Development Characterization and Optimization of Self-Micro-emulsifying Drug Delivery System to Enhance Solubility of Antihypertensive Drug

A Thesis

Submitted towards the Requirements for the Award of Degree of

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In
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By

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Under the Supervision of

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2026

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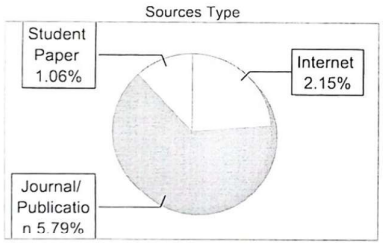
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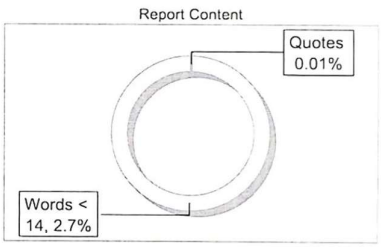
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ABSTRACT

This study focuses on the design and development of a solid Self-Microemulsifying Drug Delivery System (SMEDDS) for Azilsartan Medoxomil (AM), a poorly water-soluble drug. Excipients were selected through screening studies based on drug solubility and emulsification efficiency. Castor oil, Tween 20, and Carbitol were identified as the optimal oil, surfactant, and co-surfactant, respectively, due to their superior solubilizing and emulsifying properties. A pseudo-ternary phase diagram was constructed using these components to determine suitable formulation ratios. Among the tested surfactant/co-surfactant ratios (1:1, 1:2, and 2:1), the 1:1 ratio demonstrated the best stability and was selected for further formulation development. The optimized SMEDDS successfully produced a transparent emulsion and was capable of incorporating up to 80 mg of Azilsartan Medoxomil per milliliter of formulation without drug precipitation. The developed solid SMEDDS is expected to improve the solubility and dissolution characteristics of Azilsartan Medoxomil, potentially enhancing its oral bioavailability.

CHAPTER-1

INTRODUCTION

In oral route, drugs are administered through the mouth and absorbed primarily from the gastrointestinal tract to produce systemic effects. Oral dosage forms include tablets, capsules, syrups, suspensions, powders, and emulsions, which are designed to provide accurate dosing and ease of administration[1].

The popularity of oral drug delivery is mainly attributed to its non-invasive nature and suitability for self-medication. Compared with parenteral administration, oral formulations are easier to manufacture, transport, and store, making them economically advantageous for both patients and pharmaceutical industries. Furthermore, oral dosage forms can be formulated for immediate, delayed, or sustained release to achieve desired therapeutic outcomes[2].

After oral administration, the drug undergoes disintegration, dissolution, and absorption through the gastrointestinal mucosa. The extent and rate of absorption depend on several factors such as drug solubility, permeability, gastric emptying time, pH of the gastrointestinal tract, presence of food, and first-pass metabolism in the liver. Drugs with poor aqueous solubility often exhibit limited oral bioavailability, which has led to the development of advanced delivery systems such as nanoparticles, solid dispersions, liposomes, and Self-Microemulsifying Drug Delivery Systems (SMEDDS) [3].

Despite its advantages, the oral route also has certain limitations. Some drugs may undergo degradation in the acidic gastric environment or enzymatic metabolism before reaching systemic circulation. Additionally, drugs with poor permeability or extensive first-pass metabolism may show reduced therapeutic efficacy. Nevertheless, continuous advancements in pharmaceutical technology have significantly improved the effectiveness of oral drug delivery systems[4].

The Biopharmaceutical Classification System (BCS) is a scientific framework used to classify drug substances based on their aqueous solubility and intestinal permeability. It was developed to predict the in vivo performance of orally administered drugs and to support drug development and regulatory decisions. The BCS plays a significant role in formulation development, bioavailability

studies, and biowaiver applications for immediate-release oral dosage forms [5].

To overcome solubility-related limitations, several formulation techniques have been explored and implemented. These include [6, 7]:

- Adjustment of pH to enhance solubility
- Microemulsion systems for improved dispersion
- Self-emulsifying drug delivery systems (SEDDS)
- Modification of the solid-state properties of drugs
- Reduction of particle size to increase surface area
- Use of supercritical fluid (SCF) technology
- Formation of inclusion complexes (e.g., cyclodextrins)
- Use of co-solvents to improve drug solubility

Additional advanced approaches include:

- Micellar solubilization
- Hydrotropic solubilization techniques
- Solid dispersion systems
- Nano suspensions
- Floating drug delivery systems (e.g., floating granules)
- Cryogenic processing techniques
- Nano crystallization

These strategies aim to enhance the dissolution rate, improve bioavailability, and ultimately ensure better therapeutic outcomes for poorly soluble drugs.

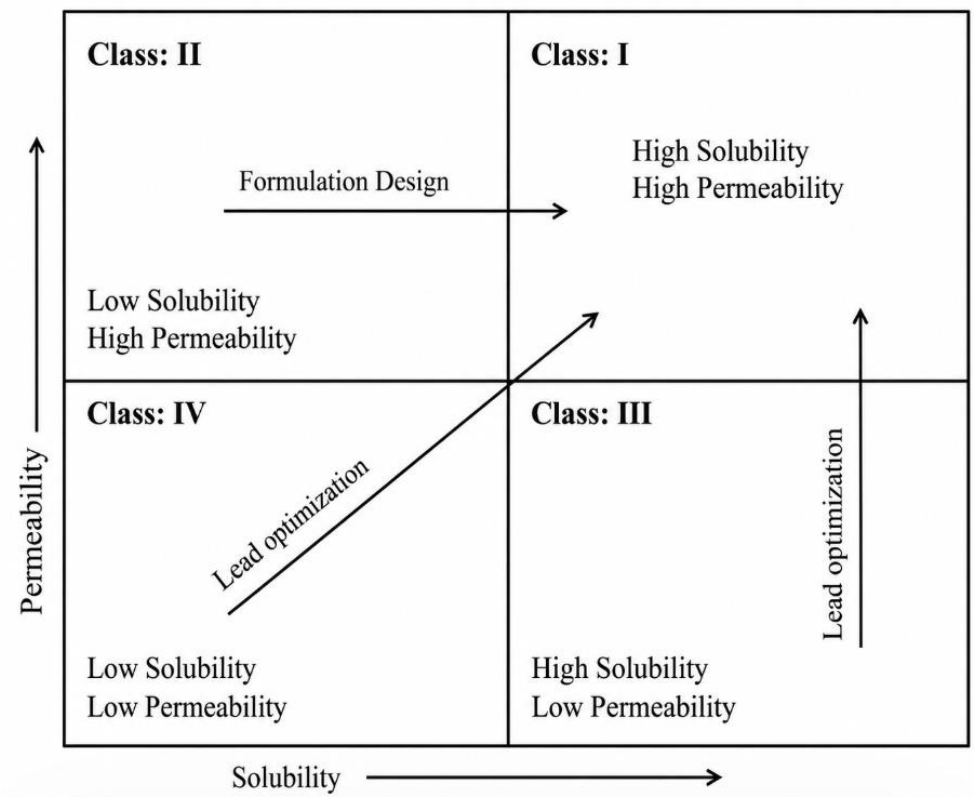


Figure 1.1: Biopharmaceutical Classification System (BCS)

1.1 Lipid Formulation Classification System

A substantial proportion of newly developed therapeutic molecules exhibit limited water solubility, which often results in inadequate dissolution in gastrointestinal fluids and consequently poor and variable oral bioavailability[8]. Lipid-based formulations address this limitation by improving drug solubilization within the gastrointestinal environment, thereby facilitating enhanced dissolution, improved permeability, and greater systemic availability following oral administration.

A wide range of lipid-based delivery systems has been developed, including simple lipid solutions, emulsions, microemulsions, self-emulsifying drug delivery systems, and dry emulsions. These systems differ in their composition, physicochemical properties, mechanism of dispersion, and interaction with

gastrointestinal fluids.

Because of the extensive variety of excipients and the numerous possible combinations available for developing lipid-based formulations, particularly self-emulsifying systems, a structured and scientifically sound classification framework became necessary. It enables formulation scientists to better understand formulation performance, predict in vivo behavior, and design optimized delivery systems using a rational, evidence-based approach rather than relying solely on empirical trial-and-error methods.

In addition to its value in formulation development, the LFCS (Lipid formulation classic system) serves as an important tool for evaluating the likelihood of drug precipitation following dilution, the extent of lipid digestion, and the overall capacity of a formulation to sustain drug solubilization during gastrointestinal transit. These attributes are particularly critical for ensuring consistent drug absorption and therapeutic efficacy. The classification system also facilitates communication among researchers, formulators, and regulatory agencies by providing a common framework for the assessment and comparison of lipid-based delivery systems[9].

Originally proposed by Colin W. Pouton in 2000 and subsequently refined in 2006, the LFCS reflects significant advances in lipid formulation science and technology[5]. In summary, the Lipid Formulation Classification System provides a comprehensive and practical framework for the development, optimization, and evaluation of oral lipid-based drug delivery systems (table 1.1). By categorizing formulations according to their composition and functional characteristics, the LFCS plays a vital role in guiding formulation design, improving predictability of in vivo performance.

Table 1.1: Lipid formulation classification system (LFCS) showing typical proportions of lipid formulations

LFCS Type	Composition	Typical Proportions (%)	Dispersion Characteristics	Examples
Type I	Oils only (triglycerides or mixed glycerides)	Oil: 100	Requires digestion; coarse emulsion formed	Simple oils, edible oils
Type II	Oils + water-insoluble surfactants	Oil: 40–80; Surfactant: 20–60	Self-emulsifying systems producing fine emulsions	SEDDS
Type IIIA	Oils + high HLB surfactants + co-solvents	Oil: 40–80; Surfactant: 20–40; Co-solvent: <20	Self-microemulsifying systems with fine droplets	SMEDDS
Type IIIB	Low oil content with high surfactant/co-solvent levels	Oil: <20; Surfactant: 20–50; Co-solvent: 20–50	Forms transparent microemulsions with very small droplets	Advanced SMEDDS
Type IV	Surfactants and co-solvents only; no oil	Oil: 0; Surfactant: 30–80; Co-solvent: 20–50	Produces clear micellar solutions	Surfactant-based formulations

Type I lipid formulations are the simplest class of lipid-based delivery systems. In these formulations, the drug is dissolved in natural oils such as triglycerides, mixed glycerides, or incorporated into conventional oil-in-water emulsions containing only a small amount of emulsifying agent[10]. Because these systems contain little or no surfactant, they exhibit limited spontaneous dispersion when exposed to aqueous gastrointestinal fluids. As a result, their effective performance depends largely on the digestive processes occurring within the gastrointestinal tract.

Following oral administration, pancreatic lipase and co-lipase hydrolyze the lipid components to form monoglycerides and free fatty acids. These digestion products subsequently interact with bile salts and phospholipids to generate mixed micellar and other colloidal structures that facilitate drug solubilization and absorption. Type I systems are particularly suitable for highly lipophilic drug molecules that possess adequate solubility in oils and require only moderate drug loading.

Type II formulations, commonly known as self-emulsifying drug delivery systems (SEDDS), contain a higher proportion of surfactants in combination with oils. Upon contact with gastrointestinal fluids and gentle agitation provided by gastric motility, these systems spontaneously form fine oil-in-water emulsions. The presence of surfactants significantly reduces interfacial tension, enabling rapid emulsification without the need for external energy [11]. Typically, the surfactant concentration in Type II systems exceeds 25% by weight, which ensures efficient self-emulsification. However, excessively high surfactant levels, particularly above 50–60%, may adversely affect the emulsification process due to the formation of viscous liquid crystalline phases at the oil–water interface [12].

Type III formulations represent a more advanced class of self-emulsifying systems and are generally referred to as self-microemulsifying drug delivery systems (SMEDDS). These systems contain oils, relatively high concentrations of hydrophilic surfactants, and often co-surfactants or co-solvents such as ethanol, propylene glycol, or polyethylene glycol. On dilution with aqueous media, they rapidly form transparent or slightly opalescent microemulsions with extremely small droplet sizes, typically in the nanometer range [13].

Surfactants and co-solvents with correspondingly lower lipid content. As a result, Type IIIB formulations generally exhibit faster dispersion and produce smaller droplet sizes [14]. However, their reduced lipid content may compromise their ability to maintain the drug in a solubilized state after dilution, thereby increasing the risk of drug precipitation in the gastrointestinal environment.

Type IV formulations are the most hydrophilic among all classes in the Lipid Formulation Classification System. Unlike the other categories, these systems do not contain traditional lipid components such as triglycerides or mixed glycerides. Instead, they are composed entirely of hydrophilic surfactants and co-solvents.

Upon dilution, Type IV systems form clear micellar solutions capable of solubilizing substantial quantities of poorly water-soluble drugs. Their high surfactant content often allows for excellent drug-loading capacity and rapid formation of very fine dispersions [15]. Nevertheless, the absence of digestible lipids may limit their ability to sustain drug solubilization under physiological conditions, particularly after dilution and during transit through the gastrointestinal tract. Consequently, there is a greater likelihood of drug precipitation in vivo compared to lipid-containing formulations. Despite this limitation, Type IV systems have been successfully employed in several pharmaceutical products. [16,17].

Table 1.2: Characteristics, advantages & disadvantages of lipid formulations[18]

LFCS Type	Characteristics	Advantages	Disadvantages
Type I	Consists only of oils such as triglycerides and mixed glycerides; requires digestion for drug release	Simple composition; good for highly lipophilic drugs; low surfactant toxicity	Poor dispersibility; limited self-emulsification; variable drug absorption
Type II	Contains oils and water-insoluble surfactants; forms coarse or fine emulsions upon dilution	Improved drug solubilization; self-emulsifying property; enhanced bioavailability	May show drug precipitation after dilution; moderate surfactant irritation
Type IIIA	Contains oils, high HLB surfactants, and small amounts of co-solvents; forms microemulsions	Excellent self-microemulsification; improved dissolution and absorption; reduced food effect	Higher surfactant concentration may cause irritation; possible stability issues
Type IIIB	Lower oil content with high surfactant and co-solvent concentration; produces transparent dispersions	Rapid dispersion; superior drug solubilization; very small droplet size	Increased risk of drug precipitation on dilution; higher surfactant toxicity

Type IV	Contains only surfactants and co-solvents without oils; forms micellar solutions	Maximum drug solubilization; clear formulations; easy dispersion	Lack of lipid digestion pathway; high risk of precipitation; greater gastrointestinal irritation due to high surfactant levels

1.1.1 Challenges in Development of Lipid-Based Formulations [19]

The overall performance, stability, and therapeutic effectiveness of these formulations are largely determined by the physicochemical properties of the excipients employed and their compatibility with the incorporated drug. Since lipid-based systems rely on the coordinated interaction of oils, surfactants, co-surfactants, and co-solvents, each component must be selected judiciously to ensure optimal formulation performance.

An ideal excipient for lipid-based formulations should be pharmacologically safe, non-toxic, and acceptable for human use. It should possess a high degree of purity and comply with regulatory standards for pharmaceutical applications. In addition, the excipient must remain chemically inert and should not undergo degradation, oxidation, or hydrolysis during manufacturing, storage, or administration. Stability during processing and throughout the product's shelf life is essential to maintain formulation integrity and therapeutic efficacy.

Excipients with high solubilization capacity help maintain the drug in a dissolved state, thereby improving dissolution and facilitating enhanced absorption after oral administration.

Surface-active properties are also highly desirable, especially in self-emulsifying systems such as SEDDS and SMEDDS. Excipients capable of reducing interfacial tension promote rapid and spontaneous emulsification upon contact with gastrointestinal fluids. This property is crucial for the formation of fine emulsions or microemulsions, which significantly enhance the surface area available for drug release and absorption.

Furthermore, the selected excipients should consistently improve oral bioavailability in a predictable and reproducible manner. Variability in excipient performance can lead to fluctuations in drug absorption, potentially affecting therapeutic outcomes. Therefore, excipients should provide reliable performance across different batches and under varying physiological conditions.

Physical and chemical stability is another essential consideration. The excipients must be compatible not only with the drug but also with other formulation

components. Incompatibility can result in undesirable interactions, including chemical degradation, phase separation, or drug precipitation, which may compromise formulation quality and stability.

For practical manufacturing considerations, excipients should ideally be non-hygroscopic, as moisture uptake can adversely affect stability, flow properties, and encapsulation efficiency. They should also be inert toward capsule shells, container closure systems, and packaging materials to prevent interactions that could impact product quality during storage.

Finally, excipients should support ease of manufacturing and be amenable to scale-up from laboratory development to commercial production. Good processability, reproducibility, and compatibility with standard pharmaceutical manufacturing equipment are essential for successful industrial application.

In summary, the selection and optimization of excipients for lipid-based formulations require a comprehensive understanding of their physicochemical characteristics, functional performance, and compatibility. Improper excipient selection may lead to formulation instability, phase separation, drug precipitation, or reduced bioavailability. Therefore, systematic screening and optimization are indispensable for the successful development of stable, effective, and commercially viable lipid-based drug delivery systems.

Table 1.3: Comparative features of all self-emulsifying formulations [20]

Self-emulsifying formulations (SEFs)	**Self-micro emulsifying formulations (SMEFs)**	**Self-nanoemulsifying formulations (SNEFs)**
Isotropic mixture of the drug compound, surfactant, co-surfactant & lipid phase which emulsify under conditions of gentle agitation, when come in contact with gastro-intestinal fluid.		
• Oil droplet size in the dispersion ranges from 200 nm to 5 µm. • Appearance of dispersion is turbid. • Formulations formed using surfactants of HLB < 12.	• Oil droplet size in the dispersion is less than 200 nm. • Appearance of dispersion is optically clear to translucent. • Formulations formed using surfactants of HLB > 12.	• Oil droplet size in the dispersion ranges from less than 100 nm (small poly-dispersibility index). • Appearance of dispersion is optically clear. • Formulations formed using surfactants of HLB > 12.
All these formulations have high solubilizing & dispersibility capacity		
• Thermodynamically stable in physiological conditions. • Development may require characterization of ternary phase diagram.	• Thermodynamically stable in physiological conditions. • Development may require characterization of pseudo ternary phase diagram.	• No phase separation during storage. • Development may require characterization • of pseudo ternary phase diagram.

1.1.2. Marketed Lipid-Based Formulations

The successful commercialization of oral lipid- and surfactant-based formulations for poorly water-soluble drugs has significantly encouraged researchers to further explore and develop this field. These formulations have demonstrated improved solubility, enhanced dissolution, and better bioavailability compared to

conventional dosage forms. As a result, several lipid-based and self-emulsifying formulations have been successfully introduced into the pharmaceutical market. Notable examples include Sandimmune®, Sandimmune Neoral®, Norvir® (ritonavir), and Fortovase® (saquinavir), all of which have been formulated as self-emulsifying formulations (SEFs). Their pharmacokinetic profiles have been widely investigated and reviewed, particularly by Ritschel (1996), highlighting their improved and consistent bioavailability. On dilution with aqueous medium, above formulations spontaneously form polydispersed oil-in-water macro- or micro-emulsions, which enhance drug dispersion and facilitate absorption in the gastrointestinal tract [21,22]. This behavior demonstrates the effectiveness of lipid-based systems in improving the delivery of poorly soluble drugs.

Another important example is the formulation of ritonavir marketed as Norvir®. Initially, Norvir® was developed as an amorphous, semi-solid dispersion in hard gelatin capsules. This transformation adversely affected the drug's dissolution rate and bioavailability, which lead to significant therapeutic concerns and finally resulting into temporary withdrawal of the Norvir® product from the market in 1998. Subsequently. In the year, 1999 Norvir® was successfully reformulated and reintroduced as a thermodynamically stable emulsion. This new formulation contained 100 mg of Ritonavir solubilized in a self-emulsifying excipient system and was delivered in soft gelatin capsules, which improved stability, dissolution, and bioavailability [23,24].

Saquinavir provides another example of the evolution of lipid-based drug delivery systems. It was first introduced in 1996 as a conventional solid oral dosage form under the brand name Invirase®. However, due to limitations in solubility and bioavailability, it was later reformulated as a self-emulsifying lipid-based formulation in soft gelatin capsules under the brand name Fortovase®, containing 200 mg of saquinavir. This reformulation significantly improved drug solubility and absorption. Despite its advantages, Fortovase® was withdrawn from the market in 2006 due to lack of commercial demand rather than formulation issues. Currently, saquinavir continues to be available in 200 mg and 500 mg strengths in various hard gelatin capsule formulations [25].

Table 1.4: List of Selected Commercially Available Lipid-Based Formulations for Oral Administration[26,28]

Brand Name	Drug	Type of Lipid-Based Formulation	Therapeutic Use
Neoral®	Cyclosporine	Microemulsion preconcentrate (SMEDDS)	Immunosuppressant
Sandimmune®	Cyclosporine	Oil-based solution/emulsion	Immunosuppressant
Norvir®	Ritonavir	Soft gelatin lipid capsule	Antiretroviral
Fortovase®	Saquinavir	Soft gelatin lipid formulation	Antiretroviral
Kaletra®	Lopinavir + Ritonavir	Lipid-based soft gelatin capsule	Antiretroviral
Agenerase®	Amprenavir	Self-emulsifying lipid formulation	Antiretroviral
Rocaltrol®	Calcitriol	Lipid solution capsule	Vitamin D analogue
Lipirex® / Tricor®	Fenofibrate	Lipid micronized formulation	Antihyperlipidemic
Cesamet®	Nabilone	Lipid-based capsule	Antiemetic
Prograf®	Tacrolimus	Lipid-based capsule formulation	Immunosuppressant
Sporanox®	Itraconazole	Oral lipid solution in capsule	Antifungal
Accutane®	Isotretinoin	Lipid-filled soft gelatin capsule	Anti-acne agent
Absorica®	Isotretinoin	Lipid-based oral capsule	Anti-acne agent
Vesanoid®	Tretinoin	Lipid formulation capsule	Anticancer
Tipranavir® (Aptivus®)	Tipranavir	Self-emulsifying lipid capsule	Antiretroviral

1.2 Self-Emulsifying Drug Delivery Systems (SEDDS) [27,28,29]

The increasing number of drug candidates with low aqueous solubility has necessitated the development of advanced delivery systems that can overcome dissolution-limited absorption. Lipid-based formulations represent a diverse class of drug delivery systems that vary widely in their physical characteristics, ranging from simple triglyceride-based solutions to more complex and sophisticated systems such as self-emulsifying drug delivery systems (SEDDS).

When a drug dissolves slowly, only a limited amount becomes available for permeation across the gastrointestinal membrane, resulting in low and often highly variable oral bioavailability [30]. Lipid-based drug delivery systems effectively overcome this barrier by maintaining the drug in a solubilized state prior to and after administration. By bypassing the dissolution step, these systems significantly enhance the availability of the drug for absorption, thereby improving both the rate and extent of systemic uptake. This ability to sustain the drug in a dissolved form is widely regarded as one of the most important prerequisites for the successful performance of lipid-based formulations. Additionally, such systems help minimize variability in absorption caused by physiological factors such as gastrointestinal pH, motility, and the presence or absence of food.

A major advantage of lipid-based drug delivery systems is their remarkable versatility [31]. Such flexibility makes lipid-based systems highly adaptable for a diverse range of poorly soluble therapeutic agents.

The composition of these formulations can also be extensively modified to optimize performance. They may contain pure triglyceride oils or blends incorporating diglycerides and monoglycerides, depending on the required solubilization capacity and emulsification behavior. In addition, both lipophilic and hydrophilic surfactants can be employed, often in combination with co-surfactants or hydrophilic co-solvents, to improve drug solubilization and facilitate efficient emulsification. This adaptability in excipient selection enables the development of formulations with enhanced stability, improved drug-loading capacity, and superior in vivo performance.

Non-digestible lipids, such as mineral oils and sucrose polyesters, are poorly absorbed in the gastrointestinal tract. As a result, they may retain the incorporated drug within the oil phase, limiting its release and reducing absorption. This digestion produces amphiphilic molecules that interact with endogenous bile salts and phospholipids to form mixed micelles and other colloidal structures.

Upon exposure to aqueous gastrointestinal fluids and the gentle mechanical agitation provided by gastrointestinal motility, SEDDS spontaneously form fine oil-in-water emulsions. Depending on their composition, these systems may generate conventional emulsions, nanoemulsions, or microemulsions. When the resulting droplets are in the nanometer range and the dispersion is optically clear or translucent, the system is referred to as a self-microemulsifying drug delivery system (SMEDDS). When the droplet size is slightly larger but still within the nanoscale range, the formulation is often termed a self-nanoemulsifying drug delivery system (SNEDDS).

The spontaneous emulsification process is central to the effectiveness of these systems. It ensures rapid dispersion of the formulation in gastrointestinal fluids and maintains the drug in a solubilized state throughout the absorption process. The formation of extremely small droplets results in a dramatic increase in interfacial surface area, which accelerates drug release and promotes efficient absorption. This large surface area also facilitates close interaction with the intestinal epithelium, further enhancing drug uptake.

SEDDS and SMEDDS offer several distinct advantages over conventional oral dosage forms. They provide improved and more reproducible drug release profiles, reduced inter- and intra-subject variability, and decreased dependence on physiological variables such as gastric emptying rate, intestinal motility, and fed or fasted state. These attributes contribute to more predictable therapeutic outcomes. Modern formulations frequently utilize medium-chain triglycerides and non-ionic surfactants, which are preferred because of their excellent biocompatibility, lower toxicity, and superior emulsification efficiency. Conventional SEDDS typically produce emulsions approximately 200 nm to several micrometers, resulting in turbid dispersions. In contrast, SMEDDS generate droplets usually smaller than 100 nm, producing clear or slightly opalescent systems with superior solubilization efficiency[31].

Ultimately, both SEDDS and SMEDDS provide extensive interfacial surface area, creating highly favorable conditions for the lipophilic drugs. Their ability to enhance solubilization, improve bioavailability, and reduce pharmacokinetic variability has established them as highly promising and versatile platforms in contemporary pharmaceutical formulation development. These systems continue to play an increasingly important role in addressing the challenges associated with oral delivery of lipophilic therapeutic agents.

Properties of SEDDS [32]

➢ They are capable of rapidly self-emulsifying in gastrointestinal fluids. Upon dilution, they spontaneously form fine oil-in-water (o/w) emulsions with very small droplet size, which enhances drug dispersion and promotes faster dissolution and absorption.

➢ The versatility of hydrophilic and lipophilic incorporation allows improved solubilization of poorly water-soluble drugs as well as enhanced delivery of drugs with varying physicochemical properties, thereby increasing formulation flexibility.

➢ They can be formulated into both liquid and solid dosage forms, such as capsules, tablets, or powders. This adaptability provides convenience in handling, storage, and administration, and also supports large-scale manufacturing and commercialization.

➢ They require a less dose of drug compared to conventional dosage forms due to improved solubility, enhanced absorption, and increased bioavailability. This reduction in dose may help in minimizing dose-related side effects and improving patient compliance.

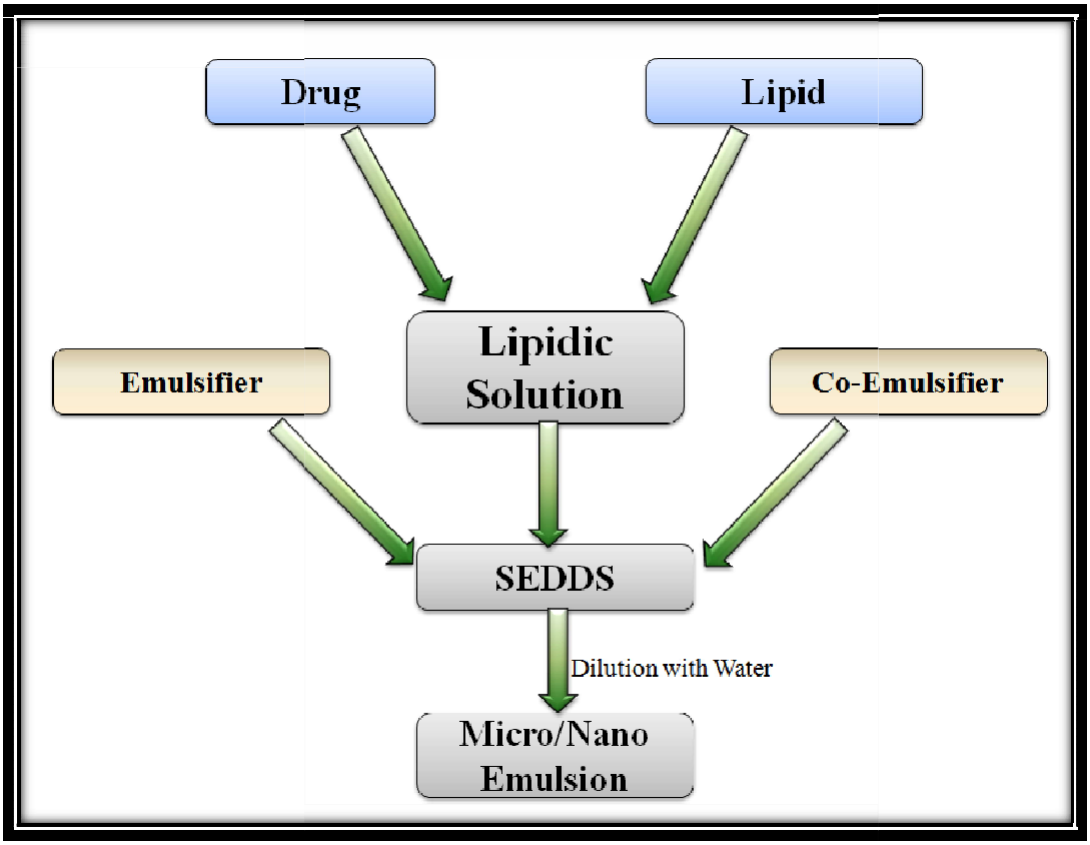


Figure 1.2: Schematic flow chart on general strategy of formulating the Self emulsifying systems and their subsequent conversion to the Micro/ Nano emulsions [12]

1.2.2 Advantages associated with SEDDS [33]

➢ SEDDS provide protection of the drug from the harsh gastrointestinal (GIT) environment, including enzymatic degradation and pH variations, thereby improving drug stability during transit through the gastrointestinal tract.

➢ They enable selective targeting of the drug toward specific absorption windows within the GIT, which can enhance the efficiency of drug absorption and improve therapeutic outcomes, especially for drugs with site-specific absorption.

➢ They significantly enhance oral bioavailability by improving drug solubilization and maintaining the drug in a dissolved state, which facilitates faster and more efficient absorption across the intestinal membrane.

➢ They offer a consistent drug absorption profile by minimizing variability caused by physiological conditions such as pH, motility, and food intake, thereby ensuring more predictable therapeutic effects.

➢ They provide better control over drug delivery profiles, allowing formulation scientists to modify release characteristics and optimize drug performance according to therapeutic requirements.

➢ They exhibit versatility in dosage form design, as they can be easily incorporated into both liquid and solid dosage forms, enhancing patient convenience and formulation flexibility.

➢ They enable more predictable therapy by reducing variability in drug absorption, including food effects, which is particularly beneficial for drugs that show significant food-dependent bioavailability.

➢ They can accommodate relatively high drug payloads, making them suitable for delivering drugs that require higher doses without compromising solubility and stability.

➢ They provide protection to sensitive drug substances, especially those prone to degradation, by encapsulating them within a lipid matrix and shielding them from external environmental factors.

1.2.3 Disadvantages

➢ Drug release from SEDDS is often dependent on digestion processes rather than simple dissolution, making conventional testing methods inadequate.

➢ The currently available in vitro models require further development and validation to accurately predict in vivo performance, and their reliability still needs to be fully established.

➢ Further formulation development depends largely on establishing in vitro–in vivo correlations (IVIVC), which requires the preparation and evaluation of multiple prototype lipid-based formulations in suitable animal models.

➢ Strong chemical instability and need of more surfactant concentration (30% approx.), which may lead to gastrointestinal irritation or toxicity upon prolonged use.

1.2.4 Mechanism of Self-Emulsification [34]

The mechanism of self-emulsification is governed by interfacial phenomena, thermodynamics, and the physicochemical properties of formulation components. The aqueous phase penetrates the formulation, allowing surfactant molecules to orient themselves at the oil–water interface. Surfactants reduce the interfacial tension between the oil and aqueous phases, thereby facilitating the spontaneous dispersion of the oil phase into tiny droplets. Co-surfactants further assist by increasing the flexibility of the interfacial film and stabilizing the newly formed droplets.

The driving force for self-emulsification is the reduction in free energy associated with the formation of the emulsion. Normally, the creation of new surfaces between oil and water requires energy input; however, in self-emulsifying systems, the entropy gain achieved during dispersion exceeds the energy required for interface formation. As a result, the system spontaneously forms a thermodynamically or kinetically stable emulsion with minimal external energy input[35].

The mechanism can be explained by the free energy equation for emulsion formation by eq. 1:

$$\Delta G = \Sigma N \pi r^2 \sigma \text{.....(1)}$$

where,

ΔG = free energy is associated with the process

r = radius of droplets

N = number of droplets

σ = represents the interfacial energy between the oil and aqueous phases.

In conventional emulsions, the oil and water phases are thermodynamically unstable and naturally tend to separate over time. This separation occurs because the system seeks to reduce its interfacial area and, consequently, minimize its free energy. To counteract this tendency, conventional emulsifying agents stabilize the emulsion by adsorbing at the oil–water interface. They form a protective monolayer around each droplet, thereby lowering the interfacial tension and creating a physical barrier that prevents droplet coalescence. Despite this stabilization, conventional emulsions remain kinetically stable rather than thermodynamically stable[36].

In contrast, self-emulsifying systems such as SEDDS and SMEDDS undergo spontaneous emulsification because the free energy required for emulsion formation is extremely low and may even approach zero or become slightly negative under optimal conditions. This unique thermodynamic advantage arises from the carefully selected combination of oil, surfactant, and co-surfactant. For spontaneous emulsification to occur, the interfacial film formed between the oil and aqueous phases must possess very low resistance to deformation. In other words, the interface should be sufficiently flexible to allow rapid disruption under the gentle agitation provided by gastrointestinal motility[36].

Subsequent water uptake leads to the formation of intermediate mesophases, such as liquid crystalline or gel-like structures, at the oil–water interface. The ease with which water penetrates these interfacial phases is directly related to the efficiency of emulsification. A more permeable and flexible interfacial structure allows rapid hydration, swelling, and eventual disintegration[37].

As hydration proceeds, the liquid crystalline structures become increasingly unstable. Gentle agitation, such as that produced by normal gastrointestinal

movements, disrupts these swollen interfacial layers. This disruption causes the bulk oil phase to fragment into extremely fine droplets, resulting in the formation of a stable microemulsion or nanoemulsion.

1.2.5. Excipients Used in SMEDDS

The selection of excipients is one of the most critical aspects in the development of SMEDDS formulations. Since these systems are intended for oral administration, all components must be pharmaceutically acceptable, non-toxic, biocompatible, and suitable for long-term use. Regulatory approval, safety profile, and compatibility with the active pharmaceutical ingredient are essential considerations during excipient selection[38].

Early investigations demonstrated that successful self-microemulsification depends on several interrelated factors. Even minor variations in these parameters can significantly affect the efficiency of emulsification, droplet size, stability, and drug-loading capacity[39]. The surfactant reduces interfacial tension and facilitates spontaneous droplet formation, while the co-surfactant further enhances interfacial fluidity and promotes the formation of ultra-fine droplets. Together, these components must be carefully balanced to achieve optimal self-emulsification performance.

Importantly, only specific combinations of pharmaceutical excipients are capable of producing efficient and stable SMEDDS. Not all oils, surfactants, and co-surfactants are mutually compatible, nor do they all possess the required emulsification characteristics. Therefore, systematic screening and optimization of excipients are essential during formulation development. This process ensures the formation of a robust system capable of rapid self-emulsification, high drug solubilization, long-term stability, and enhanced oral bioavailability.

In summary, the remarkable performance of SMEDDS arises from a delicate interplay of thermodynamic and interfacial phenomena, combined with the judicious selection of excipients [39]

1.2.5.1 Oils:

The oil phase plays a crucial role in enhancing drug solubilization, facilitating

self-emulsification, improving intestinal permeability, and promoting lymphatic transport. The incorporation of suitable oils helps maintain the drug in a dissolved state throughout its transit in the gastrointestinal tract, thereby preventing precipitation and enhancing oral bioavailability [40].

The selection of oil is a critical factor in SMEDDS formulation development and depends on several parameters such as drug solubilization capacity, compatibility with surfactants, digestibility, oxidative stability, and ability to form stable microemulsions. Oils with higher drug solubilization potential are preferred because they reduce the likelihood of drug precipitation upon aqueous dilution. Furthermore, the type and concentration of oil significantly influence droplet size, emulsification efficiency, and drug release characteristics [41].

Oils used in SMEDDS are generally classified into long-chain triglycerides (LCTs), medium-chain triglycerides (MCTs), and semi-synthetic lipid excipients. Medium-chain triglycerides are more commonly employed because of their superior solvent capacity and better self-emulsification properties compared to long-chain triglycerides [42].

Table 1.5: Type of oils used SMEDDS Formulations

Type of Oil	Marketed Product	Drug
Corn oil	Depakene Capsule	Valproic acid
Olive oil	Sand immune Oral Solution	Cyclosporine
Sesame oil	Marinol	Dronabinol
Soybean oil	Accutane	Isotretinoin
Peanut oil	Prometrium	Progesterone
Beeswax	Vesanoid	Tretinoin
Hydrogenated soybean oil	Accutane	Isotretinoin

1.2.5.2. Surfactants:

Surfactants are essential components of Self-Microemulsifying Drug Delivery Systems (SMEDDS) that facilitate the spontaneous formation of microemulsions upon dilution with gastrointestinal fluids. Their primary role is to reduce the

interfacial tension between the oil and aqueous phases, enabling the formation of fine and stable oil-in-water dispersions under mild agitation. By lowering the free energy required for emulsification, surfactants promote rapid self-emulsification and improve drug solubilization and absorption [44].

Surfactants may also enhance intestinal permeability and inhibit efflux transporters such as P-glycoprotein, thereby improving drug absorption. They are broadly classified into ionic and non-ionic surfactants, with non-ionic surfactants being most commonly used due to their lower toxicity, better biocompatibility, and greater stability over a wide pH range [45] [46].

The effectiveness of surfactants in SMEDDS depends on:

- Ability to reduce interfacial tension
- Compatibility with oil and drug
- Capacity to form stable microemulsions
- Safety for oral administration
- Influence on droplet size and stability

Higher surfactant concentrations generally improve emulsification efficiency and reduce droplet size; however, excessive levels may cause gastrointestinal irritation and toxicity, requiring careful optimization during formulation development.

Table 1.6: Type of surfactants used in SMEDDS Formulation

Surfactant	Marketed Product	Drug
Span 80, Tween 80	Gengraf soft gelatin capsule	Cyclosporine
Tween 20	Targretin Hard gelatin Capsule	Bexarotene
Cremophor RH 40	BCNU self-emulsifying implant	Carmustine
D-alpha Tocopheryl Poly ethylene Glycol 1000 Succinate (TPGS)	Agenerase Soft Gelatin capsule, Agenerase oral solution	Amprenavir
Labrafil M 1944 CS	Sand immune oral solution	Cyclosporine

1.2.5.3 Co- surfactants:

Co-surfactants and co-solvents are important excipients in Self-Microemulsifying Drug Delivery Systems (SMEDDS) that enhance the efficiency of self-emulsification and improve the stability of the microemulsion system [48].

These excipients also improve the solubilization capacity of the formulation by increasing the solubility of both the drug and surfactant within the system. This helps maintain the drug in a dissolved state and minimizes the risk of precipitation during storage or after dilution in gastrointestinal fluids. In addition, co-surfactants promote rapid dispersion and contribute to the formation of microemulsions with smaller droplet size and narrow size distribution, which enhances drug dissolution and oral bioavailability [49]. Short- and medium-chain alcohols or hydrophilic solvents are commonly used as co-surfactants and co-solvents because of their ability to improve interfacial flexibility and emulsification efficiency. They help destabilize the rigid surfactant film at the interface, thereby allowing easier curvature and formation of stable microemulsion systems.

Table 1.7: Types of Co-surfactants Used in SMEDDS Formulations [50]

Co-surfactant	Marketed Preparations
Polyethylene Glycol (PEG)	Targretin® soft gelatin capsule, Gengraf® hard gelatin capsule, Agenerase® soft gelatin capsule
Glycerin	Sand immune® soft gelatin capsule
Propylene Glycol	Neoral® soft gelatin capsule, Neoral® oral solution, Gengraf® hard gelatin capsule, Lamprene® soft gelatin capsule
Ethanol	Neoral® soft gelatin capsule, Neoral® oral solution, Sand immune® soft gelatin capsule, Sand immune® oral solution, Gengraf® hard gelatin capsule

1.3 Solid Self emulsifying drug delivery system (S-SMEDDS)

1.3.1 Significance of S-SMEDDS

This innovative approach combines the exceptional solubilization and bioavailability-enhancing properties of liquid SMEDDS with the numerous

pharmaceutical and technological advantages associated with solid dosage forms. By maintaining the drug in a molecularly dispersed or solubilized state within the lipid matrix, S-SMEDDS effectively overcome the dissolution limitations commonly associated with hydrophobic drug molecules[51].

Upon exposure to aqueous media, such as gastrointestinal fluids, S-SMEDDS rapidly disperse under the influence of gentle agitation generated by normal gastrointestinal motility. The formation of such ultra-fine droplets offers several important advantages. Most notably, the large interfacial surface area created by these droplets facilitates rapid partitioning of the drug from the dispersed phase into the surrounding aqueous environment and subsequently across the gastrointestinal membrane[52].

Because the drug is presented in a pre-dissolved state, the dissolution step is effectively bypassed. This leads to faster drug release, improved absorption, and significantly enhanced oral bioavailability. Moreover, the uniformity of droplet formation contributes to more predictable drug absorption, thereby reducing inter- and intra-subject variability. As a result, S-SMEDDS can provide more consistent therapeutic outcomes and improved clinical performance.

In addition to their biopharmaceutical advantages, S-SMEDDS offer all the practical benefits associated with solid dosage forms. These include superior physical, chemical, and microbial stability compared to liquid formulations. Solid systems are generally less susceptible to issues such as leakage, phase separation, precipitation, and oxidative degradation, which are commonly encountered with liquid SMEDDS during storage and handling.

Furthermore, S-SMEDDS provide greater flexibility in dosage form design. They can be formulated into a variety of convenient and patient-friendly dosage forms, including capsules, tablets, pellets, granules, powders, and sachets. This versatility facilitates easier manufacturing, improved portability, enhanced patient compliance, and better commercial acceptability. Solid dosage forms also simplify packaging, transportation, and large-scale industrial production.

Conventional SMEDDS are often restricted to liquid or semi-solid formulations because many of the oils, surfactants, and co-surfactants used are liquid at room

temperature. While these liquid systems are effective, they may present challenges related to stability, handling, encapsulation, and patient convenience. The development of S-SMEDDS successfully addresses these limitations by converting liquid formulations into free-flowing, compressible, and stable solid systems without compromising their self-microemulsifying properties.

