Formulation Development and Evaluation of Fast Dissolving Oral Film for the Treatment of Angina Pectoris

A Thesis
Submitted towards the Requirements for the Award of Degree of

Doctor of Philosophy

In

Pharmacy
Under the Faculty of Pharmacy

By

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Under the Supervision of

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2026

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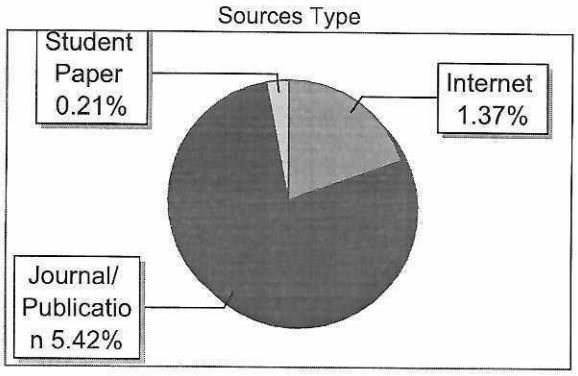
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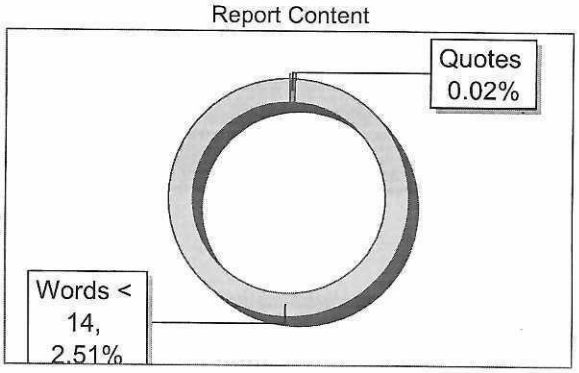
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LIST OF SYMBOLS AND ABBREVIATIONS

S. No.	Topic	Page No.
1.	%	Percentage
2.	±SD	Standard deviation
3.	µg	Microgram
4.	^{0}C	Degree Celsius
5.	API	Active pharmaceutical ingredient
6.	Cm	Centimeter
7.	i.e	That is
8.	Mg	Milligram
9.	Min	Minutes
10.	Ml	Milliliter
11.	Hrs	Hours
12.	Mm	Millimeter
13.	Nm	Nanometer
14.	PEG	Polyethylene glycol
15.	Rpm	Revolution per minute
16.	Std	Standard
17.	Sec	Seconds
18.	λ	Wavelength
19.	λ_{max}	Maximum wavelength
20.	Gm	Gram
21.	DSC	Differential Scanning Calorimetry
22.	FTIR	Fourier-transform infrared spectroscopy

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Date: **(RATNESH KUMAR MISHRA)**

Place:

INTRODUCTION

General:

In the late 1970s as an option in contrast to ordinary dose shapes for pediatric and geriatric patients who experience challenges in gulping conventional oral strong measurement frames plan the FDTS (Mouth dissolving tablets) by utilizing super disintigrants and hydrophilic fixings which has the higher bioavailability, brisk activity and most patient consistence. Numerous FDTS are set up by utilizing the costly lyophilisation process and at times hard to convey, store and handle delicacy and friability likewise dread of chocking with Fast dissolving tablet.

To dispense with the disadvantages of Fast dissolving tablet a Fast dissolving film can be set. Fast dissolving film are fundamentally the same as ultra-slim segment of postage stamp in their shape, size and thickness. Fast dissolving film are planned utilizing polymers, Programming interface (Dynamic pharmaceutical fixing), plasticizers, spit invigorating specialists, sugars, flavors, additives and hues. Fast dissolving film is just put on the patient's tongue or any oral mucosal tissue, in a split second wet by spit the film ly hydrates and follows onto the site of utilization. It at that point ly breaks down and disintegrates to discharge the prescription for oro mucosal retention or with equation changes, will keep up the snappy dissolving perspectives take into account gastrointestinal assimilation to be accomplished when gulped. (**Pandya K *et al.*, 2013**)

1.1 Characteristics of Oral Mucosa:

Oral medication conveyance has been referred to for a considerable length of time as the most broadly used course of organization among every one of the courses that have been investigated for the foundational conveyance of medications through different pharmaceutical results of various dose frames. The reason that the oral course accomplished such prevalence might be to some degree ascribed to its simplicity of organization just as the conventional conviction that by oral organization the medication is all around assimilated as the foodstuffs that are ingested day by day. (**Chien Y 2005**)

The majority of the medications are being taken as tablets and containers by practically all patients, including grown-up, pediatric and geriatric patients. Nonetheless, around 26 – half of patients think that its hard to swallow tablets and hard gelatin cases. These patients incorporate, old, pediatric patients, the rationally sick patients and patients who are unco-agent. (**Dahiya M *et al.*, 2009**)

Throughout the previous two decades, there has been and upgraded interest for increasingly persistent agreeable measurements shapes. (Patel A and Prajapati D 2010) Late improvements in the innovation have introduced feasible dose options from oral course for pediatrics, geriatric, laid up, sick or resistant patients. Buccal medication conveyance has of late turned into an imperative course of medication organization. Different bioadhesive mucosal measurements shapes have been created, which incorporates glue tablets, gels, salves, patches and all the more as of late the utilization of polymeric film for buccal conveyance, otherwise called mouth dissolving films. (**Gavaskar B *et al.*, 2010**)

Among different measurements frames that are regulated orally, strong oral dose shapes speak to the favored class as a result of their accessibility as unit dose frames, simplicity of shipment and transport and dependability.

The reasons for this preference over liquid oral dosage form are;

- Accuracy of dose administered
- Rapid action
- Enhanced bioavailability
- Taste masking
- Low shipment charges
- Absence of leakage and breakage
- Stability etc.

Anyway the primary obstruction for the oral conveyance of medications as potential helpful specialists is their broad presystemic digestion, shakiness in acidic condition coming about into deficient and flighty oral assimilation. So Parentral course of organization is the main set up course that defeats every one of these disadvantages related with the orally less/inadequate medications. Be that as it may, these definition are exorbitant, have less patient compliances, Agony at the site of organization, notwithstanding alternate unsafe impacts related with this course.

In the course of the most recent couple of decades pharmaceutical researcher all through the world are endeavoring to investigate transdermal or transmucosal courses as an option in contrast to infusions. Among the different transmucosal destinations accessible, mucosa of the buccal pit was observed to be most advantageous and simple open site for the conveyance of remedial specialists for both nearby and fundamental conveyance as retentive measurements structure, since it has territory of smooth muscles which is moderately stable, bounteous vascularization, recuperation time after introduction to stretch and the close nonappearance of langerhans cells, It has direct access to the foundational flow through the interior jugular vein sidesteps drugs from the hepatic first pass digestion prompting high bioavailability. Different favorable circumstances are as low enzymatic movement, reasonableness for medication and excipients that gently and reversibly harm or chafe the mucosa, effortless organization, simple medication withdrawal, office to incorporate saturation enhancer/chemical inhibitors or pH modifier in the detailing and adaptability in planning as multidirectional or unidirectional discharge frameworks for nearby and foundational activities and so on. (**Sudhakar et al.,2006**).

1.2 Absorption from Oral Cavity:

The oral cavity involves the lips, cheek, tongue, hard sense of taste, delicate sense of taste and floor of the mouth (Figure 1.1). The coating of the oral depression is alluded to as the oral mucosa, and incorporates the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue represents about 60% of the oral mucosal surface zone. The best quarter to 33% of the

oral mucosa is comprised of intently compacted epithelial cells (Figure 1.2). The essential capacity of the oral epithelium is to ensure the basic tissue against potential unsafe operators in the oral condition and from liquid misfortune. Underneath the epithelium are the basement layer, lamina propia and submucosa. The tongue comprises of a mass of interweaving packs of skeletal muscle fiber and is secured by mucosa. It is specific for controlling nourishment, general tangible gathering and the extraordinary tactile capacity of taste. The ventral surface of the tongue and floor of the mouth comprises about 16% of the oral mucosa (**Collins and Dawes 1987**).