Consequently, S-SMEDDS have gained considerable attention in recent years as a superior alternative to traditional liquid SMEDDS. They retain the essential advantages of lipid-based self-emulsifying systems—namely enhanced solubilization, improved dissolution, and increased bioavailability—while overcoming many of the drawbacks associated with liquid formulations. They are prepared by converting liquid or semisolid systems into solid forms using techniques such as spray drying, adsorption onto solid carriers, melt extrusion, and nanoparticle methods.

These systems may be formulated as powders, capsules, tablets, pellets, or nanoparticles [52]. They enhance the oral bioavailability of poorly water-soluble drugs while offering better portability and manufacturing convenience compared to liquid formulations [53].

Evaluation of S-SMEDDS includes both self-emulsification efficiency and conventional solid dosage parameters such as hardness, friability, flow properties, and dissolution behavior. Modern S-SMEDDS are available in various forms including capsules, tablets, pellets, microspheres, and nanoparticles.
[54,55].

1.3.2Advantages of S-SMEDDS

- Low production cost compared to liquid lipid formulations.
- Easy and convenient manufacturing process with better process control.
- Excellent physical, chemical, and microbiological stability.
- High batch-to-batch reproducibility.
- Improved patient compliance due to ease of administration.
- Available in convenient solid dosage form.
- Spontaneously forms fine oil-in-water microemulsions upon contact with gastrointestinal fluids.
- Produces thermodynamically stable systems.

- Significantly enhances the solubility of lipophilic drugs.
- Bypasses the dissolution step.
- Improves the drug absorption rate.
- Provides enhanced and reproducible oral bioavailability.
- Produces more consistent plasma concentration–time profiles.
- May reduce the required therapeutic dose.
- Facilitates faster drug release
- Protects drugs from degradation in the harsh gastrointestinal environment.
- Enables selective target specific absorption site in GIT.
- Particularly suitable for drugs exhibiting dissolution rate-limited absorption.
- Improves therapeutic efficacy and patient acceptance.

1.3.3 S-SMEDDS Overcoming the Need for Liquid SMEDDS[56]

- More preferred than liquid SMEDDS due to superior stability and convenience.
- Remains solid at room temperature while retaining liquid SMEDDS advantages.
- Rapidly forms microemulsions upon contact with aqueous media.
- Eliminates issues such as leakage, phase separation, and precipitation associated with liquid formulations.
- Avoids the need for soft gelatin capsule manufacturing.
- Reduces dependence on outsourcing during early product development.
- Can be conveniently filled into hard gelatin or HPMC capsules.
- Offers easier handling, packaging, storage, and transportation.
- Provides greater formulation stability during long-term storage.
- Exhibits better batch-to-batch reproducibility.
- Allows accurate dosing and improved content uniformity.
- Compatible with conventional solid dosage manufacturing equipment.
- Can be formulated into multiple dosage forms, including:
    - Hard gelatin capsules
    - Tablets
    - Pellets
    - Granules

- Powders
- Fast-dissolving tablets
- Oral films
- Sachets

- Improves patient convenience and compliance.
- Simplifies large-scale manufacturing and commercialization.

1.4 Solidification Techniques [57]

Solidification techniques are employed to convert liquid or semisolid Self-Microemulsifying Drug Delivery Systems (SMEDDS) into solid dosage forms while retaining their self-emulsifying properties. These techniques improve formulation stability, handling, portability, and patient compliance.

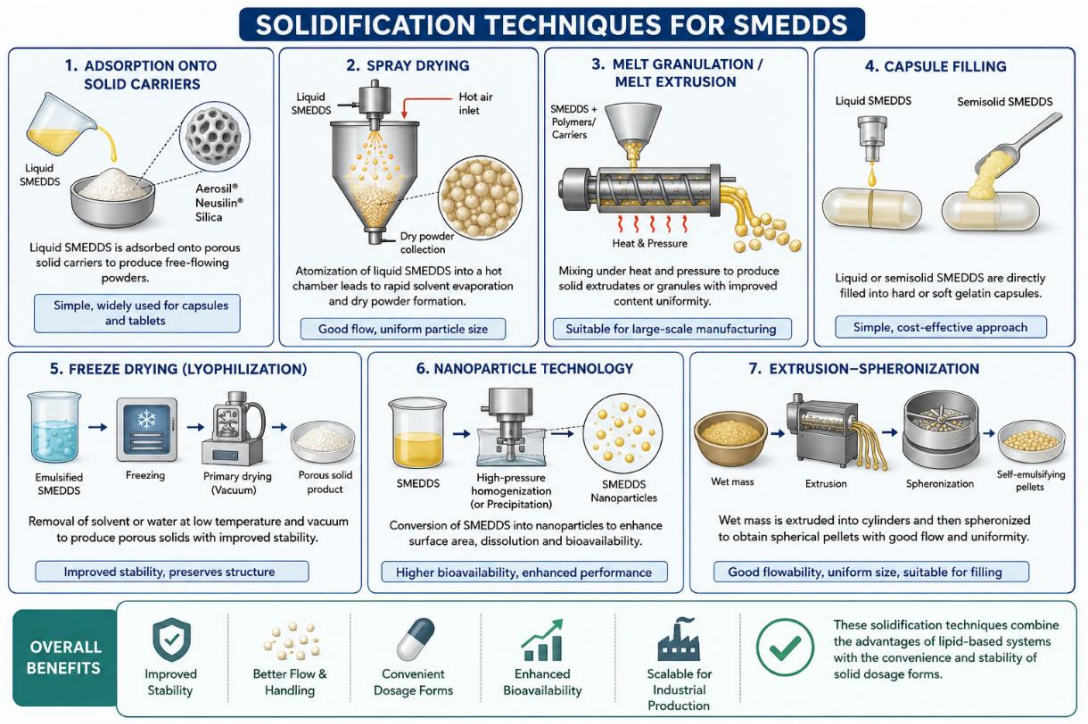


Figure 1.3: Solidification techniques for SMEEDS

1.5 Types of solid-SEDDS Formulation

Solid SEDDS are generally preferred over liquid systems due to several practical and pharmaceutical advantages. Liquid formulations, although effective, often suffer from issues such as leakage from capsules, poor stability, handling difficulties, and challenges during transportation. In contrast, solid SEDDS offer improved physical and chemical stability, ease of handling, better patient

compliance, and suitability for large-scale manufacturing. These advantages make solid SEDDS more favorable for commercial and clinical applications.

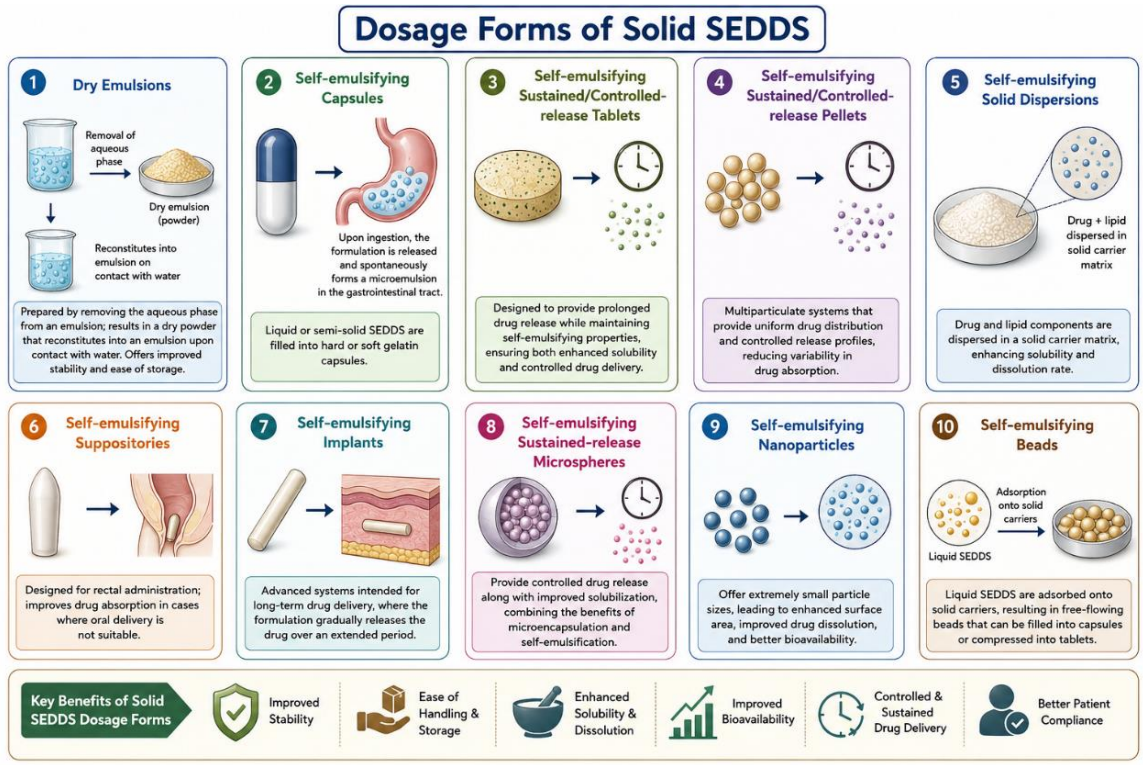


Figure 1.4: Dosage forms of Solid SEDDS

The versatility of solid SEDDS allows for the development of a wide range of dosage forms tailored to specific therapeutic needs. Their superior stability, ease of handling, and improved patient acceptability make them a promising approach for delivering poorly water-soluble drugs.

CHAPTER-2

REVIEW OF LITERATURE

Darl Norwood and colleagues provide detailed information regarding Olmesartan medoxomil (OLM), Highlighting its pharmacological importance and their therapeutic application. Olmesartan medoxomil Is identified one of the newest angiotensin 2 receptor blockers (ARBS) and is approved in the United states for effective management of hypertension. The authors emphasize that olm is generally well tolerated by patients and exhibits and advice effect profile comparable to that of a placebo however slightly higher incidence of dizziness has beed Observed in patients receiving Olmesartan medoxomil. Importantly, the drug is reported to have minimal to no Significant drug to drug interaction making it as safer option for patients who may be on multiple medications.

Furthermore, Olmesartan medoxomil Provides consistent and smooth 24 hour blood pressure control when administrator once daily which enhance patient compliance and treatment outcomes the article also discuss comparative studies involving other antihypertensive agents such as captopril, losaetan, valsartan, and irbesartan. this comparisons are just that olm demonstrates superior or at least comparable efficiency in reducing blood pressure levels as a result, Olmesartan medoxomil is considered a valuable alternative antihypertensive therapy, particularly for patients who are unable to tolerate angiotensin-covering enzyme (ACE) inhibitors, Despite its benefits, the authors nor the AC east inhibitors and certain arbs are also used in management of conditions such as heart failure ventricular dysfunction following myocardial, infraction and proteinuria. Therefore further clinical research is necessary to firmly established the role of Olmesartan medoxomil As a cardioprotective enrenum protective agent continued investigation will help determine its long term benefits and broader therapeutic potential its cardiovascular and renal disease[61].

Ketan T. Savjani et al. In another significant contribution Ketan T. Savjani and Coors discuss the concept of solubility and its critical role in pharmaceutical sciences. More than 40% of newly developed pharmaceutical compounds are poorly water-soluble, which significantly limits their bioavailability and therapeutic effectiveness. Since a drug must be in a dissolved state at the site of absorption to exert its therapeutic action, enhancing solubility has become a major focus in formulation development. Overall,

the article underscores the importance of solubility in drug development and highlights the need for innovative approaches to overcome solubility-. Related challenges in pharmaceutical research and formulation design[62].

Kyatanwar A. U. et al. discusses that the effectiveness of SMEDDS depends on the careful selection and optimization of formulation components. The oil phase provides solubilization for lipophilic drugs, while surfactants reduce interfacial tension and facilitate spontaneous emulsification. Co-surfactants further improve interfacial flexibility, promote the formation of ultra-fine droplets, and enhance system stability. Although relatively high concentrations of surfactants are often required for efficient self-emulsification, excessive amounts may cause gastrointestinal irritation or toxicity. Therefore, achieving an optimal balance between emulsification efficiency and safety is essential.

Furthermore, the self emulsification efficiency of SMEDDS Is strongly influenced by the concentration and ratio of surface cans and coarse Africans used. The authors also point out that the size and surface change of the oil droplets formed during Emulsification are critical placement that's that directly fact gastroesophageal absorption. Smaller drop table sizes increase the surface area available for drug dissolution common thereby improving observation. This droplet characteristics are, intern, dependent on the formulation composition. The article also provides insights into the mechanism by which SMEDDS Are transported through the gastrointestinal tract(git). However, it acknowledges that there is still limited understanding of the formulation parameters govern Optimal in vivo performance. Significant challenge highlighted is the lack of reliable in vitro testing method that can accurately predict in vivo performance, which has hindered the successful development and optimization of SMEDDS[64].

Sapra K. et al. Presented a comprey overview of Self-Emulsifying Drug Delivery System. This systems are part particularly beneficial for drugs classified under biopharmaceutics classification systems(BCS) Class 2 and 4, where solubility is a major limited dating factor. Upon overall administration, Saints formulation interact with gastrointestinal Fluids and for Tania sleeve form oil in water emulsion. This occurs as the system observes water from its surrounding environment, resulting in the dispersion of the formulation into fine droplets. The formation of smaller carpet

significantly enhances the surface area available for drug dissolution and permission, thereby improving drug absorption and bioavailability

The Article also explores various technological advancements related to solar SEDDS Formulation. Such as adoption onto solid carries spray drying, melt granulation and extraction spheronization are described in detail. Additionally, the preparation of other solid and semi solid dosage forms including tablets, common capsules, beads, and microspheres, is explained commonly by providing a broader perspective on the where stability of SEDDS technology[65]

Selvam P.R. et al. highlights various solidification techniques used to transform liquids seeds into solid forms well retaining their self famous fine properties. The study underscores the growing importance of seeds in modern pharmaceutical development the carbon the advantages of both liquid and solid dosage form Mrs make Kingdom Making them A highly effective strategy for addressing Solubility challenges in drug delivery

The development of solid self- Emulsifying drug delivery system has gained significant importance in recent years, as a systems enable the preparation of final dosage form in solid state while returning the advantages of liquid formulation. One of the most critical aspects in the formulation of solid SEDDS In this careful selection of excipients.

Selection of excipients also consider their functional roles just improving flow properties dancing compressibility, and maintaining the self-emulsifying characteristics of the formulation. Expanding the range of excipients Available and improving the understanding of formulation techniques and optimization strategies, it is expected that a greater number of Poly water- soluble drugs can be successfully formulated as solved SEDDS In the future this advancement holds promise for improving drug stability common scalability, and patient acceptability[66].

Sharma S. et al. demonstrated that S-SMEDDS systems are particularly effective for the oral delivery of lipophilic compounds, as they significantly enhance solubility, dissolution rate, gastrointestinal absorption, and ultimately oral bioavailability. Numerous studies cited in their work have consistently shown that S-SMEDDS can

overcome the dissolution limitations associated with hydrophobic drugs, thereby improving their therapeutic performance and ensuring more reliable clinical outcomes.

In addition to their biopharmaceutical advantages, S-SMEDDS offer several practical benefits over conventional liquid SMEDDS. These include lower production costs, simplified manufacturing processes, enhanced physical and chemical stability during storage, and improved patient compliance owing to their ease of handling, transportation, and administration. Moreover, S-SMEDDS provide exceptional flexibility in dosage form design and can be formulated into tablets, capsules, granules, pellets, and other solid oral dosage forms. Their adaptability also extends to alternative routes of administration, such as topical and parenteral delivery, thereby broadening their pharmaceutical applications and making them a versatile platform for modern drug delivery[67].

Ravel C. at al. developed an optimized SMEDDS formulation using a pseudo-temary face diagram, which help identify the ideal ratio of components of stable and sufficient emulsification. The optimise liquid SMEDDS exhibited where is small particle size(approximately 36.4 NM), is it a potential of -22.2 MV, and excellent vitro drug release (around 99.35%). This characteristics indicate improves stability and enhanced drug dissolution.

To further improve the particle of the, the optimiser liquid SMEEDS was converted into solid from using adsorbents such as Neusilin US 2 and fujicalin. Among the tester, formulation S3 containing 500 MG of Neusilin US to demonstrated the highest drug(approximately 99.02%) along with desirable mechanical tie, including good harness(3.8 KG). This result suggested that the solidified.SMEDDS not only retained the advantages of the liquid system, but also provided improved handling and stability[68].

Prajapati S. T. et al. Concluded in their study that SMEDDS formulations containing Olmesartan Medoxomil significantly enhance both the dissolution and invitro diffusion rate when compared to a plane drug suspension of Olmesartan. The research further extended to ex vivo, initial permeability studies, where it was observed that the diffusion of the drug across the intestinal member from the SMEDDS formulation was considerably higher than that of the conventional suspension. This improved

permeability can be attributed to the formation of fine oil-in-Water emulsions, which increase the surface area and facilitate better drug transport across biological membrane. Based on this findings, the author SMEDDS represent a highly promising drug delivery system. They provided a practical and effective solution for overcoming challenges associated with poor aqueous, solubility, and low systemic bioavailability of drug thereby improving overall therapeutic efficacy[66].

Mahajan H. D. et al. Conductor research on the develop SMEDDS formulation for fenofibrate, a drug known for its poor Water solubility and limited oral bio availability. The study revealed that the SMEDDS formulation of exhibitor superior performance compared to conventional marketed formulations, Pr, particularly in terms of in vitro dissolution profiles. Enhancement dissolution leads to improve absorption and bio availability consequently, the authors proposal that SMEDDS could serve a novel, efficient, and commercially viable alternative to existing fenofibrate formulations, offering better therapeutic or comes and patient benefits[67].

Chouksey R. et al. Reported that the formulation of SEDDS was optimised using various critical parameters The study demonstrated that SEDDS significantly enhance the solubility and dissolution of poorly water-soluble drugs like Atorvastatin. By reducing droplet size and improving drug dispersion in the gastrointestinal environment, SEDDS increase surface area for dissolution, resulting in improved drug release and absorption, thereby highlighting their potential as an effective delivery system for lipophilic drugs [68].

Suresh P. K. et al. Successfully developed SMEDDS formulations of Domperidone using a simple and efficient mixing method. The study found that a surfactant to co-surfactant ratio of 3.1 was ideal for achieving rapid and efficient emulsification. The optimiser formulation exhibited a very short emulsification time of less than one minute, indicating excellent self emulsifying properties. The formulation also demonstrated improve drug release characteristics compared to conventional forms. Based on this findings, the authors concluded that SMEDDS formulation prepared using oleic acid, Tween 80, and PEG 400 with an optimal surfactant or co-surfactant ratio of 3:1 represent a promising and effective approach of improving the solubility, dissolution, and bioavailability availability of domperidone

The enhancement of solubility and dissolution rate of domperidone through SMEDDS formulations highlights their significant potential in improving drug delivery performance. One of the key advantages of these systems is that the drug release profile is not significantly affected by the lipid digestion process, which ensures consistent performance within the gastrointestinal tract. Based on these observations, it can be logically concluded that SMEDDS formulations hold a promising future in the effective delivery of poorly water-soluble drugs, offering improved therapeutic outcomes and enhanced patient compliance[69].

Deshmukh A. et al. Successfully developed and optimized SMEDDS formulations of efaviren by systematically evaluating multiple formulation parameters. The optimized formulation demonstrated a marked improvement in drug solubility and dissolution rate. Droplet size analysis confirmed the formation of microemulsions with fine droplet sizes, which contributed to enhanced drug release. Additionally, the SMEDDS formulation was independent of pH, which is advantageous as it minimizes the effect of varying gastrointestinal pH conditions. This also reduces food-related variability and inter-subject differences, ultimately improving the consistency of efavirenz absorption and bioavailability[70].

Patel A. R. et al. developed an optimized formulation that exhibited significantly enhanced solubility and dissolution rate of fenofibrate, a drug known for its poor water solubility. Furthermore, the developed SMEDDS showed improved pharmacodynamic activity when compared to the plain drug. These findings confirm that SMEDDS can serve as a viable and effective alternative to traditional oral dosage forms, offering improved therapeutic performance by enhancing drug solubility and absorption[71].

Goyal U. et al. A patient-compliant SMEDDS formulation of lovastatin was developed to enhance its solubility and bioavailability. The optimized system comprised Capryol 90 as the oil phase, Cremophor RH40 as the surfactant, and Transcutol P as the co-surfactant. By varying the ratios of these components, an optimal formulation ratio of 20:40:40 (oil:surfactant:co-surfactant) was achieved.

This optimized formulation exhibited a small droplet size of approximately 42.5 nm, a low PDI of 0.15 indicating uniform droplet distribution, and a zeta potential of -4.56 mV, suggesting good physical stability. The formulation demonstrated excellent drug

release, with more than 90% of the drug being released compared to the pure drug. These results clearly illustrate the SMEDDS potential in enhancing the oral delivery of lipid-soluble drugs, making them more effective and patient-friendly[72].

Bhagwat D. A. et al. demonstrated the development of solid self-microemulsifying drug delivery systems (S-SMEDDS) for telmisartan using Aerosil 200 as an adsorbent through an adsorption technique. The resulting solid formulation exhibited desirable flow properties and uniform drug content, making it suitable for further processing into solid dosage forms. Upon reconstitution, the formulation formed microemulsions with droplet sizes in the micrometric range. This study highlights that the use of adsorption techniques with suitable carriers like Aerosil 200 can effectively convert liquid SMEDDS into solid forms while enhancing dissolution characteristics[73].

Khan F. et al. Demonstrated that the dissolution rate of atorvastatin can be significantly improved by incorporating it into SEDDS formulations. It was found that up to 12.5% of atorvastatin could be safely incorporated into the formulation without compromising stability. The construction of pseudo-ternary phase diagrams played a vital role in determining the optimal ratios of formulation components. Additionally, the use of a 3^2 factorial design helped establish the relationship between independent and dependent variables, ensuring proper optimization of the formulation. The findings suggest that SEDDS have strong potential for improving both solubility and dissolution rate of poorly soluble drugs.

Rajinikanth P. S. et al. Successfully formulated SNEDDS of valsartan by Labrafil M 1944 CS (23%), Tween 80 (58%), and Transcutol HP (19%). The developed formulation demonstrated a significant increase in dissolution rate when tested in pH 1.2 acidic buffer, showing more than a six-fold improvement in drug release compared to conventional formulations. This enhanced dissolution suggests a higher probability of improved drug absorption in the stomach, leading to better bioavailability and therapeutic effectiveness[74].

Singh G. et al. Emphasized the critical part of solubility in drug release and absorption, stating that it is a key determinant of oral bioavailability. Drugs with poor aqueous solubility often exhibit low dissolution rates, which in turn limits their absorption in the

gastrointestinal tract. As a result, many newly developed drugs pose formulation challenges due to their inadequate solubility profiles.

Solid dispersion technique involves dispersing the drug in an inert carrier matrix, which enhances wettability, reduces particle size, and may convert the drug into an amorphous form, thereby improving its solubility. The present review focuses on different aspects of solid dispersion systems, including their classification into types such as eutectic mixtures and solid solutions. It also discusses various methods of preparation, such as melting, solvent evaporation, and spray drying techniques, along with the selection of suitable carriers that play a critical role in the success of these formulations.

Furthermore, extensive research has been conducted on solid dispersions to enhance the solubility of a wide range of pharmacologically active compounds. Despite their advantages, certain challenges such as physical instability, recrystallization of the drug, and scalability issues have been encountered during their development. Recent advancements in formulation technologies, however, have addressed many of these limitations, making solid dispersions a viable and increasingly popular strategy in modern drug delivery systems[75].

Jagatap S. et al. Explained that solubility that is very much essential for drug absorption and therapeutic action. Poor aqueous solubility can prevent drug products from reaching the market, as it limits their ability to achieve the desired therapeutic concentration in systemic circulation. Even drugs with strong pharmacological activity may fail during development if their solubility and bioavailability are inadequate. Additionally, solubility influences several important properties of a drug, including its physicochemical stability, dissolution rate, absorption profile, and overall pharmacokinetics. The aqueous solubility of a drug also affects its stability within the gastrointestinal tract, its dose uniformity, and the rate at which it dissolves and becomes available for absorption.

To overcome solubility-related challenges, various solubilization techniques have been developed. These include chemical modification of drug molecules, use of solubilizing agents such as Soluplus and Povacoat, incorporation of dendrimers, and physical modification techniques like particle size reduction and solid dispersion formation.

Additionally, complexation methods and the use of surfactants have gained significant importance in enhancing drug solubility.

With the continuous advancement in pharmaceutical technologies, these solubility enhancement techniques are becoming increasingly important for the development of effective, stable, and commercially viable drug products. They provide new opportunities to formulate drugs that were previously considered unsuitable due to poor solubility. Overall, improving solubility not only enhances drug performance but also contributes to the successful development and marketability of pharmaceutical products[76].

CHAPTER-3

RATIONALE, AIM AND OBJECTIVES

3.1 RATIONALE OF DISSERTATION

On an average, 40% of newly developed drug molecules are classified as poorly water-soluble, which significantly limits their dissolution in gastrointestinal fluids and ultimately results in low and variable oral bioavailability. The formulation of such hydrophobic drugs into effective and stable solid dosage forms using conventional aqueous-based techniques remains a major challenge in pharmaceutical development. Poor solubility often leads to incomplete drug absorption, delayed onset of action, and inconsistent therapeutic outcomes[77] [78].

The formation of SMEDDS results in nanosized droplets, which provide a significantly increased surface area for drug release. By optimizing the ratio of oil to surfactant and surfactant to co-surfactant, it is possible to enhance drug solubility, improve dispersion, and facilitate rapid absorption. This approach effectively overcomes the dissolution limitations of poorly soluble drugs and enhances both the rate and extent of drug release, thereby improving bioavailability.

Furthermore, recent advancements have focused on converting liquid SMEDDS into solid dosage forms, known as Solid SMEDDS (S-SMEDDS). According to Pharmaceutical Survey and Analysis Reports (PSAR), solid SMEDDS exhibit superior stability and are more suitable for large-scale manufacturing and long-term storage. Therefore, the present dissertation focuses on the development and optimization of SMEDDS, with particular emphasis on solidification techniques [[79]].

3.2 AIM

To develop and statistically optimize a Self micro emulsifying drug delivery system (SMEDDS) for Azilsartan Medoxomil (AM) to improve its solubility, rate of dissolution and bioavailability.

3.3 OBJECTIVE

1. To develop a Self-Microemulsifying Drug Delivery System (SMEDDS) of Azilsartan Medoxomil.

2. To improve the dissolution characteristics and gastrointestinal absorption of Azilsartan Medoxomil through the formation of fine O/W microemulsions.
3. To perform solubility screening studies for the selection of suitable oils, surfactants, and co-surfactants for the formulation of SMEDDS.
4. To construct pseudo-ternary phase diagrams for identifying the efficient microemulsion region and optimizing the surfactant/co-surfactant ratio.
5. To optimize the SMEDDS formulation using the Box–Behnken statistical design with Design Expert software by evaluating the influence of formulation variables such as oil concentration, surfactant concentration, and co-surfactant concentration.
6. To evaluate the optimized formulations based on response parameters including emulsification time, percentage transmittance, droplet size, and cumulative drug release.
7. To convert the optimized liquid SMEDDS into Solid SMEDDS by employing the lyophilization (freeze-drying) technique.
8. To optimize the concentration of cryoprotectants used during lyophilization for obtaining stable and free-flowing Solid SMEDDS.
9. To evaluate the developed Solid SMEDDS for physicochemical properties, reconstitution ability, flow characteristics, stability, and in vitro drug release performance.
10. To develop a stable and patient-compliant Solid SMEDDS formulation capable of improving the therapeutic efficacy of Azilsartan Medoxomil.

3.4 PLAN OF WORK

The research work was carried out in a systematic manner through the following stages:

1. **Literature Survey:** Comprehensive review of published studies related to SMEDDS and Azilsartan Medoxomil.
2. **Preformulation Studies:** Characterization of the active pharmaceutical ingredient and compatibility assessment with excipients.
3. **Screening Studies and Phase Diagram:** Selection of suitable oils, surfactants, and co-surfactants, followed by construction of pseudo-ternary

phase diagrams to identify the microemulsion region and evaluate the effect of drug incorporation.

4. **Formulation Development:** Optimization and preparation of liquid SMEDDS formulations.
5. **Evaluation of Liquid SMEDDS:** Assessment of emulsification efficiency, drug content, droplet size, and stability parameters.
6. **Preparation of Solid SMEDDS:** Conversion of liquid SMEDDS into solid form by lyophilization using suitable cryoprotectants.
7. **Evaluation of Solid SMEDDS:** Determination of micromeritic properties including bulk density, tapped density, Carr's index, and Hausner's ratio to assess flow and compressibility characteristics.
8. **Characterization and Dissolution Studies:** Physicochemical characterization and in-vitro dissolution studies of the optimized formulation.
9. **Thesis Completion:** Statistical analysis, interpretation of results, and final thesis documentation and submission.

CHAPTER-4

DRUG AND EXCIPIENT PROFILE

4.1 Drug Profile

Azilsartan Medoxomil

Azilsartan Medoxomil (AM) belongs to the angiotensin receptor blocker (ARB) class of antihypertensive agents and is known for its high selectivity and strong binding affinity toward AT1 receptors due to Azilsartan. By inhibiting these receptors, the drug prevents vasoconstriction, reduces aldosterone secretion, and promotes vasodilation, thereby lowering blood pressure and improving cardiovascular outcomes[82].

It is considered a relatively newer antihypertensive medication and was first approved by the USFDA in February 2011 for essential hypertension. Due to its long duration of action and effective blood pressure control, it has gained importance in clinical practice.

Several international hypertension management guidelines recommend ARBs, including Azilsartan Medoxomil, as first-line therapy for the initiation of antihypertensive treatment, especially in patients who are intolerant to angiotensin-converting enzyme (ACE) inhibitors. Clinical studies have shown that ARBs provide comparable efficacy to ACE inhibitors in reducing blood pressure and minimizing cardiovascular risks, while often producing fewer side effects such as dry cough and angioedema.

Azilsartan Medoxomil is marketed under the brand name **Edarbi**. Additionally, Azilsartan Medoxomil is available as a fixed-dose combination with chlorthalidone, a thiazide-like diuretic, which enhances its antihypertensive effectiveness and provides improved therapeutic outcomes in patients with uncontrolled blood pressure[83].

By maintaining optimal blood pressure levels, Azilsartan Medoxomil contributes to the prevention of long-term cardiovascular complications and helps in reducing disease progression.

Furthermore, Azilsartan Medoxomil is believed to have a positive impact on lowering mortality rates associated with cardiovascular disorders by preventing the onset and

progression of hypertension-related complications. Although its primary indication remains hypertension, there is growing interest in its potential off-label applications, particularly in patients with a history of myocardial infarction or heart failure. While clinical evidence is still limited, ongoing research suggests that Azilsartan Medoxomil may offer additional cardiovascular protective benefits in such conditions in the future.

Structure of Azilsartan Medoxomil

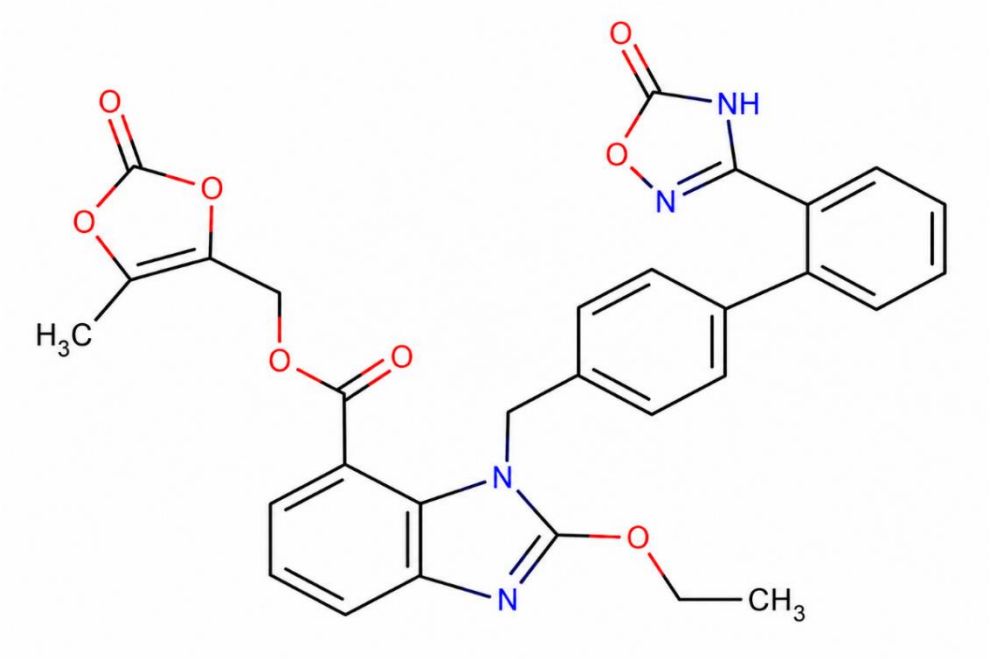


Figure 4.1: Azilsartan Medoxomil

Indication

Azilsartan Medoxomil is indicated for the treatment of hypertension in adults above 18 years of age to effectively lower and control blood pressure. In certain populations, particularly Black patients, some antihypertensive drugs may show a comparatively reduced response in blood pressure reduction; however, Azilsartan Medoxomil remains a useful option in overall hypertension management [84].

Belonging to the angiotensin receptor blocker (ARB) class, Azilsartan Medoxomil is additionally explored for certain off-label uses, such as reducing the progression of moderate-to-severe albuminuria and preventing the recurrence of atrial fibrillation in patients with diabetes mellitus and hypertension. These additional benefits highlight its potential role in broader cardiovascular and renal protection.

Pharmacodynamics

The pharmacodynamics effects of Azilsartan Medoxomil are primarily working through its active metabolite, Azilsartan, which selectively blocks angiotensin-II type-1 (AT1) receptors. A single 32 mg dose of Azilsartan has been shown to inhibit approximately 90% of the maximal precursor effect at peak plasma concentration and around 60% after 24 hours of administration, demonstrating its long-lasting antihypertensive action.

In both single and repeated dose studies in healthy individuals, Azilsartan Medoxomil increases plasma angiotensin I and II levels as well as plasma renin activity, while reducing plasma aldosterone concentration. Similar to other ARBs, Azilsartan decreases peripheral vascular resistance and reduces vascular smooth muscle tone, leading to vasodilation and improved blood pressure control. [85].

Azilsartan Medoxomil has minimal influence on serum electrolyte levels, particularly sodium and potassium, and does not interfere with the biosynthesis of angiotensin II or bradykinin metabolism. Additionally, it does not bind to ion channels involved in cardiovascular regulation, which contributes to its favorable safety and tolerability profile. No dosage adjustment is generally required based on sex, race, or mild to moderate renal or hepatic impairment, making Azilsartan Medoxomil a reliable and effective option for long-term hypertension management.

Mechanism of Action

Angiotensin II, a peptide hormone, is the primary pressor agent in Renin angiotensin system and acts as a potent vasoconstrictor. This process ultimately increases blood volume and blood pressure, while also inhibiting further secretion of renin through negative feedback mechanisms[86].

Azilsartan Medoxomil is a prodrug that is rapidly hydrolyzed in the gastrointestinal tract to its active metabolite, Azilsartan, following oral administration. It exhibits more than 10,000-fold greater affinity for AT1 receptors compared to AT2 receptors. Additionally, Azilsartan dissociates slowly from AT1 receptors compared to other angiotensin receptor blockers (ARBs), which contributes to its prolonged duration of action and sustained antihypertensive effect[87].

Absorption

During absorption, Azilsartan Medoxomil is completely converted into Azilsartan, and the parent drug is not detectable in plasma after oral administration. The absolute bioavailability of Azilsartan is approximately 60%, with peak plasma concentration (Tmax) occurring between 1.5 and 3 hours.

Volume of Distribution

Azilsartan has a volume of distribution of approximately 16 liters, indicating moderate distribution within body tissues. Animal studies have shown that only a minimal amount of the drug crosses the blood–brain barrier.

Protein Binding

Azilsartan is highly bound to plasma proteins, with more than 99% bound primarily to serum albumin. This high protein binding remains consistent even at plasma concentrations higher than those achieved with recommended therapeutic doses.

Metabolism

After conversion to Azilsartan, the drug undergoes metabolism to form two inactive metabolites. The major metabolite, M-II, is formed through O-de-alkylation mediated by the CYP2C9 enzyme and accounts for about 50% of systemic exposure. The minor metabolite, M-I, is formed through decarboxylation mediated by CYP2C8 and CYP2B6 and accounts for less than 1% of systemic exposure.

Route of Elimination

Approx. 55% of the administered dose is excreted via the feces, while about 42% is eliminated through the urine. Of the total dose administered, nearly 15% is excreted unchanged in the urine as Azilsartan, indicating partial renal elimination of the active drug.

Half-life

Azilsartan has an elimination half-life of approximately 11 hours.

Clearance

The renal clearance of Azilsartan is approximately 2.3 mL/min. This relatively low renal clearance supports its sustained plasma concentration and contributes to its prolonged antihypertensive action. The overall clearance profile allows for effective once-daily dosing without significant accumulation in patients with normal renal function.

Toxicity

The maximum toxic dose of Azilsartan has not been clearly established due to limited clinical data on overdose in humans. Available clinical trial data indicate that healthy individuals were able to tolerate once-daily doses of up to 320 mg of Azilsartan Medoxomil without significant adverse effects. In cases of overdose, treatment is mainly supportive and symptomatic, as Azilsartan cannot be effectively removed by dialysis due to its high protein-binding capacity[88].

Azilsartan is considered a teratogenic and fetotoxic agent, particularly when used during pregnancy. Similar to other angiotensin receptor blockers (ARBs), it poses a significant risk of congenital abnormalities and fetal injury, especially during the second and third trimesters. Therefore, the use of Azilsartan Medoxomil is contraindicated in pregnancy, and alternative antihypertensive therapy should be considered for pregnant patients to avoid potential harm to the developing fetus.

4.2 EXCIPIENT PROFILE [89]:

4.2.1 CASTOR OIL

Synonyms:

Oleum ricini, Ricinoleum, Ricinus communis oil, Ricinus oil, Tangantangan oil

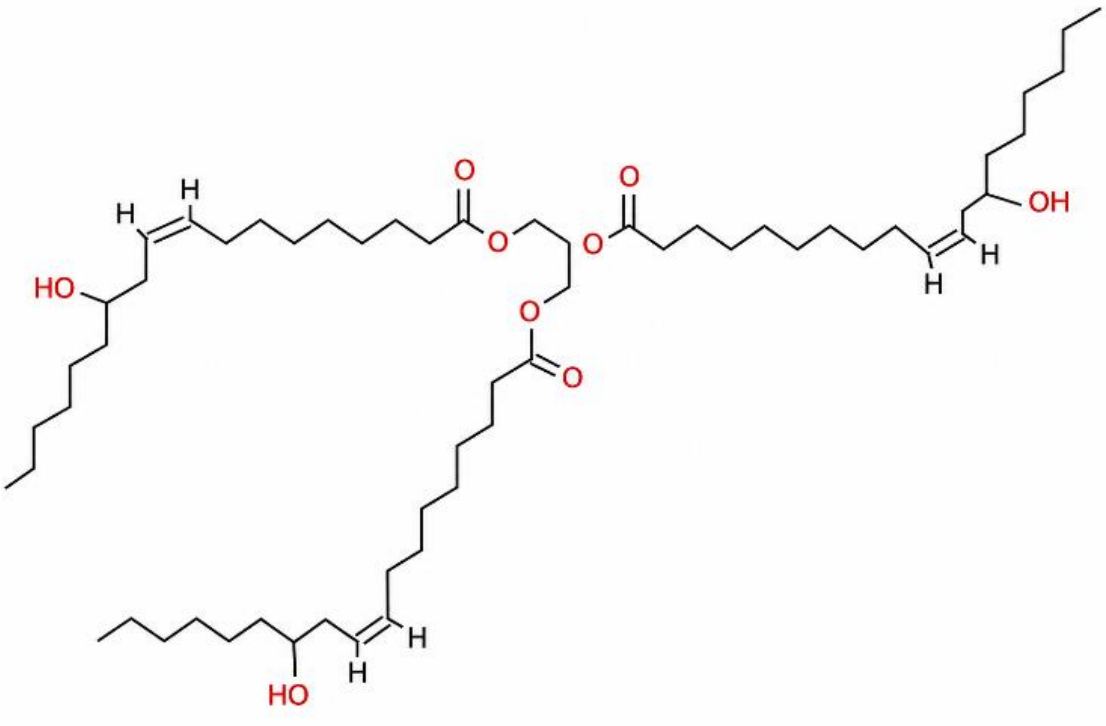


Figure 4.2: Structure of Functional Category

Table 4.1: Physicochemical properties of castor oil

Parameter	Details
Functional Role	Emollient, oleaginous vehicle, solvent, plasticizer, and solubilizing agent
Description	Castor oil is a clear, viscous liquid that appears nearly colourless to pale yellow. It has a mild characteristic odour and a bland taste that may become slightly acrid on storage. Its smooth texture and high viscosity make it suitable for pharmaceutical and topical formulations.
Boiling Point	313°C
Density	0.955–0.968 g/cm³ at 25°C
Melting Point	−12°C
Moisture Content	Not more than 0.25%
Solubility in Organic Solvents	Miscible with chloroform, diethyl ether, ethanol, glacial acetic acid, and methanol
Solubility in Alcohol & Petroleum Ether	Freely soluble in 95% ethanol and petroleum ether
Solubility in Water	Practically insoluble
Solubility in Mineral Oil	Practically insoluble unless mixed with another vegetable oil

Applications

- Widely used as an emollient in creams, ointments, and lotions
- Serves as an oleaginous vehicle in liquid and semisolid formulations
- Functions as a solvent for poorly water-soluble drugs
- Acts as a plasticizer in capsule shells and coating formulations
- Enhances drug solubilization and bioavailability in lipid-based drug delivery systems
- Commonly used in topical formulations at concentrations ranging from 5% to 12.5%

- Extensively employed in pharmaceutical, cosmetic, and food industries

Stability and Storage:

Castor oil is chemically stable under normal storage conditions and is relatively resistant to rancidity. However, prolonged exposure to excessive heat may cause polymerization. At lower temperatures, its viscosity increases significantly.

Incompatibilities

Castor oil is not compatible with strong oxidizing agents, as they may lead to degradation or chemical instability. Proper storage and handling are therefore necessary to maintain its stability and effectiveness in pharmaceutical formulations.

Olive oil

Synonyms

Gomenoleo oil, Pure olive oil, Olea europaea oil, Oleum olivae

Category

Oleaginous vehicle; emollient; solvent

Applications in Pharmaceutical Formulation and Technology

- Oleaginous vehicle in oral and topical pharmaceutical formulations.
- Serves as an effective solvent and carrier for lipophilic drugs.
- Enemas, liniments, ointments, plasters, and soaps preparation.
- Used as a vehicle in soft gelatin capsules, oral oily solutions, and injectable oily preparations.
- Enhances drug solubility, stability, and absorption in lipid-based formulations.