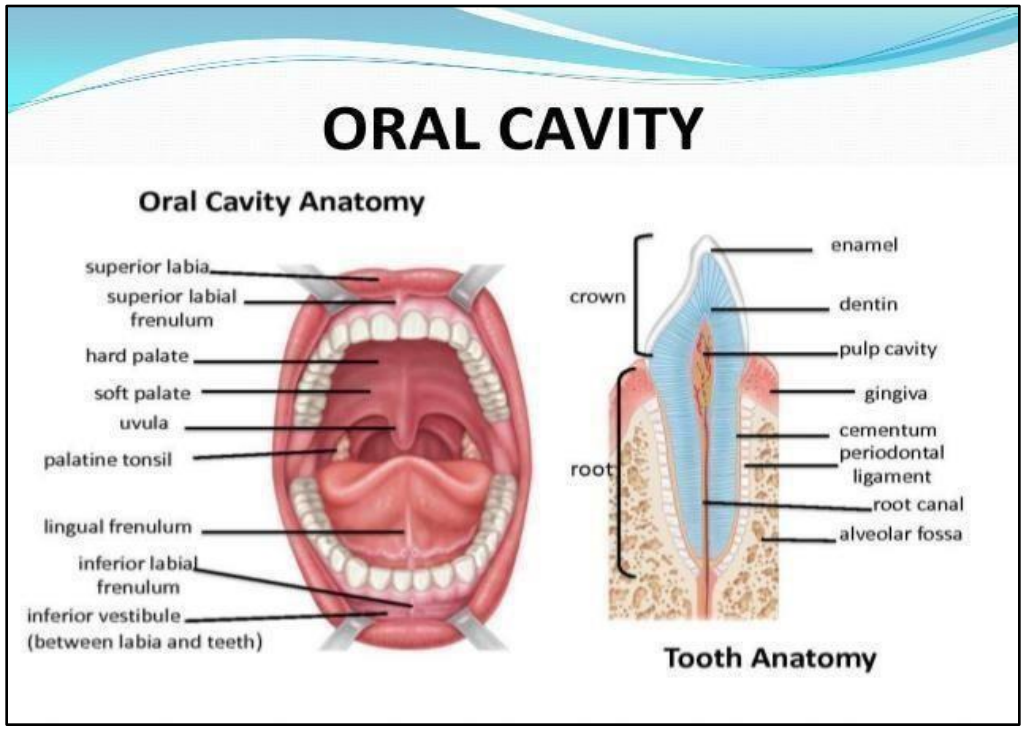


Figure 1: Anatomy of Mouth and Tooth (Oral Cavity)

Physiological Barriers for Oral Transmucosal Drug Delivery

Buccal mucosa made out of a few layers of various cells. The epithelium is like striated squamous epithelia found in rest of the body and is around 40-50 cell layers thick. Coating epithelium of buccal mucosa is the non keratinized stratified squamous epithelium that has thickness of roughly 500-600 μ and surface region of 50.2 cm2 as appeared Table 1.1 (**Patel et al. 2011; Collins 2001; Vries 1991**). Storm cellar film, lamina propria pursued by the submucosa is available underneath the epithelial layer. Lamina propia is rich with veins and vessels that open to the inward jugular vein. Lipid

investigation of buccal tissues demonstrates the nearness of phospholipids 76%, glucosphingolipid 23% and ceramide NS at 0.72%. Different lipids, for example, acyl glucosylated and ceramide like cer AH, cer AP, cer NH, Cer AS, and EOHP/NP are totally missing (Fox 1998). The earth of the oral depression introduces some noteworthy difficulties for foundational medicate conveyance. The medication should be discharged from the plan to the conveyance site (for example buccal or sublingual territory) and go through the mucosal layers to enter the fundamental dissemination. Certain physiological parts of the oral hole assume huge jobs in this procedure, including pH, liquid volume, chemical movement and the porousness of oral mucosa. [**Squier C et al.,2001**]

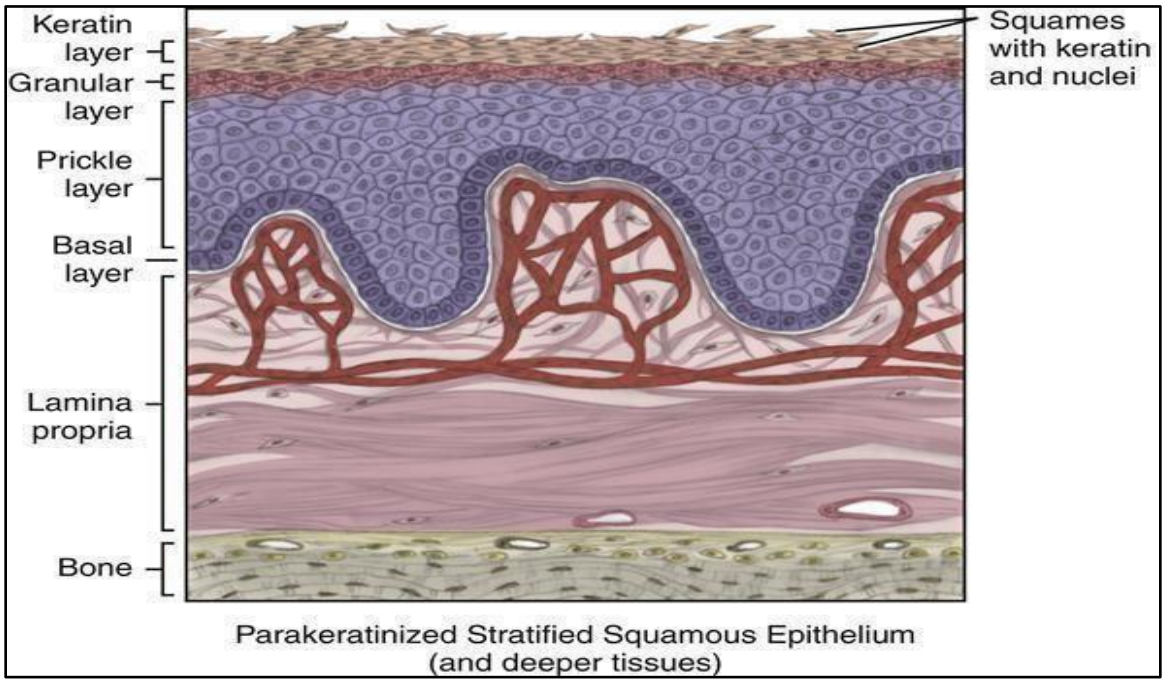


Figure 2: Structure of the oral mucosa

The oral mucosa is a squamous cell epithelium contained exceedingly multiplying basal keratinocytes which renew the overlying epithelial cells which separate and in the long run shed as the cells turn out to be increasingly shallow (Fig. 1.1). The penetrability boundary is in charge of keeping exogenous and endogenous materials from entering the body over the oral mucosa and keeps loss of liquid from the fundamental tissues to the earth. There is variety in penetrability crosswise over various locales of the oral mucosa because of the contrasting thickness of the epithelium and level of keratinisation at

various destinations. Keratinised tissues show a lower penetrability than non-keratinised tissues, this is anyway because of the lipid organization of the film covering granules in the keratinised versus non-keratinised tissues as opposed to the nearness of keratin itself. The level of porousness is least in keratinized gingiva pursued by the buccal mucosa with the most effectively saturated zone of the oral mucosa being the sublingual mucosa. [**Hernden et al.,2011**]

Table: 1 Characteristics of Oral Mucosa

Tissue	Structure	Thickness (µm)	Turn over time (days)	Surface Area (cm^2±SD)	Permeability	Blood Flow*
Buccal	NK	500-600	5-7	50±2.9	Intermediate	20.3
Sublingual	NK	100-200	20	26±4.2	Very Poor	12.2
Gingival	K	200	-	-	Poor	19.5
Palatal	K	250	24	20±1.9	Poor	7

(NK is non keratinized tissue, K is Keratinized tissue and * In rhesus monkeys (ml/min/100 g tissue).

There are three strategies for dissemination over the oral mucosa's penetrability obstruction (I) aloof dispersion including trans-cell (through cells) and para- cell (where material goes through lipid rich areas around the cells), (ii) bearer interceded transport, and (iii) endocytosis/exocytosis where material is effectively taken up and discharged by cells by means of the endocytic pathway.[**Hernden et al.,2011**]

Most investigations of buccal ingestion show that the dominating component is aloof dispersion crosswise over lipid films through either the paracellular or transcellular pathways; despite the fact that these may really be a similar pathway (figure 1.3). The hydrophilic idea of the paracellular spaces and cytoplasm gives a penetrability obstruction to lipophilic medications yet can be great for hydrophilic medications. Interestingly, the transcellular pathway includes drugs infiltrating through one cell and the following until entering the fundamental course. The lipophilic cell layer offers an ideal course for lipophilic medications contrasted with hydrophilic mixes. Medications can transverse both pathways all the while albeit one course could be overwhelming relying upon the physicochemical properties of the drug. **[Squier C et al.,2001]**

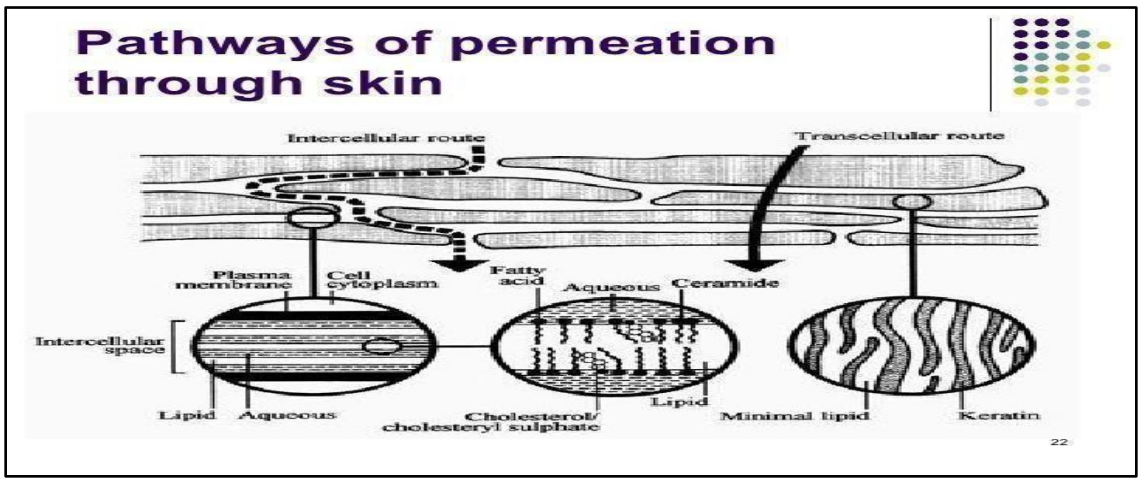


Figure 3: Pathways of Permeation through Skin Factors

Affecting Systemic Oral Mucosal Drug Delivery:

Permeability:

The oral mucosa all in all is halfway between that of the epidermis and intestinal mucosa as far as porousness. It is assessed that the porousness of the buccal mucosa is 4-4000 times more prominent than that of the skin. (Galey et al. 1976). There are extensive contrasts in penetrability between various locales of the oral hole due to the assorted structures and elements of the diverse oral mucosa. For the better assimilation of APIs in oral locale saturation enhancer assume an imperative job. So on the off chance that one needs the medication to be ingested generally from the oral pit at exactly that point there is the need of saturation enhancer. Some case of saturation enhancer are given as pursue:

- ✓ Aprotinin (Aungst BJ et al.,1988)
- ✓ 23-lauryl ether (Goodness CK et al.,1990)
- ✓ Azone (Kurosaki Y(a) et al.,1989; Kurosaki Y(b) et al.,1989)
- ✓ Benzalkonium chloride (Siegel IA(a) et al.,1985)
- ✓ Cetylpyridinium chloride (Siegel IA(b) et al.,1985)
- ✓ Dextran sulfate (Coutel-Egros An et al.,1992)
- ✓ Menthol (Goodness CK et al.,1990)

Saliva:

Saliva is the defensive liquid for every one of the tissues of the oral depression. Salivation shields the delicate tissues from scraped spot by unpleasant materials and from certain synthetic compounds. It permits the proceeding with mineralisation of the veneer of teeth after they emit and helps remineralisation of the lacquer in the beginning times of dental caries. It additionally assumes a vital antibacterial job by either helping or keeping the connection of microscopic organisms to the surfaces of the oral pit. It additionally gives an oil work which is accomplished by the nearness of the bodily fluid glycoprotein's or mucins which enable nourishment to be gulped and the development of the tissues against one another amid discourse. Up to 70% of the all out mucin found in salivation is contributed by the minor salivary organs **(Tabak et al.,1982).**

The primary job of salivary mucins is in the non-insusceptible assurance of the oral cavity by going about as an ointment, and as a particular porousness boundary against drying and different exogenous put-down. Moreover the mucins additionally assume a job in the freedom of certain microorganisms and in advancing the connection of others. Salivation is 99% water and is a mind boggling liquid containing natural and inorganic materials **(Mandel et al.,1976).** There is impressive variety between people, with time of day, stream rate of salivation and amid illness. (Tenovuo 1989) gives a point by point audit of the piece of spit. There are three noteworthy salivary organs (the parotid, sub maxillary and sublingual), which discharge spit into the oral pit. These organs are arranged far from the oral pit yet open into it by long conduits. Minor salivary or buccal organs are arranged in or ly beneath the oral mucosa. The parotid and submaxillary organs produce a watery discharge though the buccal and sublingual organs produce the fundamentally gooey spit that contains mucin with little protein the parotid and sub mandibular serous salivary organs.

Glycoproteins which structure the mucins in salivation are created solely by the sublingual and minor salivary organs. The parotid organ additionally delivers a few glycoproteins however they vary from that created in the bodily fluid organs in that they are for the most part cationic and are non-gooey in nature. There is the

potential risk that medications will tie to salivary proteins and along these lines lessen the successful grouping of medication accessible for retention. The pH of entire salivation changes somewhere in the range of 6.5 and 7.5 and will rely upon how the pH is estimated - especially whether the carbon dioxide is driven off first. The pH of salivation as it leaves the channels is distinctive to that when it is estimated in entire spit and shifts particularly relying upon the stream rate. The pH of spit as it leaves the salivary channels can be as low as 5.5 however increment to over pH 7 at high stream rates. This is chiefly because of the expansion in bicarbonate and sodium fixations which additionally happen with expanding stream. The fundamental buffering framework is the bicarbonate framework; be that as it may, phosphate and protein cradles additionally assume a job. Subsequently the ingestion of medications from the oral cavity is pH subordinate and the varieties in spit pH will impact sedate assimilation. In any case, it might be conceivable to change the pH of entire salivation or at a confined locale to advance the nearness of non ionized medication species and encourage ingestion **(Rathbone et al.,1994)**.

1.3 Introduction about Various Fast Dissolving Formulations:

Architects of medication conveyance frameworks must consider a wide range of variables including the worthiness to the patient, tranquilize discharge profile and the common sense of utilizing them. Aggravations to taste, discourse and eating must all be considered for patient agreeableness. In the event that the point is to create a self- administrable gadget this ought to be anything but difficult to control, ought to have great timeframe of realistic usability and ought to be anything but difficult to pull back on account of unfavorable impacts.

Tablet (most basic measurement structure from this course) needs to deteriorate in the gastrointestinal tract pursued by disintegration of the medication. These procedures stretch out the time until viability to some degree which is unwanted in certain conditions.

Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, visual, and oral pit) offer particular focal points over oral organization for fundamental medication conveyance. These points of interest incorporate conceivable detour of first pass impact, shirking of pre-foundational end inside the GI tract, and, low compound action. As a site for medication conveyance, intraoral course offers focal points over the ordinary gastrointestinal, parenteral and other mucosal courses of medication organization. It gives direct passage into the foundational dissemination in this way keeping away from the hepatic first pass impact, simplicity of organization and the capacity to end conveyance when required.

Intraoral drug delivery has turned into an essential course of medication organization. Different intraoral dose frames have been created, which incorporates glue tablets, gels, Treatments, patches, dissolving medication conveyance frameworks (FDDDS). A dissolving medication conveyance framework (FDDDS) is the most advantageous method of overseeing medications to conquer issues identified with gulping challenges. These conveyance frameworks break down or crumble in the mouth ly, without requiring any water to help in gulping. Disintegration inside oral depression likewise allows intra-oral assimilation, in this way bypassing first-pass impacts. FDDDS offer favorable circumstances, for example, deterioration without water, fast beginning of activity, simplicity of transportability, simplicity of taking care of, wonderful taste, and improved patient compliance.

A film or strip can be characterized as a measurements structure that utilizes a water-dissolving polymer which permits the dose structure to rapidly hydrate, follow, and break down to discharge the medication when set on the tongue or in the oral depression. They are otherwise called scattering, mouth dissolving, orally crumbling, liquefying, fast dissolving films. It enables the medication to be conveyed to the circulation system either intragastrically, buccally or sublingually. When mouth dissolving films are taken, fast assimilation of medication, through the sublingual course is conceivable, which at last prompts brisk beginning of medication action.

1.4 Fast dissolving Drug Delivery System (Film)

Late advances in Novel Medication Conveyance Framework (NDDS) means to improve security and viability of medication atom by planning an advantageous dose structure for organization and to accomplish better patient consistence. One such methodology is dissolving/deteriorating tablets and dissolving oral film develops out as a novel medication conveyance framework (**Chang 2000; Dobetti 2001**).

The idea of Dissolving Medication Conveyance Framework rose up out of the craving to give quiet a customary mean of taking their drug. Trouble in gulping (Dysphagia) is a typical issue of all age gatherings, particularly old and pediatrics, due to physiological changes related with these gatherings of patients **(Lindgren 2001)**. So dissolving film will maintains a strategic distance from the dread of gulping for the pediatric and geriatric patients.