Additional Industrial Applications

- Extensively used in the food industry as a cooking oil and salad dressing ingredient.
- Widely incorporated in cosmetic formulations as a moisturizer, emollient, and conditioning agent.
- Found in cosmetic products

Description

Olive oil is a fixed oil obtained from the ripe fruit of Olea europaea. It is a clear, oily liquid that ranges in color from nearly colorless to pale greenish-yellow and possesses a mild, characteristic odor.

Solubility

It is slightly soluble in 95% ethanol, ether soluble, chloroform, light petroleum (50–70°C), and CS_2, while being practically insoluble in water.

Stability and Storage

- Cloudy at 10°C
- Solidifies into a butter-like mass near 0°C
- Susceptible to oxidation due to its high unsaturated fatty acid content
- Store in tightly closed, well-filled containers
- Protect from light, air, and excessive heat
- Keep in a cool and dry place

Incompatibilities

- Undergoes saponification in the presence of alkali hydroxides
- Incompatible with strong oxidizing agents due to oxidative susceptibility

Safety

As a pharmaceutical excipient, it is considered nonirritant, nontoxic, and biocompatible when used within recommended concentrations. Its excellent safety profile makes it a reliable choice for oral, topical, and parenteral formulations.

4.2.3 Labrafil M 1944

Synonyms

USP–NF Name: Lauroyl polyoxyl-6 glycerides

EP Name: Lauroyl macrogol-6 glycerides

UNII Code (FDA): 8EPU9MJ01K

Preferred Substance Name (FDA): Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters

Chemical Description

Labrafil M 1944 mainly consists mono-, di-, & triglycerides along with polyethylene glycol (PEG-6, molecular weight approximately 300) mono- and diesters of lauric (C12) and stearic (C18) fatty acids.

Product Description

In aqueous media, it self-emulsifies to form a coarse dispersion or emulsion, commonly used in Self-Emulsifying Drug Delivery Systems (SEDDS). In topical formulations, it acts as a co-emulsifier to enhance emulsion stability and improve the overall performance of the formulation.

Functionality

Labrafil M 1944 CS functions primarily as a versatile lipid-based excipient.

It can serve as a single-excipient self-emulsifying system, spontaneously forming fine emulsions upon contact with aqueous gastrointestinal fluids. In such applications, it is classified as a Lipid Formulation Classification System (LFCS) Type II excipient and is widely employed in Self-Emulsifying Drug Delivery Systems (SEDDS).

When combined with surfactants or co-surfactants such as Labrasol ALF or Gelucire 44/14, it forms LFCS Type III systems, commonly known as Self-Microemulsifying Drug Delivery Systems (SMEDDS). These systems generate transparent or translucent microemulsions with very fine droplet sizes, significantly improving drug solubilization, dissolution rate, and gastrointestinal absorption.

In topical and semisolid formulations, Labrafil M 1944 CS is frequently used as a co-emulsifier, particularly in combination with Tefose 63. This combination is especially valuable in antifungal creams and other dermatological preparations, where it enhances emulsion stability, consistency, spreadability, and overall product performance.

Applications

Labrafil M 1944 is widely used as a water-dispersible surfactant, solubilizer, and bioavailability enhancer in pharmaceutical formulations. It serves as a key component in self-emulsifying and microemulsion drug delivery systems and is also utilized as an

intestinal absorption enhancer to improve drug uptake. Additionally, Labrafil M 1944 is used in capsules and sugar-coated tablets as a filler and functions as a antiadhesion or lubricating agent in tablet preparation.

4.2.4 Labrafac CC

Nonproprietary Names

Medium-chain triglycerides, triglyceride saturate media.

Synonyms

Bergabest, caprylic/capric triglyceride, Captex 300, Labrafac CC, Miglyol 810.

Chemical Name

Medium-chain triglyceride.

Functional Category

Emulsifying agent, solvent, suspending agent, and therapeutic agent.

Table 4.2: Physicochemical properties of Labrafac CC

Parameter	Details
Description	Labrafac CC is a clear, colourless to slightly yellowish oily liquid. It is practically odourless and tasteless. It solidifies at approximately 0°C and is manufactured with high purity, free from catalytic residues and cracking products, ensuring excellent stability and safety.
Relative Density	0.93–0.96 g/cm³
Refractive Index	1.440–1.452
Viscosity	25–33 mPa·s
Acid Value	Not more than 0.2
Iodine Value	Not more than 1.0
Peroxide Value	Not more than 1.0
Saponification Value	310–360
Unsaponifiable Matter	Not more than 0.5%
Heavy Metals	Not more than 10 ppm
Water Content	Not more than 0.2%
Total Ash	Not more than 0.1%

Pharmaceutical Significance

- Excellent lipid vehicle for poorly water-soluble drugs
- Enhances drug solubilization and oral bioavailability
- Suitable for use in SEDDS and SMEDDS formulations
- Offers high chemical purity and oxidative stability
- Ideal for oral, topical, and soft gelatin capsule formulations
- Provides consistent formulation performance due to its controlled physicochemical properties

Stability and Storage Conditions: Labrafac lipophile WL 1349 should be stored in tightly closed containers under standard storage conditions to maintain its stability and quality.

Incompatibilities

Preparations containing medium-chain triglycerides should not be stored in polystyrene containers, as contact with polystyrene may cause the plastic to become brittle and degrade. Suitable storage materials include low-density polyethylene, polypropylene, glass, and metal containers, which ensure stability and compatibility.

Safety

Toxicological studies have demonstrated a high margin of safety, with an oral LD_{50} value of approximately 33.3 g/kg in rats. Its excellent biocompatibility and tolerability make it a reliable excipient for a broad range of pharmaceutical applications.

Applications

In oral formulations, it serves as an effective vehicle for the preparation of emulsions, microemulsions, self-emulsifying drug delivery systems (SEDDS), and self-microemulsifying drug delivery systems (SMEDDS). It is particularly valuable for formulating drugs that are poorly water-soluble or unstable in aqueous environments, thereby enhancing their solubility, dissolution, and oral bioavailability.

It also functions as an intestinal absorption enhancer, facilitating improved drug permeation across the gastrointestinal membrane. In solid dosage forms, Labrafac CC is used as a capsule fill material, particularly in soft and hard gelatin capsules, and as a lubricant or antiadherent in tablet manufacturing.

4.2.5 Tween 80

Nonproprietary Names

Polysorbate 80, Polysorbatum 80.

Synonyms

Tween 80, Ritabate 80, Polyoxyethylene 20 oleate.

Table 4.3: Physicochemical properties and applications of Tween 80

Parameter	Details
Empirical Formula	$C_{64}H_{124}O_{26}$
Molecular Weight	1310
Functional Category	Emulsifying agent, non-ionic surfactant, solubilizing agent, wetting agent, and dispersing/suspending agent
Description	Yellow-coloured oily liquid at 25°C with a characteristic odour and a slightly bitter, warm taste.
Viscosity	400 mPa·s
Saponification Value	45–55
Hydroxyl Value	65–80
Water Content	≤ 3.0%
Acid Value	≤ 2.0%
Heavy Metals	≤ 10 ppm
HLB Value	15
Specific Gravity	1.08
Solubility	Soluble in water and ethanol; insoluble in mineral oil and vegetable oils.
Storage Conditions	Store in well-closed containers from light in a cool and dry place.
Safety	Considered safe, nonirritant, and nontoxic approximately 1.8 g/kg in rats (intravenous).
Applications	Emulsifying, solubilizing, wetting, dispersing, and stabilizing agent.
Typical Concentration Range	• Emulsifying Agent: 1–15% • Solubilizing Agent: 1–10% • Wetting Agent: 0.1–3%

4.2.6 Captex 355

Synonyms of Captex 355

Caprylic/Capric Triglyceride, Captex 300, Crodamol GTC/C, Glyceryl Tricaprylate/Caprate, MCT Oil (Medium-Chain Triglycerides), Miglyol 810, Miglyol 812, Myritol, Neobee M-5, Nesatol, Oleum Neutrale, Oleum Vegetabile Tenue, Thin Vegetable Oil, Waglinol 3/9280

These names refer to medium-chain triglyceride excipients that are widely used as lipid vehicles, solvents, and solubilizing agents in pharmaceutical, cosmetic, and nutraceutical formulations.

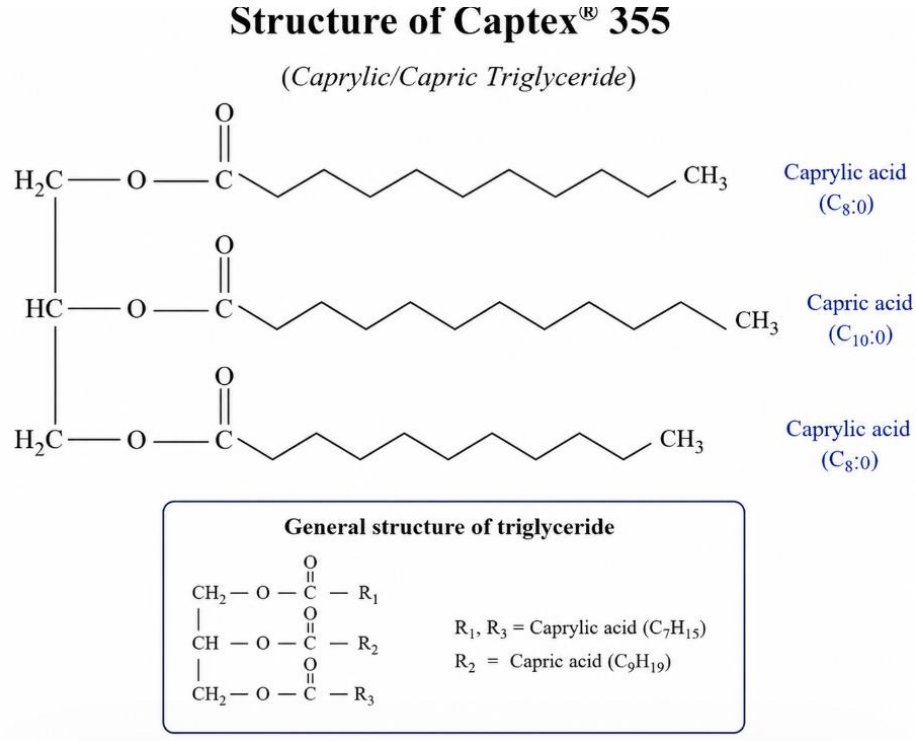


Figure 4.3: Structural Formula of Captex @355

Captex 355 consists of medium-chain triglycerides composed primarily of glycerol esterified with caprylic (C8) and capric (C10) fatty acids, forming a stable lipid-based excipient widely used in pharmaceutical formulations.

Functional Category

Emulsifying agent, solvent, suspending agent, and therapeutic agent.

Applications

Medium-chain triglycerides such as Captex 355 are extensively used in pharmaceutical formulations. They are commonly employed as vehicles in lipid-based drug delivery systems, emulsions, and suspensions, particularly for drugs that are poorly soluble in water.

Description

Captex 355 is a clear, colorless to slightly yellowish oily liquid that is practically odorless and tasteless. It possesses excellent organoleptic properties, making it particularly suitable for oral, topical, and cosmetic formulations.

This excipient solidifies at approximately 0°C and is characterized by its high purity, being free from catalytic residues and thermal cracking products. Its chemical neutrality contributes to excellent compatibility.

Captex 355 exhibits low viscosity and outstanding physicochemical stability, which facilitate easy handling, processing, and incorporation into various dosage forms.

Stability and Storage Conditions

Medium-chain triglycerides are stable over a wide range of storage temperatures commonly encountered in both tropical and temperate climates. However, for optimal stability, Captex 355 should be stored between 25°C to 40°C for prolonged periods. It should be kept in tightly closed containers and protected from excessive heat and light.

Incompatibilities

Formulations containing Captex 355 should not be stored or kept in polystyrene containers as this is highly interactive with polystyrene it will corrode the container and make it brittle easy to brake. Not only polystyrene even low density polystyrene is not at all suitable for storage since medium-chain triglycerides can penetrate the material, particularly at elevated temperatures, forming an oily film on the container surface. Suitable packaging materials include glass, metal, and compatible polymer containers that ensure stability and prevent leakage or degradation.

4.2.7 Polyethylene Glycol 400 (PEG 400)

Chemical Name

α-Hydroxy-ω-hydroxy-poly(oxy-1,2-ethanediyl)

Chemical Formula

$C_2nH_4n+2O_n+1$

Molecular Weight

380–420 (average)

Physical State

Colorless, viscous liquid

Specific Gravity

its specific gravity is estimated to be 1.1254

Solubility

Polyethylene Glycol 400 is freely soluble in water, acetone, alcohol, glycerin, and benzene, making it a versatile solvent and cosolvent in pharmaceutical formulations.

Applications in Pharmaceutical Formulation and Technology

PEG 400, being a liquid grade polyethylene glycol, is commonly used as a water-miscible cosolvent with excellent solvent properties for poorly water-soluble drugs. Due to its ability to enhance solubility and stability, PEG 400 is extensively used in lipid-based drug delivery systems such as solid dispersions, self-emulsifying drug delivery systems (SEDDS), and microemulsions.

Recent research in nanoparticle-based drug delivery systems has demonstrated that PEG can support sustained and controlled drug release. PEG-coated nanoparticles, known as mucus-penetrating particles (MPP), are designed to overcome the protective mucus barrier present on mucosal surfaces. The PEG coating prevents adhesion to mucus and allows the nanoparticles to penetrate mucosal layers effectively, thereby improving drug distribution, bioavailability, and therapeutic efficacy in mucosal drug delivery.

Incompatibilities

When used in soft gelatin capsules, PEG 400 may cause hardening of capsule shells due to moisture absorption from the gelatin, which can affect capsule stability and shelf life. Therefore, careful formulation and compatibility studies are required when incorporating qPEG 400 in soft gelatin dosage forms.

Transcutol® (Diethylene Glycol Monoethyl Ether)

Description

Transcutol® is a clear liquid commonly used as a co-surfactant and penetration enhancer in various drug delivery systems. Additionally, it is utilized in ocular and intranasal delivery systems, enhancing drug absorption and bioavailability.

It is also an important component in nanoemulsions, dermal formulations, and cosmetic products such as sunless tanning formulations and hair-coloring products (especially rinse-off products). Its multifunctional properties make it a valuable excipient in modern pharmaceutical and cosmetic technologies.

4.2.8 Propylene Glycol

Chemical Name

1,2-Propanediol

CAS Registry Number

57-55-6

Description

Propylene glycol is a clear, colorless, viscous, hygroscopic liquid with a faint characteristic odor and a slightly sweet taste.

Common Synonyms

1,2-Propanediol, Propane-1,2-diol, Methyl glycol, Methylethylene glycol, Trimethyl glycol, α-Propylene glycol, Propylene alcohol.

Functional Roles in Pharmaceutical Formulations

- Solvent for poorly water-soluble drugs
- Humectant to retain moisture
- Plasticizer in coatings and capsules
- Preservative enhancer
- Cosolvent in oral, topical, and parenteral formulations
- Stabilizer in various liquid dosage forms

Its versatility, safety, and compatibility with numerous pharmaceutical ingredients make propylene glycol one of the most widely used excipients in modern drug formulation.

Empirical Formula and Molecular Weight

Propylene glycol has the molecular formula $C_3H_8O_2$ and a weight of 76.09 g/mol. It is a dihydric alcohol with two hydroxyl functional groups that contribute to its solubility and stability in various pharmaceutical systems.

Structural Formula

Propylene glycol consists of a three-carbon chain with two hydroxyl groups attached, making it highly miscible with water and many organic solvents.

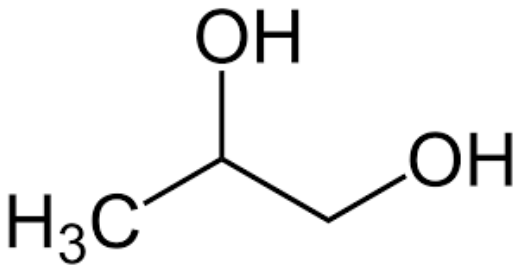


Figure 4.4: Structure of Propylene glycol

Applications

Propylene glycol is commonly employed in oral solutions, topical preparations, injectables, and ophthalmic formulations due to its ability to dissolve poorly soluble drugs and enhance drug stability. Additionally, it is used as a vehicle in syrups, elixirs, creams, ointments, and gels, and serves as a penetration enhancer in transdermal drug delivery systems.

Stability and Storage Conditions

Propylene glycol remains compatible and stable when mixed with ethanol (95%), glycerin, and water. Aqueous solutions containing propylene glycol can be sterilized by autoclaving without significant decomposition, making it suitable for sterile pharmaceutical preparations.

Incompatibilities

Contact with oxidizing agents may cause oxidation, chemical degradation, and loss of formulation stability.

Safety

Propylene glycol is considered a relatively nontoxic, nonirritant, and well-tolerated excipient when used within recommended limits. Its long history of safe use in oral, topical, parenteral, and other pharmaceutical formulations underscores its excellent safety profile and broad acceptability as a multifunctional excipient.

4.2.9 Carbitol

Chemical Name

Diethylene glycol monoethyl ether.

Description

Carbitol is a fast-acting solvent characterized by a high boiling point and low vapor pressure, making it suitable for applications that require efficient penetration and uniform distribution. Its strong solvency and stability make it a valuable component in various industrial and pharmaceutical applications.

Carbitol is also used as an important solvent in non-grain-raising wood stains and coatings, where it helps maintain smooth surface finishing. In addition, it serves as a component in industrial and household cleaners due to its excellent coupling and dispersing properties. In mineral oil–soap and mineral oil–sulfonated oil mixtures, small amounts of Carbitol act as a mutual solvent, producing clear or translucent dispersions instead of turbid mixtures, thereby improving solubility and formulation stability.

Table 4.4: Properties, Applications, and Benefits

Parameter	Details
Boiling Point	202°C
Specific Gravity	Approximately 0.98–1.00 (20/20°C)
Solubility	Completely miscible with water and many organic solvents
Appearance	Clear liquid with high solvency and low volatility
Applications	Solvent for non-grain-raising wood stains and coatings
	Carrier solvent in textile dyeing and printing processes
	Coupling agent and solvent in household and industrial cleaning products
	Mutual solvent in mineral oil–soap and mineral oil–sulfonated oil mixtures
Benefits	Excellent solvency power
	High chemical stability
	Compatibility with water and various organic solvents
	High boiling point and low vapor pressure, ensuring efficient industrial performance

4.2.10 Mannitol

Synonyms

Cordycepic acid, PharmMannidex, E421, manna sugar, D-mannite, mannite, Mannogem, Pearlitol.

Empirical Formula and Molecular Weight

$C_6H_{14}O_6$; Molecular weight: 182.17 g/mol.

Functional Category

Diluent, lyophilized preparation diluent, sweetening agent, tablet and capsule diluent, and tonicity agent.

Applications in Pharmaceutical Formulation and Technology

- Widely used as a diluent or filler in tablet formulations, typically at concentrations of 10–90% w/w.
- Particularly suitable for moisture-sensitive drugs due to its non-hygroscopic nature.
- Commonly employed in chewable tablets, orally disintegrating tablets (ODTs), and rapidly dispersing dosage forms because of its pleasant cooling sensation and sweet taste.
- Used in aqueous aluminum hydroxide antacid suspensions (usually below 7% w/v) to prevent viscosity increase and thickening during storage.
- Functions as a plasticizer in soft gelatin capsule formulations.
- Serves as a carrier in dry powder inhalers (DPIs), ensuring uniform drug delivery.
- Incorporated into sustained-release formulations and lyophilized pharmaceutical products.
- Also used as a bulking agent, sweetener, and texturizer in food and nutraceutical products.

Description

Mannitol is a hexa hydric sugar alcohol derived from mannose and is structurally related to sorbitol. It occurs as a white, odorless, crystalline powder or free-flowing granules with a pleasantly sweet taste and cooling mouthfeel. Its excellent flow properties and low hygroscopicity make it particularly valuable in solid dosage form development.

Stability and Storage Conditions

Mannitol is highly stable in both dry powder form and aqueous solution. Its solutions withstand repeated autoclaving cycles without significant physical or chemical degradation. For optimal stability, it should be stored in tightly closed containers in a cool, dry place, protected from excessive moisture.

Incompatibilities

- Concentrated mannitol solutions (20% w/v or higher) may exhibit **salting out** in the presence of sodium chloride or potassium chloride.

- Precipitation may occur when highly concentrated solutions (e.g., 25% w/v) come into contact with certain plastic materials.
- Incompatibilities have been reported with some drugs, particularly certain antibiotics such as Cephapirin sodium, which may result in precipitation or reduced solution stability.

CHAPTER -5

Materials and methods

5.1. Materials used

Table 5.1: List of materials

S. No.	Materials	Manufacturer
1	Azilsartan Medoxomil (AM)	Zydus Cadila Healthcare, Ahmadabad
2	Castor Oil	Chiti-Chem Corporation
3	Olive oil	Chiti-Chem Corporation
4	Oleic acid	Chiti-Chem Corporation
5	Labrafil-M1944	HiMedia Laboratories Pvt. Ltd, Mumbai
6	Labrafac CC	HiMedia Laboratories Pvt. Ltd, Mumbai
7	Tween 80	Chiti-Chem Corporation
8	Tween 20	Chiti-Chem Corporation
9	Captex 355	AaturInstru-chem
10	Cremophor EL	HiMedia Laboratories Pvt. Ltd, Mumbai
11	Labrafac PG	HiMedia Laboratories Pvt. Ltd, Mumbai
12	Polyethylene glycol-400	Chiti-Chem Corporation
13	Transcutol	AaturInstru-chem
14	Propylene glycol	Chiti-Chem Corporation
15	Carbitol	AaturInstru-chem
16	Mannitol	Balaji Drugs, Surat
17	Dialysis Membrane	HiMedia Laboratories Pvt. Ltd, Mumbai

5.2. Equipment employed

Table 5.2: List of equipment

S. No.	Name of equipment	Make and Model	Purpose
1	Digital Weight Balance	Shimazdu ATX224	For weighing materials
2	Vortex Mixter	REMI, Mumbai	Mixing of components
3	Mechanical Shaker	EiE instruments Pvt. Ltd, Ahamdabad	For solubility study
4	Hot Plate	DurgaSintific	For screening study
5	Magnetic Stirrer	REMI, Mumbai	Mixing of liquid SMEDDS
6	Cooling Centifugator	REMI-CM-12 PLUS	For thermodynamic stability study
7	Spray Dryer	Labultima LU 222 Advanced	To convert liquid SMEDDS to solid SMEDDS
8	Brookfild Viscometer	DV-ll+ PRO	Determine Viscosity
9	Dissolution Apparatus	LabIndia DS-8000	For In vitro drug release
10	UV-Visible spectrophotometer	Shimazdu UV-1800 with UV Prob-2.33 software	For Quantitative Analysis of formulation
11	Malvern Zetasizer	Malvern Zetasizer NS90	Determination of zeta potential, droplet size and

			PDI
12	Fourier transform Infrared spectroscopic studies	Bruker, Mumbai, India	For identification and compatibility study
13	Freeze Dryer	Freeze Dryer	For Lyophilization of powder

Preformulation

Fourier transforms infrared spectroscopic studies (FTIR)

Fourier transform infrared (FTIR) spectroscopic analysis was conducted for the pure drug as well as for the drug in combination with selected excipients in order to evaluate possible interactions and asses compatibility. The analysis was carried out using an FITR spectrophotometer equipped with potassium bromide (KBr) pellet technique. This method was specifically employed to investigate potential drug-excipient as well as excipient-excipient interactions by identifying characteristic functional group peaks and possible shifts or changes in the infrared spectra.

The FITR studies were performed using a standard pressed pellet technique. For pellet preparation, the drug and KBr were accurately weighed and mixed in ratio of 1:100, ensuring uniform distribution of the sample within the matrix. The obtained spectra were analyzed to confirm the presence of characteristic peaks and to detect any possible interaction or incompatibilities between the drug and excipients.

Analytical Method Development

The analytical method for the quantitative estimation of Azilsartan Medoxomil was developed using UV–Visible spectrophotometry. This method was selected because of its simplicity, accuracy, sensitivity, and suitability for routine analysis during formulation development and evaluation.

Determination of λmax

A standard solution of Azilsartan Medoxomil having a concentration of 10 µg/mL was prepared separately in two different solvent systems and scanned at 200-400nm range by UV-Visible spectrometer.

- Methanol
- 0.1 N Hydrochloric acid (HCl)

This wavelength was selected as the analytical wavelength for subsequent quantitative estimation and calibration studies.

Standard Calibration Curve of Azilsartan Medoxomil

Preparation of Standard Calibration Curve in Methanol

Accurately weighed 10 mg of Azilsartan Medoxomil was transferred into a 100 mL volumetric flask and dissolved in methanol and volume was made upto mark with methanol.

Suitable aliquots were withdrawn and diluted with methanol to prepare working standard solutions containing 2, 4, 6, 8, 10, 12, 14, 16, and 18 µg/mL of Azilsartan Medoxomil. The absorbance of each solution was measured at obtained absorption maxima.

Preparation of Standard Calibration Curve in 0.1 N HCl

Accurately weighed 10 mg of Azilsartan Medoxomil was transferred into a 100 mL volumetric flask. The drug was dissolved in 0.1 N hydrochloric acid, and the volume was adjusted to the mark with the same solvent to prepare the stock solution.

Appropriate aliquots from the stock solution were further diluted with 0.1 N HCl to obtain standard solutions containing 5, 10, 15, 20, 25, 30, 35, and 40 µg/mL of Azilsartan Medoxomil. The absorbance of these solutions was recorded at 275 nm using 0.1 N HCl as the blank.

A standard calibration curve was then plotted by graphing absorbance versus concentration, which demonstrated the linearity of the analytical method.

Screening Study

Solubility of Drug in Various Oils, Surfactants, and Co-surfactants

This screening step is crucial for identifying excipients with maximum solubilizing capacity, thereby ensuring efficient drug loading and formulation stability. An excess amount of Azilsartan Medoxomil was added to 2 mL of each selected excipient in separate glass vials to ensure saturation. The mixtures were vortexed for approximately 5 minutes to achieve uniform dispersion of the drug within the excipient.

The vials were then placed in a mechanical shaker maintained at 25 ± 1℃ for 72 hours to attain equilibrium solubility. This prolonged shaking period ensured complete interaction between the drug and the excipient.

Following equilibration, the samples were centrifuged using an R-4C DX laboratory centrifuge at 8000 rpm for 25 minutes at 25 ± 1℃ to separate undissolved drug particles from the saturated supernatant.

The clear supernatant was carefully collected and filtered through a 0.45 µm membrane filter to remove any residual particulate matter. The filtrate was then suitably diluted with methanol to bring the concentration within the measurable range of the spectrophotometric method.

The absorbance of the diluted samples was measured at 257 nm using a UV–Visible spectrophotometer. The concentration of Azilsartan Medoxomil dissolved in each excipient was calculated using the corresponding standard calibration equation. Based on the solubility results, excipients exhibiting the highest drug solubilization were selected for further formulation development.

Table 5.3: List of material used in screening study

S. No.	Category	Excipient	HLB Value
1	Oils	Castor Oil	14
2		Olive Oil	7
3		Oleic Acid	1
4		Labrafil M 1944 CS	4
5		Labrafac CC	1
6	Surfactants	Tween 20	16.7
7		Tween 80	15
8		Cremophor EL	12–14
9		Captex 355	13
10		Labrafac PG	2
11	Co-surfactants	PEG 400	13
12		Transcutol	4.7
13		Propylene glycol	12
14		Carbitol	17

Screening of Oils

Oils exhibiting higher solubilization capacity were considered more suitable, as they can efficiently dissolve larger amounts of the drug and facilitate improved drug loading. Therefore, only those oils demonstrating maximum solubility were shortlisted for subsequent formulation and optimization studies.

Screening of Surfactants

The selection of an appropriate surfactant was carried out using well-defined criteria to ensure optimal formulation performance. Among the various surfactants evaluated, the primary selection criterion was their ability to solubilize Azilsartan Medoxomil effectively.

Based on Drug Solubilization Capacity

The surfactant exhibiting the highest solubilization potential for Azilsartan Medoxomil was identified as the most suitable candidate. A higher solubilization capacity is essential for enhancing drug incorporation, improving emulsification efficiency, and promoting the formation of a stable microemulsion system. Consequently, the surfactant demonstrating superior drug solubility was selected for further formulation development and optimization studies.

Based on % oil solubilizing different surfactants

Screening of surfactants was performed by evaluating percentage of oil solubilization in various surfactants. The surfactants were assessed further capacity to form microemulsions. Surfactant such as twin 20, tween 80, cremophor El, CapEx 355, and Labrafac PG were analysed. Among these 15% w/v Concentration of each surfactants was prepared and 2.5 ml of solution was taken for testing. To this solution, 4µl of oils was added gradually with continuous vortex mixing to ensure proper blending. If the mixture in a Clear and transparent solution, it indicated successful solubilization and micro emulsion formation the point at which the solution turned cloudy was noted as it indicated the limit of oil solubilization capacity for that particular surfactant.

Based on Ease of Emulsification

Various surfactants were systematically evaluated for their ability to efficiently emulsify the selected oil phase. The choice of surfactant is critical, as it directly influences the formation, stability, and uniformity of the emulsion. For this study, 300 µL of each surfactant was mixed with 300 µL of the selected oil to maintain an equal ratio. The mixture was gently heated to approximately 50°C to reduce viscosity, enhance miscibility, and promote uniform blending of the components. After obtaining a homogeneous mixture, a 50 µL aliquot was withdrawn and diluted to 50 mL with distilled water in a volumetric flask.

The resulting emulsion was allowed to stand undisturbed for 2 hours to assess its stability. Percentage transmittance was then measured at 650 nm using a double-beam UV–Visible spectrophotometer, with distilled water as the blank. In addition, the emulsions were visually examined for clarity, turbidity, and any evidence of phase

separation. The surfactant producing the highest transmittance, rapid emulsification, and a clear, stable emulsion was selected for further studies.

Screening of Co-surfactants

Co-surfactants, including PEG 400, Transcutol, propylene glycol, and Carbitol, were evaluated for their suitability in the formulation. Their selection was based on three important criteria: drug solubilization capacity, ability to form a clear system, and ease of emulsification.

Based on Drug Solubilization Capacity

The co-surfactant capable of dissolving the highest amount of Azilsartan Medoxomil was considered most suitable. Higher drug solubility ensures improved drug loading and enhances formulation efficiency.

Based on Ability to Form a Clear Solution

For this evaluation, approximately 80 µL of surfactant was mixed with 200 µL of the selected oil phase to obtain a uniform blend. This mixture was then diluted with distilled water to a total volume of 400 µL. From this, a 20 µL aliquot was carefully titrated with distilled water under continuous stirring. The point at which turbidity first appeared was recorded. A co-surfactant that maintained clarity for a longer duration was considered superior, as it indicates a greater capacity to sustain microemulsion formation.

Based on Ease of Emulsification

To assess emulsification efficiency, 200 µL of surfactant was mixed with 100 µL of each co-surfactant, followed by the addition of 300 µL of the selected oil phase. The mixture was stirred thoroughly and gently heated to about 50°C to improve homogenization. A 50 µL sample was then diluted to 50 mL with distilled water.

The ease of emulsification was evaluated by counting the number of flask inversions required to form a uniform emulsion. The prepared emulsions were allowed to stand for 2 hours and then analyzed for percentage transmittance at 650 nm using a double-beam UV spectrophotometer. Visual examination was also performed to detect

turbidity, phase separation, or any signs of instability. The co-surfactant showing the highest clarity, least number of flask inversions, and greatest stability was selected for formulation development.

Construction of Pseudo-Ternary Phase Diagram

Pseudo-ternary phase diagrams were constructed to identify the microemulsion region and optimize the proportions of oil, surfactant, and co-surfactant. The surfactant (Tween 20) and co-surfactant (Carbitol) were combined to form surfactant mixtures (Smix) in different volume ratios of 1:1, 2:1, and 1:2.

For each Smix ratio, the selected oil phase (Castor oil) was mixed with Smix in varying ratios ranging from 1:9 to 9:1. These mixtures were prepared in separate glass vials and thoroughly mixed. The pseudo-ternary phase diagrams were developed using the aqueous titration method, in which water was added gradually to each oil–Smix mixture.

Water was incorporated in increments of approximately 5%, covering a concentration range from 5% to 95% of the total system. After each addition, the mixture was visually examined and classified according to its appearance.

These observations were systematically recorded for each oil-to-Smix ratio and for each Smix composition. Based on the collected data, pseudo-ternary phase diagrams were constructed using CHEMIX software. These diagrams helped identify the largest microemulsion region, thereby facilitating the selection of the optimum formulation composition for the development of a stable self-microemulsifying drug delivery system.

Effect of drug on phase diagram

The study was conducted with primary objective of investigating the influence of AM On the self-microemulsion dying drug delivery system (SMEDDS). In this experiment, predetermined quantity of AM was incorporated into the boundary formulations that define the self-microemulsion region within ternary phase diagrams. The performance of the developed self microemulsifying systems was subsequently evaluated through

visual observation after subjecting them to infinite dilution with purified water this step helped in assessing the efficiency, clarity, and spontaneity of microemulsion formation.

Formulation development

Optimization of formulation variables:

Formulation development process primarily focused on 3 critical variables that significantly influenced the self-microanalysis sign properties as well as the solubility of the drug. These variables include the concentration of oil, surfactant, and Co surfactant, all of which play a crucial role in determining the efficiency of self-emulsification and the extent of drug solubilization. Since these factors are the direct and substantial impact on the overall performance of the formulation, they were selected as key independent variables for systematic investigation.

To better understand the quantitative relationship between these formulation components and their effect on drug solubility and emulsification behaviour, response surface methodology (RSM) was employed. This statistical and mathematical tool enables the evaluation of multiple variables simultaneously and helps in identifying optimal conditions.

For the purpose of optimization, a "Box Behnken Design" (BBD) Was utilized. experimental design is widely recognised for its efficiency and studying formulation parameters, as it requires fever experimental run compared to full factorial designs while still providing reliable and comprehensive results. One of the advantages of BBB is that it involves only two levels for each factor and explores a limited yet effective set of possible combinations.

Within this design framework, experimental space is considered as multidimensional cube, were experiments were conducted at the midpoint of each edge as well as at the centre of the cube. Additionally replicate experiments were performed at the centre point ensure reproducibility and accuracy of the data. Task structured approach allows for a robust analysis of interaction effects between variables.

The Box–Behnken design is a highly efficient experimental design used in response surface methodology for evaluating quadratic response surfaces and developing second-order polynomial models. It is particularly valuable for optimization studies, as

it requires fewer experimental runs compared to full factorial designs while still providing reliable information about the individual, interaction, and quadratic effects of formulation variables.

In the present study, a total of **17 experimental runs** were carried out using the Box–Behnken design. These included **12 unique experimental combinations** representing different levels of the independent variables, along with **5 replicate runs at the center point**. The center point replicates were incorporated to assess experimental error, ensure reproducibility, and validate the consistency and reliability of the obtained results. This design approach enabled systematic optimization of the formulation variables and facilitated the identification of the optimum formulation conditions.

To design the experiments and analyse the resulting data, Design Expert software (Version 9, State Ease Inc., USA) Was employed. This software facilitated the construction of the experimental model, statistical analysis, and the generation of 3 dimensional response surface plots and contour plots. The associated Tables present the independent and dependent variables used in box behnken design, along with the experimental matrix outlining all formulation combinations.

Table 5.4: Dependent and independent variables of BBD:

Independent variable	**Variable level**	
	Low (-1)	**High (+1)**
Oil (ml) A	1	9
Surfactant (ml) B	0.5	4.5
Co-surfactant (ml) C	0.5	4.5
Dependent variables	Self-Emulsification Time (Sec) % Transmittance (%) % cumulative Drug Release (%)	

Preparation of liquid SMEDDS

In this study, Castor oil was selected as the oil phase, while Tween 20 served as surfactant and Carbitol was employed as Co surfactant. The specific proportions of

these components were determined based on the experimental design and are represented in 5.5 table. Across all these prepared formulations, quantity of Azilsartan Medoxomil (AM) is maintained at a standard level of 20 mg keeping the drug concentration fixed allowed for a clearer evaluation of how variations in the formulation components influenced the overall performance of the SMEDDS. The selected amount of SMEDDS was optimizer to ensure complete solubilization of the drug, enabling effective delivery in a single dose. For the preparation process Azilsartan Medoxomil (20mg) was accurately weighed and then incorporated into the mixture containing the oil, surfactant, and Co surfactant. The components were blended together using gentle and continuous sterling to achieve a uniform and homogeneous mixture. To facilitate proper dissolution and enhance disability among the ingredients the mixture was slightly heated and maintained at approximately 40 degrees Celsius during the mixing process. After achieving clear and consistent formulation the prepared SMEDDS Was allowed to cool and subsequently stored at room temperature until further use and evaluation. Overall, the developed SMEDDS Consisted of a carefully optimized combination of oil, surfactant, co-surfactant and drug, designed to improve solubility, enhance bioavailability and promote efficient self emulsification upon dilution.

Table 5.5: Matrix of Box-Behnken Design for SMEDDS formulation

S. No.	Standard Order	Run Order	Batch No.	Oil (mL)	Surfactant (mL)	Co-surfactant (mL)
1	8	1	B1	9	2.5	4.5
2	17	2	B2	5	2.5	2.5
3	16	3	B3	5	2.5	2.5
4	10	4	B4	5	4.5	0.5
5	15	5	B5	5	2.5	2.5
6	1	6	B6	1	0.5	2.5
7	3	7	B7	1	4.5	2.5
8	13	8	B8	5	2.5	2.5
9	9	9	B9	5	0.5	0.5
10	4	10	B10	9	4.5	2.5
11	6	11	B11	9	2.5	0.5
12	7	12	B12	1	2.5	4.5
13	2	13	B13	9	0.5	2.5
14	14	14	B14	5	2.5	2.5
15	12	15	B15	5	4.5	4.5
16	5	16	B16	1	2.5	0.5
17	11	17	B17	5	0.5	4.5

Evaluation of Liquid SMEDDS Formulation

Dispersibility Test

The Dispersibility test is an important evaluation parameter used to assess the ability of a Self-Microemulsifying Drug Delivery System (SMEDDS) to disperse rapidly and spontaneously upon dilution in an aqueous medium. This test provides valuable information regarding the efficiency of self-emulsification, the clarity of the resulting emulsion, and the approximate size of the formed globules. Based on these characteristics, the formulation can be classified and its suitability as an effective SMEDDS can be determined.

The test is performed using the **USP Dissolution Apparatus II (Paddle Type)**. In this method, 1 mL of the SMEDDS formulation is introduced into 500 mL of distilled water maintained at **37 ± 0.5°C**, simulating physiological conditions. The dissolution medium is stirred at a paddle rotation speed of **50 rpm**. Upon gentle agitation, the formulation disperses spontaneously, forming an emulsion, microemulsion, or gel depending on its composition and self-emulsifying efficiency.

The nature of the dispersion formed—such as its clarity, homogeneity, and rate of emulsification—is carefully observed. Formulations that rapidly produce a clear or slightly bluish microemulsion are considered superior, as they indicate efficient self-emulsification and the formation of fine globules. In contrast, formulations that yield milky emulsions, exhibit poor dispersibility, or form gels are considered less desirable. Thus, the dispersibility test serves as a simple yet reliable method for predicting the **in vitro performance**, emulsification behavior, and overall suitability of SMEDDS formulations for oral drug delivery.

Table 5.6: Type of formulation depending upon visual observation

Mixture/Gel	Type of formulation	Grade
Transparent mixture	Micro emulsion	A
Transparent Gel	Micro emulsion gel	B
Milky or cloudy mixture	Emulsion	C
Milky Gel	Emulgel	D

Robustness on dilution

The robustness of the liquid SMEDDS Formulation upon dilution was evaluated by subjecting it to extensive dilution studies. The formulation was diluted 100-fold and 1000-fold using different aqueous media specifically distilled water and 0.1 and hydrochloric acid to stimulate physiological conditions. After dilution, the samples for carefully observed for any signs of instability such as face separation, turbidity or precipitation of the drug. These observations were carried out immediately after dilution and also after a storage period of up to 12 hours under controlled conditions. A

formulation was considered to exhibit good robustness to dilution if it remained clear, homogeneous, and free from any visible drug precipitation or face separation through the observation This test is crucial to ensure that the formulation maintains integrity end performance upon exposure to gastrointestinal fluids after oral administration.

Emulsification time

The Emulsification time of the SMEDDS Formulation was determined to assess its efficiency in forming microemulsion upon dilution. This parameter was evaluated by visually monitoring the rate at which the formulation dispersed and formed a uniform abortion which introduced into an aqueous medium. The test was conducted in triplicate to ensure accuracy and reproducibility of results. In estimating emulsification time procedure in 30ml distilled water 1ml of formulation was added and maintained at 37°C. The time required for the formulation to completely emulsify, along with the clarity and uniformity of the resulting microemulsion was carefully recorded. Additionally, the formation and progression of emulsion droplets were visually examined to evaluate the self emulsification efficiency of the formulation.

Percentage Transmittance

The percentage transmittance of the diluted SMEDDS formulation was determined to assess the clarity and transparency of the resulting microemulsion. This parameter serves as an indirect indicator of droplet size, uniformity, and the efficiency of self-emulsification. Generally, higher transmittance values correspond to the formation of smaller and more uniformly distributed droplets, which are characteristic of a stable microemulsion system.

For this evaluation, the SMEDDS formulation was diluted 100-fold with distilled water to simulate aqueous dispersion under physiological conditions. The transmittance of the diluted sample was measured at a wavelength of **650 nm**. Distilled water was used as the blank. Formulations exhibiting high transmittance values were considered to possess superior clarity, finer droplet size, and better emulsification characteristics.

Drug Content

The drug content of the SMEDDS formulation was determined to ensure uniform distribution and accurate incorporation of the active pharmaceutical ingredient, Azilsartan Medoxomil. This test is essential for confirming dose uniformity and formulation reliability.

For analysis, an accurately measured quantity of the formulation was taken, and the drug was extracted using methanol as a suitable solvent. The extraction process was facilitated by sonication to ensure complete dissolution of the drug from the lipid matrix. The resulting solution was then filtered through watman filter paper to remove any insoluble excipients or particulate matter. The clear methanolic extract was analyzed using a UV–Visible spectrophotometer at **257 nm**, corresponding to the maximum absorbance (λmax) of Azilsartan Medoxomil in methanol. The drug concentration was calculated using the previously established standard calibration curve.

In Vitro Dissolution Study

The in vitro dissolution study was performed to evaluate the rate and extent of drug release from the SMEDDS formulation under simulated gastrointestinal conditions. This study provides insight into the formulation's ability to enhance drug dissolution and improve bioavailability.

The dissolution study was carried out using the **dialysis bag method**. An accurately measured quantity of the SMEDDS formulation equivalent to **20 mg of Azilsartan Medoxomil** was placed into a dialysis membrane bag, and one end was securely tied to prevent leakage. The dialysis bag was then immersed in **900 mL of 0.1 N hydrochloric acid**, which served as the dissolution medium. The medium was maintained at **37 ± 0.5°C** to simulate physiological temperature.

The study was conducted using a **USP Dissolution Apparatus II (Paddle Type)** operated at a paddle speed of **100 rpm** to ensure uniform agitation. At predetermined intervals (0, 5, 10, 15, 20, 25, 30, 35, 40, and 45 minutes), **5 mL** aliquots were withdrawn from the dissolution medium. To maintain constant volume and sink conditions, an equal volume of fresh pre warmed 0.1 N HCl was immediately replaced after each sampling at **257nm.** The amount of drug released at each time point was

calculated using the standard calibration curve, and the cumulative percentage drug release was determined. This study enabled assessment of the dissolution enhancement achieved by the SMEDDS formulation compared to the pure drug or conventional dosage forms.

Thermodynamic stability studies

Devaluation of thermodynamic stability is critical step in determining the overall performance and reliability of formulation. Add primarily assess the physical stability of the drug within the XP and matrix and ensures that the formulation remains uniform and effective throughout its shelf life. Instability Mein lead to drug precipitation com of phase separation or degradation which can significantly affect the bioavailability and therapeutic efficacy of the drug. Poor physical stability can also result in incompatibility between formulation components leading to undesirable changes such as brittleness, softening, or defamation of capsule shells when the formulation is filled. To evaluate stability, the formulation is subjected to a series of stress tests design to stimulate environmental changes and handling conditions. These include heating cooling cycles, centrifugation tests, and freeze thaw cycles as described below.

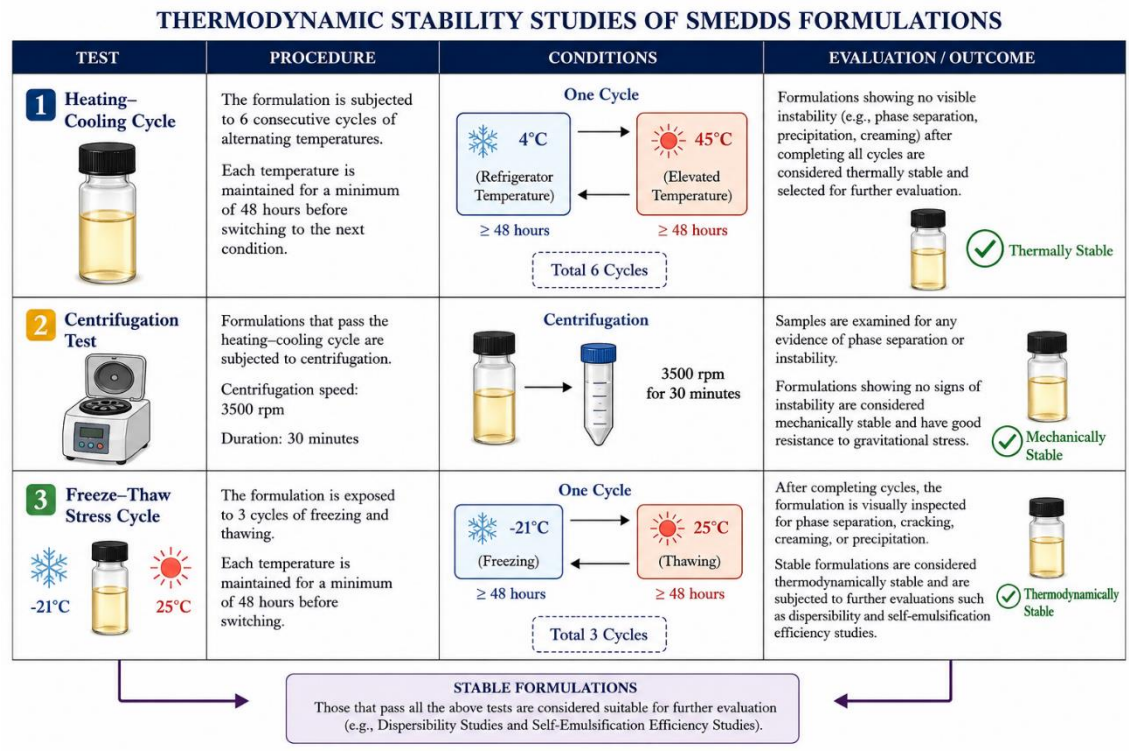


Figure 5.1: Thermodynamic studies of SMEDDS formulations

Viscosity

The viscosity of the SMEDDS Formulation was determined as an important rheological parameter to understand their flow behaviour and consistency. The measurements were carried out using Brookfield DV-II+ Pro viscometer, which is widely used for evaluating the viscosity of liquid and semi solid formulations. The analysis was performed at controlled temperature of 30 degrees Celsius to maintain uniform testing conditions and to simulate near physiological environments. Spindle number 62 was selected for the measurement, and the rotational speed was maintained at 5:00 rpm to ensure accurate and reproducible readings.

Globule size measurement

The globule size of the microemulsion formed from the SMEDDS Formulation was measured to evaluate the efficiency of self emulsification and quantity of resulting dispersion. The measurement of globule was carried out using Malvern Zetasizer NS90, An advanced instrument based on dynamic light scattering (DLS) technique. Prior to analysis the emulsion was diluted appropriately(1-1.5 ml) With a suitable medium to avoid multiple scattering effects and to obtain accurate particles as distribution. the prepared sample was done subjected to analysis and the average droplet size along with size distribution was recorded in addition to globule size polydispersity index (PDI) May also be evaluated to assess the uniformity of droplet distribution. Furthermore, the surface charge of the droplets represented by Zeta potential, was determined to assess the stability of the formulation. Zeta potential of the optimized SMEDDS formulation was measured using **Doppler velocimetry coupled with Phase Analysis Light Scattering (PALS)**. The analysis was performed at a **90° scattering angle** and a temperature of **25°C**. This technique determines the surface charge of emulsion droplets, which is an important indicator of colloidal stability. Higher absolute zeta potential values suggest better stability by preventing droplet aggregation.

Polydispersity index (PDI)

The polydispersity index of the optimized SMEDDS formulation Was determined to evaluate the uniformity and homogeneity of oil globules present in the system. The PD I value generally ranges from 0.0 to 1.0, where values closer to zero represent highly uniform dispersion with minimal variation in droplet size. In contrast, values

approaching one indicate ferocity and poor uniformity. The polydispersity index was determined by Malvern Zetasizer NS90

Zeta potential

Zeta potential is an important parameter used to assess the surface charge and physical stability of colloidal systems such as SMEDDS. The zeta potential of the formulation was determined using a Malvern Zetasizer, which measures the electrical potential at the surface of dispersed globules and helps predict the stability of the emulsion system.

For conversion of liquid SMEDDS into a solid form, mannitol was employed as a cryoprotectant. Different concentrations of mannitol—1%, 1.5%, 2%, and 2.5% w/v—were incorporated into the liquid SMEDDS to optimize the formulation. The resulting mixtures were subjected to freeze-drying using a lyophilizer. Initially, samples were frozen at –50°C, followed by lyophilization at –75°C under a vacuum pressure of 50 mmHg. The obtained lyophilized powder was then collected and further evaluated for its physicochemical properties.

Solid Self Micro Emulsifying Drug Delivery System Pre Formulation Evaluation

Solid state Preformulation parameters include Bulk density, Tapped density, Hausner's ratio and Carr's Index.

Table 5.7: Carr's Index and Hausner's ratio as an indication of powder flow and compressibility index

Type of flow	Carr's Index (%)	Hausner's Ratio
Excellent	≤ 10	1.00 – 1.11
Good	11-15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passible	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very Poor	32 – 37	1.46 – 1.59
Extremely Poor	>38	>1.60

Angle of Repose

Table 5.8: Correlations between angles of repose & flow property

Angle of repose (Ɵ)	Predicted flow property
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair
23 – 28	Poor
28 – 35	Poor
35 – 38	Very poor
>40	Extremely poor

Characterization of solid SMEDDS Formulation

Drug content

The drug content of the solid SMEDDS Formulation was determined by accurately 20mg of freeze-dried powder of Azilsartan Medoxomil was weighed. This weight sample was then carefully transferred into a volumetric flask and diluted with methanol to make up is final volume of 100 ml, insuring complete dissolution of the drug. From this prepared stop solution one ml was precisely withdrawn using puppet and further diluted to 10 ml with methanol to obtain a suitable concentration for analysis. The absorbance of this diluted solution was when measured at a wavelength of 257 nm Using UV spectrophotometer. the obtained absorbance value were used to calculate the drug content and the results are shown in corresponding table.

Zeta Potential

The zeta potential of the prepared SMEDDS formulation was measured using a Malvern Zetasizer Nano ZS90. Zeta potential is a critical physicochemical parameter that indicates the surface charge present on the oil globules. It plays a vital role in predicting the physical stability of emulsion systems. A sufficiently high positive or negative zeta potential value helps prevent droplet aggregation by electrostatic repulsion, thereby enhancing formulation stability. Conversely, low zeta potential values may lead to globule aggregation, phase separation, and instability of the emulsion.

Globule Size

The globule size of the optimized formulation was determined using the Malvern Zetasizer Nano ZS90, a widely employed instrument for particle size analysis. A small volume of the diluted emulsion sample (approximately 1–1.5 mL) was carefully transferred into a clean disposable polystyrene cuvette, ensuring the absence of air bubbles and contaminants. The average globule size and size distribution were analyzed using laser Doppler velocimetry in combination with photon correlation spectroscopy. Measurements were performed at a fixed scattering angle of 90° and a controlled temperature of 25°C. These parameters provide valuable information regarding the uniformity, dispersion characteristics, and stability of the SMEDDS formulation.

Polydispersity Index (PDI)

The polydispersity index (PDI) is an important parameter used to assess the uniformity of droplet size distribution in an emulsion system. Lower PDI values indicate a more homogeneous and stable formulation. Generally, PDI values ranging from 0.0 to 0.5 are considered indicative of a narrow size distribution and good uniformity. The PDI of the prepared SMEDDS formulation was determined using a Malvern Zetasizer Nano ZS90.

Self-Emulsification Time of Powder

The self-emulsification time of the freeze-dried solid SMEDDS powder was determined by gradually adding a measured quantity of the powder into a specified volume of water under gentle agitation. The time required for the complete formation of a clear or slightly bluish emulsion was recorded in seconds. A shorter self-emulsification time indicates rapid emulsification efficiency and better performance of the solid SMEDDS formulation.

In Vitro Dissolution Study

In vitro drug release studies of the solid SMEDDS formulation were carried out using a USP dissolution apparatus. The dissolution medium consisted of 900 mL of 0.1 N hydrochloric acid maintained at 37 ± 0.5°C, with the paddle rotation speed set at 50 rpm to simulate physiological conditions. A capsule containing freeze-dried powder equivalent to 20 mg of azilsartan medoxomil was placed in the dissolution apparatus.

At predetermined time intervals, 5 mL samples were withdrawn through a 0.45 µm membrane filter. An equal volume of fresh dissolution medium was immediately replaced after each sampling to maintain constant volume and sink conditions. The filtered samples were analyzed spectrophotometrically at 257 nm using a UV-visible spectrophotometer. The dissolution profile of the solid SMEDDS was compared with that of the pure drug and the marketed tablet formulation to evaluate the enhancement in drug release.

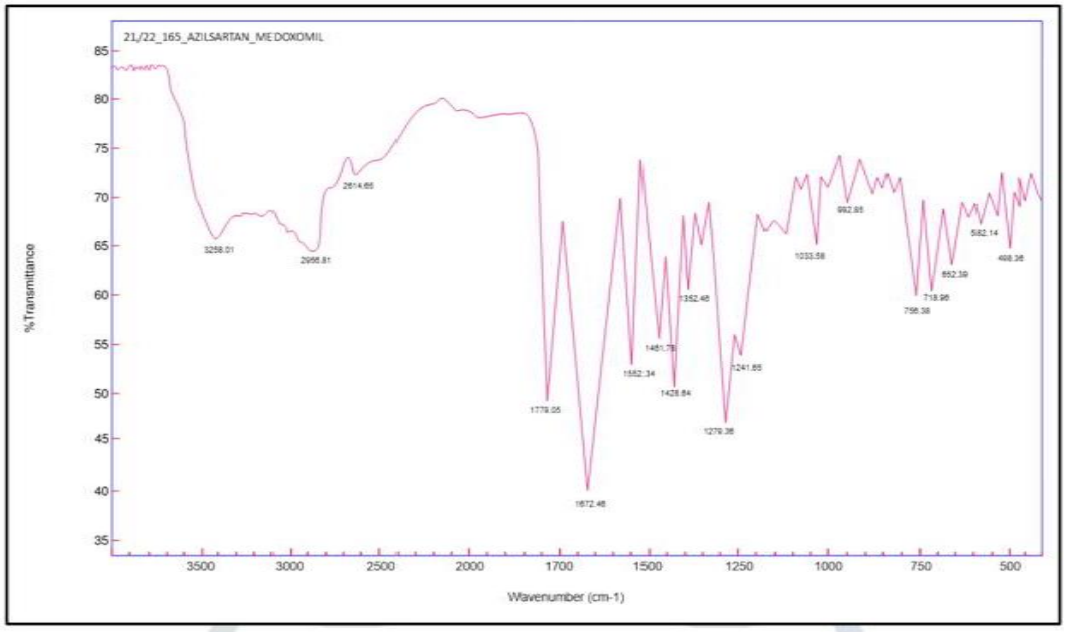
CHAPTER-6
RESULTS AND DISCUSSIONS

6.1 Pre-formulation Studies:

6.1.1 Fourier Transform Infrared spectroscopic studies (FTIR):

The FTIR spectra of the pure drug and the final freeze-dried SMEDDS powder were recorded and compared. Evaluation of these spectra helps identify any significant changes, such as shifts in peak positions, disappearance of characteristic peaks, or appearance of new peaks, which could indicate possible interactions between formulation components. In table 6.1. Spectral data of the drug alone and in a combination of drug and freeze dried powder mixture is elucidated.

Figure 6.1: FTIR Spectra of Azilsartan Medoxomil (AM)



The results indicated that there were no significant changes in the characteristic peaks of the drug, confirming no chemical interaction and demonstrating compatibility between the drug and selected excipients.

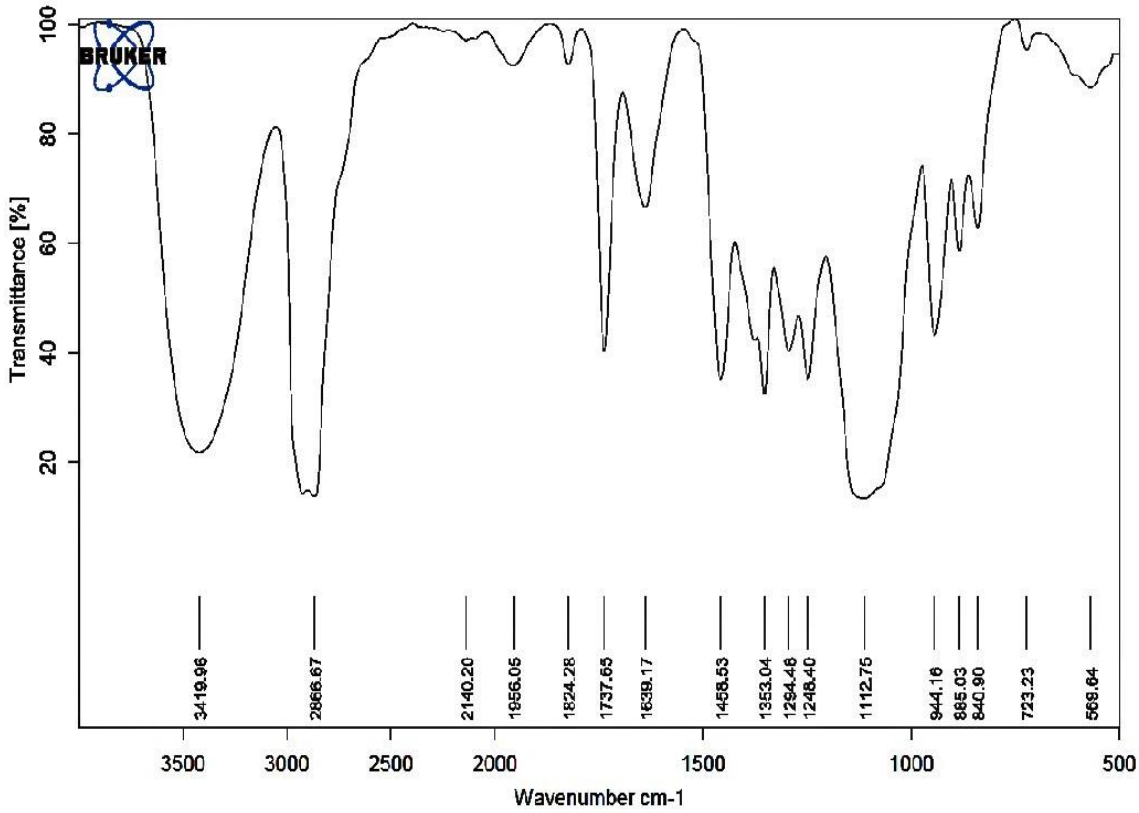


Figure 6.2 FTIR of Final Freeze Dried Product Along With Drug

Table 6.1: FTIR Peaks

Functional Group	**Principal Peak of Pure Azilsartan Medoxomil (cm^{-1})**	**Peak in Freeze-Dried SMEDDS Powder (cm^{-1})**
C=O stretching (carboxyl group)	1776.3	1737
C–O stretching	1280.7, 1309.0	1458, 1639
C–O–C stretching	1083.9	1112
N–H bending (amine group)	1467.0	3419
C=N stretching	1691.5	1639
C–H bending (out-of-plane)	761.8	1294
Aromatic C–H stretching	761.8	Retained*

*The characteristic aromatic C–H peak was retained in the freeze-dried formulation, though it may overlap with adjacent excipient peaks.

The FTIR spectrum of pure azilsartan medoxomil exhibited characteristic absorption peaks corresponding to its major functional groups. A prominent peak at 1776.3 cm^{-1} was attributed to C=O stretching of the carboxyl group. Peaks observed at 1280.7 and 1309 cm^{-1} corresponded to C–O stretching vibrations, while the peak at 1083.9 cm^{-1} indicated C–O–C stretching. The N–H bending vibration of the amine group appeared at 1467 cm^{-1}. A characteristic C=N stretching peak was observed at 1691.5 cm^{-1}, and the aromatic C–H out-of-plane bending vibration was identified at 761.8 cm^{-1}.

In the FTIR spectrum of the freeze-dried SMEDDS powder, the major characteristic peaks of azilsartan medoxomil were retained, although slight shifts in peak positions were observed. Peaks appeared at 1737 cm^{-1}, 1639 cm^{-1}, 1458 cm^{-1}, 1294 cm^{-1}, and 1112 cm^{-1}, corresponding to the drug's functional groups. A broad peak around 3419 cm^{-1} was attributed to N–H stretching or hydrogen bonding interactions. The presence of these characteristic peaks confirms that the chemical structure of azilsartan medoxomil remained intact after formulation and freeze-drying.

The minor shifts in absorption bands may be attributed to physical interactions, such as hydrogen bonding or molecular dispersion within the excipient matrix, rather than chemical incompatibility. These findings confirm the compatibility of azilsartan medoxomil with the selected formulation components and support the stability of the developed freeze-dried SMEDDS formulation.

6.1.1 Analytical Method Development

6.1.2 Determination Of λ_{max}

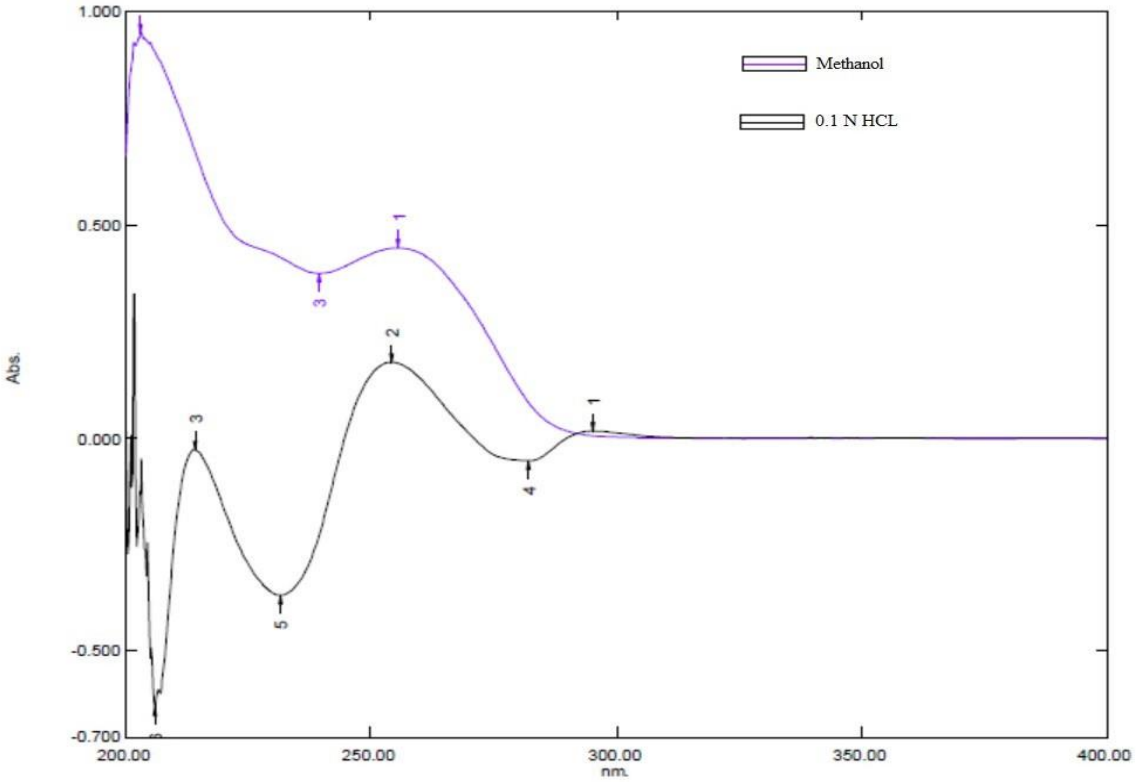


Figure 6. 3: overlay of spectra

A standard drug solution of azilsartan medoxomil (10 µg/mL) was scanned in wavelength range of 200–400 nm to determine its maximum absorption wavelength (λmax). The analysis was carried out in both methanol and 0.1 N hydrochloric acid to assess the drug's absorption behavior in analytical and simulated physiological media. Azilsartan medoxomil exhibited a distinct absorption maximum within the range of 239–259 nm in both media, indicating excellent suitability for spectrophotometric estimation.

6.1.2.2 Calibration Curve of Azilsartan Medoxomil in Methanol

A calibration curve of azilsartan medoxomil was constructed in methanol over a concentration range of 2–18 µg/mL. The absorbance of each standard solution was measured at 248 nm, corresponding to the λmax of the drug in methanol. The calibration plot demonstrated a linear relationship between concentration and absorbance within

the selected range, confirming adherence to Beer–Lambert's law. This validated method was subsequently employed for the quantitative estimation of azilsartan medoxomil in formulation development and analytical studies.

The regression coefficient (R^2) was found to be 0.996, which confirms a strong linear relationship between concentration and absorbance. This high degree of linearity indicates the accuracy and reliability of the method for estimating drug concentration. The calibration curve thus obtained can be effectively used for the quantitative determination of Azilsartan Medoxomil in various formulations and dissolution studies. The detailed results are presented in Table 6.2 and the corresponding calibration curve is illustrated in Figure 6.4.

Table 6.2: Calibration curve of Azilsartan Medoxomil in methanol

Concentration (µg/ml)	Absorbance			Mean Absorbance ± SD
	I	II	III	
2	0.097	0.095	0.096	0.096±0.0010
4	0.187	0.184	0.188	0.186±0.0021
6	0.265	0.268	0.264	0.266±0.0021
8	0.359	0.361	0.36	0.360±0.0010
10	0.443	0.44	0.441	0.441±0.0015
12	0.546	0.549	0.544	0.546±0.0025
14	0.642	0.641	0.643	0.642±0.0010
16	0.726	0.726	0.724	0.725±0.0012
18	0.867	0.868	0.866	0.867±0.0010

*Mean ± SD, n=3

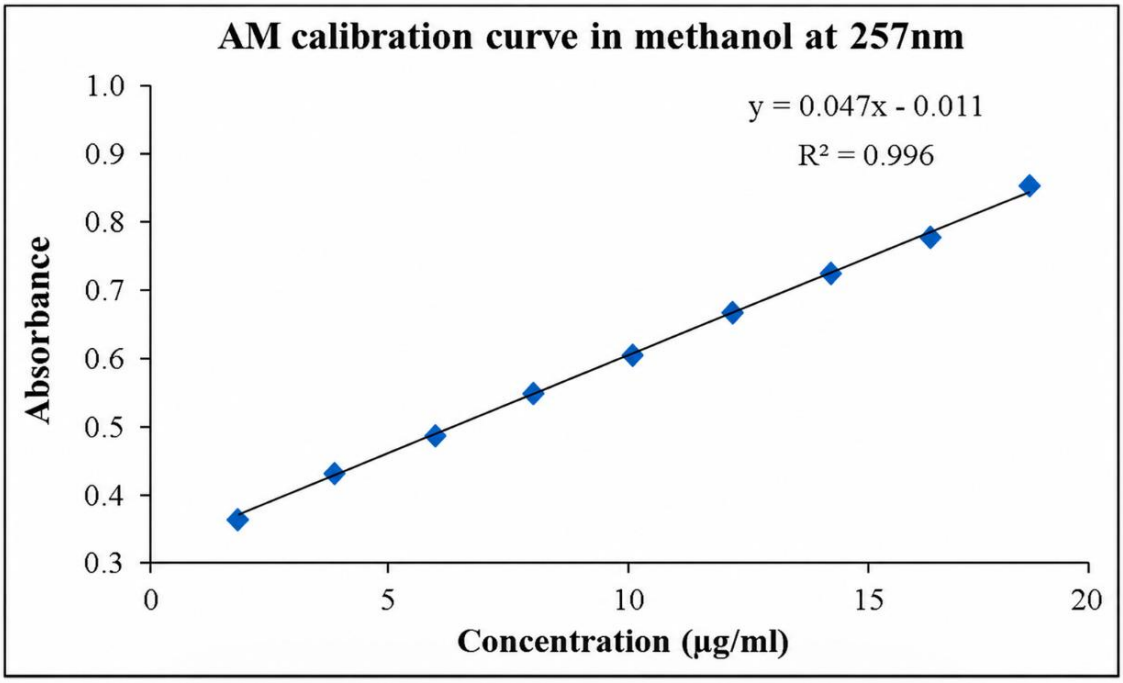


Figure 6.4: Calibration curve of Azilsartan Medoxomil in methanol

6.1.2.2.3. Calibration Curve of Azilsartan Medoxomil in 0.1 N HCl

A standard calibration curve of Azilsartan medoxomil was constructed in **0.1 N hydrochloric acid** over a concentration range of **5–40 µg/mL**. The absorbance of each prepared standard solution was measured at **248 nm** using a UV–Visible spectrophotometer, corresponding to the drug's maximum absorbance in the selected medium.

The selected concentration range exhibited excellent linearity as per Beer-Lamberts law, indicating a direct proportional relationship between drug concentration and absorbance within this range. The regression analysis of the calibration data yielded a correlation coefficient (R^2) of 0.999, demonstrating a high degree of accuracy and reliability of the analytical method. The detailed results of the calibration curve, including absorbance values and corresponding concentrations, are presented in Table 6.3, while the graphical representation of the standard curve is illustrated in Figure 6.5.

Table:6.3-calibration curve of Azilsartan Medoxomil in 0.1N HCl

Conc. (µg/mL)	Abs. I	Abs. II	Abs.III	Mean Abs. ± SD
5	0.132	0.130	0.134	0.132 ± 0.0022
10	0.223	0.224	0.224	0.224 ± 0.0005
15	0.364	0.366	0.364	0.365 ± 0.0012
20	0.477	0.482	0.479	0.479 ± 0.0025
25	0.596	0.587	0.596	0.593 ± 0.0052
30	0.717	0.718	0.715	0.717 ± 0.0015
35	0.846	0.845	0.844	0.845 ± 0.0010
40	0.965	0.963	0.965	0.964 ± 0.0012

Note: Abs = Absorbance, Conc. = concentration.

*Mean ± SD, n=3

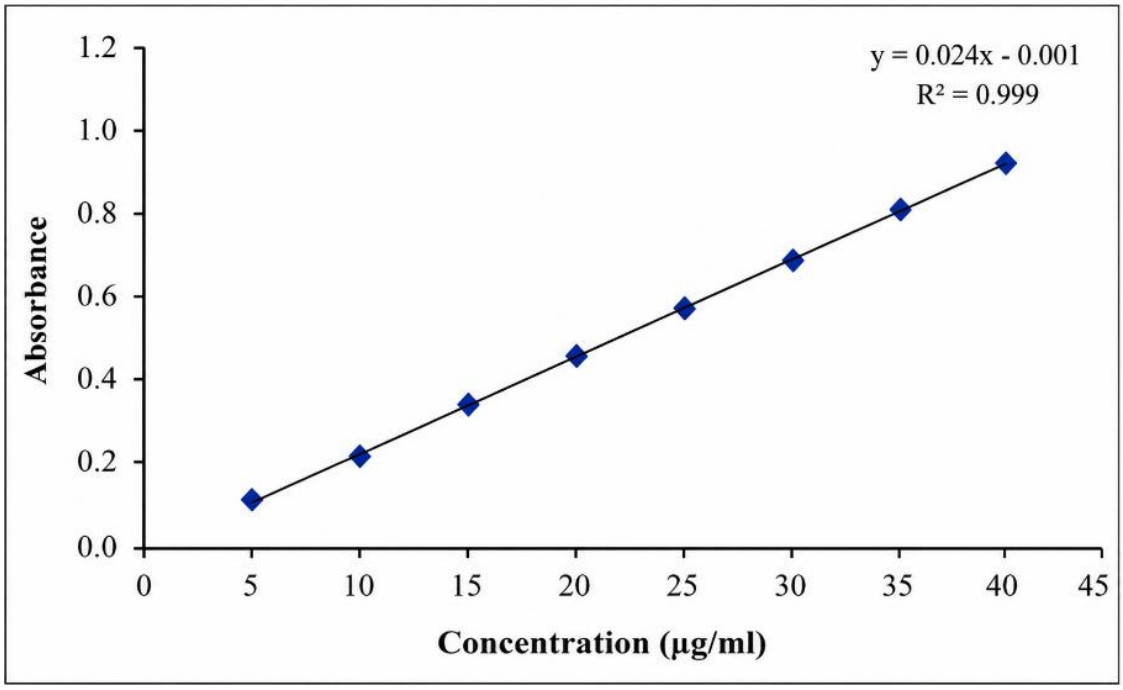


Figure 6.5: Calibration Curve of Azilsartan Medoxomil in 0.1 N HCl

The regression coefficients (R^2) were found to be 0.996 in methanol and 0.999 in 0.1 N HCl, indicating excellent linearity, accuracy, and precision of the analytical method. These values, being very close to unity, confirm the reliability, reproducibility, and sensitivity of the developed spectrophotometric method for quantitative analysis.

Furthermore, the calibration data clearly obeyed Beer–Lambert's law, as evidenced by the proportional increase in absorbance with increasing drug concentration. This confirms that the method is highly suitable for the quantitative estimation of Azilsartan Medoxomil in bulk drug analysis, formulation development studies, and in vitro dissolution or drug release investigations.

6.1.3 Screening Study

The selection was based on the solubility profile of Azilsartan Medoxomil (AM) in various excipients. For this purpose, an excess amount of the drug was added separately to different oils, surfactants, and co-surfactants to prepare saturated solutions. These mixtures were subjected to continuous agitation for a sufficient period to attain equilibrium solubility, followed by appropriate separation of the undissolved drug. The supernatant obtained was then analyzed to determine the amount of drug solubilized in each excipient.

The excipients exhibiting the highest solubilizing capacity for the drug were selected as potential candidates for formulation development. This systematic screening approach ensured the selection of components capable of enhancing drug solubility, thereby contributing to improved formulation performance and bioavailability

6.1.3.1 Screening of oils based on solubility of drugs

6.1.3 Based on solubility of drug

Table 6.4: Solubility study in different oils

S. No	Oils	Solubility (mg/ml)
1	Castor Oil	19.23±0.08
2	Olive Oil	12.37±0.28
3	Oleic Acid	8.45±0.24
4	Labrafil M 1944	7.84±0.23
5	Labrafac CC	9.54±0.21

*Mean ± SD, n=3

The solubility of Azilsartan Medoxomil (AM) was evaluated in various oil phases to identify the most suitable oil for the development of the SMEDDS formulation. An excess amount of the drug was added to different oils, and the mixtures were subjected to continuous shaking to achieve equilibrium solubility. After equilibration, the samples were centrifuged or filtered to remove any undissolved drug, and the supernatant was analyzed to determine the solubility of the drug in each oil.

Among the oils screened, castor oil exhibited the highest solubilizing capacity, with a solubility value of 19.63 ± 0.08 mg/mL. This significantly higher solubility compared to other tested oils indicates its superior ability to dissolve Azilsartan Medoxomil effectively. Based on these results, castor oil was selected as the oily phase for the SMEDDS formulation, as it is expected to enhance drug loading and improve the overall efficiency of the delivery system.

The detailed solubility data of Azilsartan Medoxomil in various oils are presented in Table 6.4.

6.1.3.2 Screening of Surfactants Based on Drug Solubility

A surfactant with high drug solubilization capacity can enhance drug loading, improve emulsification efficiency, and contribute significantly to the overall stability and performance of the formulation.

To identify the most suitable surfactant, the solubility of Azilsartan Medoxomil was determined in various surfactants under standardized experimental conditions. The surfactant exhibiting the highest solubilization potential was considered optimal for further formulation development. The results of the solubility study in different surfactants are presented in Table 6.5.

Table 6.5: solubility data in various surfactants

S. No.	Surfactant	Solubility of Azilsartan Medoxomil (mg/mL)
1	Tween 20	80.56 ± 0.125
2	Tween 80	34.62 ± 0.202
3	Cremophor EL	38.60 ± 0.259
4	Labrafac PG	41.61 ± 0.271
5	Captex 355	27.52 ± 0.231

*Mean ±SD, n=3

Azilsartan Medoxomil was solubilized in various surfactants to identify the most suitable one for the development of the SMEDDS formulation. The mixtures were then subjected to centrifugation or filtration to remove any undissolved drug, and the clear supernatant was analyzed to determine the solubility of the drug in each surfactant.

Among the surfactants investigated, Tween 20 exhibited the highest solubilizing capacity, with a solubility value of 80.56 ± 0.125 mg/mL. This high solubility indicates its excellent ability to dissolve Azilsartan Medoxomil, making it a suitable candidate for enhancing drug dispersion and improving formulation efficiency.

Based on these findings, Tween 20 was selected as the surfactant phase for the SMEDDS formulation. The detailed solubility profile of Azilsartan Medoxomil in different surfactants is presented in Table 6.5.

6.1.3.2 Screening of Surfactants Based on Oil Solubilization Capacity

The efficiency of a surfactant in a SMEDDS formulation depends not only on its ability to solubilize the drug but also on its capacity to emulsify and solubilize the selected oil phase. Therefore, various surfactants were further evaluated based on the percentage of oil they could effectively solubilize. This parameter is essential, as it reflects the

surfactant's emulsification potential and its ability to form a stable and homogeneous microemulsion upon dilution.

A higher percentage of oil solubilization indicates better compatibility between the surfactant and the oily phase, which in turn facilitates rapid self-emulsification, improved drug dispersion, and enhanced formulation stability. The surfactant demonstrating the highest oil solubilization capacity was considered most suitable for further optimization of the SMEDDS formulation. The percentage of oil solubilized by different surfactants is presented in Table 6.6.

Table 6.6: Screening of Surfactants Based on Oil Solubilization Capacity

S. No.	Surfactant	Oil Solubilization Capacity (%)
1	Tween 20	5.4
2	Tween 80	2.3
3	Cremophor EL	3.3
4	Labrafac PG	1.5
5	Captex 355	1.3

*Mean ± SD, n=3

The results indicated that the oily phase, castor oil, demonstrated the highest solubilization efficiency, exhibiting approximately 5.3% solubilization in combination with Tween 20. This enhanced solubilization behavior suggests a favorable interaction between the selected oil and surfactant, leading to improved drug incorporation capacity.

Based on these findings, the combination of castor oil as the oily phase and Tween 20 as the surfactant was considered optimal and selected for further formulation development studies. This selection is expected to contribute to improved drug solubility, stability, and overall performance of the SMEDDS formulation.

6.1.3.4 Screening of Surfactants Based on Ease of Emulsification

Ease of emulsification is a crucial parameter in the selection of an appropriate surfactant for the development of a self-microemulsifying drug delivery system (SMEDDS). It

reflects the ability of the surfactant to rapidly and spontaneously emulsify the oil phase upon dilution with an aqueous medium under mild agitation. Efficient self-emulsification is essential for the formation of a fine and stable microemulsion, which directly influences drug dissolution, absorption, and bioavailability.

A lower number of flask inversions indicates faster emulsification, while a higher percentage transmittance suggests the formation of a clear or translucent microemulsion with smaller droplet size and better uniformity. The surfactant combination exhibiting the least number of flask inversions and the highest transmittance was considered most suitable for further formulation development. The results are presented in Table 6.7.

Table 6.7: Number of Flask Inversions and Percentage Transmittance of Oil with Different Surfactant Combinations

S. No.	Surfactant	Number of Flask Inversions	% Transmittance at 650 nm
1	Tween 20	8	93.1
2	Tween 80	13	86.6
3	Cremophor EL	17	63.0
4	Labrafac PG	23	34.8
5	Captex 355	22	26.0

Efficient emulsification is essential for ensuring rapid drug dispersion, enhanced dissolution, and improved oral bioavailability. In the present study, different surfactants were screened for their emulsification efficiency with the selected oily phase, castor oil. The evaluation was based on two important parameters: the number of flask inversions required to produce a uniform emulsion and the percentage transmittance measured at 650 nm. A lower number of flask inversions indicates faster self-emulsification, while a higher transmittance value signifies the formation of a clearer microemulsion with smaller and more uniformly distributed globules.

Among the surfactants evaluated, Tween 20 demonstrated the highest emulsification efficiency. It required the fewest flask inversions and produced the highest

transmittance value, indicating rapid emulsification and the formation of a transparent microemulsion with very fine droplet size. This superior performance can be attributed to its optimal hydrophilic-lipophilic balance (HLB) value, which makes it highly suitable for the formation of oil-in-water microemulsions. Its excellent ability to reduce interfacial tension ensures uniform dispersion of the oil phase throughout the aqueous medium.

In comparison, other surfactants such as Tween 80, Cremophor EL, Labrafac PG, and Captex 355 exhibited relatively lower emulsification efficiency. These surfactants required a greater number of flask inversions and produced dispersions with lower transmittance values, indicating slower emulsification, larger droplet size, and reduced clarity. Such differences may be attributed to variations in their HLB values and their comparatively weaker interaction with castor oil.

Overall, the findings clearly establish that Tween 20 is the most suitable surfactant for the formulation of azilsartan medoxomil SMEDDS. Its superior emulsification properties, excellent clarity, and ability to form a stable microemulsion make it an ideal choice for further formulation optimization and development.

Screening of Co-surfactants

6.1.3.5 Based on Solubility of Drug

In the present study, various co-surfactants were screened based on their ability to solubilize Azilsartan medoxomil. The co-surfactant exhibiting the highest solubilization capacity was considered most suitable for incorporation into the SMEDDS formulation. A higher drug solubility in the co-surfactant ensures better drug loading, minimizes the risk of precipitation upon dilution, and contributes to enhanced formulation stability and performance.

Therefore, the solubility of Azilsartan Medoxomil was determined in different co-surfactants under standardized conditions. The results obtained from this screening study were used to identify the most appropriate co-surfactant for further formulation development and optimization.

Table: 6.8 Solubility of Azilsartan Medoxomil in Various Co-surfactants

S. No.	Co-surfactant	Solubility of Azilsartan Medoxomil (mg/mL)
1	PEG 400	42.60 ± 0.31
2	Transcutol	73.55 ± 0.23
3	Propylene Glycol	12.73 ± 0.63
4	Carbitol	82.63 ± 0.16

*Mean ± SD, n=3

In this study, the solubility of Azilsartan Medoxomil was evaluated in different co-surfactants such as PEG-400, Transcutol, Propylene Glycol, and Carbitol. The results indicated significant variation in solubility among the tested co-surfactants.

Carbitol demonstrated the highest solubility for the drug, indicating its superior solubilizing capacity. This high solubility can be attributed to its chemical structure, which allows better interaction with both hydrophilic and lipophilic components of the drug molecule. Transcutol also showed good solubility, but it was comparatively lower than Carbitol. PEG-400 exhibited moderate solubility, whereas Propylene Glycol showed the least solubilizing ability.

The higher solubility of the drug in Carbitol ensures that a greater amount of drug can be incorporated into the SMEDDS formulation without the risk of precipitation. This is particularly important for poorly water-soluble drugs like Azilsartan Medoxomil, where enhancing solubility directly correlates with improved bioavailability.

Based on these findings, Carbitol was selected as the co-surfactant for further formulation studies due to its superior drug solubilization capacity.

6.1.3.6 Screening of Co-surfactants Based on Ability to Form a Clear Solution

A clear solution indicates efficient solubilization of the drug and excipients, proper reduction of interfacial tension, and the formation of a homogeneous isotropic system. This characteristic is essential for achieving rapid self-emulsification, enhanced drug dispersion, and improved formulation stability.

In this study, different co-surfactants were evaluated based on the minimum quantity required to form a clear solution when combined with the selected oil and surfactant. A lower amount of co-surfactant required to achieve clarity reflects superior solubilization efficiency and better compatibility with the other formulation components. Such co-surfactants are preferred, as they enable the development of an optimized formulation with minimal excipient concentration while maintaining excellent emulsification properties.

The co-surfactant that required the least amount to produce a clear, transparent, and stable system was considered the most suitable for further formulation development. The results of this evaluation are summarized in Table 6.9.

Table 6.9: Minimum Amount of Co-surfactant Required to Form a Clear Solution

S. No.	Co-surfactant	Minimum Amount Required for Clear Solution (µL)
1	PEG 400	150
2	Transcutol	117
3	Propylene Glycol	140
4	Carbitol	104

Ability of cosurfactant to form a clear and homogeneous solution with oil and surfactant is another important selection criterion. This property reflects the efficiency of the co-surfactant in reducing interfacial tension and facilitating the formation of a stable microemulsion system.

In this evaluation, different co-surfactants were tested to determine the minimum quantity required to produce a clear solution when combined with castor oil and Tween 20. The formation of a clear solution indicates the formation of a thermodynamically stable system with uniform distribution of components.