The real downsides of MDT are dread of gulping, biting or stifling. As they are progressively friable or delicate, they require unique and costly bundling, exceptional transportation and putting away conditions. Above downsides of Mouth dissolving tablets can be overwhelmed by the methodology of growing snappy/mouth dissolving films. **(Indurwade 2002)**. All the more as of late dissolving film as an option for dissolving tablets since it certainly take out the patients dread of stifling and conquer patent obstacles. Such a significant number of Pharmaceutical organizations and customers alike have grasped oral meager film (OTFs) as a down to earth and acknowledged option in contrast to customary OTC drug structures, for example, fluids, tablets, and containers.

Oral film is the oral conveyance of the medications, was created dependent on the innovation of the transdermal fix. The conveyance framework comprises of a dainty oral strip, which is just set on the patient's tongue or any oral mucosal tissue, in a flash wet by spit; discharging the medication, which disintegrate or scatters in the salivation. A few medications are retained from the mouth, pharynx and throat as the salivation goes down into the stomach. In such cases, bioavailability of medication is altogether more prominent than traditional tablet dose structure (Biradar 2006). The film can be delivered with an assembling procedure that is focused with the assembling expenses of customary

tablets. Presently days, Numerous pharmaceutical organizations have been changing their items from ordinary strong measurement structure to dissolving advancements OTFs likewise have a built up time span of usability of 2-3years, contingent upon the Programming interface yet are very touchy to natural dampness **(Malke et al. 2007)**. Innovation Impetuses gauges the market for medication items in oral meager film definitions to be esteemed at $500 million of every 2007 and could reach $2 billion in not so distant future as indicated by Innovation Impetus **(http://www.technologycatalysts)**.

The (OTFs) place as an option in the market because of the customer's inclination for a dissolving item over customary tablets/containers. The oral dainty film innovation is still first and foremost stages and has splendid future ahead on the grounds that it satisfies all the need of patients. In the long run, film definitions having drug/s will be financially propelled utilizing the OTF innovation. In North America in excess of 80 oral slim film brands propelled since 2003, the market stays restricted when contrasted with ODTs. Anyway for future development perspective the OTF part is all around situated. In US advertise the OTC film of agony the board and movement ailment are marketed. All the more significantly, solution OTFs have now been affirmed in US, EU, and Japan which are the three noteworthy locales. These affirmed Rx films, can possibly rule over other oral measurement types of similar medications. It appears that the estimation of the general oral dainty film market will develop altogether (Orally Breaking down Tablet and Film Innovations, 2006).The advancement of oral strong measurement structure from regular to activity strong dose structure is appeared (**Siddiqui. 2011**).

Patents

Every pharmaceutical organization needs to plan the novel oral dose structure which has the higher bioavailability, speedy activity and most patient consistence so they detail the dissolving definition by utilizing superdisintigrants and hydrophilic ingredients.

Table 2: Survey of Pharmaceutical Wafers Launched in Recent Years

Trade Name	Manufacturer
Eclipse Flash Strips	Wrigley's
Cool Mint/ Fresh Burst Listerine Pocket Paks	Pfizer
Neocitran® Thin Strips™ Cough And Night time Cough	Novartis
Health Strips	Mattel/Momentus Solutions, LLC™
Thera Flu Thin Strips	Novartis
Suppress Cough Herbal	Innozen
Suppress Cough	Innozen
Chloraseptic Sore Throatrelief Strips	Prestige Brand/ Zengen(Innozen)
Ora Film Pain Relieving Strips	Apothecus Pharmaceutical Corp.
Sudafed PE™	Pfizer/Johnson & Johnson

Improved patient consistence is an essential advantage of the dissolving medication conveyance frameworks. Different advantages of dissolving film incorporate simplicity of gulping, no water fundamental for organization, and exactness of measurements. These extra, better advantages permit patients than take their medicine whenever and wherever under all conditions. The dissolving film tranquilize conveyance framework offers a mammoth jump forward in medication organization by giving another and simple method for taking prescription (**Mahajan A et al. 2011**).

Ideal Characteristics of A Drug To Be Selected: (Bhyan B 2011)

- ✓ The drug should have pleasant taste.
- ✓ The drug to be incorporated should have a low dose upto 40mg.
- ✓ The drugs with smaller and moderate molecular weight are preferable.
- ✓ The drug should have good stability and solubility in water as well as saliva.
- ✓ It should be partially unionised at the pH of oral cavity.
- ✓ It should have the ability to permeate the oral mucosal tissue.

Special features of fast dissolving films (Arya Arun et al., 2010)

- Thin elegant film.
- Available in various size and shapes.
- Unobstructive.
- Excellent mucoadhesion.
- Fast disintegration.
- Rapid release

Advantages

Fast dissolving film combines all the advantages of tablets such as accurate dose, self administration with those of liquid dosage forms like easy swallowing, bioavailability. Oral films have some special advantages over other oral dosage forms given as follows:

- Rapidly dissolved and disintegrated in the oral cavity because of large surface area which lowers dosage interval, improves onset of action, efficacy and safety profile of therapy.
- Oral films are more flexible, compliant and are not brittle as ODTS.
- Easily handled, storage and transportation.
- Accuracy in the administered dose is assured from every strip or film.
- Pharmaceutical companies and customers practically accepted OTFs as an alternative of conventional OTC dosage forms such tablets and capsules etc. (Frey, 2006).
- Oral film is desirable for patient suffering from motion sickness, dysphagia, repeated emesis and mental dis-orders.
- From commercial point of view, oral films provide new business opportunity like product differentiation, promotion etc. **(Manivannan, 2009)**

Disadvantage:

- The disadvantage of OTF is that high dose cannot be incorporated into the strip e.g. rifampin (600 mg), ethambutol (1000 mg) etc. Hence researchers have proven that the concentration level of active can be improved up to 50 percent; per dose

weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip.

- Expensive packaging of oral film.
- Dose uniformity is a technical challenge.
- Most bitter drugs should be avoided or taste masking is required.
- Proteinaceous drugs should be avoided if used then co-administration of enzyme inhibitors such as aprotinin, bestatin, puromicin and bile salts required for the inhibition of proteolytic enzymes present in saliva (http://www.gas-x.com/).

1.5 Composition of the film Formulation

Oral dissolving film is a flimsy film with a territory of 1-20 cm2 (rely upon portion and medication stacking) containing drug. Medications can be stacked up to a solitary portion of 30 mg. Detailing contemplations (plasticizers and so forth.) have been accounted for as imperative variables influencing mechanical properties of the films (**Kouji I, et al.,1987**).

Table 3 Composition of fast dissolving films

S. No.	Category	Amount (%)
1	Drug	1-30
2	Polymer	40-50
3	Plasticizer	0-20
4	Surfactant	q.s
5	Saliva Stimulating agent	2-6
6	Sweetening agent	3-6
7	Flavoring agent	0-10
8	Coloring agent	q.s
9	Stabilizer or thickening agent	0-5

A typical composition contains the following **[Saini S et 2011]**

I. Active Pharmaceutical Ingrediant 1-25%

II. Water soluble polymer 40-50%

III. Plasticizers 0-20%

IV. Fillers, colors, flavors etc. 0-40%

Active Pharmaceutical Ingredients (API)

Several classes of drugs can be formulated as oral dissolving films which includes antiulcers (e.g. omeprazole), antiasthamatics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAIDs (e.g. paracetamol, meloxicam, valdecoxib). Less bitter, potent and highly lipophilic drug should be preferred for mouth dissolving film. Most advanced research has proven that the concentration level of API per dose can extend up to 50% per dose weight. Novartis Consumer Health's Gas-X thin film has proven this by loading 62.5 mg of simethicone per thin film (**Kouji I, et al.,1987**).

The ideal characteristics of a drug to be selected are as follows-

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose generally less than 30 mg.
- The drugs with smaller and moderate molecular weight should be preferable.
- The drug has should be stable and soluble in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Polymers

The polymers can be used alone or in combination to obtain the desired film properties. The film obtained should be tough enough so that there won't be any damage while

handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation.

The various polymers to make mouth dissolving films include cellulose or cellulose derivatives, pullulan, gelatin, hydroxyl- propylmethyl cellulose hydroxyethyl cellolose, hydroxypropylmethyl cellulose, hydroxyethylcellolose, hydroxypropyl- cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, methyl methacrylate copolymer and hypromellose. Modified starches are also used for preparation. Due to low cost of natural polymers, excipients are used in combination of natural polymers to decrease the overall cost of the product. Combination of microcrystalline cellulose and maltodextrin has also been used to formulate fast dissolving films. Kulkarni et al., 2010 has explored different polymers for use in formulation of oral fast dissolving strips. Different polymers viz., HPMC E15, HPMC K4M, HPMC E5, PVP, PVA, gelatin, eudragit RL100 and pullulan were used to formulate fast dissolving films; by solvent casting method.