Among the tested co-surfactants, Carbitol required the least amount to produce a clear and transparent solution. This suggests that Carbitol has a strong ability to penetrate the interfacial film and enhance its fluidity, thereby promoting efficient emulsification. Transcutol also performed relatively well but required a slightly higher quantity. PEG-

400 and Propylene Glycol required larger amounts, indicating lower efficiency.
The requirement of a lower quantity of co-surfactant is advantageous as it minimizes the risk of toxicity and improves formulation acceptability. Therefore, Carbitol was identified as the most suitable co-surfactant based on its ability to form clear solutions efficiently.

6.1.3.7 Screening of Co-surfactants Based on Ease of Emulsification

Table 6.10: Number of Flask Inversions and Percentage Transmittance of Oil–Surfactant Systems Containing Different Co-surfactants

S. No.	Co-surfactant	Number of Phase Inversions	% Transmittance at 650 nm
1	PEG 400	24	31.5
2	Transcutol	14	76.8
3	Propylene Glycol	27	64.4
4	Carbitol	11	88.5

The combined influence of the oil, surfactant, and co-surfactant on the emulsification efficiency of the SMEDDS was systematically evaluated to identify the most effective formulation components. This assessment is essential, as the interaction among these components directly affects the spontaneity of emulsification, clarity of the resulting emulsion, droplet size, and overall stability of the system. The study also provides valuable insight into the role of the selected co-surfactant in enhancing the performance and robustness of the SMEDDS formulation.

The results demonstrated that the combination of castor oil, Tween 20, and Carbitol exhibited superior emulsification characteristics compared to other combinations. This optimized system required the fewest phase inversions to form a homogeneous emulsion and showed the highest percentage transmittance, indicating rapid self-emulsification and the formation of a clear, transparent microemulsion.

Other co-surfactants such as PEG-400, Transcutol, and Propylene Glycol showed comparatively poorer performance. These systems required more energy (higher inversions) and resulted in lower clarity, suggesting inefficient emulsification and larger droplet size.

The superior performance of Carbitol can be attributed to its ability to further reduce interfacial tension and increase the flexibility of the surfactant film. This facilitates the spontaneous formation of microemulsions with minimal energy input. Thus, the combination of castor oil, Tween 20, and Carbitol was finalized for further studies due to its excellent emulsification efficiency and stability.

6.2 Construction of pseudo ternary phase diagram

A pseudo ternary phase diagram represents the relationship between three components: oil, surfactant/co-surfactant mixture (Smix), and water. By systematically varying the ratios of these components, different regions such as microemulsion, emulsion, and phase separation zones can be identified.

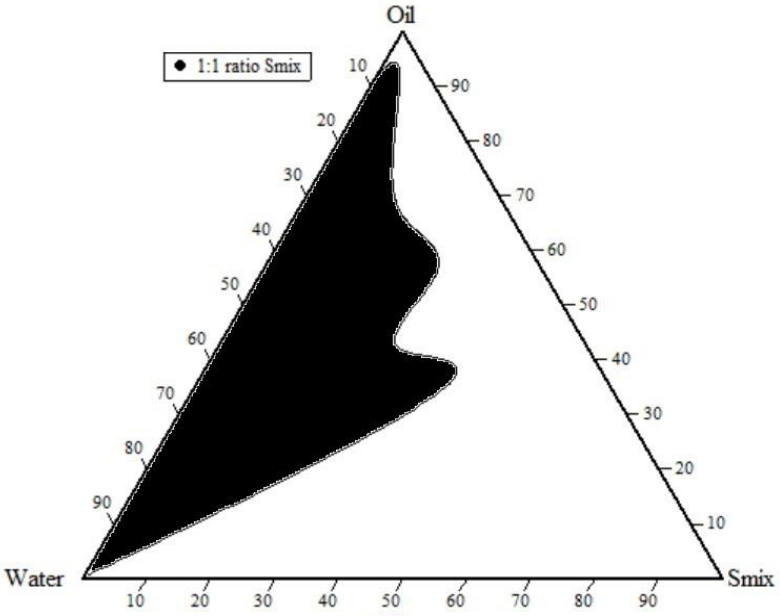
In this study, castor oil was used as the oil phase, Tween 20 as the surfactant, and Carbitol as the co-surfactant. The Smix was prepared in different ratios (1:1, 1:2, and 2:1) to evaluate their effect on microemulsion formation.

The results revealed that higher proportions of co-surfactant (1:2 ratio) enhanced emulsification efficiency but compromised stability. Conversely, higher surfactant ratios (2:1) also showed good emulsification but were not optimal in terms of stability. The 1:1 ratio provided a balanced system with both good emulsification efficiency and stability.

The phase diagram clearly indicated that the microemulsion region was most stable and extensive at the 1:1 ratio of surfactant to co-surfactant. This ratio ensures optimal interfacial film formation and prevents phase separation.

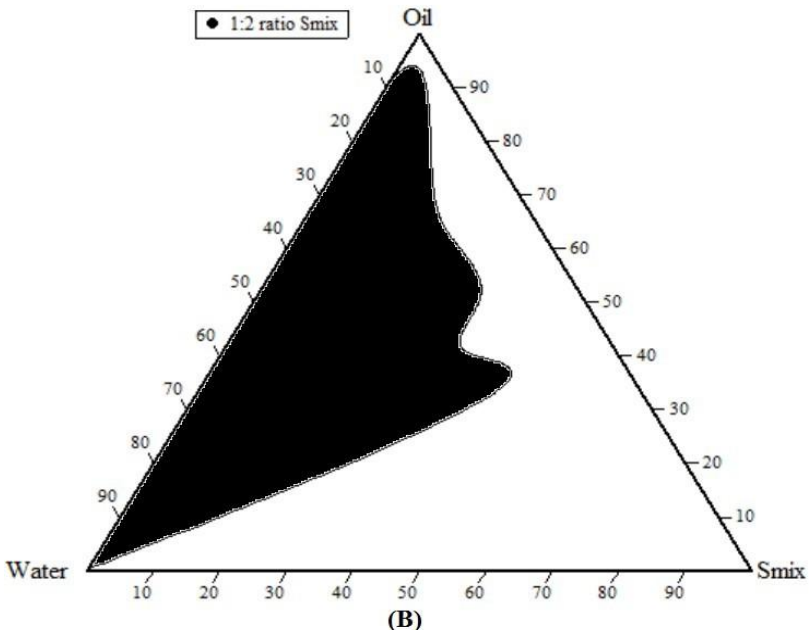
Therefore, the 1:1 Smix ratio was selected for further formulation development due to its superior stability and performance.

Psudo Ternaty Phase Diagram



(A)

Psudo Ternaty Phase Diagram



(B)

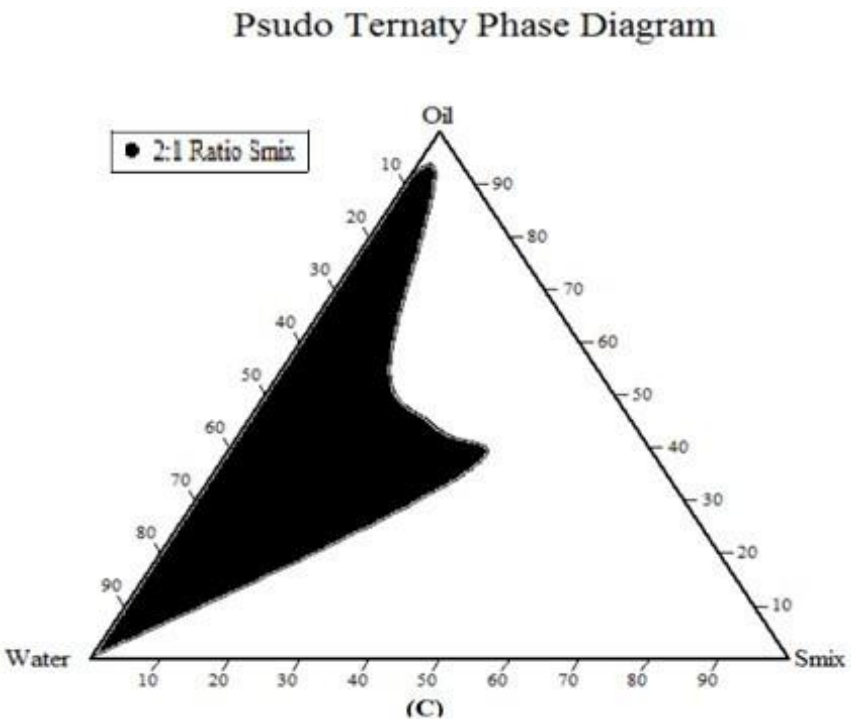


Figure 6.6: Pseudo-ternary phase diagrams illustrating the microemulsion region of the system comprising castor oil, Tween 20, Carbitol, and water at different surfactant-to-co-surfactant (Smix) ratios: (A) 1:1, (B) 1:2, and (C) 2:1.

6.3 Effect of Drug on the Phase Diagram

In the present study, the effect of Azilsartan Medoxomil incorporation on the phase behavior of the selected SMEDDS system—comprising castor oil, Tween 20, and Carbitol—was systematically evaluated. The pseudo-ternary phase diagrams constructed before and after drug incorporation were compared to assess any changes in the self-microemulsifying region.

The results revealed that the optimized formulation maintained a substantial microemulsion region even after the addition of the drug, indicating excellent compatibility of Azilsartan Medoxomil with the selected excipients. This suggests that the drug was efficiently solubilized within the lipid matrix without significantly disrupting the self-emulsification process. A slight reduction in the microemulsion

region may be observed following drug incorporation, which is commonly attributed to the occupation of solubilization space by drug molecules and minor changes in interfacial film flexibility. However, the retained broad microemulsion area confirms the robustness of the selected formulation and its ability to accommodate the drug while preserving its spontaneous emulsification characteristics.

Therefore, the optimized combination of castor oil, Tween 20, and Carbitol demonstrated excellent drug-loading capacity and maintained desirable phase behavior, making it a suitable system for the development of a stable and efficient SMEDDS formulation of Azilsartan Medoxomil.

Table 6.11: Effect of Azilsartan Medoxomil Incorporation on the Pseudo-Ternary Phase Diagram of the Optimized SMEDDS System

Amount of Drug (mg)	Visual Observation
10	Transparent
20	Transparent
30	Transparent
40	Transparent
50	Transparent
60	Transparent
70	Transparent
80	Transparent
90	Precipitation Observed
100	Precipitation Observed

The results demonstrated that the optimized SMEDDS formulation remained clear and transparent with drug loading up to 80 mg, indicating efficient solubilization of Azilsartan Medoxomil within the lipid-based system. The transparent appearance confirms the formation of a stable, isotropic system in which the drug is completely dissolved. However, at drug concentrations of 90 mg and above, precipitation was observed, suggesting that the solubilization capacity of the formulation had been

exceeded. This precipitation indicates saturation of the lipid matrix, resulting in the inability of the system to maintain the drug in a solubilized state.

Therefore, the maximum drug-loading capacity of the optimized SMEDDS was determined to be 80 mg. This finding confirms the excellent solubilizing efficiency of the selected combination of castor oil, Tween 20, and Carbitol, making it highly suitable for the formulation of Azilsartan Medoxomil with improved solubility and stability.

6.4 Formulation Development

6.4.1. Optimization of Formulation variables:

Optimization of formulation variables is a crucial step in SMEDDS development, as the performance of the system is highly dependent on the precise balance between oil, surfactant, and co-surfactant. Each of these components contributes uniquely to the overall behavior of the formulation, and even slight variations in their concentrations can significantly impact the final product characteristics.

The oil phase primarily serves as a reservoir for the lipophilic drug and plays an essential role in enhancing solubility and facilitating lymphatic transport. However, excessive oil concentration can lead to poor emulsification and increased droplet size, thereby reducing the efficiency of the system. On the other hand, surfactants are responsible for reducing interfacial tension and enabling the formation of stable microemulsions. High surfactant concentration improves emulsification but may cause irritation or toxicity concerns, which must be carefully balanced.

Co-surfactants act by increasing the flexibility of the interfacial film, allowing the system to achieve ultra-low interfacial tension. They also help in reducing the amount of surfactant required, thereby minimizing potential side effects. The synergistic interaction between surfactant and co-surfactant is critical for achieving spontaneous emulsification and stable droplet formation.

To systematically evaluate the effect of these variables, a statistical approach using Box-Behnken Design (BBD) was employed. The inclusion of center points allows for estimation of experimental error and ensures reproducibility.

Through this optimization process, it becomes possible to identify not only the individual effects of formulation variables but also their interaction effects. This holistic understanding is essential for designing a robust formulation that consistently

delivers optimal performance.

6.4.2 Optimization of Formulation Variables

Matrix of Box–Behnken Experimental Design for Optimization of Formulation Variables and Evaluation of Response Parameters

The improvement of oil, surfactant, and co-surfactant concentrations was carried out with a focus on achieving desirable formulation characteristics such as rapid emulsification, high clarity, and maximum drug release. These parameters are interdependent and are significantly influenced by the ratio and concentration of formulation components. Emulsification time is a direct indicator of the efficiency of the system to form a microemulsion upon dilution. Faster emulsification indicates better self-emulsifying properties, which is essential for oral drug delivery. It was observed that formulations with lower oil content and higher surfactant/co-surfactant concentrations exhibited faster emulsification due to improved interfacial activity.

Percentage transmittance reflects the optical clarity of the system and is inversely related to droplet size. High transmittance values indicate the formation of nanosized droplets, which are essential for enhanced drug dissolution and absorption. The presence of adequate surfactant and co-surfactant ensures uniform dispersion and prevents aggregation of droplets.

Cumulative drug release is the most critical parameter, as it determines the therapeutic efficiency of the formulation. The optimized formulations demonstrated significantly higher drug release compared to non-optimized systems. This enhancement can be attributed to improved solubilization, reduced droplet size, and increased surface area. The optimization process revealed that a balanced combination of low oil concentration and relatively higher surfactant and co-surfactant concentrations yields the best results. This balance ensures efficient emulsification, high clarity, and maximum drug release, thereby achieving the desired formulation objectives.

Table 6.12 Matrix of Box-Behnken Design for formulation and its evaluation

S. No	Std	Run	Batch No	Oil (ml)	Surfactant (ml)	Co-surfactant (ml)	Emulsification time (Sec)	% Transmittance (%)	% CDR (%)
1	8	1	B_1	9	2.5	4.5	46±5.28	80.96±1.76	92.1±0.028
2	17	2	B_2	5	2.5	2.5	64±42	74.82±1.07	68.52±0.024
3	16	3	B_3	5	2.5	2.5	65±5.55	75.82±1.26	66.16±0.021
4	10	4	B_4	5	4.5	0.5	86±2.60	59.15±0.90	52.35±0.022
5	15	5	B_5	5	2.5	2.5	63±2.60	74.83±1.07	69.74±0.026
6	1	6	B_6	1	0.5	2.5	50±3.35	88.12±0.76	80.6±0.029
7	3	7	B_7	1	4.5	2.5	37±3.65	91.27±0.99	86.41±0.032
8	13	8	B_8	5	2.5	2.5	64±44	75±1.11	69.52±0.026
9	9	9	B_9	5	0.5	0.5	90±42	43.05±0.79	50.1±0.026
10	4	10	B_{10}	9	4.5	2.5	67±2.54	62.9±0.88	63.35±0.018
11	6	11	B_{11}	9	2.5	0.5	112±2.60	32.06±0.51	44.08±0.028
12	7	12	B_{12}	1	2.5	4.5	18±2.64	99.07±0.23	99.53±0.015
13	2	13	B_{13}	9	0.5	2.5	83±2	51.48±0.47	68.82±0.030
14	14	14	B_{14}	5	2.5	2.5	64±2.64	76.83±1.07	70.58±0.028
15	12	15	B_{15}	5	4.5	4.5	23±2.64	95.35±0.77	96.62±0.011
16	5	16	B_{16}	1	2.5	0.5	73±3.50	64.13±0.74	61.10±0.028
17	11	17	B_{17}	5	0.4	4.4	38±3.62	90.8±1.82	94.35±0.028

6.5 Statistical Analysis

Statistical analysis plays a pivotal role in formulation development by offering a systematic, scientific, and quantitative approach to understand the relationship between formulation variables and critical response parameters. It enables researchers to evaluate the individual as well as interactive effects of independent variables on the performance of the formulation. Through statistical tools and experimental design techniques, it becomes possible to optimize formulation components efficiently, minimize the number of experimental trials, and develop a robust product with the desired quality attributes. This approach not only enhances the reliability and reproducibility of the formulation process but also facilitates the identification of the optimal formulation composition with improved performance, stability, and therapeutic efficacy. In the present study, the Box–Behnken Design (BBD), a response surface methodology, was employed to evaluate the influence of key formulation variables—namely oil, surfactant, and co-surfactant concentrations—on critical response parameters such as emulsification time, percentage transmittance, and cumulative drug release. This design is particularly advantageous as it reduces the number of experimental runs while still providing comprehensive information about variable interactions and optimization.

The use of Design Expert software facilitated the development of mathematical models that accurately describe the behavior of the SMEDDS formulation system. Among the various models evaluated, the quadratic model was found to be the most appropriate for representing the experimental data. This was evidenced by high coefficient of determination (R^2) values, indicating a strong correlation between predicted and observed responses, along with statistically significant p-values that confirm the validity of the model. These parameters collectively demonstrate the robustness, reliability, and predictive capability of the developed model.

Further validation was achieved through Analysis of Variance (ANOVA), which confirmed the overall significance of the model and identified the contribution of each independent variable. The results revealed that all three formulation components—oil, surfactant, and co-surfactant—had a significant impact on the response parameters, not only individually but also through their interaction effects. Such interactions are

critical in SMEDDS formulations, as the balance between these components determines the efficiency of self-emulsification and the stability of the resulting microemulsion.

Additionally, the statistical analysis generated polynomial equations that quantitatively describe the relationship between variables and responses. These equations serve as valuable predictive tools, allowing formulation scientists to estimate the behavior of the system under different conditions without the need for extensive experimental trials. This significantly reduces time, cost, and resource utilization during the optimization process.

Overall, the application of statistical design and analysis provided a comprehensive understanding of the formulation system. It enabled the identification of optimal formulation conditions that achieve the desired performance characteristics, thereby enhancing the efficiency and scientific rigor of the development process.

Response 1: Emulsification Time

In the present study, the emulsification time of batches B1 to B17 ranged from **18 ± 2.64 seconds to 112 ± 3.60 seconds**. This variation demonstrates the significant effect of formulation composition on emulsification behavior.

ANOVA results showed that oil (A), surfactant (B), and co-surfactant (C) significantly affected emulsification time, as evidenced by a **P-value less than 0.05**. Among these variables, oil concentration had a positive effect, indicating that increasing oil content prolonged emulsification time. In contrast, surfactant and co-surfactant concentrations had negative effects, showing that their increase reduced emulsification time.

Polynomial Equation for Emulsification Time

$$=63.80+16.25A-5.75B-29.25C-0.50AB-3.00AC-2.50BC-1.15A^2-3.65B^2-0.65C^2$$

The equation indicates that higher oil concentration increases emulsification time, while higher surfactant and co-surfactant concentrations promote faster emulsification. Therefore, an optimal balance of these components is essential to achieve rapid and efficient self-emulsification.

Table 6.13: Analysis of Variance (ANOVA) for Emulsification Time

Source	Sum of Squares	df	Mean Square	F Value	p-value (Prob > F)	Remark
Model	9350.75	9	1038.96	299.24	<0.0001	Significant
Lack of Fit	21.54	3	7.15	10.25	0.0229	Significant
Pure Error	2.70	4	0.70	–	–	–
Core Total	9375.05	16	–	–	–	–

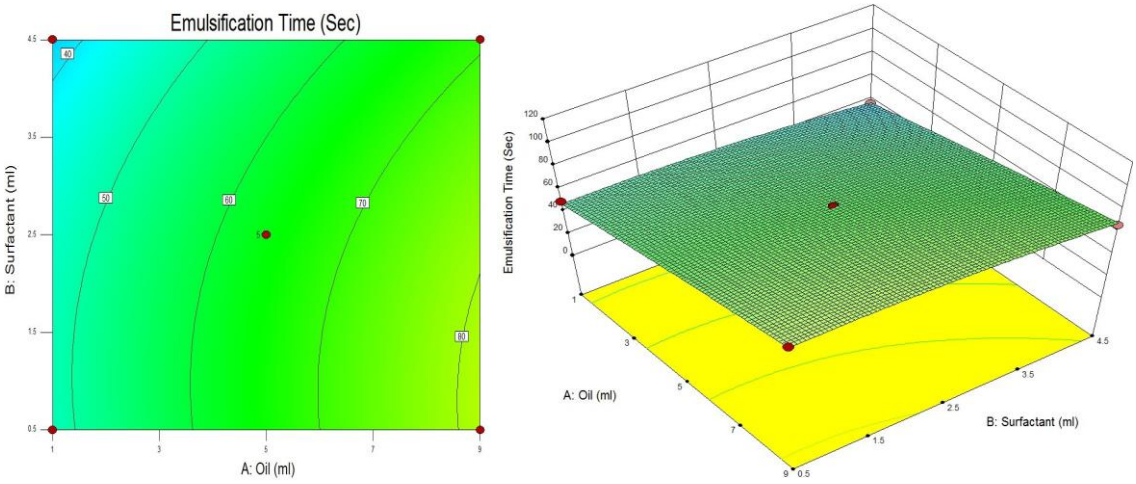
- **R^2 = 0.9975**
- **Adjusted R^2 = 0.9942**
- **Predicted R^2 = 0.9627**

The ANOVA results indicate that the quadratic model developed for emulsification time is highly significant, as evidenced by the high F-value (299.24) and a p-value of less than 0.0001. The model explains 99.75% of the variability in emulsification time, demonstrating an excellent fit between the experimental data and the predicted values.

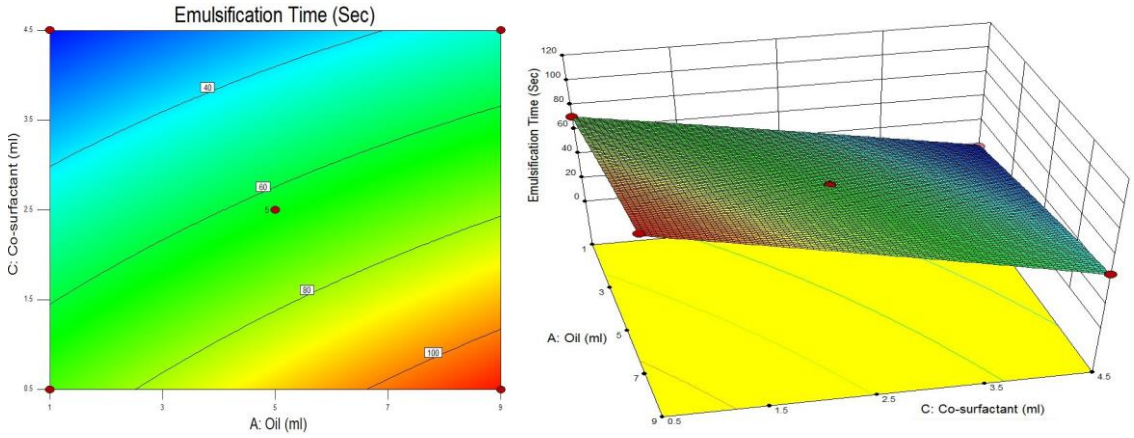
The adjusted R^2 value of 0.9942 confirms the reliability of the model after accounting for the number of variables included. Similarly, the predicted R^2 value of 0.9627 indicates strong predictive ability and good agreement with the adjusted R^2 value.

Although the lack-of-fit was found to be significant, the very high R^2 values and strong predictive performance suggest that the model is robust and suitable for optimization and prediction of emulsification time within the studied design space.

(i) Effect of Oil (A) and Surfactant (B) on Emulsification Time



(ii) Oil (A) and co-surfactant (C)



(iii) Surfactant (B) and Co-surfactant (C)

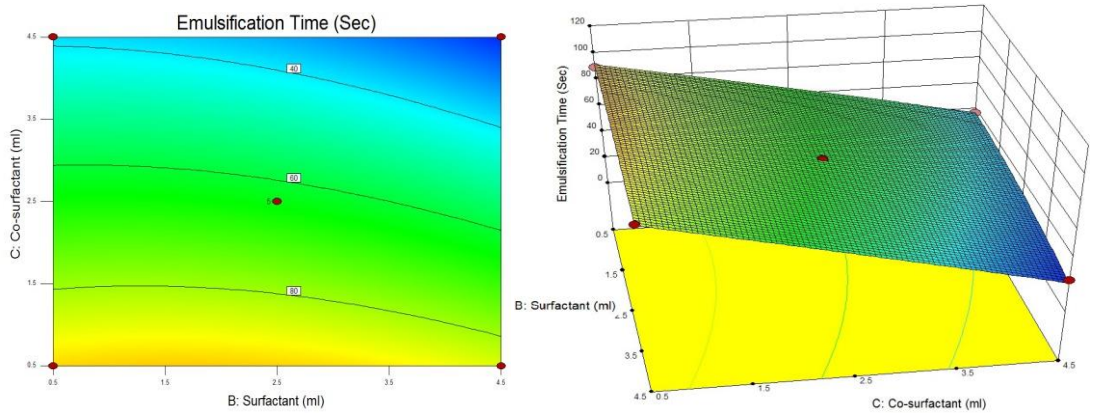


Figure 6.7: Contour plots and response surface plots illustrating the effect of formulation variables on emulsification time: (i) oil (A) and surfactant (B), (ii) oil (A) and co-surfactant (C), and (iii) surfactant (B) and co-surfactant (C).

Response 2: Percentage Transmittance

In the present study, the percentage transmittance of batches B1 to B17 ranged from **32.06 ± 0.51% to 99.08 ± 0.23%**. This wide range reflects the significant influence of formulation variables on the clarity and quality of the microemulsion.

Statistical analysis showed that oil (A), surfactant (B), and co-surfactant (C) significantly affected percentage transmittance, as indicated by a **P-value less than 0.05**. Oil concentration exhibited a negative effect, suggesting that increasing the oil content reduced transmittance. In contrast, surfactant and co-surfactant concentrations showed positive effects, indicating that their increase enhanced the clarity of the emulsion.

Polynomial Equation for Percentage Transmittance

$$\%\text{Transmittance}=75.25-14.40A+4.40B+20.98C+2.07AB+3.49AC-2.89BC-2.52A^2+0.51B^2-3.87C^2$$

The equation demonstrates that increasing the concentrations of surfactant and co-surfactant improves transmittance, while increasing oil concentration decreases it. Thus, an optimized balance of these components is essential for obtaining a clear and stable microemulsion.

Table 6.14: Analysis of Variance (ANOVA) for Percentage Transmittance

Source	Sum of Squares	df	Mean Square	F Value	p-value (Prob > F)	Remark
Model	5527.29	9	614.15	122.52	< 0.0001	Significant
Lack of Fit	32.10	3	10.72	14.28	0.0132	Significant
Pure Error	3.00	4	0.75	–	–	–
core Total	5562.38	16	–	–	–	–

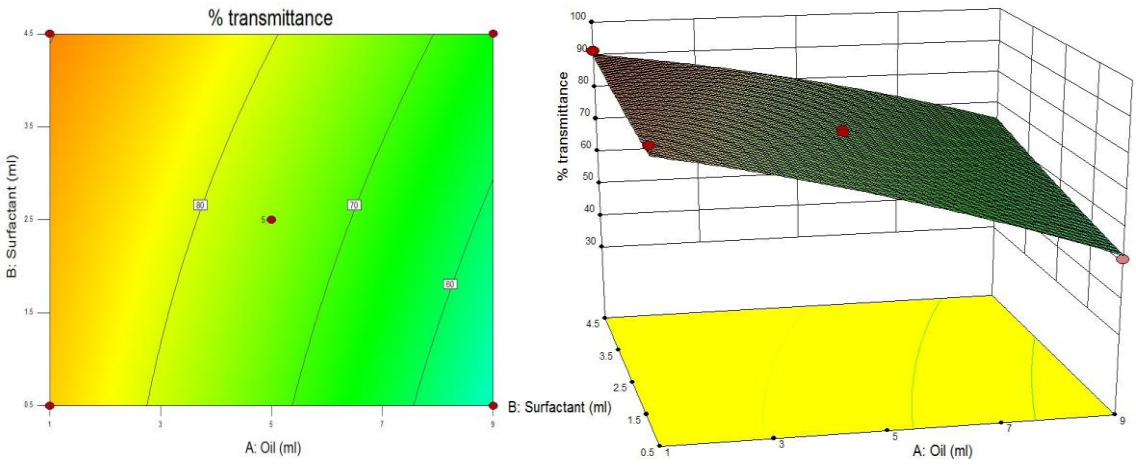
- **$R^2 = 0.9936$**
- **Adjusted $R^2 = 0.9855$**
- **Predicted $R^2 = 0.9067$**

The ANOVA results indicate that the quadratic model for percentage transmittance is highly significant, as shown by the high F-value (122.52) and a p-value of less than 0.0001. The model explains 99.36% of the variability in percentage transmittance, indicating an excellent fit.

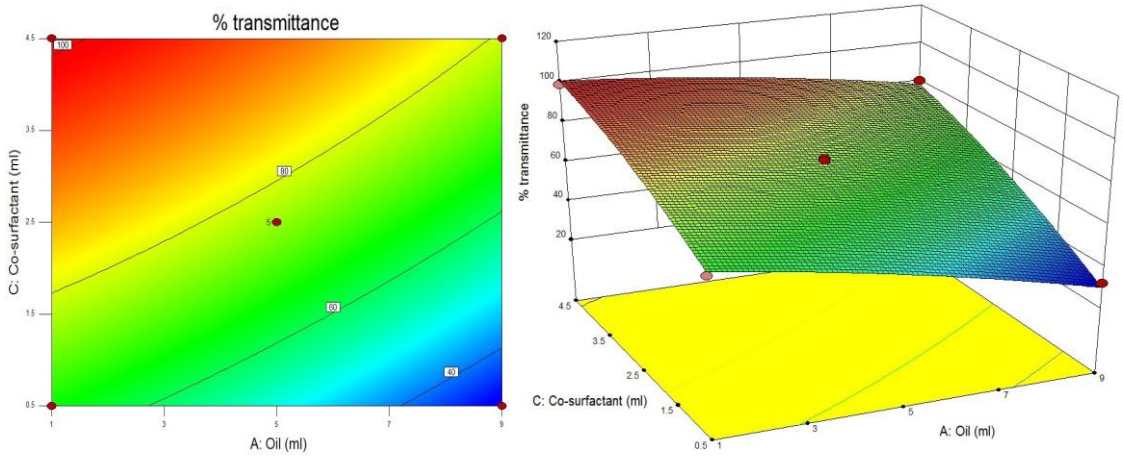
The adjusted R^2 value of 0.9855 confirms the reliability of the model, while the predicted R^2 value of 0.9067 demonstrates good predictive capability. The close agreement between the adjusted and predicted R^2 values further supports the adequacy of the model.

Although the lack-of-fit is significant, the high R^2 values and strong predictive performance indicate that the model is suitable for optimization and prediction of percentage transmittance within the selected experimental range

(i) Effect of Oil (A) and Surfactant (B) on Emulsification Time



(ii) Oil (A) and Co-surfactant (C)



(iii) Surfactant (B) and Co-surfactant

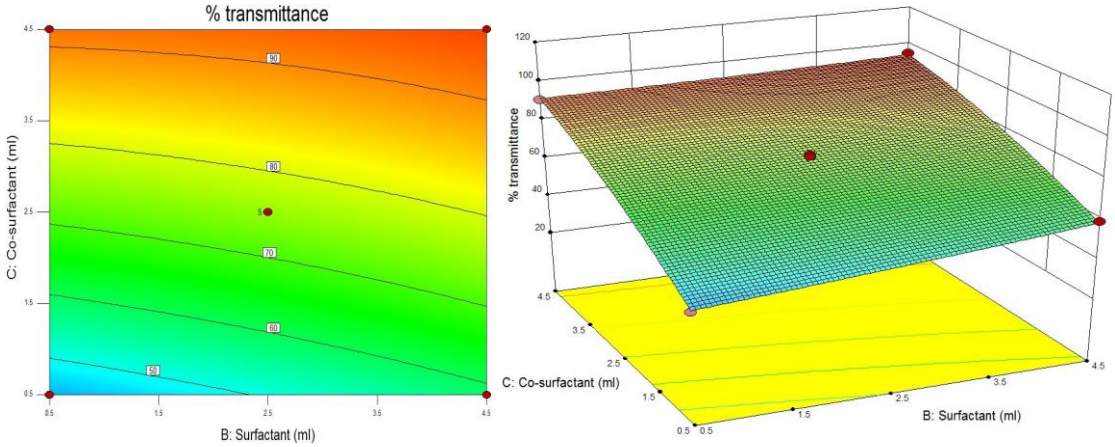


Figure 6.8: Contour plot and Response surface of % transmittance (i) Effect of Oil

(A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

Response 3: Percentage Cumulative Drug Release

In the present study, the percentage cumulative drug release of batches B1 to B17 ranged from **44.08 ± 0.028% to 99.43 ± 0.015%**. This wide range demonstrates the significant influence of formulation variables on drug release performance.

Statistical analysis revealed that oil (A), surfactant (B), and co-surfactant (C) significantly affected percentage cumulative drug release, as indicated by a **P-value**

less than 0.05. Oil concentration showed a negative effect, indicating that increasing oil content reduced drug release. In contrast, surfactant and co-surfactant concentrations exhibited positive effects, suggesting that their increase enhanced drug release.

Polynomial Equation for Percentage Cumulative Drug Release

$=68.90-7.37A+0.66B+21.90C-2.80AB+2.45AC-0.078BC+3.42A^2+2.49B^2+1.88C^2$

The equation indicates that co-surfactant had the most pronounced positive effect on drug release, followed by surfactant, whereas oil concentration negatively influenced the response. Therefore, an optimized combination of lower oil content and higher surfactant and co-surfactant concentrations is essential to achieve maximum drug release.

Table 6.15: Analysis of Variance (ANOVA) for Percentage Cumulative Drug Release

Source	Sum of Squares	df	Mean Square	F Value	p-value (Prob > F)	Remark
Model	4431.18	9	492.38	121.33	< 0.0001	Significant
Lack of Fit	17.82	3	5.50	1.92	0.2663	Not Significant
Pure Error	11.61	4	2.80	–	–	–
core Total	4450.60	16	–	–	–	–

- **R^2 = 0.9936**
- **Adjusted R^2 = 0.9854**
- **Predicted R^2 = 0.9357**

The ANOVA results indicate that the quadratic model for percentage cumulative drug release is highly significant, as evidenced by the high F-value (121.33) and a p-value of less than 0.0001. The model explains 99.36% of the variability in drug release, demonstrating an excellent fit.

The adjusted R^2 value of 0.9854 confirms the reliability of the model, while the predicted R^2 value of 0.9357 indicates strong predictive ability. The close agreement between these values further supports the adequacy of the model.

Importantly, the lack-of-fit was found to be non-significant ($p = 0.2663$), indicating that the model fits the experimental data well. Therefore, the developed model is highly suitable for optimization and prediction of percentage cumulative drug release within the studied formulation range.

Effect of Oil (A) and Surfactant (B) on Emulsification Time

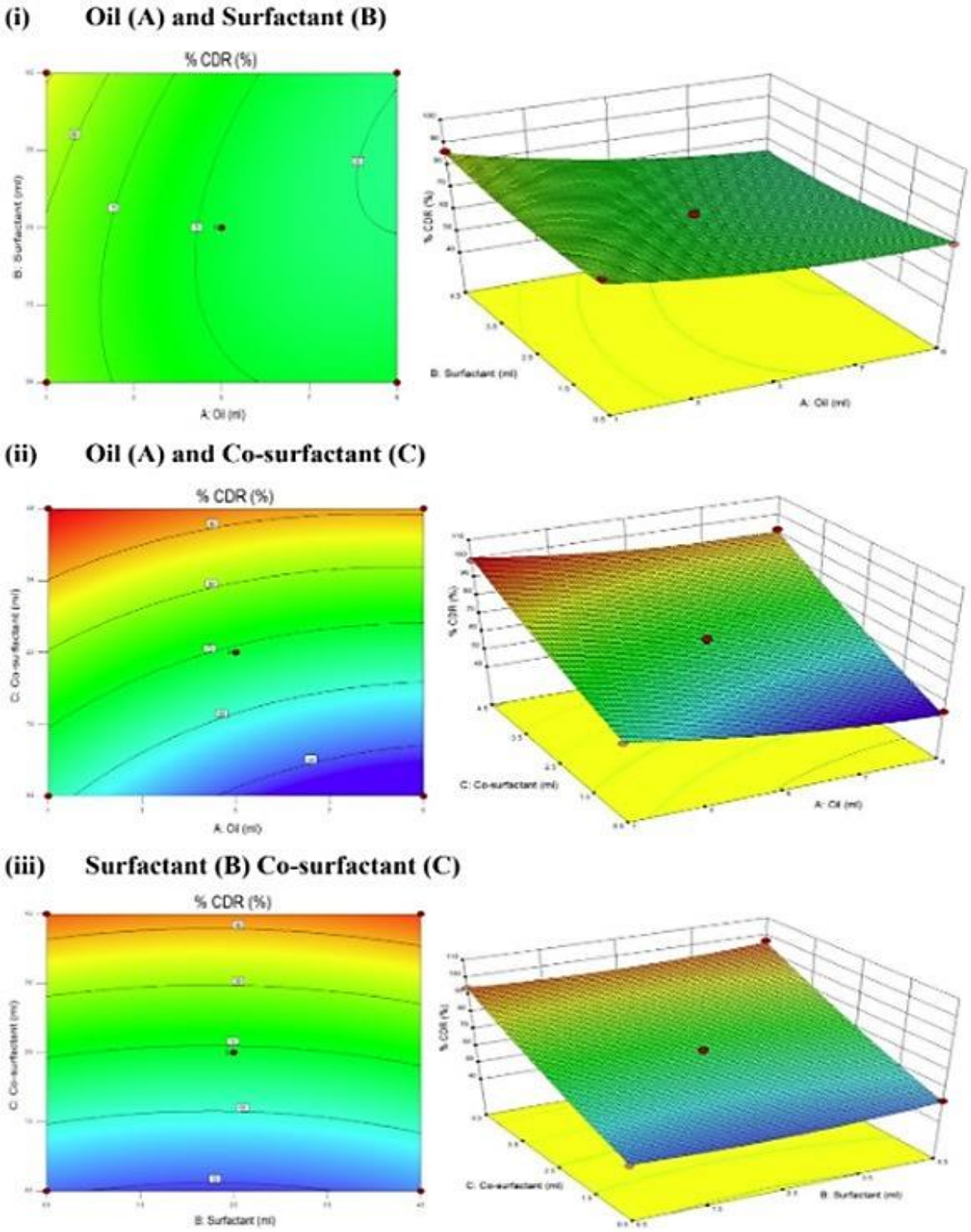


Figure 6.9: Contour plots and response surface plots showing the effect of formulation variables on percentage cumulative drug release: (i) effect of oil (A) and surfactant (B), (ii) effect of oil (A) and co-surfactant (C), and (iii) effect of surfactant (B) and co-surfactant (C).

At constant levels of surfactant and co-surfactant, increasing the concentration of oil from 1 mL to 9 mL resulted in an increase in emulsification time from **18 ± 2.64 sec to 112 ± 3.60 sec**. Simultaneously, percentage transmittance decreased from **99.08 ± 0.23% to 32.06 ± 0.51%**, and percentage cumulative drug release declined from **99.43 ± 0.015% to 44.08 ± 0.028%**. This indicates that higher oil concentrations adversely affect self-emulsification efficiency, clarity, and drug release.

Conversely, at fixed levels of oil and co-surfactant, increasing the surfactant concentration from 0.5 mL to 4.5 mL significantly improved formulation performance. Emulsification time decreased from **112 ± 3.60 sec to 18 ± 2.64 sec**, while percentage transmittance increased from **32.06 ± 0.51% to 99.08 ± 0.23%**. Similarly, percentage cumulative drug release improved markedly from **44.08 ± 0.028% to 99.43 ± 0.015%**. This enhancement can be attributed to the ability of surfactants to reduce interfacial tension and promote rapid emulsion formation.

Likewise, increasing the concentration of co-surfactant from 0.5 mL to 4.5 mL, while maintaining constant levels of oil and surfactant, also led to substantial improvements. Emulsification time decreased, whereas percentage transmittance and cumulative drug release increased significantly. These findings confirm that co-surfactants enhance interfacial fluidity, facilitate spontaneous emulsification, and improve drug solubilization.

Overall, the response surface analysis demonstrates that lower oil concentration combined with higher concentrations of surfactant and co-surfactant produces an optimized SMEDDS with rapid emulsification, excellent clarity, and maximum drug release.

6.5 Evaluation of Liquid SMEDDS Formulation

6.5.1 Dispersibility Test

Table 6.16: Dispersibility test results of Box–Behnken design formulations.

S. No.	Batch No.	Distilled Water	0.1 N HCl
1	B1	Grade A	Grade A
2	B2	Grade B	Grade B
3	B3	Grade B	Grade B
4	B4	Grade D	Grade D
5	B5	Grade B	Grade B
6	B6	Grade B	Grade B
7	B7	Grade B	Grade B
8	B8	Grade B	Grade B
9	B9	Grade D	Grade D
10	B10	Grade C	Grade C
11	B11	Grade D	Grade D
12	B12	Grade A	Grade A
13	B13	Grade C	Grade C
14	B14	Grade B	Grade B
15	B15	Grade A	Grade A
16	B16	Grade C	Grade C
17	B17	Grade A	Grade A

These evaluations provide detailed insights into how the formulation behaves under various conditions, including dilution, agitation, and environmental stress. Such information is essential for predicting in vivo performance and ensuring that the formulation can consistently deliver the desired therapeutic effect.

Key parameters evaluated include dispersibility, robustness to dilution, emulsification time, and clarity of the resulting microemulsion. Dispersibility testing helps determine how efficiently the formulation can form a microemulsion in aqueous media, while robustness to dilution ensures that the system remains stable even after significant dilution in gastrointestinal fluids. Emulsification time indicates the speed at which the formulation self-emulsifies, and clarity reflects the formation of fine, uniformly distributed droplets. Together, these parameters serve as important indicators of formulation quality, stability, and efficiency.

Furthermore, the evaluation process plays a crucial role in understanding the influence of formulation variables. By analyzing these effects, it becomes possible to optimize the formulation composition to achieve the best balance between stability and drug release. This systematic approach ensures that only the most promising formulations are selected for further development.

Overall, the evaluation of liquid SMEDDS formulations provides a strong foundation for formulation optimization and development. It enables the identification of robust, efficient, and reproducible systems, ultimately contributing to the successful design of an effective drug delivery system with improved bioavailability and therapeutic performance.

6.6.2 Robustness to Dilution

Table 6.17: Robustness to Dilution of Box–Behnken Design Formulations

S. No.	Batch No.	Distilled Water	0.1 N HCl
1	`	Stable, no precipitation	Stable, no precipitation
2	B2		
3	B3		
4	B4		
5	B5		
6	B6		
7	B7		
8	B8		
9	B9		
10	B10		
11	B11		
12	B12		
13	B13		
14	B14		
15	B15		
16	B16		
17	B17		

Upon oral administration, SMEDDS are exposed to extensive and rapid dilution in the gastrointestinal tract due to the presence of gastric and intestinal fluids. Such dilution can potentially disrupt the system, leading to phase separation or drug precipitation if the formulation is not properly optimized.

In the present study, the developed formulations demonstrated excellent robustness to dilution, as they remained clear and stable without any signs of phase separation, turbidity, or precipitation. This indicates that the formulations are capable of forming

stable microemulsions over a wide range of dilution conditions, which is essential for consistent in vivo performance.

The observed stability can be attributed to the optimal ratio and selection of formulation components, particularly the oil, surfactant, and co-surfactant. These components work synergistically to form a strong and flexible interfacial film around the droplets, which prevents coalescence and maintains the dispersion even under highly diluted conditions. Additionally, the ability of the system to rapidly self-emulsify into fine droplets ensures that the drug remains uniformly distributed and solubilized. Therefore, the excellent robustness to dilution observed in the optimized SMEDDS formulation confirms its suitability for oral delivery and its potential to provide consistent therapeutic outcomes.

6.6.3 Emulsification Time

In the present study, the optimized formulation exhibited the shortest emulsification time among all the developed batches, indicating its superior self-emulsifying efficiency. This rapid emulsification behavior suggests that the formulation can readily disperse under mild agitation conditions, similar to those present in the gastrointestinal tract, without the need for external energy input.

Rapid emulsification not only enhances the dissolution rate but also ensures that the drug is presented in a solubilized and readily absorbable form. This contributes significantly to improved bioavailability and consistent therapeutic performance.

Overall, the results confirm that the optimized SMEDDS formulation possesses excellent self-emulsifying properties, characterized by minimal emulsification time, which is a critical factor in achieving efficient drug delivery and improved pharmacokinetic outcomes.

6.6.4 Transmittance

Percentage transmittance is a key parameter used in the characterization of Self-Microemulsifying Drug Delivery Systems (SMEDDS), as it provides indirect information about the clarity of the system and the size of the formed droplets. It is measured using a spectrophotometer and reflects the ability of light to pass through

the microemulsion. Higher transmittance values are typically associated with smaller droplet sizes and a more homogeneous dispersion, which are indicative of an efficient microemulsion system.

In the present study, the optimized formulation exhibited very high percentage transmittance, suggesting the formation of a clear and transparent microemulsion upon dilution. This clarity confirms that the droplets are present in the nanometer range and are uniformly distributed throughout the system. The absence of turbidity or cloudiness further indicates that there is no phase separation or aggregation of droplets, highlighting the physical stability of the formulation.

Such high transmittance is a desirable characteristic in SMEDDS, as it correlates with enhanced drug solubilization and improved dissolution behavior. Smaller and uniformly distributed droplets provide a larger surface area, which facilitates rapid drug release and efficient interaction with the dissolution medium. This ultimately contributes to improved absorption and bioavailability of the drug.

Overall, the high percentage transmittance observed in the optimized formulation confirms the successful formation of a fine, stable, and homogeneous microemulsion system. This characteristic plays a crucial role in ensuring consistent performance and supports the effectiveness of SMEDDS as an advanced drug delivery approach for poorly water-soluble drugs.

6.7 Drug Content

Table 6.18: Drug Content of Box-Behnken Design formulation

S. No	Batch No	Drug Content
1	B_1	90.72±0.012
2	B_2	93.57±0.0154
3	B_3	95.50±0.0145
4	B_4	83.79±0.0298
5	B_5	96.23±0.021
6	B_6	94.82±0.018
7	B_7	97.62±0.011
8	B_8	94.40±0.016
9	B_9	88.01±0.020
10	B_{10}	89.29±0.011
11	B_{11}	83.82±0.029
12	B_{12}	99.01±0.009
13	B_{13}	94.06±0.016
14	B_{14}	92.78±0.019
15	B_{15}	98.86±0.013
16	B_{16}	90.24±0.017
17	B_{17}	93.78±0.019

*Mean ± SD, n=3

In the present study, drug content analysis was performed using a UV spectrophotometric method at a specific wavelength, based on a previously constructed and validated calibration curve. This analytical approach provides precise and reproducible quantification of the drug present in the formulation.

The results of the drug content analysis indicated that the majority of the developed formulations exhibited high drug loading efficiency, suggesting that there was minimal loss of drug during the formulation process. This observation reflects the excellent compatibility between the drug and the selected excipients, including the oil phase, surfactant, and co-surfactant. These components effectively solubilize the drug and maintain it in a stable, dissolved state within the system. Notably, the optimized formulation showed nearly complete drug content, confirming the efficiency of the

formulation design as well as the precision and reproducibility of the preparation method.

Uniform drug content is crucial for ensuring dose accuracy and consistency in therapeutic performance. Any variation in drug distribution within the formulation can result in dose fluctuations, leading to suboptimal efficacy or potential safety concerns. In the case of SMEDDS, this aspect becomes even more critical, as the drug is molecularly dispersed within the lipid matrix. Any instability, such as phase separation or precipitation, can disrupt this uniformity and adversely affect the formulation's performance.

Furthermore, the high drug content observed in the optimized formulation indicates a strong solubilization capacity of the system, which is a highly desirable attribute for improving oral bioavailability. A formulation with high solubilization efficiency ensures that the drug remains in a dissolved state even after dilution in gastrointestinal fluids, thereby minimizing the risk of precipitation and promoting efficient absorption.

Overall, the findings confirm that the optimized SMEDDS formulation achieves excellent drug content uniformity and high loading efficiency. These characteristics not only validate the robustness of the formulation strategy but also support its potential for delivering consistent, effective, and reproducible therapeutic outcomes.

6.8 In-vitro Drug Release

Table 6.19: *In-vitro* Drug release of batch B1 to B8

Time (min)	Batch No							
	B1	B2	B3	B4	B5	B6	B7	B8
0	0	0	0	0	0	0	0	0
5	10.35±0.025	6.65±0.018	5.88±0.016	3.70±0.012	6.23±0.018	13.65±0.027	8.64±0.023	5.36±0.017
10	17.35±0.038	17.33±0.025	12.56±0.027	8.95±0.017	15.00±0.027	22.95±0.025	21.70±0.022	14.50±0.014
15	23.32±0.031	25.59±0.027	21.01±0.021	19.47±0.024	23.57±0.035	29.10±0.025	31.11±0.029	25.62±0.022
20	32.86±0.021	34.05±0.026	30.04±0.030	26.85±0.020	32.73±0.034	38.59±0.031	43.97±0.018	33.54±0.019
25	43.82±0.025	40.10±0.029	41.02±0.029	32.00±0.019	37.01±0.028	47.88±0.027	54.15±0.034	39.52±0.025
30	61.62±0.028	47.57±0.027	48.20±0.029	37.37±0.024	43.83±0.025	58.58±0.034	65.09±0.021	46.88±0.018
35	74.43±0.036	55.52±0.024	53.60±0.038	41.17±0.029	55.13±0.029	69.85±0.028	73.54±0.027	53.43±0.028
40	87.64±0.028	62.07±0.023	60.47±0.024	45.42±0.020	61.36±0.027	76.78±0.038	84.49±0.035	63.16±0.025
45	92.41±0.029	68.52±0.024	66.16±0.021	52.36±0.022	69.74±0.027	80.53±0.029	86.41±0.031	69.53±0.025

*Mean ± SD, n=3

Table 6.20: *In-vitro* drug Release of batch B9 to B17

Time (min)	Batch No								
	B9	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**	**B16**	**B17**
0	0	0	0	0	0	0	0	0	0
5	3.84±0.014	4.62±0.011	4.25±0.010	15.15±0.021	4.39±0.020	8.09±0.022	13.08±0.012	8.11±0.024	10.59±0.021
10	8.95±0.018	11.12±0.022	9.84±0.022	30.12±0.017	10.57±0.024	14.56±0.024	28.28±0.015	15.38±0.029	21.19±0.030
15	13.23±0.021	19.75±0.019	13.87±.013	45.13±0.018	18.75±0.033	24.88±0.026	41.70±0.012	24.74±0.023	30.38±0.024
20	22.37±0.020	27.94±0.018	17.00±0.020	56.25±0.012	26.53±0.026	33.16±0.029	54.47±0.018	28.48±0.011	42.75±0.021
25	28.78±0.022	34.64±0.029	20.14±0.026	73.67±0.018	32.92±0.030	39.45±0.027	71.93±0.012	35.65±0.025	52.97±0.022
30	31.55±0.015	41.81±0.023	24.84±0.013	85.61±0.018	36.69±0.027	45.71±0.022	81.98±0.015	43.03±0.020	65.57±0.023
35	40.93±0.013	50.21±0.024	32.22±0.019	96.21±0.016	47.67±0.022	53.20±0.025	92.61±0.023	49.68±0.026	78.56±0.026
40	45.41±0.013	55.67±0.020	39.38±0.025	99.24±0.005	52.86±0.026	62.30±0.025	95.65±0.018	59.04±0.028	91.95±0.024
45	50.10±0.024	63.45±0.016	45.08±0.027	99.43±0.015	68.83±0.020	70.59±0.038	96.60±0.012	61.11±0.027	94.35±0.028

*Mean ± SD, n=3

In the present investigation, dissolution studies were conducted using appropriate media that simulate physiological conditions of the gastrointestinal tract. This approach ensures that the obtained results closely reflect the behavior of the formulation upon oral administration.

The optimized SMEDDS formulation demonstrated rapid and nearly complete drug release within a short duration, indicating its superior dissolution performance. This enhanced behavior can be primarily attributed to the spontaneous formation of fine microemulsion droplets upon contact with aqueous media. These nanosized droplets provide an extensive surface area, which facilitates faster drug diffusion into the dissolution medium. Moreover, the presence of surfactants and co-surfactants improves the wetting properties of the drug and maintains it in a solubilized state, thereby eliminating dissolution as a limiting step and promoting efficient release.

In contrast, formulations containing a higher proportion of oil and relatively lower concentrations of surfactants exhibited slower and incomplete drug release. This can be explained by the formation of larger droplets and less efficient dispersion, which reduces the available surface area and hinders drug diffusion. These observations clearly indicate that an optimal balance between formulation components is essential to achieve efficient self-emulsification and enhanced drug release.

6.9 Thermodynamic Stability Studies

Table 6.21: Thermodynamic stability studies of Box-Behnken Design formulation

Batch No	Hearing Cooling Cycle	Centrifugation	Freeze – thaw cycles	Inference
B_1	Stable	No phase separation	Stable	Passed
B_2	Stable	phase separation	Unstable	Failed
B_3	Stable	phase separation	Unstable	Failed
B_4	Unstable	Phase separation	Unstable	Failed
B_5	Unstable	Phase separation	Unstable	Failed
B_6	Stable	No phase separation	Unstable	Failed
B_7	Stable	No phase separation	Unstable	Failed
B_8	Stable	phase separation	Unstable	Failed
B_9	Unstable	Phase separation	Unstable	Failed
B_{10}	Stable	Phase separation	Unstable	Failed
B_{11}	Unstable	Phase separation	Unstable	Failed
B_{12}	Stable	No phase separation	Stable	Passed
B_{13}	Stable	Phase separation	Unstable	Failed
B_{14}	Stable	phase separation	Unstable	Failed
B_{15}	Stable	No Phase separation	stable	Passed
B_{16}	Unstable	Phase separation	Unstable	Failed
B_{17}	Stable	No Phase separation	stable	Passed

Unlike conventional emulsions, which are only kinetically stable and may eventually undergo phase separation, microemulsions formed by SMEDDS are expected to be thermodynamically stable systems.

In the present study, the developed SMEDDS formulations were subjected to a series of rigorous stress tests, including heating–cooling cycles, centrifugation, and freeze–

thaw cycles. Together, these tests provide a comprehensive assessment of the formulation's robustness and stability under adverse conditions.

The results of these studies revealed that only a select number of formulations were able to successfully withstand all applied stress conditions. These optimized formulations exhibited no visible signs of instability such as phase separation, creaming, cracking, or precipitation. The absence of such changes confirms that the internal structure of the microemulsion remained intact, even under extreme conditions, thereby demonstrating excellent thermodynamic stability.

The remarkable stability of SMEDDS can be attributed to the ultra-low interfacial tension between the oil and aqueous phases, achieved through the combined action of surfactants and co-surfactants. These components form a flexible and dynamic interfacial film around the droplets, which not only facilitates spontaneous emulsification but also prevents droplet coalescence and aggregation. This structural arrangement ensures that the system remains stable without the need for external energy input.

Thermodynamic stability is a critical requirement for any pharmaceutical formulation, as it directly impacts product quality, consistency, and safety. A stable formulation ensures uniform drug distribution, predictable performance, and an extended shelf life, which are essential for patient compliance and therapeutic efficacy. Based on these findings, only the formulations that demonstrated superior stability were selected for further characterization and development, ensuring the reliability and effectiveness of the final SMEDDS product.

6.10 Viscosity

Table 6.22: Viscosity of optimize SMEDDS formulation

Batch no.	Viscosity in Centi poise
B_{12}	0.8872
B_{15}	0.9176
B_{17}	0.9244
B_1	0.9277

The viscosity measurements in this study revealed that all formulations exhibited very low viscosity, closely resembling that of water. This observation indicates that the systems predominantly form oil-in-water (o/w) microemulsions upon dilution, where the aqueous phase acts as the continuous medium and the oil phase is dispersed as fine droplets. Such low-viscosity systems are highly desirable, as they promote rapid dispersion and spontaneous emulsification when introduced into aqueous environments, such as gastrointestinal fluids.

Among the evaluated batches, the optimized formulation demonstrated the lowest viscosity, suggesting the formation of a highly efficient and finely dispersed microemulsion system. This reduced viscosity is often associated with smaller and uniformly distributed droplet sizes, which contribute to enhanced surface area and improved drug solubilization. Consequently, this leads to faster drug release and better absorption, ultimately improving the bioavailability of the drug.

In addition to its impact on drug delivery performance, low viscosity also offers practical advantages in terms of formulation handling and manufacturability. Such systems are easier to pour, mix, and fill into dosage forms like capsules, ensuring uniform dosing and minimizing processing challenges. Furthermore, low-viscosity formulations enhance patient acceptability by enabling smooth administration without issues related to thickness or resistance to flow.

Overall, the results confirm that the developed SMEDDS formulations possess favorable rheological properties, characterized by low viscosity and efficient flow behavior. These attributes not only support the formation of stable and effective

microemulsions but also contribute to the practicality and scalability of the formulation for pharmaceutical applications.

6.11 Globule Size Measurement

Table 6.23: Globule size of optimize SMEDDS formulation

Batch no	Size of globule in nm
B_{12}	92.27
B_{15}	124.8
B_{17}	170.3
B_1	283.1

Globule size is one of the most critical parameters in the design and evaluation of Self-Microemulsifying Drug Delivery Systems (SMEDDS), as it has a direct and profound influence on drug release, absorption, and overall bioavailability. The size of the droplets formed upon dilution determines the surface area available for drug diffusion; therefore, smaller droplet sizes significantly enhance drug dissolution and facilitate rapid absorption across the gastrointestinal membrane.

In the present study, the optimized SMEDDS formulation exhibited globule sizes in the nanometer range, confirming the successful formation of a true microemulsion system. This nanoscale droplet size is a defining characteristic of SMEDDS and is primarily responsible for its superior performance compared to conventional dosage forms. The extremely fine droplets provide a vastly increased interfacial surface area, allowing the drug to remain in a solubilized state and enabling faster and more efficient release into the dissolution medium.

Maintaining a small and uniform globule size is also crucial for preventing physical instability such as aggregation or phase separation. A stable nanosized system ensures that the formulation retains its integrity during storage and upon dilution, thereby delivering consistent therapeutic outcomes.

6.12 Poly Dispersity Index (PDI)

In this study, the optimized SMEDDS formulation exhibited a low PDI value, clearly indicating a narrow and uniform droplet size distribution. Such a low PDI reflects a homogeneous system in which the droplets are evenly dispersed without significant variation in size. This uniformity is highly desirable, as it ensures that the formulation behaves consistently during storage, handling, and upon dilution in biological fluids. A well-defined and uniform droplet population is crucial for ensuring predictable performance, stability, and reproducibility of the formulation.

Uniform droplet size distribution plays a vital role in achieving consistent drug release and absorption. When the droplets are similar in size, the surface area available for drug release remains uniform, leading to predictable dissolution and bioavailability. Moreover, a low PDI reduces the likelihood of instability phenomena such as droplet aggregation, flocculation, or coalescence, which are more common in systems with a broad size distribution. In contrast, a high PDI value indicates heterogeneity within the system, suggesting the presence of droplets of varying sizes, which can compromise stability and lead to inconsistent performance.

The obtained results confirm that the optimized SMEDDS formulation possesses excellent homogeneity and physical stability. The narrow droplet size distribution not only enhances the reliability and reproducibility of the formulation but also supports its suitability for pharmaceutical applications. Overall, the low PDI value reinforces the effectiveness of the formulation strategy in producing a stable, uniform, and high-performance drug delivery system.

Table 6.24: Poly Dispersity Index of optimize SMEDDS formulation

Batch No	Poly Dispersity Index
B_{12}	0.242
B_{15}	0.333
B_{17}	0.417
B_1	0.484

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 92.28	Peak 1:	92.28	36.3	48.17
PdI: 0.243	Peak 2:			
Intercept: 0.683	Peak 3:			

Result quality : Refer to quality report

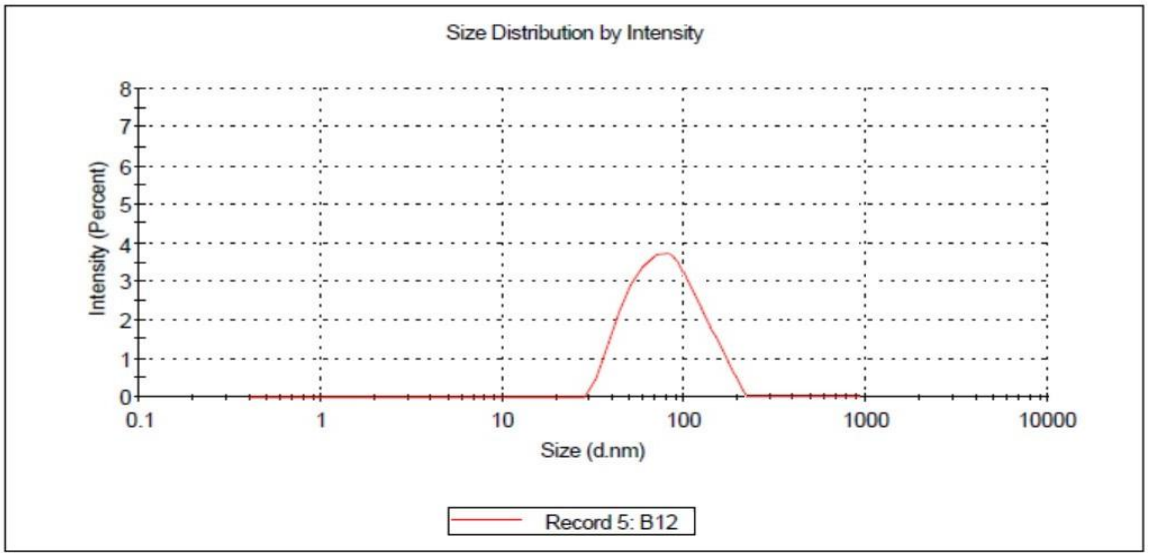


Figure 6.10 : Droplet size and PDI of Batch B_{12}

6.13 Zeta Potential

Zeta potential provides valuable insight into the degree of electrostatic repulsion between dispersed droplets, which is essential in preventing their aggregation or coalescence. A higher magnitude of zeta potential, whether positive or negative, generally indicates stronger repulsive forces and, consequently, better stability of the system.

In the present study, the optimized SMEDDS formulation exhibited a moderately negative zeta potential, suggesting that the droplets possess sufficient surface charge to repel each other effectively. This negative charge generates electrostatic repulsive forces between adjacent droplets, thereby minimizing the likelihood of collision-induced aggregation and ensuring the maintenance of a stable dispersion. As a result, the formulation is able to retain its fine droplet size distribution over time, which is crucial for consistent drug release and absorption.

It is important to note that SMEDDS formulations predominantly employ nonionic surfactants, which stabilize the system primarily through steric hindrance rather than electrostatic mechanisms. In such systems, the surfactant molecules form a protective layer around the droplets, preventing them from coming into close proximity and coalescing. Despite this, zeta potential still contributes as a supportive factor by adding an additional layer of electrostatic stabilization, further enhancing the overall robustness of the formulation.

Table 6.25: Zeta potential of optimize SMEDDS formulation

Batch No	Zeta potential (mv)
B_{12}	-27.4
B_{15}	-22.9
B_{17}	-15.0
B_1	-14.2

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -27.5	**Peak 1:**	-27.5	100.0	4.63
Zeta Deviation (mV): 4.63	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm): 0.0810	**Peak 3:**	0.00	0.0	0.00

Result quality : See result quality report

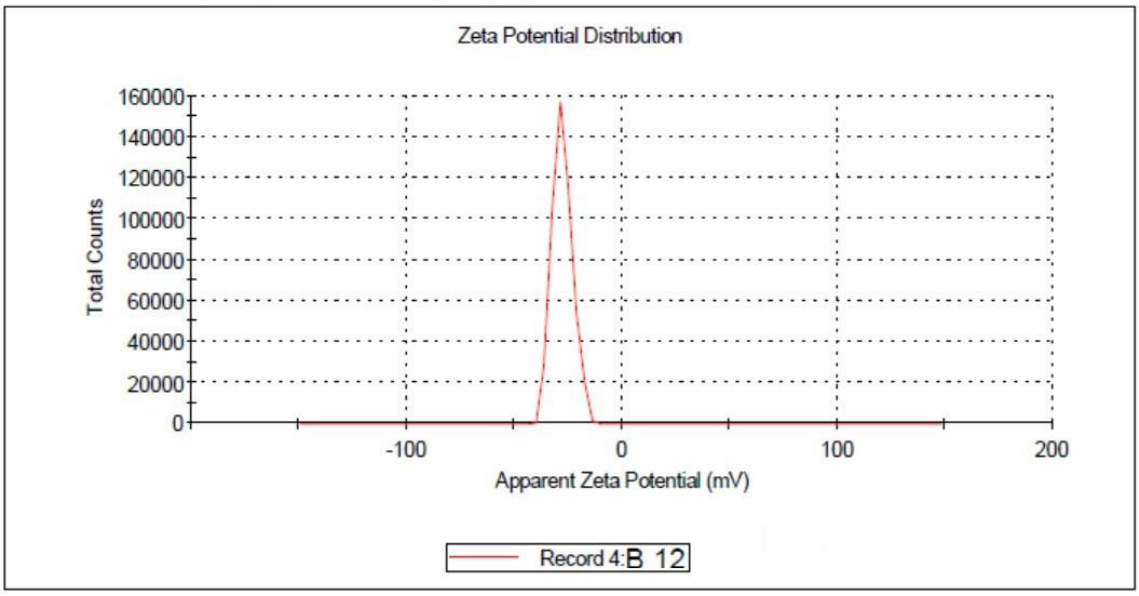


Figure 6.11: Zeta potential of batch B_{12}

The obtained zeta potential values confirm that the optimized formulation possesses adequate stability to resist droplet aggregation and phase separation. This stability is essential for maintaining uniformity, reproducibility, and performance of the SMEDDS, particularly during storage and upon dilution in biological fluids. Therefore, the results substantiate that the formulation is well-designed to ensure consistent behavior and improved therapeutic efficacy.

6.13 Preparation of Solid SMEDDS Formulation

The conversion of liquid Self-Microemulsifying Drug Delivery System (SMEDDS) into a solid form represents a significant advancement in formulation development, primarily aimed at enhancing stability, ease of handling, portability, and patient compliance. While liquid SMEDDS offer excellent solubilization and bioavailability advantages, they often suffer from limitations such as leakage, poor stability, and difficulties in encapsulation. To overcome these challenges, the present study successfully employed the lyophilization (freeze-drying) technique to transform the liquid system into a solid dosage form. Mannitol was utilized as a cryoprotectant,

playing a vital role in preserving the structural and functional integrity of the formulation during the freezing and sublimation stages.

Mannitol acts by forming a protective matrix around the microemulsion droplets, thereby preventing their aggregation or structural collapse during the stress conditions of freeze-drying. It stabilizes the formulation by maintaining the spatial arrangement of the components and ensuring that the self-emulsifying properties are retained upon reconstitution. Without an effective cryoprotectant, the formulation could undergo phase separation or irreversible damage, leading to loss of performance. In this study, different concentrations of mannitol were systematically evaluated to identify the optimal level required to achieve efficient solidification while maintaining the desired physicochemical properties.

The optimization results revealed that a specific concentration of mannitol provided the best balance between structural stability and functional performance. At this optimized level, the formulation exhibited minimal collapse during lyophilization, retained its microemulsion-forming capability, and ensured rapid reconstitution in aqueous media. The resulting solid SMEDDS was obtained as a fine, free-flowing powder with good physical stability. Importantly, upon contact with aqueous fluids, it readily formed a microemulsion similar to the original liquid formulation, confirming the success of the solidification process.

6.14 valuation of Solid SMEDDS Formulation

6.14.1. Solid State characterization

6.14.2. Bulk Density

Table 6.26: Bulk Density of freeze-dried powder

Sr No.	Weight of Powder (mg)	Volume of Powder (ml)	Bulk Density (mg/ml)	Avg±SD
1	15	26	0.58	0.59±0.012
2	15	25	0.61	
3	15	25	0.61	

*Mean ± SD, n=3

The evaluation of solid SMEDDS formulations is a critical step in determining their suitability for further development into solid dosage forms such as capsules or tablets. This evaluation primarily focuses on micromeritic properties, which provide insight into the flow behavior, packing ability, and handling characteristics of the powder. These properties are essential for ensuring uniformity during large-scale manufacturing processes.

6.14.3. Tapped Density

Table 6.27: Tapped Density of freeze-dried powder

S. No.	Weight of Powder (mg)	Volume of Tapped Powder (ml)	Tapped Density (mg/ml)	Avg±SD
1	15	21	0.65	0.68±0.03
2	15	22	0.67	
3	15	23	0.71	

*Mean ± SD, n=3

The optimized solid SMEDDS formulation demonstrated favorable values for all these parameters, indicating good flow properties and minimal cohesiveness.

6.14.4. Carr's Index and Hausner's ratio

Table 6.28: Carr's Index and Hausner's ratio of freeze dried powder

S. No.	Tapped Density (mg/ml)	Bulk Density (mg/ml)	Carr's Index	Avg±SD	Hausner's ratio	Avg±SD
1	0.65	0.57	17.14	14.80±2.76	1.12	1.14±0.03
2	0.68	0.61	11.76		1.13	
3	0.71	0.61	15.49		1.18	

*Mean ± SD, n=3

Good flowability is particularly important for ensuring uniform die filling during tablet compression or consistent capsule filling, which directly influences dose uniformity and product quality. The observed micromeritic properties confirmed that the solid SMEDDS formulation possesses excellent handling and processing characteristics. Overall, these results validate that the developed solid SMEDDS not only retains its

functional performance but also exhibits desirable physical attributes, making it highly suitable for further pharmaceutical development and large-scale production.

6.14.4 Angle of Repose

Table 6.29: Angle of Repose of freeze dried powder

S. No.	Height of Pile (cm)	Radius of Pile (cm)	Angle of Repose (θ)	Avg±SD
1	1.7	4.2	24.48	24.91±1.25°
2	1.5	3.4	23.93	
3	1.8	4.2	26.32	

*Mean ± SD, n=3

Angle of repose was measured by determined radius of pile of self-emulsified freeze dried powder using equation:

Angle of repose = $\tan^{-1}$ (h/r)

Angle of repose of optimized freeze dried powder was found to be 24.91±1.25°. Result of angle of repose of freeze dried powder.

6.15 Characterization of Solid SMEDDS Formulation

Characterization of the solid Self-Microemulsifying Drug Delivery System (SMEDDS) is a crucial step in confirming that the transformation from liquid to solid state does not compromise its performance. This process involves a comprehensive evaluation of various physicochemical properties and a direct comparison with the original liquid formulation. The results demonstrated that the solid SMEDDS successfully retained its essential characteristics, including high drug content uniformity, rapid emulsification ability, and the formation of a stable microemulsion with consistent droplet size upon reconstitution.

6.15.1. Drug Content

The preservation of drug content indicates that the drug remained uniformly distributed within the formulation during the solidification process, with minimal degradation or loss. Additionally, the rapid emulsification observed upon reconstitution confirms that the self-emulsifying efficiency of the system was not affected by the freeze-drying (lyophilization) process. The droplet size analysis further supported these findings, showing that the reconstituted formulation produced fine droplets comparable to those of the liquid SMEDDS, which is essential for maintaining enhanced drug solubilization and absorption.

6.15.2. Zeta Potential

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -22.5	Peak 1:	-22.5	100.0	4.57
Zeta Deviation (mV): 4.57	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm): 0.0242	Peak 3:	0.00	0.0	0.00
Result quality : Good				

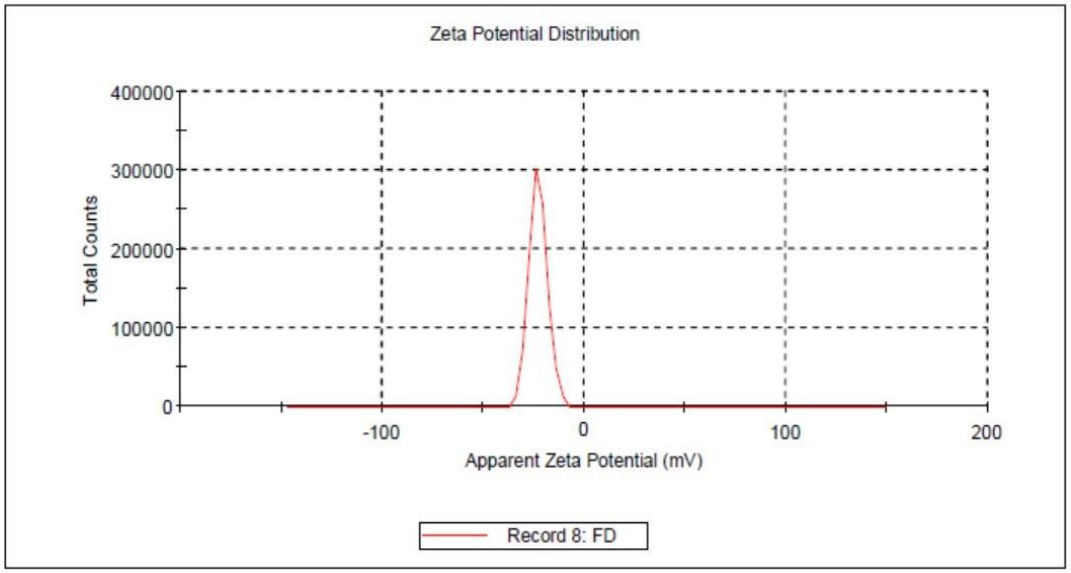


Figure 6.12: Zeta potential of Freeze Dried Powder Globule Size

The globule size of the emulsion was measured by Malvern Zetasizer NS90. The globules size of optimized freeze dried powder was found to be 98.24 nm. The zeta potential values suggested adequate electrostatic stabilization, which helps prevent

droplet aggregation, while the low PDI values indicated a uniform droplet size distribution. Together, these results confirm that the formulation remained physically stable and homogeneous even after undergoing solidification.

Importantly, the ability of the solid SMEDDS to spontaneously reconstitute into a microemulsion upon contact with aqueous media is a critical performance criterion. This ensures that the advantages associated with the liquid SMEDDS—such as enhanced solubility, improved dissolution, and better bioavailability—are fully retained in the solid form. Therefore, the successful characterization of the solid SMEDDS demonstrates that lyophilization is a suitable and effective approach for converting liquid SMEDDS into a stable, convenient, and efficient solid dosage form without compromising its functional properties.

6.15.3. Poly Disperbility Index

Poly dispersity index of the emulsion was measured by Malvern Zetasizer NS90. PDI of optimized freeze dried powder was found to be 0.304. Result of freeze dried power was shown below.

			Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	98.24	Peak 1:	98.24	38.37	48.17
PdI:	0.304	Peak 2:			
Intercept:	0.683	Peak 3:			
Result quality :	Refer to quality report				

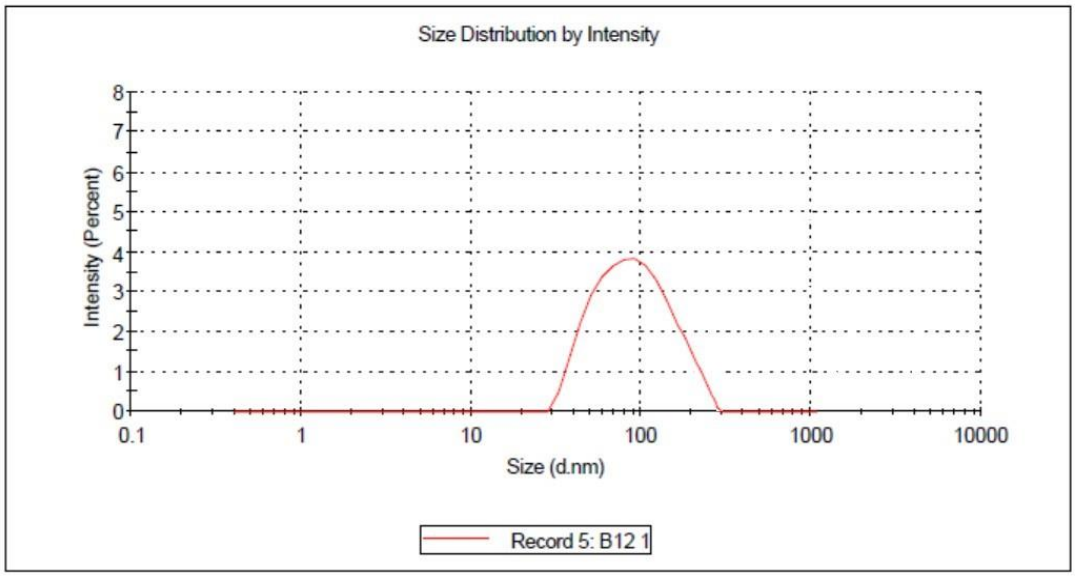


Figure 6.13: Droplet size and PDI of Freeze Dried Powder

6.15.4. Self emulsification time of powder

Self-emulsification time was measured using stop watch. It was found to be 20±3.60 second. Result of self-emulsification time is shown in table 6.30.

6.16 In vitro Drug Release

Table 6.30: in vitro drug release of freeze dried power

Sr No	Time (Min)	Plain Drug	Marketed Formulation	% CDR of 2% w/v mannitol freeze dried powder
1	0	0	0	0
2	5	1.31±0.009	3.38±0.017	12.73±0.021
3	10	5.05±0.014	7.50±0.016	27.22±0.017
4	15	14.06±0.025	14.05±0.019	41.71±0.027
5	20	21.19±0.024	21.94±0.019	54.23±0.011
6	25	25.12±0.012	27.65±0.011	71.08±0.024
7	30	28.69±0.015	35.26±0.018	79.98±0.023
8	35	31.87±0.022	44.53±0.012	90.08±0.020
9	40	34.69±0.030	51.00±0.017	97.73±0.014
10	45	37.88±0.025	58.21±0.015	99.28±0.013

*Mean ± SD, n=3

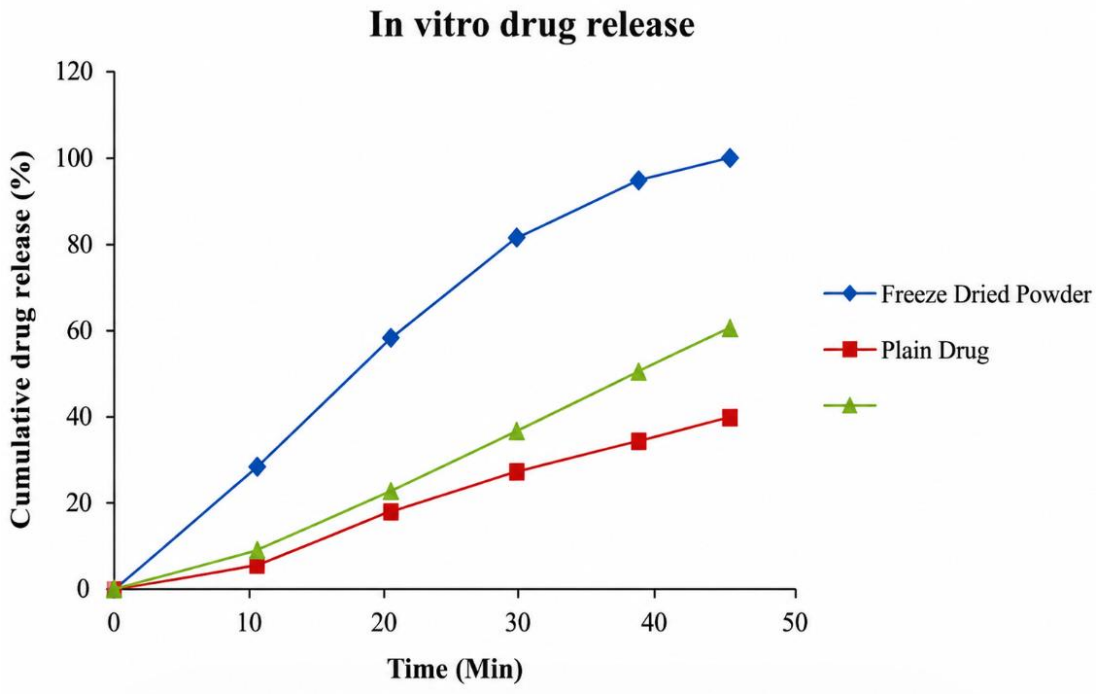


Figure 6.14: In vitro drug release of freeze dried powder, Plain drug and Marketed Tablet

The freeze-dried SMEDDS powder exhibited a rapid onset of drug release, achieving nearly complete dissolution within a significantly shorter time period. This improvement highlights the efficiency of the formulation in overcoming the inherent solubility limitations of the drug.

The enhanced dissolution behavior of the solid SMEDDS can be primarily attributed to its ability to spontaneously form fine oil-in-water microemulsions upon reconstitution in aqueous media. These microemulsions consist of extremely small droplet sizes, which provide a substantially increased surface area for drug release. As a result, the drug is presented in a solubilized form, eliminating the need for dissolution as a rate-limiting step and thereby facilitating faster and more efficient release.

Furthermore, the presence of surfactants and co-surfactants in the formulation plays a crucial role in improving the wetting properties of the drug particles. These components reduce interfacial tension and enhance the dispersion of the drug within the dissolution medium, promoting better interaction with gastrointestinal fluids. This improved wettability, combined with the solubilization capacity of the formulation, significantly contributes to the observed increase in dissolution rate. By enhancing

dissolution and maintaining the drug in a readily absorbable form, the formulation has the potential to significantly improve oral bioavailability and therapeutic performance.

6.17 Optimized Freeze Dried Powder Formulation and Its Evaluation

Table 6.31: Optimized freeze-dried powder formulation and its evaluation results

S. No	Parameters		Inference
1	Composition of batch		Drug (AM): 20 mg + Oil: 1 ml + Surfactant: 2.5 ml + Co-surfactant: 4.5 ml + Mannitol: 2 % w/v
2	Bulk density (mg/ml)		0.58±0.012
3	Tapped density (mg/ml)		0.66±0.03
4	Carr's Index (%)		14.80±2.75
5	Hausner's Ratio		1.14±0.03
6	Angle of Repose (θ)		24.91±1.25^0
7	Zeta Potential (mv)		-22.5
8	Globule Size (nm)		97.24
9	Poly Dispersibility Index (PDI)		0.304
10	Emulsification Time (Sec)		20±3.60
11	Drug Content (%)		96.15±0.14
12	In vitro drug release (%)	Freeze Dried Powder	99.28±0.012
		Plain Drug	36.88±0.025
		Marketed Tablet	58.32±0.014

*Mean ± SD, n=3

The optimized freeze-dried formulation demonstrated excellent flow properties, which are essential for ensuring uniformity during processing, handling, and filling into dosage forms. This improved flowability can be attributed to the successful conversion of the liquid SMEDDS into a solid, free-flowing powder through the freeze-drying process, without compromising its inherent self-emulsifying capacity.

In addition to its favorable flow characteristics, the formulation showed rapid and efficient emulsification upon dilution in aqueous media, forming a fine microemulsion with a large surface area. This rapid emulsification is a key factor in enhancing drug solubilization and absorption in the gastrointestinal tract. The optimized formulation also exhibited high drug content uniformity, indicating efficient drug incorporation and minimal drug loss during formulation and processing steps. Furthermore, stability studies revealed that the formulation remained physically and chemically stable under various storage conditions, with no significant changes in appearance, drug content, or emulsification efficiency over time.

A significant improvement in dissolution profile was observed for the optimized SMEDDS formulation when compared to both the plain drug and conventional marketed formulations. The enhanced dissolution rate can be attributed to the increased surface area provided by the microemulsion droplets, improved wettability, and the presence of surfactants and co-surfactants that facilitate drug solubilization. This study, therefore, achieves its primary objective of formulating a stable, efficient, and performance-enhanced delivery system capable of addressing the challenges associated with the bioavailability of Azilsartan Medoxomil.

CHAPTER-7

SUMMARY AND CONCLUSION

7.1. Summary

Azilsartam Modemoxil active form selectively blocks angiotensin II type-1 receptors, thereby producing a potent antihypertensive effect through vasodilation and reduction of peripheral vascular resistance. It is administered as a prodrug and undergoes rapid de-esterification in the gastrointestinal tract during absorption to yield its active metabolite. Its low aqueous solubility significantly limits its dissolution in gastrointestinal fluids, resulting in incomplete absorption and an oral bioavailability of only about 26% in healthy individuals. Such poor dissolution behavior can lead to delayed onset of action, variable plasma drug concentrations, and inconsistent therapeutic outcomes. Therefore, improving its solubility and dissolution profile is essential for enhancing oral absorption, maximizing bioavailability, and ensuring optimal clinical efficacy.

The spontaneous formation of nanosized droplets provides an exceptionally large interfacial surface area, which greatly enhances drug dissolution and facilitates rapid absorption across the intestinal membrane. In addition, the drug remains in a solubilized state throughout its transit in the gastrointestinal tract, thereby preventing precipitation and minimizing variability in absorption. Owing to these advantages, Self emulsifying drug delivery system (SMEDDS) have emerged as an efficient and reliable approach to enhance bioavailability of lipophilic drugs such as Azilsartan Medoxomil.