Ideal properties of the polymers used in the oral film

- Polymers should be non toxic and non- irritant.
- It should be non- bitter.
- Polymers should be tasteless.
- It should be devoid of leachable impurities.
- It should be inexpensive and readily available.
- It should not be an obstacle in the disintegration time.
- It should have good wetting and spreadibility property.
- It should exhibit sufficient peel, shear and tensile strength.
- It should have sufficient shelf life.
- It should not cause secondary infection in the oral cavity

Plasticizers

Plasticizer helps to improve the flexibility of the film and reduces the brittleness of the film. Plasticizer significantly improves the strip properties by reducing the glass

transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. However inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the film. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug. [Adeoti AG et 1998]

Sweetening Agents

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the fast dissolving formulations. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are also less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. The sweetness property of most of the polyols is less than half of that of sucrose except xylitol and mannitol which have similar sweetness as that of sucrose (scale of 0.8–1.0).

However, it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients. The flavor quality of these artificial sweeteners is different than the natural sweeteners and may not be acceptable to the patients who are accustomed to the natural sugars. The amalgamation of sweeteners may lead to synergism and improvement in the taste of the formulations. Aspartame was used for the preparation of oral strips of valdecoxib. For the oral strip of piroxicam, maltodextrin was employed as sweetening agent. Generally

sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.[Adeoti AG et 1998]

Table 4 Artificial sweeteners

First Generation	Second Generation
Saccharin	Acesulfame-K
Cyclamate	Sucralose
Aspartame	Alitame

1.6 Saliva Stimulating Agent:

More saliva production helps in the faster disintegration of the fast dissoving film formulations so the formulations may contain acids which are used in the preparation of food as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them (Israel and Leo 1989). These agents are used alone or in combination between 2 to 6%w/w of weight of the strip. Other film ingredients such as sweeteners also act as salivary stimulants. Food grade sugars as well as synthetic sugars are useful salivary stimulants along with acidulents. Glucose, fructose, xylose, maltose, lactose are few examples of such sweeteners (Chapdelaine et al.,2004).

Flavour

Perception for the flavours changes from individual to individual depending upon the ethnicity and liking. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. The selection of flavor is also dependant on the type of drug to be incorporated in the formulation. For example, mint flavor is generally added in products used for gastric related ailments like indigestion.

Flavouring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the flavor type and its strength. Preferably up to 10%w/w flavors are added in the film formulations.

Color

Pigments such as titanium dioxide or a full range of colors are available, including FD&C colors, EU Colours, Natural Colours and custom Pantone-matched colours (Chapdelaine et al.,2004).

Stabilizing and Thickening Agents

The stabilizing and thickening agents are employed to improve the viscosity and consistency of dispersion or solution of the strip preparation solution or suspension before casting. Natural gums like xanthan gum, locust bean gum, carragenan and cellulosic derivatives can be used in the concentration up to 5%w/w as thickening agents and stabilizing agents.

Method of Preparation

One or more of the following process can be used to manufacture the fast dissolving films-

1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Rolling methods

Solvent Casting Method

Fast dissolving buccal films are preferably formulated using the solvent casting method, whereby the water soluble ingredients are dissolved to form a clear viscous

solution and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried. (Instrumentation of Solvent Casting Method show below in Fig. 1.2

Advantages

- Better uniformity of thickness and better clarity than extrusion.
- Film has fine gloss and freedom from defects such as die lines.
- Film has more flexibility and better physical properties.
- The preferred finished film thickness is typically 12-100 µm, although various thicknesses are possible to meet API loading and dissolution needs.

Disadvantages

- The polymer must be soluble in a volatile solvent or water.
- A stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.

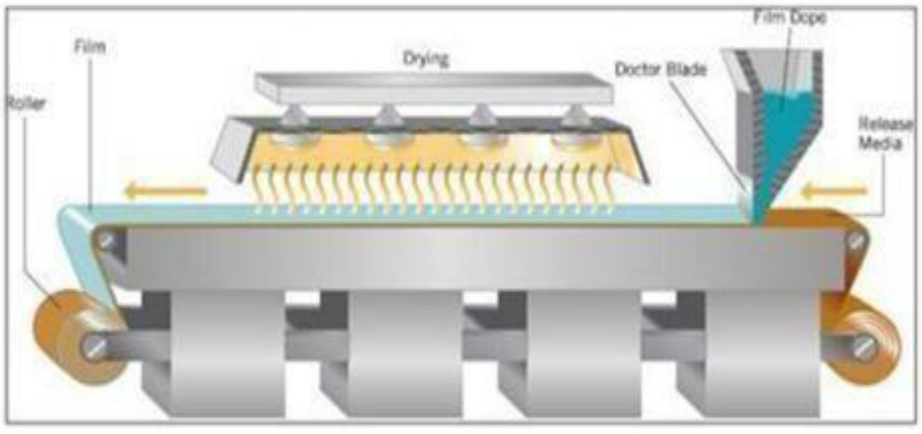


Fig. 4: Solvent Casting Method

In this method, solution of water soluble film forming polymer is mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate and cellulose acetate butyrate). After sonication, it is coated on non- treated casting film. On drying the thickness of the film should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

Hot Melt Extrusion

In this method the polymers which have low molecular weight and low viscosity are preferred. Drug is mixed with the carrier in the solid form so that granular material is formed. These granules are then dried and then introduced into the extruder. The speed of the screw should be around 15rpm so that the granules reside inside the extruder for about 3-4min. The processing temperatures should be 80°C (zone1), 115°C (zone 2), 100°C (zone 3), and 65°C (zone 4). The extrudate (T= 65°C) then pressed into a cylindrical calendar to obtain a film. (Instrumentation of Hot Melt Extrusion show below in Fig. 1.3)

Advantages

- Without use of any solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Better alternative for poorly soluble drugs.
- More uniform dispersion because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages

- Thermal degradation due to use of high temperature.
- Flow properties of the polymer are essential to processing.
- Limited number of available polymers.
- All excipients must be devoid of water or any other volatile solvent.

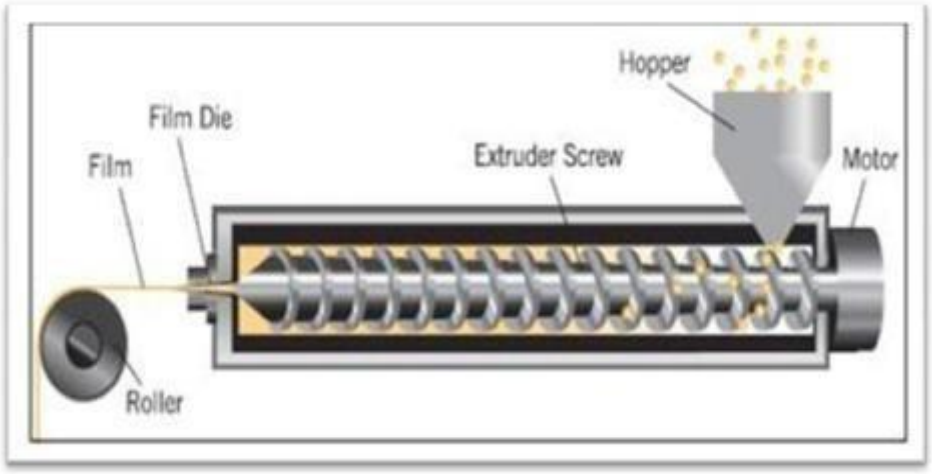


Figure 5: Hot Melt Extrusion

Rolling Method

In rolling method, a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes. Other ingredients including active agent are dissolved in small portion of aqueous solvent using high shear processor. Water soluble hydrocolloids dissolved in water to form homogenous viscous solution. (Instrumentation of Three Roll Coating Unit show below in Fig. 1.4)

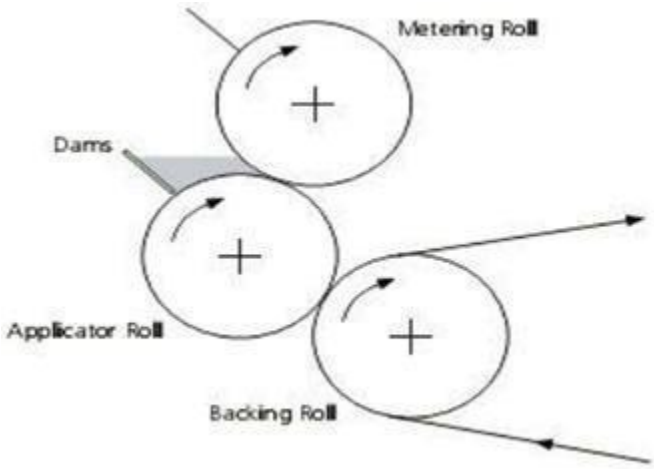


Figure 6: Rolling Method

1.7 Solid Dispersion Extrusion

The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Drug is dissolved in a suitable liquid solvent. Then solution is incorporated into the melt of PEG, obtainable below 700C. Finally the solid dispersions are shaped into the films by means of dies.

Technologies

SOLULEAVES™ technology is used to produce a range of oral delivery films that can incorporate active ingredients, colours and flavours. SOLULEAVES™ films can be designed to dissolve rapidly on contact with saliva, ly releasing the active ingredients and flavours. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses this method of administration is especially useful for paediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as delivering nutritional products. SOLULEAVES™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 minutes.

WAFERTAB™ is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The WAFERTAB™ filmstrip can be flavoured for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a pre-manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The WAFERTAB™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. WAFERTAB™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release, or for use by patients who have difficulty swallowing.

FOAMBURST™ is a special variant of the SOLULEAVES™ technology where an inert gas is passed into the film during production. This results in a film with ahoneycombed structure, which dissolves rapidly giving a novel mouth sensation. FOAMBURST™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavours.

XGEL™ film is at the heart of Meldex International's intellectual property, used in all its film systems and its ingestible dosage delivery technologies. XGEL™ film provides unique product benefits for healthcare and pharmaceutical products: it is non animal-derived, approved on religious grounds and is suitable for vegetarians; the film is GO free and continuous production processing provides an economic and competitive n economic and competitive manufacturing platform. XGEL™ film can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate APIs. The XGEL™ film systems can be made to encapsulate any oral dosage form, and can be soluble in either cold or hot water. XGEL™ film is comprised of a range of different water-soluble polymers, specifically optimised for the intended use.use.(Chandrika K. Mani et al., 2014).

Table 5: Recent patents on fast dissolving strips/films

Title	Patent number	Inventor	Issued	Assignee
Water soluble film for oral administration with instant wettability	5,948,430	Zerbe *et al.*	Sep 7, 1999	LTS Lohman Therapie-systeme GmbH
Bioerodable films for delivery of pharmaceutical compounds to mucosal surface	6159498	Tapolsky *et al.*	Dec 12, 2000	-
Fast dissolving orally consumable films containing sweetner	2003/0211136	Lori *et al.*	Nov 13, 2003	Warner Lambert company LLC
Fast dissolving films for oral administration of drug	2004/0208931	Friend *et al.*	Oct 21, 2004	William Squire, Esq.
Fast dissolving consumable films containing a modified starch for improved heat and moisture resistance	2004/0247648	David *et al.*	Dec 9, 2004	Pfizer, Inc.
Fast dissolving orally consumable films	7,025,983	Leung *et al.*	April 11, 2006	Warner Lambert company LLC
Dissolving thin film xanthone supplement	7182964B2	Kupper *et al.*	Feb 27, 2007	-
Thin film strips	7,241,411	Berry *et al.*	Jul 10, 2007	Acupac packaging, Inc.
Disintegratable films for diagnostic devices	7,470,397	Meathrel *et al.*	Dec 30, 2008	Adhesive research, Inc.
Pharmaceutical carrier devices suitable for delivery of pharmaceutical compounds to mucosal surface	7579019B2	Tapolsky *et al.*	Aug 25, 2009	-
Film comprising nitroglycerin	20100215774	Maibach and Todd	Aug. 26, 2010	-
Dissolvable tobacco film strips and method of making the same	7946296B2	Wern *et al.*	May 24, 2011	-

LTS: Lohman therapie-systeme

Table 6: List of some marketed products available as fast dissolving strips

Product	API	Manufacturer	Use
Listerine®	Cool mint	Pfizer, Inc.	Mouth ulcer
Benadryl	Diphenyhydramine HCL	Pfizer	Antiallergic
Suppress®	Menthol	InnoZen®, Inc.	Cough suppressant
Klonopin wafers	Clonazepam	Solvay pharmaceuticals	Antianxiety
Theraflu	Dextormethorphan	Novartis	Antiallergic
Orajel	Menthol/pectin	Del	Mouth freshner
Gas-X	Simethicone	Novartis	Antiflatuating
Chloraseptic	Benzocain/menthol	Prestige	Sore throat
Sudafed PE	Phenylepinephrine	Wolters Kluwer Health, Inc.	Congestion
Triaminic	Diphenhydramine	Novartis	Antiallergic

API: Active pharmaceutical ingredient, PE: Polyethylene

Angina Pectoris:

Angina pectoris or angina is temporary chest pain or discomfort as a result of decreased blood flow to the heart muscle. Angina is not a heart attack, but it is a sign of increased risk for heart attack. Angina may be stable (develops during physical activity and lasts five minutes or less) or unstable (occurs during periods of rest, lasts longer and symptoms may be more severe). Your doctor may perform an electrocardiogram (ECG), a stress test without imaging or blood tests to help diagnose your condition. Additionally, chest x-ray, chest CT, coronary CT angiography, cardiac MRI, coronary angiography, echocardiogram or stress test with imaging may be performed. Your physician may treat your condition by recommending certain lifestyle changes. Other treatment options may include medication, surgery, or angioplasty and vascular stenting.

What is angina pectoris?

Angina pectoris, or just angina, is temporary chest pain or discomfort caused by decreased blood flow to the heart muscle. Because of the decreased flow of blood, there is not enough oxygen to the heart muscle resulting in chest pain. Coronary artery disease , which can result in narrowing of the coronary arteries that carry blood and oxygen to the heart muscle, is one of the most common causes of angina. While angina is not a heart attack, it does signal an increased risk for a heart attack. Seek immediate medical attention if you experience any chest pain or discomfort.

There are two main types of angina—stable and unstable. Stable angina, the most common type, develops during physical activity and usually lasts a short time (approximately five minutes or less) if the physical activity has ended. Unstable angina is less common and usually occurs during periods of rest. Unstable angina usually lasts longer and symptoms may be more severe.

Symptoms of Angina Include:

- Chest pain or discomfort, such as tightening of the chest
- Discomfort in the jaw, neck, arms, upper abdomen, shoulder or back
- Fatigue
- Sweating
- Nausea
- Dizziness
- There are many risk factors associated with angina including, but not limited to, high blood pressure, diabetes, obesity, family history, tobacco use, stress and age.

How is angina pectoris diagnosed and evaluated?

In order to diagnose the cause of angina, the following tests may be performed:

Stress test without imaging: This heart-monitoring test is used to help evaluate how well the heart performs with activity. During a stress test, you will usually be asked to perform physical exercise, like walking on a treadmill. An ECG is recorded during the period of exercise. The ECG is assessed by your doctor to see if your heart reached an appropriate heart rate and if there were any changes to suggest decreased blood flow to your heart. If you are unable to perform exercise, pharmaceuticals that mimic the heart‘s response to exercise may be used.

Blood Tests: The tests can identify certain enzymes such as troponin that leak into the blood after your heart has suffered severe angina or a heart attack. Blood tests can also identify elevated cholesterol, LDL and triglycerides that place you at higher risk for coronary artery disease and therefore angina.

Additionally, the following imaging tests may be performed:

Chest x-ray: This noninvasive imaging test helps your doctor rule out other sources of chest pain such as pneumonia. Imaging with x-rays involves exposing the chest to a small dose of radiation to produce pictures of the chest and heart. See the Safety page for more information about x-rays.

CT of the chest: Chest CT is a more sensitive test than chest x-ray that can identify other causes of chest pain such as aortic disease or blood clots in the blood vessels of the lungs. This imaging test combines special x-ray equipment with sophisticated computers to produce multiple images of the chest and heart. See the Safety page for more information about x-rays.

Coronary computed tomography (CT) angiography: This imaging test can determine if plaque buildup has narrowed the coronary arteries and resulted in decreased blood flow to the heart, without the need for a catheter feed through the arteries into the heart. Contrast material is injected through a small line in the arm vein, similar to the ones used to draw blood.

Magnetic resonance (MR) imaging/angiography: This exam is usually performed with contrast Magnetic resonance (MR) imaging/angiography: This exam is usually performed with contrast material. The primary purpose of this exam is to determine whether there is good blood flow to the heart muscle. If there are areas with decreased blood flow, this could indicate plaque with blood vessel narrowing. This blood flow evaluation may be done twice during the exam. The first time may be performed after the administration of a pharmaceutical, which stresses the heart like exercise. The second time will be at rest. Performing the evaluation both with stress and rest helps determine if the decreased blood flow only occurs with exercise. The coronary arteries

(blood vessels that supply blood and oxygen to the heart) can also be imaged similar to CT angiography to look for any plaque buildup, which may result in narrowing of the blood vessels. MRI machines use a powerful magnetic field, radio waves and a computer to produce detailed images. See the Safety page for more information about MRI.