Preformulation studies were done to ensure the suitability of the drug - excipient for SMEDDS development. Fourier Transform Infrared Spectroscopy (FTIR) was employed to investigate potential drug–excipient and excipient–excipient interactions. The FTIR spectra of the pure drug, excipients, and their physical mixtures showed no significant shifts, disappearance, or appearance of new characteristic peaks. This confirmed the absence of chemical incompatibility and established the compatibility of Azilsartan Medoxomil with the selected formulation components. Furthermore, analytical method validation was performed for accurate quantification of the drug. Calibration curves constructed in methanol and 0.1 N HCl demonstrated excellent linearity, with regression coefficients (R^2) of 0.996 and 0.999, respectively. These

results validated the analytical method as precise, reliable, and suitable for subsequent drug estimation and dissolution studies.

Among the oils evaluated, castor oil exhibited the highest solubility for Azilsartan Medoxomil, making it the preferred oil phase. Among the surfactants screened, Tween-20 demonstrated superior performance, showing excellent drug solubilization, high oil emulsification capacity, and the ability to produce a clear and transparent microemulsion. It exhibited a high percentage transmittance of 93.2% and required only a few flask inversions, indicating rapid emulsification. Similarly, Carbitol was selected as the co-surfactant because of its excellent solubilizing capacity, low interfacial tension, and ability to facilitate rapid and efficient emulsification. The combined use of castor oil, Tween-20, and Carbitol provided an ideal system for the development of a stable and efficient SMEDDS formulation.

To identify the optimal composition range for microemulsion formation, using castor oil, Tween-20, and Carbitol, a pseudo ternary phase diagram was constructed. This study enabled the identification of the self-microemulsifying region and facilitated the selection of suitable component ratios. Three different surfactant-to-co-surfactant ratios (1:1, 1:2, and 2:1) were investigated. Although the 1:2 and 2:1 ratios exhibited faster emulsification and smaller droplet formation, they showed comparatively lower thermodynamic stability. In contrast, the 1:1 ratio demonstrated the most favorable balance between rapid emulsification, clarity, and long-term stability. Therefore, the 1:1 ratio was selected as the optimized Smix ratio.

Box–Behnken experimental approach, a robust statistical approach that allows systematic evaluation of formulation variables with a reduced number of experiments. A total of 17 experimental runs, including five center points, were generated and analyzed using Design Expert software. Statistical analysis revealed that the quadratic model provided the best fit for the observed data. Among all the formulations, batch B12 was identified as the optimized formulation, exhibiting an emulsification time of 18 ± 2.64 seconds, percentage transmittance of 99.08 ± 0.23%, and cumulative drug release of 99.43 ± 0.015% within 45 minutes. These findings confirmed the significant influence of formulation variables on SMEDDS performance.

The prepared SMEDDS formulations were further evaluated for dispersibility, robustness to dilution, drug content, and In-vitro drug release. Dispersibility testing revealed that batches B1, B12, B15, and B17 exhibited Grade A performance, indicating rapid self-emulsification and the formation of clear or slightly bluish microemulsions within a short time. Robustness to dilution studies demonstrated that all formulations remained stable without any evidence of phase separation, drug precipitation, or turbidity when diluted with distilled water and 0.1 N HCl. This confirmed their stability under conditions simulating the gastrointestinal environment. Drug content analysis showed excellent drug incorporation across all formulations, with batch B12 exhibiting the highest drug content of 99.01 ± 0.009%, reflecting uniform distribution and minimal drug loss during formulation.

Thermodynamic stability studies are essential to predict long-term stability and identify formulations resistant to phase separation or precipitation. Among all the formulations, batches B1, B12, B15, and B17 successfully passed these tests, demonstrating excellent thermodynamic stability. These stable formulations were further characterized for zeta potential, globule size, polydispersity index, and viscosity. Batch B12 exhibited the most desirable physicochemical characteristics, with a zeta potential of −27.5 mV, indicating excellent electrostatic stability; a globule size of 98.28 nm, indicating nanosized droplets; and a PDI of 0.243, reflecting a narrow and uniform droplet size distribution. These parameters are indicative of a stable microemulsion system with minimal risk of droplet aggregation and enhanced potential for gastrointestinal absorption.

To improve the stability, handling, and patient acceptability of the optimized SMEDDS, it was converted into a solid dosage form by lyophilization technique. Mannitol was employed as a cryoprotectant to preserve the structural integrity of the microemulsion droplets during the freeze-drying process. Various concentrations of mannitol were evaluated, and 2% w/v was found to be optimal for producing a stable, free-flowing freeze-dried powder. The resulting solid SMEDDS exhibited excellent micromeritic properties, including Bulk density of 0.59 ± 0.012 g/cm³, Tapped density of 0.68 ± 0.03 g/cm³, Carr's index of 14.80 ± 2.76%, Hausner's ratio of 1.14 ± 0.03, and an angle of repose of 24.91 ± 1.25°. These values indicate good flowability, compressibility, and suitability for further processing into solid dosage forms such as capsules or tablets.

The freeze-dried solid SMEDDS retained the essential characteristics of the original liquid formulation. Its drug content was found to be 96.15 ± 0.15%, indicating minimal drug loss during the lyophilization process. The self-emulsification time was 20 ± 3.60 seconds, demonstrating rapid and efficient reconstitution upon contact with aqueous media. Upon reconstitution, the formulation formed a stable microemulsion with a zeta potential of −22.5 mV, 98.4 nm globule size, and 0.304 PDI value. These values confirm that the freeze-drying process did not adversely affect the microemulsifying properties or droplet characteristics of the formulation.

In-vitro dissolution studies of the freeze-dried solid SMEDDS demonstrated a remarkable enhancement in drug release. The solid SMEDDS achieved a cumulative drug release of 99.28 ± 0.013% within 45 minutes, whereas the plain drug and marketed product exhibited only 37.88 ± 0.025% and 58.31 ± 0.015% drug release, respectively, over the same period. Consequently, dissolution is no longer the rate-limiting step, leading to faster and more complete drug release.

In conclusion, the developed solid SMEDDS of Azilsartan Medoxomil successfully addressed the major challenges associated with its poor aqueous solubility and limited oral bioavailability. The solid SMEDDS exhibited superior in-vitro performance, indicating its strong potential to improve oral absorption and therapeutic efficacy compared to plain drug and marketed one. Thus, the developed solid SMEDDS can be considered a promising and effective oral delivery system for Azilsartan Medoxomil, with significant potential for future pharmaceutical development and clinical application.

7.2 Conclusion

Azilsartan Medoxomil, being a lipophilic drug with poor aqueous solubility, exhibits limited oral bioavailability, which can adversely affect its therapeutic performance. Therefore, the development of a Self microemulsifying drug delivery system - SMEDDS formulation was undertaken as a rational and efficient strategy to overcome these limitations. By promoting rapid dispersion in gastrointestinal fluids, SMEDDS offers a significant advantage in improving the dissolution and absorption characteristics of Azilsartan Medoxomil.

The selection of suitable formulation components was accomplished through systematic screening based on solubility and emulsification efficiency. Castor oil, Tween-20, and Carbitol were identified as the best combination owing to their superior solubilizing capacity and excellent emulsification properties. These components collectively enabled the formation of a stable, clear, and efficient microemulsion system capable of maximizing drug solubilization and minimizing the risk of precipitation.

The pseudo-ternary phase diagram played a vital role in identifying the optimal microemulsion region and determining the most suitable ratio of surfactant to co-surfactant. Among the ratios investigated (1:1, 1:2, and 2:1), the 1:1 ratio demonstrated the best balance between rapid emulsification, clarity, and thermodynamic stability. This optimized ratio ensured a stable micro emulsion which upon dilution effectively prevented drug precipitation, thereby confirming its suitability for SMEDDS development.

Optimization of the formulation using the Box–Behnken statistical design successfully established the influence of formulation variables on critical quality attributes. Among the 17 experimental batches prepared, batch B12 was identified as the optimized formulation. It exhibited excellent performance, with an emulsification time of 18 ± 2.64 seconds, percentage transmittance of 99.08 ± 0.23%, and cumulative drug release of 99.43 ± 0.015% within 45 minutes. These results confirm that the optimized SMEDDS possesses rapid self-emulsification, high optical clarity, and superior drug release characteristics.

To enhance stability, ease of handling, and patient acceptability, the optimized liquid SMEDDS was successfully converted into a solid dosage form by lyophilization using 2% w/v mannitol as a cryoprotectant. Mannitol effectively preserved the structural integrity of the microemulsion during freeze-drying and produced a stable, free-flowing powder with excellent micromeritic properties. The solid SMEDDS retained its rapid self-emulsification ability and reconstituted efficiently upon contact with aqueous media.

Comparative in-vitro dissolution studies demonstrated the remarkable superiority of the freeze-dried SMEDDS over both the plain drug and the marketed formulation. The solid SMEDDS achieved 99.28 ± 0.013% drug release within 45 minutes, whereas the plain

drug and marketed formulation released only 37.88 ± 0.025% and 58.31 ± 0.015%, respectively, over the same period. This substantial enhancement in dissolution can be attributed to the spontaneous formation of nanosized microemulsion droplets, which provide a large surface area and maintain the drug in a solubilized state.

In conclusion, the developed freeze-dried SMEDDS of Azilsartan Medoxomil successfully met the challenges with poor water solubility and limited oral bioavailability. The optimized formulation demonstrated rapid self-emulsification and excellent stability, droplet size distribution, and significantly enhanced dissolution performance. It has substantial potential to improve therapeutic efficacy, enhance patient outcomes, and serve as a viable platform for future large-scale manufacturing and clinical application in the treatment of hypertension.

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Design And Development Of Azilsartan Medoxomil Solid Self Microemulsifying Drug Delivery System

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Design and development of Azilsartan Medoxomil solid Self Microemulsifying drug delivery system. The selection of oil, surfactant and co-surfactant was carried out using screening study. AM is more soluble in castor oil, tween-20 and carbitol. The solubility was found to be 19.63±0.08 mg/ml, 80.56±0.125 mg/ml and 83.62±0.165 mg/ml in olive oil, tween- 80 and carbitol respectively. For the selection of the surfactant % oil solubilize in different surfactant and ease of emulsification study was carried out, in this study tween-20 highest 5.3% oil solubilize in castor oil and 9 no of flask inversion required for mix tween-20 with castor oil and % transmittance was found to be 93.2. According to that result tween 20 selected for the surfactant phase for further study. The co-surfactant selected according to the minimum amount of co-surfactant required to form clear solution and ease of emulsification, in this study the carbitol 130 (µl) required to form clear solution with castor oil and tween-20, 11 phase inversions required for mixing with castor oil and tween-20, % transmittance of that mixture 89.6 %, so carbitol was selected for the co surfactant phase. The pseudo ternary phase diagram was constructed using castor oil as oil phase, tween-20 as surfactant phase and carbitol as co-surfactant phase. For this the different three ratio 1:1, 1:2 and 2:1 surfactant and co-surfactant was selected. The different trial has shown that the emulsifying effect is good if the ratio of the surfactant to the co-surfactant is 1:2 and 2:1 but stability properties are inferior at this ratio, so fixed the 1:1 ratio of surfactant and co-surfactant according to stability. The transparent emulsion was produce at the concentration of 80 mg of AM /1ml of SMEDDS formulation.

Keywords: Biopharmaceutical Classification System (BCS), Super critical fluid (SCF), Self emulsifying drug delivery systems (SEDDS**),** Azilsartan medoxomil (AM), PEG **.**

INTRODUCTION

Oral route is the easiest & most suitable way of noninvasive administration. Oral drug delivery systems being the most cost-effective have always lead the worldwide drug delivery market[1]. Conventional oral dosage forms for poorly water soluble drugs present the drug in a solid form to the gastrointestinal tract which means the drug has to dissolve in the GI fluids before it can be absorbed[2]. Thus, their rate & extent of absorption is largely dependent on the rate of dissolution. The formulation technique plays an important role in overcoming this shortcoming

of poorly water soluble drugs. According to the Biopharmaceutical Classification System (BCS) shown in Figure-1, drugs are classified on the basis of their solubility & permeability into four classes, two classes of drugs show poor aqueous solubility namely BCS II & BCS IV. BCS II drugs possess poor aqueous solubility but have good permeation properties. BCS class IV drugs are poorly water soluble & poorly permeable[3]. Developing a formulation for a class IV drug is nearly impossible unless the dose necessary is very small[5]. Most of the times, such drugs are withdrawn at its lead optimization stage of drug discovery & reworked to improve its physico-chemical properties. Developing a formulation for a drug belonging to BCS II is often challenging as it requires improved dissolution characteristics. Popular formulation techniques used for delivering a poorly water soluble drug include. pH adjustment[4], Micro-emulsion, Self-emulsifying drug delivery systems, Manipulation of solid state, Particle size reduction, Super critical fluid (SCF) process, Inclusion complexes/complexation, Co-solvency, Miceller solubilization, Hydrotrophy, Solid Dispersions, Nano-suspension, Floating Granules, Cryogenic techniques, Nano-crystallization.

In recent years, much attention has turned to lipid-based formulations with the aim of improving the oral bioavailability of poorly water soluble drugs. Lipid-based formulations encompass a diverse group of formulations, very different in physical appearance, ranging from a simple tri-glyceride vehicle to more sophisticated formulations such as Self emulsifying drug delivery systems (SEDDS)[5].

MATERIAL AND METHOD

Fourier transforms infrared spectroscopic studies (FTIR)

FTIR spectra for drug alone and with excipients were performed using a FTIR spectrophotometer with KBR pellets to study drug-excipients and excipient-excipient compatibility. Drug excipient interaction was analysed by performing infrared spectroscopy using FTIR (Bruker, Mumbai).

The FTIR studies were carried out by the pressed pellet technique using a KBr press in which the KBr was taken and kept in a hot air oven for two hours for the discard any moisture. The above dried KBr was taken for the preparation of pellets of drug, and the selected formulations. The pellet was prepared by taking drug: KBr in 1: 100 ratios. The prepared pellet was placed in the sample holder and kept in the instrument to confirmation the FTIR peaks[6].

Analytical Method development

Method was performed by UV Spectrophotometer.

Determination of λ_{max}

The Standard drug solution concentration of 10 µg/ml was preparing following media**,**

- ✓ Methanol
- ✓ 0.1 N HCl

The Solution was scanned in UV visible spectrophotometer in wavelength 200-400 nm. From this scan, the peak of maximum absorbance as identified (λ_{max}) in each media and used for further analysis

Standard calibration curve of Azilsartan medoxomil (AM) in various solvents

Preparation of Standard calibration Curve for AM in Methanol[7]

Weighed precisely 10 mg of Azilsartan medoxomil and placed in 100 ml of volumetric flask and volume was made up to the mark with methanol. Aliquots were taken from prepared stock solution and were appropriately diluted to prepare 2, 4, 6, 8…. 18 µg/ml and then absorbance were taken at 257 nm, keeping methanol as a blank solution.

Preparation of Standard Curve for AM in 0.1 N HCl

Weighed accurately 10 mg of Azilsartan medoxomil and placed in 100 ml of volumetric flask and volume was made up to the spot with 0.1 N HCl. Aliquots were taken from prepared stock solution and were appropriately diluted to prepare 5, 10, 15, …. 40µg/ml and then absorbance were taken at 257 nm, keep 0.1 N HCl as blank solution.

Screening study

Solubility of drug in the various oils, surfactants and co-surfactants

Screening of excipients can be done by determining the equilibrium solubility of Azilsartan medoxomil in different oils, surfactants and co-surfactants[8]. Excessive amount of Azilsartan medoxomil was added to 2 ml of each excipients. Both components were mixed in a vial for 5 min using vortex mixer (REMI, Mumbai, India). The mixtures in vials were shaken at 25 ±1.0ºC for 72 hour using controlled temperature mechanical shaker. The mixtures centrifuged using R-4C DX Laboratory Centrifuge (REMI, Mumbai, India) at 8000 rpm for 25 minutes at 25 ±1.0ºC. The supernatant was filtered through membrane filter by using 0.45 μmfilter disk. Filtered solution was appropriately diluted by methanol, and UV absorbance was measured at 257 nm. Concentration of dissolved drug was determined by using standard equation.

Screening of Oils

The oils in which the solubility of drug was more were selected for further study.

Screening of Surfactants

Surfactants were selected based on the following criteria.

Based on ability to solubilize the drug

The surfactant which could solubilized highest amount of AM was considered.

Based on % oil solubilize in different surfactants

Surfactants were screened as per their ability to from microemulsion, like Tween 20, Tween 80, Cremophor EL, Captex 355, Labrafac PG. on behalf of this surfactant solution was prepared in concentration like 15% wt/v. 2.5 ml of this solution was taken and 4 µl of oil was added with vigorous vortexing. If a one-phase clear solution was obtained, the addition of oil was repeated until the solution became like cloudy[9].

Based on ease of emulsification

Different surfactants were screened for emulsification capability of the selected oil phase. Surfactant selection was performed on the basis of % transparency and ease of emulsification. In brief, 300 µl of the surfactant was added to 300 µl of selected oil phase. The mixture was gently heated at 50^0 c for homogenization of the components. 50 µl of the mixture was diluated with distilled water to 50 ml in a to volumetric flask. Ease of emulsification was evaluator by the number of flask inversions required to yield a homogenous emulsion[10]. The emulsion was allowed to stand for 2 hours and their % transparency or transmittance was determined at

650 nm by a double-beam UV spectrometer using distilled water as a blank. The emulsion was further more observed visually for any turbidity and phase separation[11].

Screening of Co-surfactants

The co-surfactants namely, PEG-400, Transcutol, Propylene Glycol, Carbitol were subjected to the following mentioned tests and the best co-surfactant which satisfied all the criteria was selected.

Based on solubility of drug

The co-surfactant which could solubilize highest amount of AM was considered.

Based on ability to form clear solution

The co-surfactant was added to get more efficient self-micro emulsion systems. The screening of the co-surfactant was performed as follows. After mixing 80 µl of surfactant with 200 µl oil phase, the surfactant/oil mixture was diluated to 400 µl by using distilled water. 20 µl of the once mentioned resultant solution was titrated with increasing amount of co-surfactant until the system turned clear and the amount of co-surfactant used was recorded as a minimum amount[12].

Based on ease of emulsification

Different co-surfactants were screened for emulsification ability of the selected oil phase and surfactant. Co-surfactant selection easy performed on the basis of % transparency & ease of emulsification. The procedures carried out are as follows .

Briefly, 200 µl of the surfactant was added in to 100 µl of each co-surfactant. Then 300 µl of selected oil phase was added to the mixture. The mixture was smoothly heated at 50^0 c for homogenization of the components[13]. 50 µl of the mixture was diluated with distilled water to 50 ml in volumetric flask. Ease of emulsification was judged by the number of flask inversions required to yield to become homogenous emulsion. The emulsion was allowed to stand for 2 hours and their % transparency or transmittance was evaluated at 650 nm by a double-beam UV spectrometer using distilled water as a blank. The emulsions were furthermore observed visually for any turbidity and phase separation[14].

Construction of pseudo ternary phase diagram

Surfactant (Tween 20) and co-surfactant (Carbitol) were mixed (Smix) in special volume ratios (1:1, 2:1, 1:2). For each phase diagram, oil (Castor oil) and specific surfactant/co-surfactant (Smix) ratio were mixed thoroughly with different volume ratios from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) in different glass vials. Pseudo ternary phase diagrams were developed using the aqueous titration method. Slow titration with the aqueous phase was performed for each mixture of oil and Smix individually. The amount of aqueous phase added was varied to produce a water concentration in the range of 5% to 95% of total volume at around 5% time intervals[15]. The calculation for the addition with aqueous phase was done by calculating the % of each component of the microemulsion present at each 5% addition. The advantage of this system is that the scale-up of the proportions is easy, as the system is thermodynamically stable. After each 5% addition of the aqueous phase to the oil: Smix mixture, visual observation was made and recorded. Through visual observation, the following categories were assigned: (1) Transparent and make flowable: Oil/water microemulsions; (2) Transparent gel: Microemulsion gel; (3) Milky or cloudy: Emulsion; (4) Milky gel: Emulgel.

In a similar, calculations for the other ratios of oil and S mix were also done. For each Smix ratio, a separate phase diagram was constructed, and for each phase diagram visual observations were recorded. The pseudo ternary phase diagram Figure-6.3was constructed by using CHEMIX software based on the visual observations noted[16].

Effect of drug on phase diagram

The experiment was carried out to investigate the effects of AM on the SMEDDS. The formulation amount of AM was added to the boundary formulations of the self microemulsifying domain of ternary phase diagrams. The self-microemulsifying system performance was visually assessed after infinite dilution using purified water.

Formulation Development

Optimization of Formulation Variables:

Mainly 3 formulation variable that effect on self-microemulsifying properties and solubility[17]. Concentration of oil, surfactant and co-surfactant were taken as critical formulation variables have major impact on the self-emulsification and solubility of drug. Quantitative aspects of the effects and relationships among various formulation parameters affecting solubility of drug are investigated using response surface (RSM). To revision this, we performed, "Box Behnken Design" (BBD) used for optimization of formulation parameters known to affect their result. The BBD is a popular for RSM because it requires only two-levels of each and every process factor and only a fraction of all the possible combinations[18].

In this design, the experimental region is assumed to be a cube, and experiments are performed at points corresponding to midpoint of each edge and replicated experiments at the center of this multidimensional dice.

This design is suitable for exploring quadratic response surfaces and constructing second-order polynomial models. The complete design consisted of 17 experimental run that included 12 single run and 5 replications run at the center point.

The Design Expert (Version 9, State Ease Inc., USA) program was used for design of experiment and analysis of this second-order model & for drawing of three dimensional response surface and contour plots. Table shows dependent and independent variables of BBD and table matrix of BBD of formulation variables[19].

Table: Dependent and independent variables of BBD:

Independent variable	Variable level	
	Low (-1)	**High (+1)**
Oil (ml) A	1	9
Surfactant (ml) B	0.5	4.5
Co-surfactant (ml) C	0.5	4.5

Dependent variables	Self-Emulsification Time (Sec) % Transmittance (%) % cumulative Drug Release (%)

Preparation of liquid SMEDDS

A series of SMEDDS formulations were prepared by oil (Castor oil), Surfactant Tween 20) and Co-surfactant (Carbitol) as shown in Table 5.5. In all the formulations, the level of Azilsartan medoxomil (AM) was set aside constant (i.e. 20 mg). The amount of SMEDDS should be such that it should solubilize the drug (single dose) completely [104]. The Azilsartan medoxomil (20 mg) was added in the mixture. Next the components were mixed by gentle stirring and mixing, and heated at 40˚C.The mixture was stored at room temperature until used. So, prepared SMEDDS was the concentrate of oil, surfactant, co-surfactant and drug[20].

Table: Matrix of Box-Behnken Design for formulation parameters

S. No	Std.	Run	Batch No	Oil (ml)	Surfactant (ml)	Co-surfactant (ml)
1	8	1	AMB1	9	2.5	4.5
2	17	2	AMB2	5	2.5	2.5
3	16	3	AMB3	5	2.5	2.5
4	10	4	AMB4	5	4.5	0.5
5	15	5	AMB5	5	2.5	2.5
6	1	6	AMB6	1	0.5	2.5
7	3	7	AMB7	1	4.5	2.5
8	13	8	AMB8	5	2.5	2.5
9	9	9	AMB9	5	0.5	0.5
10	4	10	AMB10	9	4.5	2.5
11	6	11	AMB11	9	2.5	0.5
12	7	12	AMB12	1	2.5	4.5
13	2	13	AMB13	9	0.5	2.5
14	14	14	AMB14	5	2.5	2.5
15	12	15	AMB15	5	4.5	4.5
16	5	16	AMB16	1	2.5	0.5
17	11	17	AMB17	5	0.5	4.5

Evaluation of liquid SMEDDS formulation

Dispersibility Test

The dispersibility test of SMEDDS is carried out to evaluate its capability to disperse into emulsion and the size of resulting globules to categorize them as SMEDDS. It is carried by using a standard USP dissolution apparatus 2 (Paddle Type). 1 ml of every formulation is added to 500 ml of water at 37 ± 0.5 ºC and the paddle is rotated at 50 rpm[21]. Then titration

with water the SMEDDS formulation forms a mixture or gel which is of different type depending upon which the in vitro performance of formulation can be assessed.

Robustness on dilution

Robustness to dilution was conducted by diluting liquid SMEDDS formulation, 100 and 1000 times with various media like distilled water and 0.1 N HCl and verify out any phase separations or precipitation of drug even after 12 hrs of storage space, that formulation is considered as robust to dilution[22].

Emulsification time

The emulsification time was monitored by visually analyze the disappearance of SMEDDS and the final appearance of the microemulsion in triplicate. A visual test to evaluate the self-emulsification properties of SMEDDS formulation was performed by visual evaluation as previously reported. In this method, a predetermined volume of formulation 1 ml was introduced into 300 ml of water in a glass beaker that was maintained at 37^{o}C, and the contents mixed gently using a magnetic stirrer. The time to emulsify spontaneously and progress of emulsion droplets were observed.

Percentage Transmittance

The % transmittance of the liquid SMEDDS after the 100 times dilution with distilled water measured at 650 nm using UV visible double beam spectrophotometer keeping water as with blank Solution[23].

Drug Content

AM from SMEDDS formulation was extracted in methanol using sonication method. The solutions were filtered, using Whatman paper. The methanolic extract was analyzed for the AM content spectrophotometrically (UV-1800, Shimadzu, Japan) at 257 nm using standard curve.

In-vitro Dissolution Study

The quantitative in vitro dissolution studies are carried out to by dialysis bag method. The SMEDDS formulation was instilled in Dialysis beg equal to 20 mg AM and one end was tied with thread and was placed in 900 ml of 0.1 N HCL as dissolution medium at 37±0.5˚C. The revolt speed of paddle was maintained at a rate of 100 rpm. Samples (5ml) were withdrawn at regular time intervals (0, 5, 10, 15, 20, 25, 30, 35, 40 and 45 min.) and aliquot amount of 0.1 N HCL was replaced. The samples were analyzed for the drug content using UV spectroscopic method at 257nm

Thermodynamic stability studies

The physical stability of a formulation is very important for its performance as it can be adversely affected by precipitation of the drug in excipient matrix. Poor physical stability of formulation can direct to phase separation of excipients which affects bioavailability as well as therapeutic efficacy. as well the incompatibilities between formulation & gelatin shell of capsule (if formulation filled in capsule) may cause brittleness, softness and delayed disintegration or incomplete release of drug. The following cycles are carried out for these studies[24].

- **Heating cooling cycle:** - Six cycles of cooling and heating between refrigerator temperature (4°C) and elevated temperature (45°C) with coverage at each temperature

for not less than 48 hours are carried. Those formulations, which are stable, are then subjected to centrifugation test.

- **Centrifugation:-** Formulations which pass the heating cooling cycle are centrifuged at 3500 r/ min for 30 min. That formulation that doesn't confirm any phase separation is taken for the freeze thaw stress test.
- **Freeze thaw stress cycle:-** Three freeze thaw cycles b/w -21° C & 25° C with storage at each temperature for not less than 48 hours. Those formulations which pass this test show good stability with no phase separation, cracking or creaming. The formulations that pass this test are then further taken for dispensability test for assessment of self-emulsification efficiency[25].

Viscosity

The viscosities were measured to determine rheological properties of formulations. Brookfield DV-11+ Pro viscometer at 30˚C with a 62 spindle at 5 rpm was used to serve this purpose

Globule size measurement

The globule size of the emulsion was measured by Malvern Zetasizer NS90. The emulsion (1-1.5 ml) was transferred to a disposable polystyrene cuvette with the help of plastic syringe or micropipette and the globule size of the emulsion was determined via a combination of laser Doppler velocimetry and phase analysis light scattering (PALS) at an angle of 90°at 25°C.

Poly Disparity Index (PDI):

PDI value from 0.0 to 0.5 indicates that the uniformity of oil globules is more. So emulsion is more uniform. Poly disparity index was determined by Malvern ZetasizerNS90.

Zeta Potential:

Zeta potential was determined by Malvern Zetasizer. Zeta potential shows an electric charge there on the oil globule. Since zeta potential we can conclude that whether emulsion is stable or not. If zeta potential is not reliable then separation occurs in emulsion[26].

Preparation of Solid Self Microemulsifying Drug Delivery System

The Solid-SMEDDS prepared with lyophilization technique. Mannitol used as the cryoprotectant. Mannitol used in different ratio by means of liquid SMEDDS to optimize the formulation. The 1%, 1.5%, 2% & 2.5% w/v Mannitol (1, 1.5, 2 and 2.5 gm mannitol/ 100 ml liquid SMEDDS) mixed in liquid SMEDDS. The mixture was solidified in lyophilizer at -50 ^{0}C, and Lyophilization was performed at -75°C temperature and 50 mm-Hg vaccum pressure. Prepared lyophilized powder was evaluated[27]

Evaluation of Solid SMEDDS Formulation

Characterization of Solid SMEDDS Formulation

Drug Content

Required quantity of freeze dried powder equivalent to 20 mg of Azilsartan medoxomil (AM) was diluted by using Methanol up to 100 ml. Withdraw 1 ml of above solution and again diluted up to 10 ml with methanol and measured the absorbance at 257 nm using UV spectrophotometer[28].

Zeta Potential

Zeta potential was determined by Malvern Zetasizer NS90. Zeta potential shows an electric charge present on the oil globule. From zeta potential we can conclude that whether emulsion is stable or not. If zeta potential is not reliable then separation occurs in emulsion..

Globule Size

The globule size of the emulsion was measured by Malvern Zetasizer NS90. The emulsion (1-1.5 ml) was transferred to a disposable polystyrene cuvette with the help of plastic syringe or micropipette & the globule size of the emulsion was determined via a combination of laser Doppler velocimetry and phase analysis light scattering (PALS) at an angle of 90°at 25°C.

Poly Dispersity Index

PDI value from 0.0 to 0.5 indicates that the uniformity of oil globules is more. So emulsion is more consistent. Poly dispersity index was determined by Malvern Zetasizer NS90.

Self-emulsification time of powder

It was measured by added a water slowly in self-emulsified freeze dried powder and measure the time (sec) until the emulsion was formed.

In-Vitro Dissolution Study

In vitro drug release studies from Solid SMEDDS were performed by means of USP Type I dissolution apparatus with number of paddle rotations set to 50 rpm. The dissolution medium consisted of 900 ml of 0.1N HCL maintained at 37 ±0.5°C. The freeze dried powder containing 20 mg of Azilsartan medoxomil put it in capsule and it was introduced into the dissolution medium[29].

At predetermined time intervals 5ml of aliquot was withdrawn, filtered using 0.45µm syringe filter and an equivalent volume of fresh dissolution medium was immediately added. An amount of drug released was estimated by measuring absorbance @ 257 nm using a UV spectrophotometer. The dissolution reading was carried out with similar procedure as mentioned above for plain drug and marketed tablet with aim of comparison study[30].

RESULT AND DISCUSSION

Fourier Transform Infrared spectroscopic studies (FTIR):

FTIR study was done for the identification of the drug and excipients and to study drug - excipients and excipients - excipients compatibility. FTIR spectra of drug and final freeze dried powder mixture are shown in figure 3 and 4 respectively. The spectral elucidations for drug alone and with freeze dried powder mixture are shown in table 1.

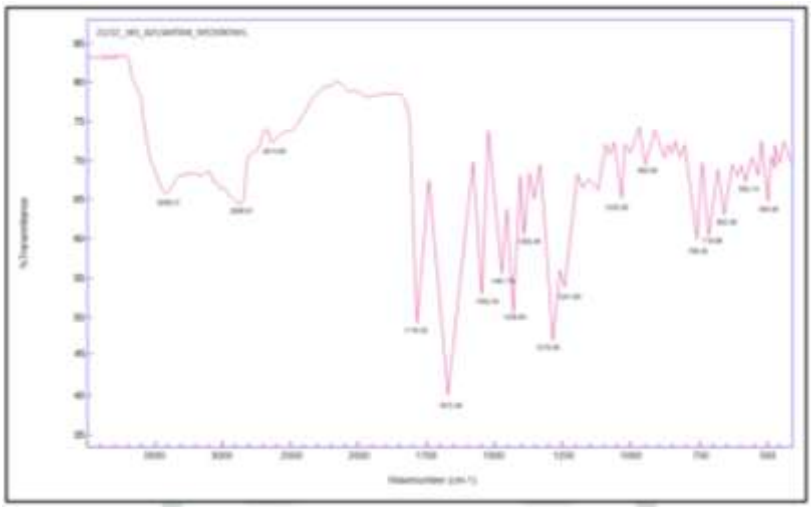


Figure 1: FTIR Spectra of Azilsartan Medoxomil (AM)

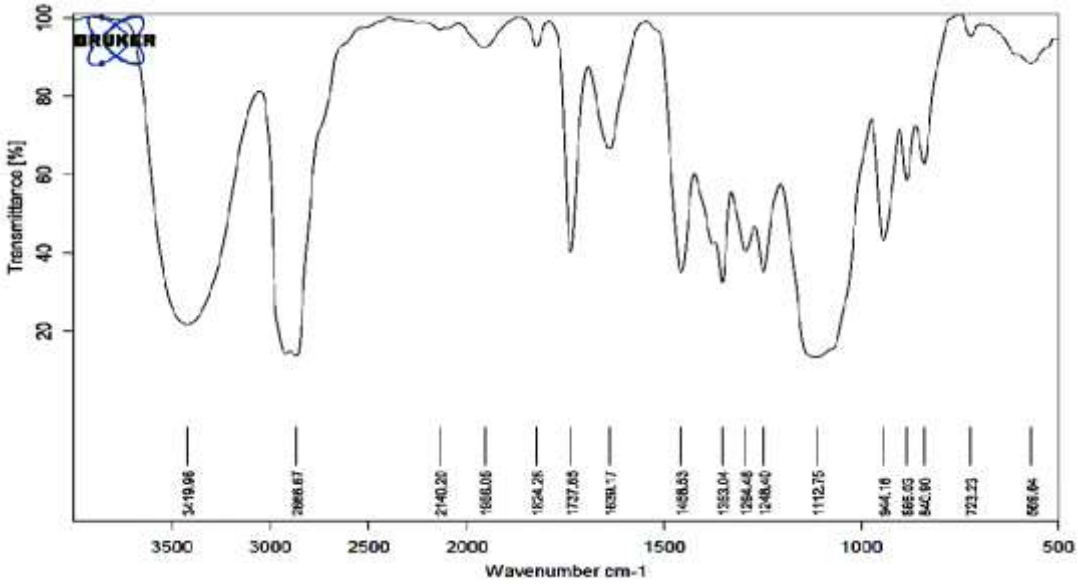


Figure 2: FTIR Spectra of Final freeze dried powder of AM

Table 1: FTIR peaks

Principle Peaks(cm-1)	Functional group stretching	Wave number (cm^{-1})	freeze dried powder of Azilsartan Medoxomil (AM) Wave number (cm^{-1})

	C=O stretching (carboxyl group)	1776.3	2866
	C–O stretching	1280.7, 1309	1458 and 1639
	C–O–C stretching	1083.9	1737
	N–H bending (amine group)	1467	1112
	C–H bending (out-of-plane)	761.8	1294
	C=N stretching	1691.5	3419
	C-H Aromatic	761.8	

Frequencies of principle peaks in FTIR spectra of physical mixture of drug with other excipients were nearly similar to the frequency of principle peaks present in FTIR spectra of pure drug[31]. So, these results revealed that the drug was compatible with excipients and neither drug decomposition nor drug-excipients and excipients-excipients interactions occurred in the formulation.

Analytical Method Development:
Determination of λ_{max}

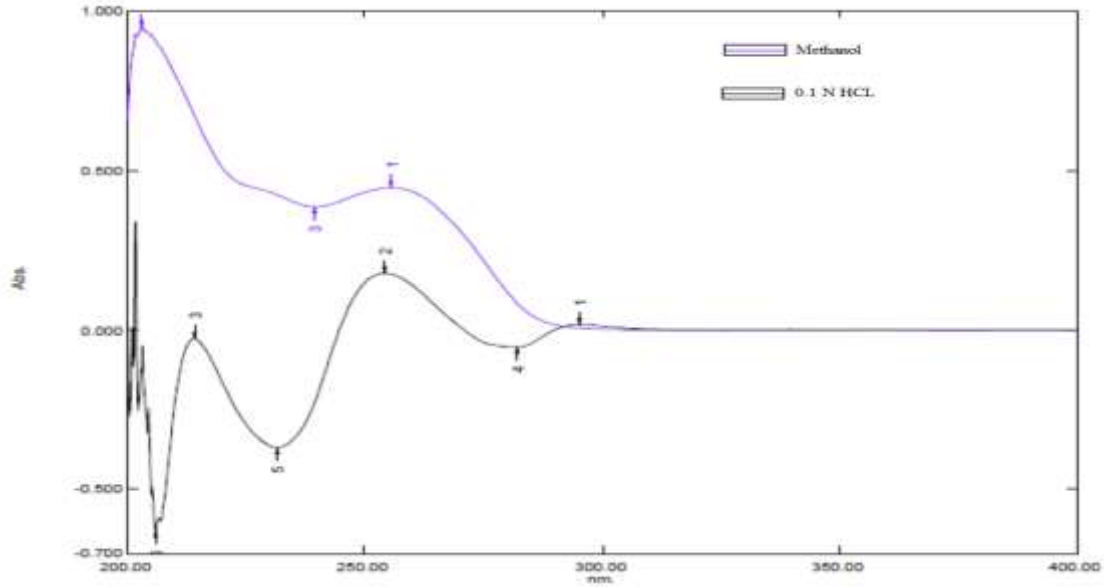


Figure 3: Overlay spectra

The standard drug solution of 10 µg/ml concentration was scanned in UV visible in the range of 200-400 nm. From this scanned spectra, the peak of maximum absorbance was identified (λ_{max}) at m 239-259 nm in both methanol and 0.1 N HCl media.

Calibration curve of Azilsartan Medoxomil in methanol

A standard curve of Almesartan Medoxomil(AM) in methanol was analyzed in the range of 2-18 µg/ml. The selected range of AM was found to be linear. A regression coefficient (R^2) at 248 nm was found to be 0.996.

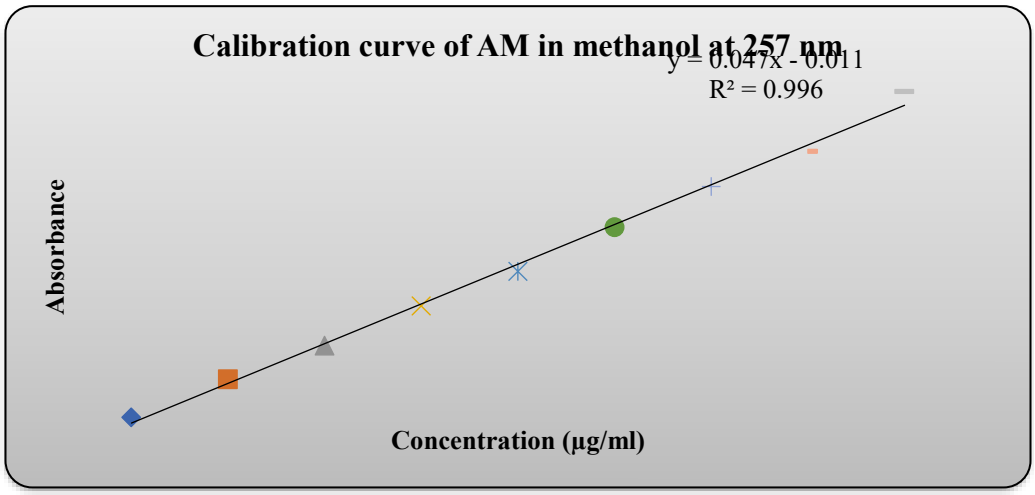


Figure 4: Calibration curve of Azilsartan medoxomil in methanol

Calibration curve of Azilsartan medoxomil in 0.1 N HCL

A standard curve of Azilsartan medoxomil in 0.1 N HCL was analyzed in the range of 5-40 µg/ml. The selected range of AM was found to be linear. A regression coefficient (R^2) at 248 nm was found to be 0.999.

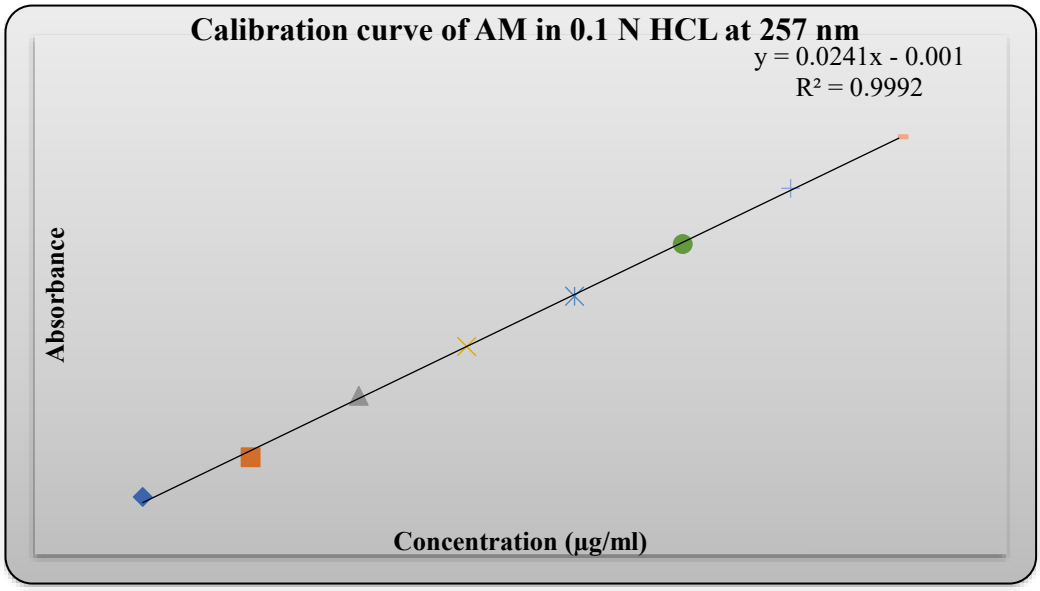


Figure 5: Calibration curve of Azilsartan medoxomil in 0.1 N HCL

Standard curves of Azilsartan medoxomil in methanol and 0.1 N HCL were analyzed in the range of 2-18 µg/ml and 5-40 µg/ml respectively. The selected range of AM was found to be linear. Regression co-efficient at 248 nm were found to be 0.996 and 0.999 respectively[32]. Regression co-efficient for the drug in methanol and in 0.1 N HCL was found to be near to one and in the linearity range. This standard concentration method obeys Beers law and found to be suitable for the determination of drug content and In vitro drug release study.

Screening Study

Screening study was performed for selection of oil, surfactant and co-surfactant for development of formulation by preparing saturated solution of drug in oil, surfactant and co-surfactant[33].

Screening of Oils (Based on solubility of drug)

Table 6: Solubility study in different oils

Sr No	Oils	Solubility (mg/ml)
1	Castor Oil	19.23±0.08
2	Olive Oil	12.37±0.28
3	Oleic Acid	8.45±0.24
4	Labrafil M 1944	7.84±0.23
5	Labrafac CC	9.54±0.21

*Mean ± SD, n=3

The solubility of the drug was tested in different oils phases and maximum solubility was determined in castor oil 19.63±0.08 mg/ml and was selected as oily phase for SMEDDS formulation.