Catheter angiography: In this invasive imaging test, a thin, long plastic tube, called a catheter, is inserted into an artery in your groin using a needle. The catheter is guided with a wire into the coronary arteries and is used to inject contrast material directly into the coronary arteries to determine whether there is any narrowing of the blood vessels. Images of the contrast material in the blood vessels are captured using x-rays.

Echocardiogram: During this test, a transducer that produces high-frequency sound waves is used to create moving images of the heart. The motion of the walls of the heart is evaluated. If there is decreased motion within a portion of the wall of the heart, this could indicate decreased blood flow from narrowing of the coronary artery. An echo contrast material, which is a fluid with very tiny bubbles, may be injected in a vein of your arm to see if there is decreased blood flow to any area of your heart.

Stress Test with Imaging: Imaging may be performed with a nuclear medicine tracer, echocardiography, CT or MRI. During an imaging stress test, the patient is usually asked to perform some kind of physical exercise like walking on a treadmill. If the patient is unable to perform exercise for any reason, drugs that mimic the heart‘s response to exercise may be used. If nuclear medicine is used for imaging, a radioactive tracer will be injected into the blood during the peak of exercise and images of the heart will be taken. The radioactive tracer flows with the blood and will show whether there is an area of the heart with decreased blood flow. During echocardiography, you will be asked to stop and lie down on a table during the peak of exercise so the wall of the heart can be imaged. The physician will look for any area that does not move well, which may indicate decreased blood flow from narrowing in the coronary artery. MRI stress testing is performed similar to MR angiography.

How is angina pectoris treated?

Many doctors may first recommend certain lifestyle changes such as maintaining a healthy weight, consuming a balanced diet low in fats, discontinuing the use of tobacco products and finding ways to reduce stress **(http://www.radiologyinfo.org.)**

Other Treatments Options Include:

- Medication: Various medications can be recommended or prescribed such as aspirin, statins,
- Medication: Various medications can be recommended or prescribed such as aspirin, statins, beta-blockers, calcium channel blockers, or nitrates.
- Angioplasty and vascular stenting: This procedure, which uses balloons and/or stents, is performed to open the blockage in the coronary arteries and improve blood flow to the heart.
- Coronary artery bypass graft surgery (CABG): This surgery increases blood flow to the heart by using a vein, or an artery from elsewhere in the body to divert blood flow around the area of narrowing or blockage in the coronary arteries of the heart.

Needs:

The need for fast dissolving drug delivery system continues due to patient‘s poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

The current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of poorly absorbed drugs. Key issues facing the biopharma industry are to improve safety and efficacy for organ targeting, and improved compliance via sustained release or easy to swallow dosage forms.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. The most popular solid dosage forms are tablets and capsules; important drawback of these dosage forms for some patients is the difficulty to swallow **(Indurwade 2002)**.

Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablets when water is not available as in the case of motion sickness (kinetosis) and sudden episodes of coughing during common cold, allergic conditions and bronchitis. For these reasons, rapidly dissolving oral dosage form which can rapidly dissolve or disintegrate in the oral cavity has attracted a great deal of attention. Rapidly dissolving or disintegrating tablets films are not only indicated for people who have swallowing difficulties, but also are ideal for active people **(Yonezawa1999).**

Recently in pharmaceutical industry pediatric and geriatric be considered as a separate and unique medicare population. Thus fast dissolving drug delivery systems are gaining more demand and popularity from last few years **(Yeola 2000).**

Pharmaceutical marketing is another reason for the increase in available fast-dissolving products. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, fast-dissolving/disintegrating tablet formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient population.

REVIEW OF LITERATURE

Many articles have been published in various reputed journals on mouth dissolving films. Some of the important articles. I have reviewed for method development for my project and all the articles are described below to understand the critical point for preparation of mouth dissolving film formulation.

- **Mashru et al. (2005)** prepared fast dissolving films for sublingual route containing salbutamol sulphate and polyvinyl alcohol as polymer. The films were evaluated for mechanical properties, in vitro release study and morphology study. A 33 factorial design was applied to study the effect of polyvinyl alcohol, glycerine and mannitol on % drug release and mechanical properties of the films. It was observed that polyvinyl alcohol had positive effect on tensile strength and mannitol had negative effect on tensile strength. Mannitol produced positive effect on drug release where as polyvinyl alcohol produced negative effect on drug release.

- **Onishi et al. (2005)** developed novel mucoadhesive patch of diazepam to achieve its rapid absorption for the emergency treatment of epileptic seizure or anxiety disorder. The patch consisted of outer mucoadhesive region of carbopol 934, central drug region and tegaderm as backing layer. Diazepam was dissolved in propylene glycol alone or propylene glycol containing oleic acid at 5.6%w/w.

- **Chen et al. (2006)** formulated fast dissolving films using water soluble polymers for achieving rapid disintegration, good mouth feel and mechanical properties. Desired fast disintegration and mechanical properties could be tailored with polyethylene oxide and HPMC. Films had good mouth feel and no sticky feeling. Film strength of films containing PEO and HPMC ranged between 3000 kg/m2 to 17000 kg/m2. Increase in glycerin content resulted in marked decrease in film strength.

- **Chen et al (2006)** was carried out a Study to determine the dissolution rates based on disintegration and total dissolution time of the oral films by mouth and by visual method. Films were prepared by solvent casting method using various film forming polymers such as HPMC E3 ,HPMC K3; HPMC A3, A5, A6 and A15 ; and

POLYOX N10, N80, N750 and 205. Films were evaluated for mechanical properties, effect of molecular weight on disintegration and dissolution time and effect of plasticizer concentration on tensile strength. The in vitro dissolution study showed that the disintegration rate of polymers was decreased by increasing the molecular weight of the polymer film bases.

- **Ali and Anisul (2007)** examined high molecular weight povidone K-90 polymer as a film forming excipient for fast dissolving drug delivery applications. It was evaluated in combination with povidone K-30 and other kollidon SR polymers. Fast dissolving films suitable for delivery of highly potent drugs and vitamins could be formulated using the polymer povidone K 90 with auxiliary polymers. K-90 films with increased amount of polyvinyl acetate and acrylic acid based kollidon SR and MAE 100P respectively showed significant flexibility and elongation. Increased amount of K-30 and kollidon VA 64 showed good flexibility. All films were highly hydrophilic and dissolved in 60 s or less except K90/kollicoat MAE 100P which dissolves in 6-7 min.

- **Sharma et al. (2007)** was made an attempt to develop taste masked films of Valdecoxib using Eudragit EPO (5, 10, 15% w/v), Hydroxy propyl methylcellulose (1, 2, 3% w/v) and combination of Eudragit EPO/HPMC (500:300mg and 800:300mg) by solvent casting method. Films were evaluated for hydration study, folding endurance and in-vitro dissolution study. Glycerol played a critical role in imparting flexibility, improving the drug release from the film. Water uptake by films was found to be dependent both on the amount of Eudragit EPO and glycerol. Films containing higher proportion of glycerol showed higher water uptake and faster drug release. Optimum plasticity was obtained using the required concentration of HPMC and glycerol.

- **Bhise (2008)** Studied carried out to prepare taste masked effervescent and dispersible tablet of Diphenhydramine Hydrochloride (DPH) using cation exchange resins Indion 234 and Tulsion 343. The drug resin complexes (DRC) were prepared by batch process by taking drug: resin ratios 1:1, 1:2, and 1:3. The drug resinates were

evaluated for the drug content, taste, micromeritic properties, drug release and X-ray diffraction. Effervescent and dispersible tablets were developed from optimum drug: resin ratio of 1:2 and 1:1. The formulations were evaluated for uniformity of dispersion, disintegration time, and in vitro dissolution. The taste evaluation depicted the successful taste masking of DPH with drug resin complexes. The drug release of 95% in 15 min was observed for effervescent and dispersible tablets.

- **Cilurzo et al. (2008)** studied maltodextrins with a low dextrose equivalent as a film forming material and its application in the design of fast dissolving films of piroxicam. The effect of plasticizer concentration was studied on the mechanical property of the film. Flexible films were obtained by using 16-20 % w/w glycerin. It was observed that microcrystalline cellulose decreased film ductility and affected in-vitro and in-vivo film disintegration. The dissolution rate of piroxicam was significantly improved in films prepared by casting and solvent evaporation independently of piroxicam to maltodextrin ratio.

- **Mishra et al. (2009)** developed a taste-masked rapid dissolving film of Cetirizine hydrochloride. Low viscosity grades of Hydroxypropylmethyl cellulose (E3, E5, El5) in a concentration range of 1-4% were used as film-forming polymers, and solvent casting was selected as the manufacturing method. RDFs containing taste-masked CTZ showed acceptable properties such as tensile strength, elasticity, percentage elongation, in vitro disintegration, and in vitro dissolution characteristics. The RDFs were transparent, without any air entrapment. The drug-release profiles indicated that it could be used for the oral delivery of CTZ in chronic and acute urticaria as well as perennial rhinitis.