Screening of Surfactants (Based on solubility of drug)

Table 7: Solubility study in different Surfactants

S. No	Surfactants	Solubility (mg/ml)
1	Tween 20	80.56±0.125
2	Tween 80	34.62±0.202
3	Cremophor EL	38.60±0.259
4	Labrafac PG	41.61±0.271
5	Captex 355	27.52±0.231

*Mean ± SD, n=3

The solubility of the drug was tested in different surfactants phases and maximum solubility was determined in tween 20 is 80.56±0.125 mg/ml and was selected as surfactant phase for SMEDDS formulation.

Based on % oil solubilize in different surfactants

Table 8: % oil solubilize in different surfactants

S.No.	Surfactants	% oil solubilize
1	Tween 20	5.4%
2	Tween 80	2.3%
3	Cremophor EL	3.3%
4	Labrafac PG	1.5%
5	Captex 355	1.3%

*Mean ± SD, n=3

Results inferred that the oily phase Castor oil exhibited the highest 5.3% solubilize with Tween 20. The mentioned results suggested the use of Castor oil as an oily phase with Tween 20 as a surfactant for further study

Based on ease of emulsification

Table 9: Number of flask inversion and % transmittance oil and different surfactant combination

S. No.	Surfactants	No. of flask inversions	% Transmittance at 650 nm
1	Tween 20	8	93.1
2	Tween 80	13	86.6
3	Cremophor EL	17	63
4	Labrafac PG	23	34.8
5	Captex 355	22	26

Results inferred that the oily phase Castor oil exhibited the highest emulsification efficiency with Tween 20 for the homogenous emulsion formation. On the other hand, Castor oil showed poor emulsification properties with other surfactants employed, requiring a higher number of flask inversions. The aforementioned results suggested the use of Castor oil as an oily phase with Tween 20 as a surfactant for further study.

Screening of Co-surfactants

Based on solubility of drug

Table 10: Solubility study in different Co-surfactants

S. No	Co-surfactants	Solubility (mg/ml)
1	PEG-400	42.60±0.31

2	Transcutol	73.55±0.23
3	Propylene Glycol	12.73±0.63
4	Carbitol	82.63±0.16

*Mean ± SD, n=3

The solubility of the drug was tested in different Co-surfactants phases and maximum solubility was determined in Carbitol is 83.62±0.165 mg/ml and was selected as Co-surfactant phase for SMEDDS formulation.

Based on ability to form clear solution

Table 11: Minimum amount of co-surfactant required to form clear solution

S. No.	Co-surfactants	Minimum co-surfactant required for clear solution (µl)
1	PEG-400	150
2	Transcutol	117
3	Propylene Glycol	140
4	Carbitol	104

Results inferred that the co-surfactant phase Carbitol exhibited the minimum amount of co-surfactant required to form clear solution with castor oil as oily phase and tween 20 as a surfactant phase in combination. The mentioned results suggested the use of Carbitol as a Co-surfactant phase with Castor oil as an oil and Tween 20 as a surfactant for further study

Based on ease of emulsification

Table 12: Number of flask inversion and % transmittance oil, surfactant and different co-surfactant combination

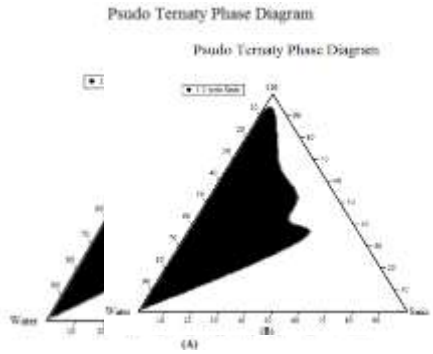
S. No	Co-surfactants	No. of phase inversions	% Transmittance at 650 nm
1	PEG-400	24	31.5
2	Transcutol	14	76.8
3	Propylene Glycol	27	64.4
4	Carbitol	11	88.5

Results inferred that the oily phase Castor oil and surfactant phase Tween 20 exhibited the highest emulsification efficiency with Carbitol as co-surfactant for the homogenous emulsion formation. On the other hand, Castor oil and Tween 20 showed poor emulsification properties with other co-surfactants employed, requiring a higher number of flask inversions. The aforementioned results suggested the use of Castor oil as an oily phase and Tween 20 as a surfactant with Carbitol as a co-surfactant phase for further study[33].

Construction of pseudo ternary phase diagram

Constructing phase diagrams is time consuming, particularly when the aim is to accurately delineate a phase boundary. Care was taken to ensure that observations are not made on metastable systems, although the free energy required to form a microemulsion is very low, the formation is thermodynamically spontaneous. The relationship between the phase behavior of a mixture and its composition can be captured with the aid of a phase diagram. Castor oil (oil), Tween 20 (surfactants) and Carbitol (co-surfactant) were put in different groups based on the ratio of surfactant to co-surfactant (1:1, 1:2, 2:1) under test to study the phase diagrams in detail[34].

From the trial has shown that the emulsifying effect is good if the ratio of the surfactant to the co-surfactant is higher than 1:2 but stability properties are inferior at this ratio. Fixing the surfactant/co-surfactant ratio at 1:1 is a better choice from the stability point of view.



(A)

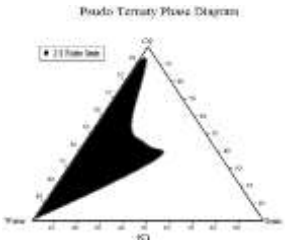


Figure 6: (A) Surfactant/co-surfactant 1:1, (B) surfactant/co-surfactant 1:2 and (C) surfactant/co-surfactant 2:1. Pseudo ternary phase diagram of the system, Castor oil, Tween 20: Carbitol, and water

Effect of drug on phase diagram

Effect of drug on the phase diagram is shown in table 13. The drug was incorporated in the formulation gradually and the emulsion was visually assessed. The results concluded that the transparent emulsion was produce at the concentration of 80 mg of AM/1ml of SMEDDS formulation. After 80 mg precipitation of AM occurs. So, results show that 80mg of AM loaded in 1ml of SMEDDS formulation.

Table 13: Effect of Drug on Phase Diagram

Amount of drug	Visual inspection
10mg	Transparent
20mg	Transparent
30mg	Transparent
40mg	Transparent
50mg	Transparent
60mg	Transparent
70mg	Transparent
80mg	Transparent
90mg	Precipitation
100mg	Precipitation

Formulation Development
Optimization of Formulation variables:

Mainly 3 formulations variables that affect on self-microemulsifying properties and solubility.

1. Concentration of oil
2. Concentration of surfactant
3. Concentration of Co-surfactant

All the batches were analyzed using the Design Expert 9 software. Box Behnken statistical design with 3 factors, 2 levels was prepared by Design expert 9 with 5 center point and 17 runs was selected for the optimization study. The optimization design consists of a set of points lying at the midpoint of each edge.

Optimization of oil, surfactant and Co-surfactant concentration:
Matrix of Box-Behnken Design for formulation parameters and its evaluation:
For optimization of formulation parameters such as concentration of oil, surfactant and co-surfactant was carried out by evaluating emulsification time, % transmittance and % cumulative drug release. Matrix of Box-Behnken Design for formulation parameters and its evaluation[35].

Table 14: Matrix of Box-Behnken Design for formulation and its evaluation

Sr No	Std	Run	Batch No	Oil (ml)	Surfactant (ml)	Co-surfactant (ml)	Emulsification time (Sec)	% Transmittance (%)	% CDR (%)
1	8	1	AMB 1	9	2.5	4.5	46±5.28	80.96±1.76	92.1±0.028
2	17	2	AMB 2	5	2.5	2.5	64±42	74.82±1.07	68.52±0.024

3	16	3	AMB 3	5	2.5	2.5	65±5.55	75.82±1.26	66.16±0. 021
4	10	4	AMB 4	5	4.5	0.5	86±2.60	59.15±0.90	52.35±0. 022
5	15	5	AMB 5	5	2.5	2.5	63±2.60	74.83±1.07	69.74±0. 026
6	1	6	AMB 6	1	0.5	2.5	50±3.35	88.12±0.76	80.6±0.0 29
7	3	7	AMB 7	1	4.5	2.5	37±3.65	91.27±0.99	86.41±0. 032
8	13	8	AMB 8	5	2.5	2.5	64±44	75±1.11	69.52±0. 026
9	9	9	AMB 9	5	0.5	0.5	90±42	43.05±0.79	50.1±0.0 26
1 0	4	10	AMB 10	9	4.5	2.5	67±2.54	62.9±0.88	63.35±0. 018
1 1	6	11	AMB 11	9	2.5	0.5	112±2.60	32.06±0.51	44.08±0. 028
1 2	7	12	AMB 12	1	2.5	4.5	18±2.64	99.07±0.23	99.53±0. 015
1 3	2	13	AMB 13	9	0.5	2.5	83±2	51.48±0.47	68.82±0. 030
1 4	14	14	AMB 14	5	2.5	2.5	64±2.64	76.83±1.07	70.58±0. 028
1 5	12	15	AMB 15	5	4.5	4.5	23±2.64	95.35±0.77	96.62±0. 011
1 6	5	16	AMB 16	1	2.5	0.5	73±3.50	64.13±0.74	61.10±0. 028
1 7	11	17	AMB 17	5	0.4	4.4	38±3.62	90.8±1.82	94.35±0. 028

Statistical Analysis:

For optimization Box-Behnken design was employed to study the effect of independent variables (i) oil (ml) (A), (ii) surfactant (ml) (B) and (iii) co-surfactant (ml) (C) on dependent variable (Y1) emulsification time, (Y2) % transmittance and (Y3) % cumulative drug release. All the batches were prepared according to the design. All the batches were analyzed using the design expert 9 software. The software itself suggests Quadratic Model and also gave model equation for dependent variables. The ANOVA of emulsification time, % transmittance and % cumulative drug release.

Response 1 – Emulsification Time

Emulsification time from the batch AMB1 to AMB17 of emulsion varied from 18±2.64 sec to 112±3.60 sec. From the P-value, it was concluded that the effect of oil (A), surfactant (B) and co-surfactant (C) had the prominent effect (P<0.05) on emulsification time.

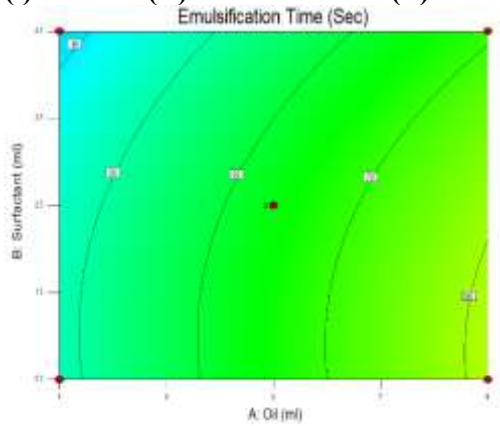
Polynomial Equation for Emulsification Time:

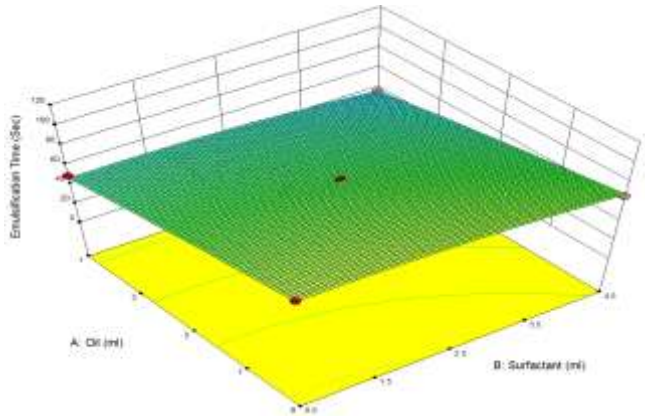
Emulsification time = +63.80 + 16.25 × A - 5.75 × B - 29.25 × C - 0.50 × AB - 3.00 × AC - 2.50 × BC -1.15 × A^2 - 3.65 × AMB2- 0.65 × C^2

Table 15: ANOVA of Emulsification Time

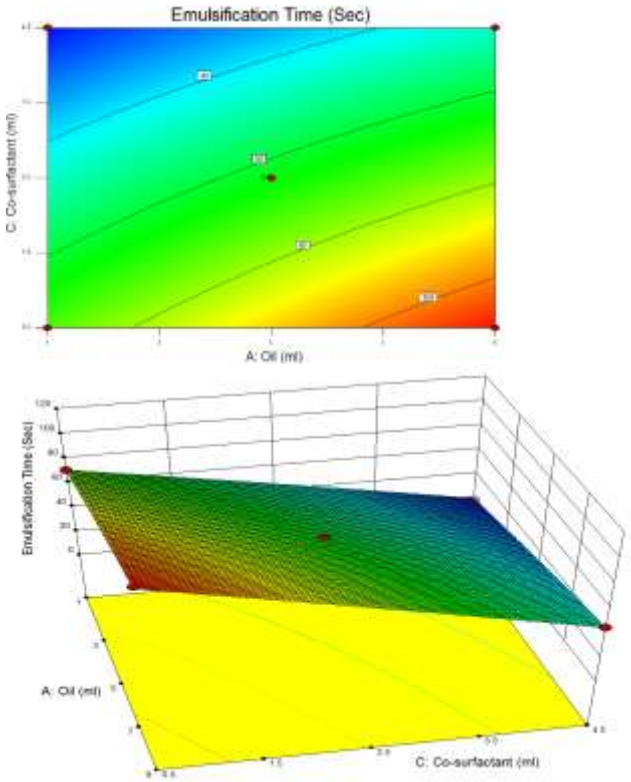
Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	
Model	9350.75	9	1038.96	299.24	<0.0001	Significant
Lack of Fit	21.54	3	7.15	10.25	0.0229	Significant
Pure Error	2.70	4	0.70	-	-	
Cor Total	9375.05	16	-	-	-	
R-Squared		**0.9975**				
Adj R-Squared		**0.9942**				
Pred R-Squared		**0.9627**				

(i) Oil (A) and Surfactant (B)





(ii) Oil (A) and co-surfactant (C)



(iii) Surfactant (B) and Co-surfactant (C)

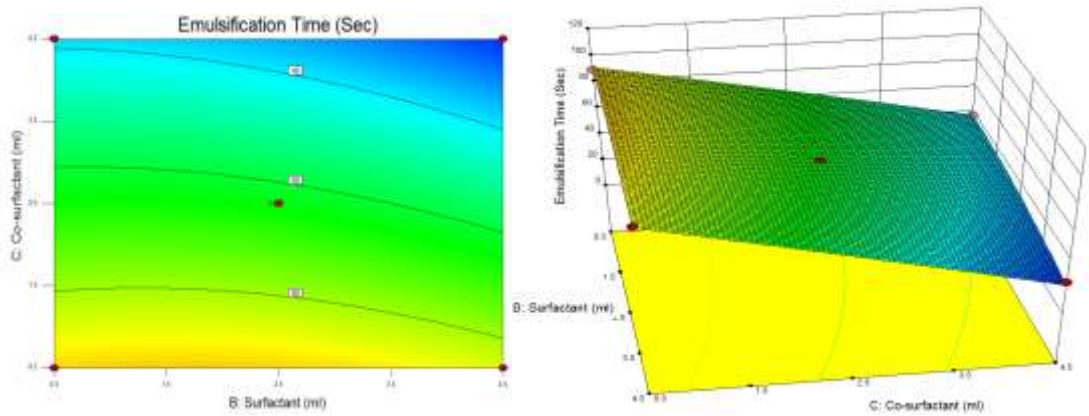


Figure 7: Contour plot and Response surface of emulsification time (i) Effect of Oil (A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

Response 2 – % Transmittance

% Transmittance from the batch AMB1 to AMB17 of emulsion varied from 32.06±0.51 % to 99.08±0.23 %. From the P-value, it was concluded that the effect of oil (A), surfactant (B) and co-surfactant (C) had the prominent effect ($P<0.05$) on % transmittance.

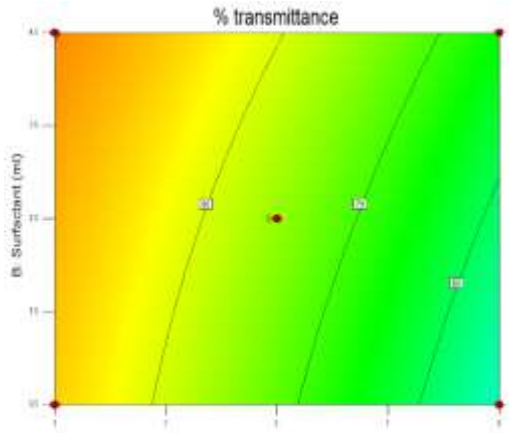
Polynomial Equation for % Transmittance:

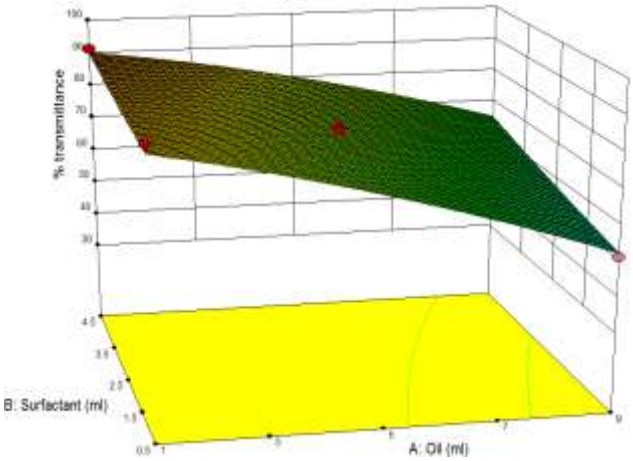
% Transmittance = $+75.25 - 14.40 \times A + 4.40 \times B + 20.98 \times C + 2.07 \times AB + 3.49 \times AC - 2.89 \times BC - 2.52 \times A^2 + 0.51 \times AMB2 - 3.87 \times C^2$

Table 16: ANOVA of % Transmittance

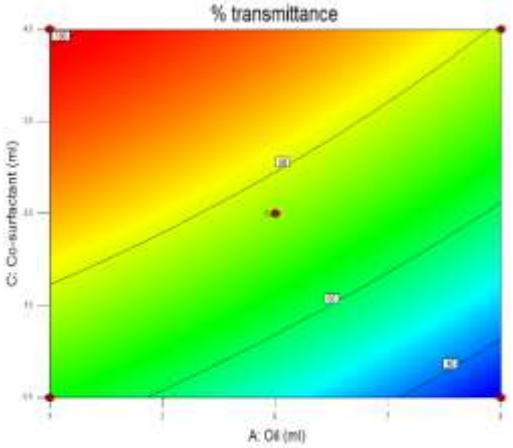
Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	
Model	5527.29	9	614.15	122.52	< 0.0001	Significant
Lack of Fit	32.10	3	10.72	14.28	0.0132	Significant
Pure Error	3.00	4	0.75	-	-	
Cor Total	5562.38	16	-	-	-	
R-Squared		**0.9936**				
Adj R-Squared		**0.9855**				
Pred R-Squared		**0.9067**				

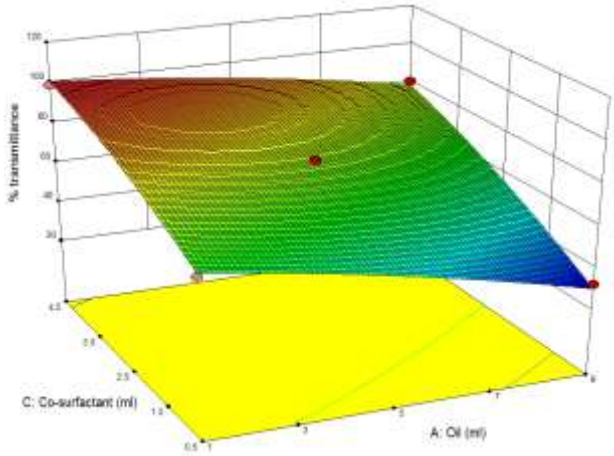
(i) Oil (A) and Surfactant (B)





(ii) Oil (A) and Co-surfactant (C)





(iii) Surfactant (B) and Co-surfactant

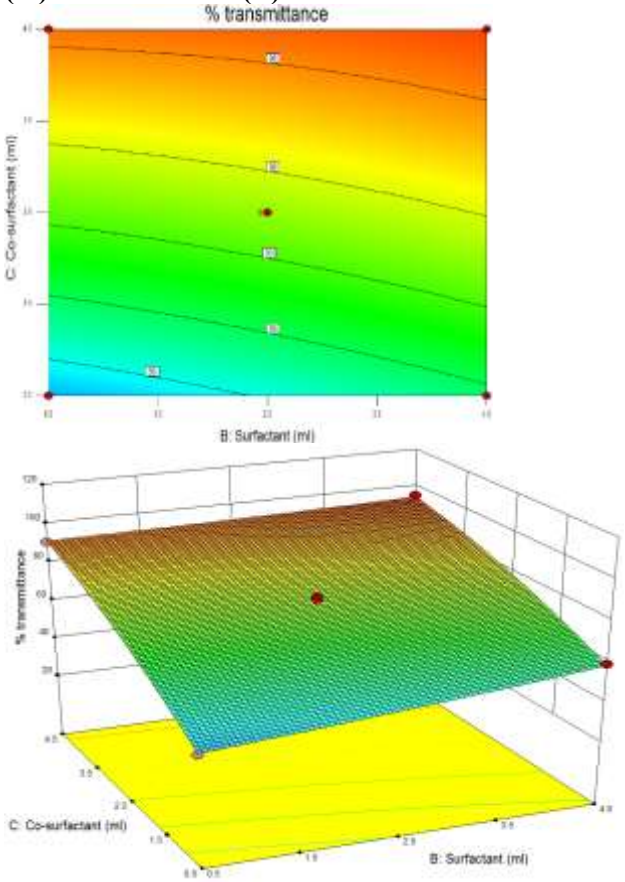


Figure 8: Contour plot and Response surface of % transmittance (i) Effect of Oil (A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

Response 2 – % Cumulative Drug Release

% Cumulative drug release from the batch AMB1 to AMB17 of emulsion varied from 44.08±0.028 % to 99.43±0.015 %. From the P-value, it was concluded that the effect of oil (A), surfactant (B) and co-surfactant (C) had the prominent effect ($P<0.05$) on % cumulative drug release.

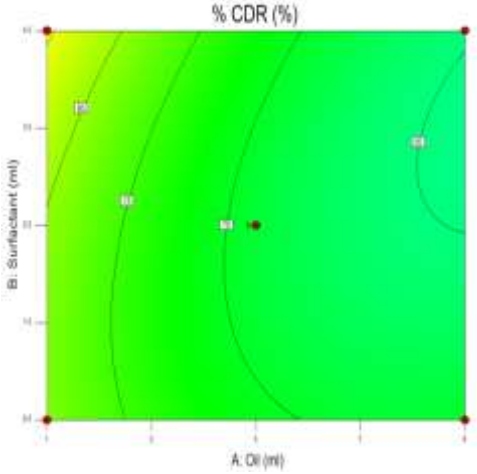
Polynomial Equation for % Cumulative Drug Release:

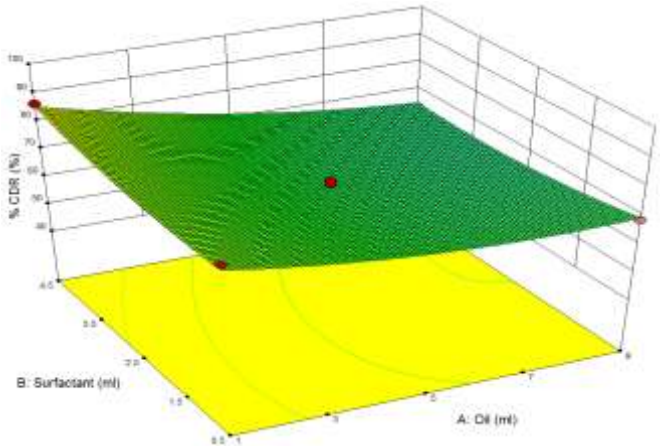
% Cumulative Drug Release = $+68.90 - 7.37 \times A + 0.66 \times B + 21.90 \times C - 2.80 \times AB + 2.45 \times AC - 0.078 \times BC + 3.42 \times A^2 + 2.49 \times AMB2 + 1.88 \times C^2$

Table 17: ANOVA of % Cumulative Drug Release

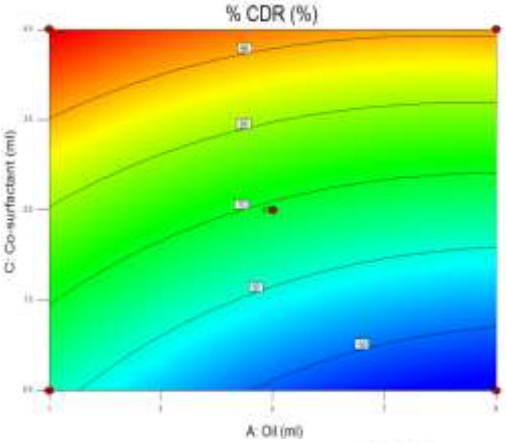
Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	
Model	4431.18	9	492.38	121.33	< 0.0001	Significant
Lack of Fit	17.82	3	5.50	1.92	0.2663	Not Significant
Pure Error	11.61	4	2.80	-	-	
Cor Total	4450.60	16	-	-	-	
R-Squared		0.9936				
Adj R-Squared		0.9854				
Pred R-Squared		0.9357				

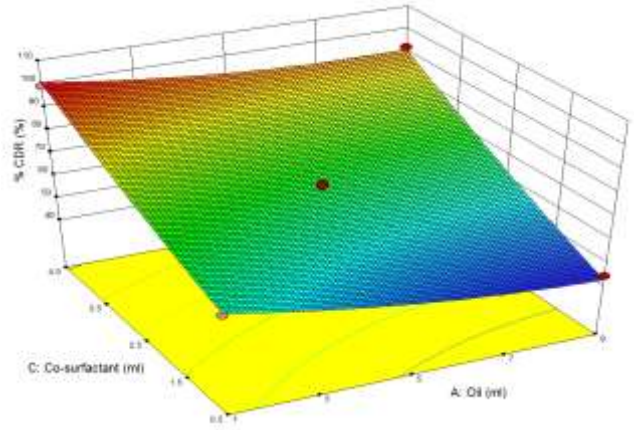
(i) Oil (A) and Surfactant (B)





(ii) Oil (A) and Co-surfactant (C)





(iii) Surfactant (B) Co-surfactant (C)

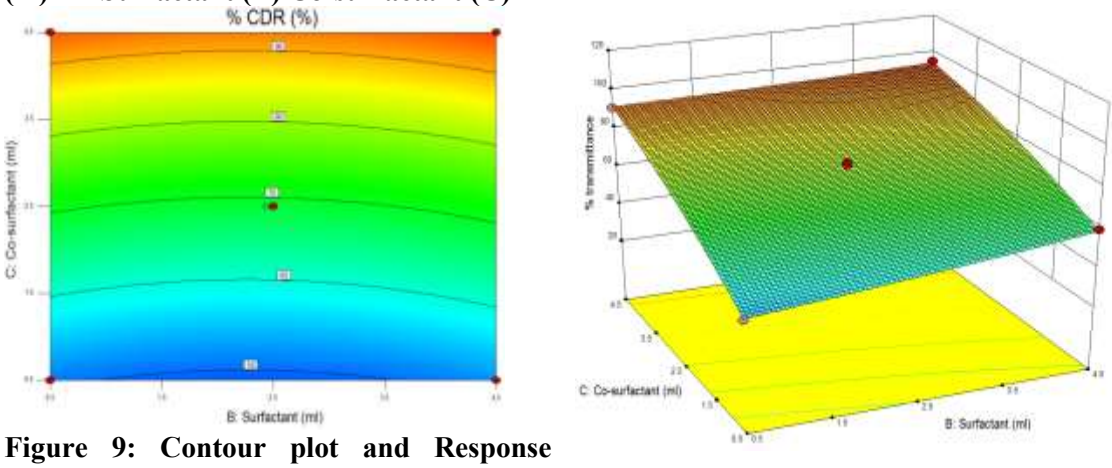


Figure 9: Contour plot and Response surface of % cumulative drug release (i) Effect of Oil (A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

Discussion:

The effect of oil (A), surfactant (B) and co-surfactant (C) on emulsification time (Sec), % transmittance (%) and % cumulative drug release are shown in figure 16 to 18 in the form of response surface plots and contour plots.

A mean level of surfactant (B) and co-surfactant (C) on emulsification time was found to be increased from 18±2.64 sec to 112±3.60 sec, % transmittance was found to be decreased from 99.08±0.23% to 32.06±0.51%, % cumulative drug release was found to be decreased from 99.43±0.015% to 44.08±0.028%, when increasing in oil (A) from 1 ml to 9 ml.

A mean level of oil (A) and co-surfactant (C) on emulsification time was found to be decreased from 112±3.60 sec to 18±2.64 sec, % transmittance was found to be increased from 32.06±0.51% to 99.08±0.23%, % cumulative drug release was found to be increased from 44.08±0.028% to 99.43±0.015%, when increasing in surfactant (B) from 0.5 ml to 4.5ml.

A mean level of oil (A), surfactant (B) on emulsification time was found to be increased from 112±3.60 sec to 18±2.64 sec, % transmittance was found to be increased from 32.06±0.51% to 99.08±0.23%, % cumulative drug release was found to be increased from 44.08±0.028% to 99.43±0.015%, when increasing in co-surfactant (C) from 0.5 ml to 4.5ml.

Evaluation of liquid SMEDDS Formulation

Dispersibility Test

Table 18: Dispersibility tests of Box-Behnken Design formulation

S. No	Batch No	Dispersibility Grade	
		Distilled Water	0.1 N HCl
1	AMB1	Grade A	Grade A

2	AMB2	Grade B	Grade B
3	AMB3	Grade B	Grade B
4	AMB4	Grade D	Grade D
5	AMB5	Grade B	Grade B
6	AMB6	Grade B	Grade B
7	AMB7	Grade B	Grade B
8	AMB8	Grade B	Grade B
9	AMB9	Grade D	Grade D
10	AMB10	Grade C	Grade C
11	AMB11	Grade D	Grade D
12	AMB12	Grade A	Grade A
13	AMB13	Grade C	Grade C
14	AMB14	Grade B	Grade B
15	AMB15	Grade A	Grade A
16	AMB16	Grade C	Grade C
17	AMB17	Grade A	Grade A

When infinite dilution is done to microemulsion formulation, there is every possibility of it to phase separate leading to precipitation of a poorly soluble drug as microemulsion are formed at a particular concentration of oil, surfactant, co-surfactant and water. For oral microemulsions the process of dilution by the GI fluids will result in the gradual desorption of surfactant located at the globule interface. The process is thermodynamically driven by the requirement of the surfactant to maintain an aqueous phase concentration equivalent to its CMC. In the present study, we used distilled water and 0.1 N HCl as a dispersion medium because it is well reported that there is no significant difference in the microemulsions prepared using nonionic surfactants, dispersed in either water or simulated gastric or intestinal fluid. Formulations that passed Dispersibility test in Grade A and B were taken for further study, as Grade A and B formulations will remain as microemulsions when dispersed in GIT. All the formulation that were falling in Grade C and D of Dispersibility tests were discarded for further study.

Robustness on dilution

Table 19: Robustness on dilution of Box-Behnken Design formulation

S. No	Batch No	Dispersibility Grade	
		Distilled Water	0.1 N HCl
1	AMB1	Stable, No precipitation	Stable, No precipitation
2	AMB2	Stable, No precipitation	Stable, No precipitation
3	AMB3	Stable, No precipitation	Stable, No precipitation
4	AMB4	Stable, No precipitation	Stable, No precipitation
5	AMB5	Stable, No precipitation	Stable, No precipitation
6	AMB6	Stable, No precipitation	Stable, No precipitation
7	AMB7	Stable, No precipitation	Stable, No precipitation

8	AMB8	Stable, No precipitation	Stable, No precipitation
9	AMB9	Stable, No precipitation	Stable, No precipitation
10	AMB10	Stable, No precipitation	Stable, No precipitation
11	AMB11	Stable, No precipitation	Stable, No precipitation
12	AMB12	Stable, No precipitation	Stable, No precipitation
13	AMB13	Stable, No precipitation	Stable, No precipitation
14	AMB14	Stable, No precipitation	Stable, No precipitation
15	AMB15	Stable, No precipitation	Stable, No precipitation
16	AMB16	Stable, No precipitation	Stable, No precipitation
17	AMB17	Stable, No precipitation	Stable, No precipitation

The prepared formulation diluated when 100 times with distilled water and 0.1 N HCL were found to be stable without any precipitation.

Emulsification Time

Self-emulsification time was measured using stop watch. It was measure by adding water in liquid SMEDDS and measured time for formed an emulsion. The formulation AMB12 has less self-emulsification time was found to be 18±2.64 second as compared as other formulation. Result of self-emulsification time is shown in table

% Transmittance

The clarity of microemulsions was checked by transparency, measured in terms of transmittance (%T). SMEDDS forms o/w microemulsion since water is external phase. Formulation AMB12 has % transmittance value greater than 99%.These results indicate the high clarity of microemulsion. In case of other systems %T values were about 80% suggesting less clarity of microemulsions. This may be due to greater particle size of the formulation. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of %T.

Drug Content

Table 20: Drug Content of Box-Behnken Design formulation

S. No	Batch No	Drug Content
1	AMB1	90.72±0.012
2	AMB2	93.57±0.0154
3	AMB3	95.50±0.0145
4	AMB4	83.79±0.0298
5	AMB5	96.23±0.021
6	AMB6	94.82±0.018
7	AMB7	97.62±0.011
8	AMB8	94.40±0.016
9	AMB9	88.01±0.020
10	AMB10	89.29±0.011
11	AMB11	83.82±0.029
12	AMB12	99.01±0.009

13	AMB13	94.06±0.016
14	AMB14	92.78±0.019
15	AMB15	98.86±0.013
16	AMB16	90.24±0.017
17	AMB17	93.78±0.019

*Mean ± SD, n=3

Drug content was measured using UV spectrophotometer at 257 nm. Drug content was measured using linearity equation of methanol. The formulation AMB12 has maximum drug content of liquid SMEDDS was found to be 99±0.009 % of optimized batch.

Time (min)	**Batch No**							
	AMB1	**AMB2**	**AMB3**	**AMB4**	**AMB5**	**AMB6**	**AMB7**	**AMB8**
0	0	0	0	0	0	0	0	0
5	10.35±0.025	6.65±0.018	5.88±0.016	3.70±0.012	6.23±0.018	13.65±0.027	8.64±0.023	5.36±0.017
10	17.35±0.038	17.33±0.025	12.56±0.027	8.95±0.017	15.00±0.027	22.95±0.025	21.70±0.022	14.50±0.014
15	23.32±0.031	25.59±0.027	21.01±0.021	19.47±0.024	23.57±0.035	29.10±0.025	31.11±0.029	25.62±0.022
20	32.86±0.021	34.05±0.026	30.04±0.030	26.85±0.020	32.73±0.034	38.59±0.031	43.97±0.018	33.54±0.019
25	43.82±0.025	40.10±0.029	41.02±0.029	32.00±0.019	37.01±0.028	47.88±0.027	54.15±0.034	39.52±0.025
30	61.62±0.028	47.57±0.027	48.20±0.029	37.37±0.024	43.83±0.025	58.58±0.034	65.09±0.021	46.88±0.018
35	74.43±0.036	55.52±0.024	53.60±0.038	41.17±0.029	55.13±0.029	69.85±0.028	73.54±0.027	53.43±0.028
40	87.64±0.028	62.07±0.023	60.47±0.024	45.42±0.020	61.36±0.027	76.78±0.038	84.49±0.035	63.16±0.025
45	92.41±0.029	68.52±0.024	66.16±0.021	52.36±0.022	69.74±0.027	80.53±0.029	86.41±0.031	69.53±0.025

Table 21: In-vitro drug release of batch AMB9 to AMB17

Table 21: In-vitro drug release of batch AMB9 to AMB17
*Mean ± SD, n=3

Dissolution studies were performed for the SMEDDS formulations in 0.1 N HCL. The maximum drug release of batch no AMB12 was 99.43±0.015 % within the 45 min in case of SMEDDS.

Time (min)	Batch No								
	AMB9	**AMB10**	**AMB11**	**AMB12**	**AMB13**	**AMB14**	**AMB15**	**AMB16**	**AMB17**
0	0	0	0	0	0	0	0	0	0
5	3.84±0.014	4.62±0.011	4.25±0.010	15.15±0.021	4.39±0.020	8.09±0.022	13.08±0.012	8.11±0.024	10.59±0.021
10	8.95±0.018	11.12±0.022	9.84±0.022	30.12±0.017	10.57±0.024	14.56±0.024	28.28±0.015	15.38±0.029	21.19±0.030
15	13.23±0.021	19.75±0.019	13.87±.013	45.13±0.018	18.75±0.033	24.88±0.026	41.70±0.012	24.74±0.023	30.38±0.024
20	22.37±0.020	27.94±0.018	17.00±0.020	56.25±0.012	26.53±0.026	33.16±0.029	54.47±0.018	28.48±0.011	42.75±0.021
25	28.78±0.022	34.64±0.029	20.14±0.026	73.67±0.018	32.92±0.030	39.45±0.027	71.93±0.012	35.65±0.025	52.97±0.022
30	31.55±0.015	41.81±0.023	24.84±0.013	85.61±0.018	36.69±0.027	45.71±0.022	81.98±0.015	43.03±0.020	65.57±0.023
35	40.93±0.013	50.21±0.024	32.22±0.019	96.21±0.016	47.67±0.022	53.20±0.025	92.61±0.023	49.68±0.026	78.56±0.026
40	45.41±0.013	55.67±0.020	39.38±0.025	99.24±0.005	52.86±0.026	62.30±0.025	95.65±0.018	59.04±0.028	91.95±0.024
45	50.10±0.024	63.45±0.016	45.08±0.027	99.43±0.015	68.83±0.020	70.59±0.038	96.60±0.012	61.11±0.027	94.35±0.028

Conclusion

Azilsartan medoxomil (AM) is a novel selective angiotensin II receptor blocker USFDA approved drug for the treatment of hypertension. It is the prodrug that is rapidly de-esterified during absorption from the gastrointestinal tract to produce an active metabolite Azilsartan medoxomil is a poorly water soluble drug due to this poor solubility the oral bioavailability of is about 26% in healthy humans. The selection of oil, surfactant and co-surfactant was carried out using screening study. AM is more soluble in castor oil, tween-20 and carbitol. The solubility was found to be 19.63±0.08 mg/ml, 80.56±0.125 mg/ml and 83.62±0.165 mg/ml in olive oil, tween- 80 and carbitol respectively. For the selection of the surfactant % oil solubilize in different surfactant and ease of emulsification study was carried out, in this study tween-20 highest 5.3% oil solubilize in castor oil and 9 no of flask inversion required for mix tween-20 with castor oil and % transmittance was found to be 93.2. According to that result tween 20 selected for the surfactant phase for further study. The co-surfactant selected according to the minimum amount of co-surfactant required to form clear solution and ease of emulsification, The pseudo ternary phase diagram was constructed using castor oil as oil phase, tween-20 as surfactant phase and carbitol as co-surfactant phase. For this the different three ratio 1:1, 1:2 and 2:1 surfactant and co-surfactant was selected. The different trial has shown that the emulsifying effect is good if the ratio of the surfactant to the co-surfactant is 1:2 and 2:1 but stability properties are inferior at this ratio, so fixed the 1:1 ratio of surfactant and co-surfactant according to stability. The transparent emulsion was produce at the concentration of 80 mg of AM /1ml of SMEDDS formulation. After 80 mg precipitation of AM occurs.

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डिजाइन सं. / Design No. : 450113-001

तारीख / Date : 03/03/2025

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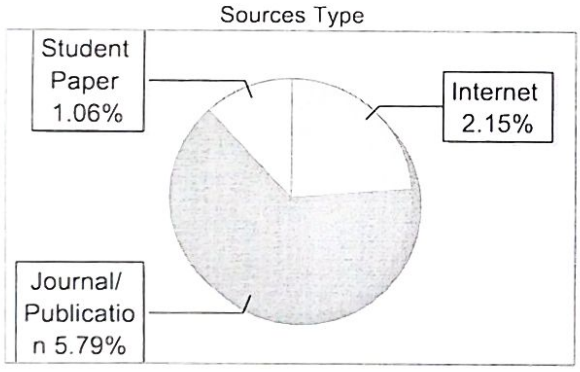
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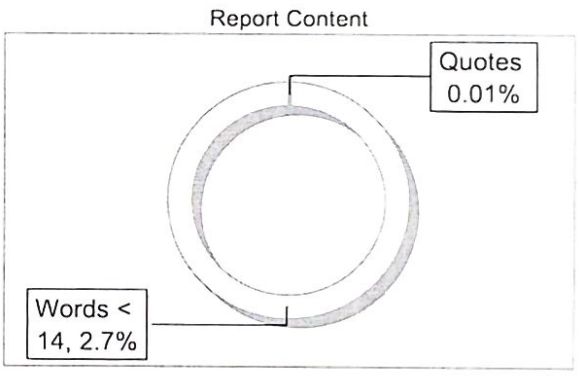
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About the Authors :



Dr. Gaurav Singh Sikarwar is an Assistant Professor at Sharda School of Pharmacy, Sharda University, Agra. With over 11 years of academic and research experience, he has made significant contributions to pharmaceutical education. His expertise spans across pharmacology and drug development, with a focus on innovative teaching methodologies. Based at the university's Keetham campus in Arsena, Agra (PIN 282007), he is actively involved in mentoring students and guiding research projects. Dr. Sikarwar is known for his commitment to academic excellence and advancing pharmaceutical sciences. His work reflects a blend of knowledge, experience, and a passion for education.



Dr.Surendra Pratap Singh M. Pharm PhD working as a Professor in Faculty Of Pharmacy PK University Shivpuri (M.P.) He is published approx. 40 research Paper in national and international journals. He has 15 years' experience in teaching and research. He is guided 45 students of post graduate. He has a good working experience of Clinical SAS Programming.



Mrs. Asha Parveen has completed M.pharm and currently pursuing PhD in PK University Shivpuri (M.P.). She has published 5 research papers in national and international journals. She Have 3 patents and presented in more than 10 conferences and attended more than 20 conferences and FDPs . She has 11 years' experience in teaching and research. She has guided more than 50 students of graduates and post graduate.



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Dr. Deepak Singh is an Assistant Professor at Teerthanker Mahaveer University, Moradabad, specializing in Pharmaceutics. With an academic background in M.Pharm and Ph.D., he brings over 10.5 years of teaching experience to the field of pharmaceutical sciences. Dr. Singh has contributed extensively to research, having published 10 research and review articles in reputed journals. His innovative work is further reflected in two patents to his credit. He is dedicated to guiding students and advancing formulation research. His expertise and commitment make him a valued figure in pharmaceutical education and innovation.

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