- **M. Nishimura et al. (2009)** developed Oral disintegrating film containing prochlorperazine, a dopamine D2 receptor antagonist with anti-emetic property, using microcrystalline cellulose, polyethlene glycol and hydroxypropylmethyl cellulose as the bases. The film showed an excellent stability at least for 8 weeks when stored at 40 ◦C and 75% in humidity. The dissolution test revealed a rapid

disintegration property, in which most of prochlorperazine dissolved within 2 min after insertion into the medium. These findings suggest that the prochlorperazine-containing oral film is potentially useful to control emesis induced by anti-cancer agents or opioid analgesics in patients who limit the oral intake.

- **Bukka et al. (2010)** worked to prepare and evaluate a buccal film for intraoral delivery of Rasagiline. Formulations were prepared using 32 full factorial design to explore the effects of carbopol P 940 and sodium alginate (as independent variables) on mucoadhesive strength and drug release (as dependent variables). The Rasagiline release was decreased with increase in both the polymers. Carbopol has more pronounced effect than sodium alginate on the mucoadhesive strength. The experimented values are in good agreement with expected values for the optimized formulation which demonstrate the feasibility of the model in the development of buccal film.

- **Dahima R et al. (2010)** made an attempt to develop the taste masked orodispersible tablet of metoclopramide hydrochloride using ion exchange resin Indion 204. The effects of variables were observed on maximum amount of the drug loading. Resinate was evaluated for taste masking, characterized by differential scanning calorimeter and infra red spectrometer. In vitro drug release study of taste masked tablet showed that more than 85 % of the drug released within 10 minutes. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

- **Dhere P.M et al. (2011)** studied that recent modification are done in the conventional tablet to avoid the acceptance problem of paediatrics, psychotics and bed ridden patient by improving disintegration capacity of formulation on that basis researcher prepare fast dissolving tablet by using super disintegrant on behalf of that patient having chocking problem, they prepare oral disintegrating film/ wafer for quick release of drug within few second. Without need of water formulation takes place in any condition like travelling or other emergency conditions. These are the

formulation having thin film and larger surface area which is easily dissolves in the mouth saliva. API containing formulation having avoided first pass metabolism effect this is easily given by (ODF) preparation.

- **Ammanage et al. (2011)** studied that dicyclomine hydrochloride is anticholinergic drug used as an antispasmodic. It is very bitter in taste. The purpose of this research was to develop a bitterless oral disintegrating tablet of Dicyclomine hydrochloride. Taste masking was done by complexing Dicyclomine hydrochloride with Eudragit E-100. Drug polymer complexes were prepared in the ratio 1:1, 1:2 and 1:3 by solvent evaporation method and 1:3 ratio was selected which shows least drug release in SSF (4.9 ± 0.31%). Three superdisintegrants were used while preparing the tablets e.g. crosscarmellose sodium, sodium starch glycolate and crospovidone. The tablets were evaluated for different parameters like thickness, weight variation, hardness, friability, disintegration time, in vitro dispersion time, wetting time and drug content uniformity for tablets was found to be within the official limits. Tablets that were formulated by direct compression method using Crospovidone (6%) i.e. optimized formulation F9 exhibited quicker disintegration of tablets than compared to those of Crosscarmellose sodium and Sodium starch glycolate.

- **Gupta et al. (2011)** studied that Dicyclomine HCL is an antispasmodic drug which is widely used in treatment of smooth muscle spasm of the gastrointestinal tract but it undergoes to first pass Metabolism. So that to develop mouth-dissolving tablet of Dicyclomine HCL to avoid first pass metabolism and increase bioavailability. This offers a new range of product having desired characteristics and intended benefits. In this study, the mouth dissolving tablets were prepared using direct compression method. Tablets produced by direct compression method contain D-Mannitol as diluent, crospovidone as a superdisintegrant and aspartame as a sweetener. The dissolution study was performed on PBS 6.8 (salivary pH) and the In-vitro release was found 99.80% without leaving residue for F6 Batch. Moreover the drug release was found to be comparable to the marketed tablet.

- **Sapkal NP. et al., (2011)** have developed fast dissolving oral thin films of ambroxol hydrochloride a mucolytic agent, and investigated the effect of the formulation variables like concentration of film forming polymer, emulsifying agent and plasticizer on the physico chemical properties and in vitro dissolution studies. Hydroxylpropyl methylcellulose was used as a film former, Tween 80 as an emulsifying agent and polyethylene glycol (PEG) 4000 as a plasticizer. These three variables were studied at two levels thus, a 23 full factorial design was applied and eight different formulations were developed by solvent casting method and evaluated. The film that contained HPMC (15 mg /film i.e. 2x3 cm2) in low levels and Tween 80 (5 mg/film i.e. 2x3 cm2) and PEG 4000 (8 mg/film i.e. 2x3 cm2) in high levels was found to be suitable for film formation with desirable physicochemical properties, faster disintegration and optimum in vitro release.

- **Gupta MM. et al., (2011)** have enhanced the dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of Meclizine hydrochloride with þ-cyclodextrine. The fast dissolving films were prepared by solvent casting method using Methocel E-5 as a primary film former. Meclizine HCl, a poorly water soluble and bitter drug could be successfully incorporated in the fast dissolving films with the help of solubilizers such as þ-Cyclodextrine and PEG-400. The fast dissolving films had suitable appearance, mechanical strength, peelability and disintegration time.

- **Nishigaki et al. (2012)** developed a fast dissolving oral film containing 4 mg dexamethasone and examined the clinical effect of the film as the antiemetic by a randomized controlled crossover study in breast cancer patients receiving a combination chemotherapy with anthracycline and cyclophosphamide, a highly emetogenic chemotherapy. The film was prepared as reported previously using microcrystalline cellulose, polyethylene glycol, hypromellose, polysorbate 80 and 5% low substituted hydroxypropylcellulose as base materials. Patients were administered with 8 mg dexamethasone as oral film or tablet on days 2–4 after chemotherapy in addition to the standard antiemetic medication. The rates of

complete protection from vomiting during acute and delayed phases were not different between film-treated group and tablet-treated group. The time course of the complete protection from nausea or vomiting during 0–120 h was also similar between the two groups. Patient‘s impressions on the oral acceptability in respect of the taste and ease in taking were significantly better for film than for tablet.

- **Shelke PV. et al., (2012)** have developed a rapidly disintegrating film of psychostimulant drug Amlodipine besylate using sodium alginate as film forming polymer and sodium starch glycolate as disintegrating agent. Aspartame was used as the taste masking agent to mask the bitter taste of the drug. Glycerine was used as a plasticizer. Solvent casting method was used as the method of preparation. A full 32 design was applied to study the effect of independent variables (conc. of sodium alginate and conc. of sodium starch glycolate) on the dependent variable (disintegration time and % cumulative drug release after 6 min). Response surface plots showed that the % cumulative drug release after 6 minutes inversely proportional to the concentration of sodium alginate and directly proportional to concentration of sodium starch glycolate. The disintegration time is inversely proportional to concentration of SSG and directly proportional to concentration of sodium alginate. It was concluded that the fast dissolving strips of amlodipine besylate can be made by solvent casting technique with enhanced dissolution rate, taste masking, and hence better patient compliance and effective therapy.

- **Buchi N Nalluri et al., (2013)** formulating mouth dissolving films (MDFs) of the anti-asthmatic drug, Salbutamol Sulfate (SAL) to enhance convenience and compliance to the elderly and pediatric patients for better therapeutic efficacy. Film former, Hydroxy propyl Methylcellulose (HPMC) of different viscosity grades along with film modifier/solubilizing agents, polyvinyl pyrrolidone K30 (PVP K30) and sodium lauryl sulphate (SLS) were used to formulate MDFs. The MDFs were prepared by wet film applicator technique and were evaluated for in vitro dissolution characteristics, in vitro disintegration time, and their physico- mechanical properties. MDFs with 13% (w/w) of HPMC E5 gave better dissolution properties when

compared to HPMC E15.MDFs with 0.04% (w/w) of SLS gave superior dissolution properties when compared to MDFs without SLS. MDFs with 0.04% (w/w) PVP did not peel off from glass plate and hence were excluded from study.

- **Sumedha Bansal et al., (2013)** formulated a fast dissolving film of Losartan potassium films of were prepared by solvent casting method using polymers such as PVA and Maltodextrin in different ratios. Propylene glycol was used as a plasticizer. Films were subjected to physicochemical characterization such as thickness, weight uniformity, folding endurance, drug content, surface pH study, in vitro drug release, ex vivo permeation study and stability studies. The in-vitro drug release in optimized formulation F8 was found to be 78.62 % in 4 min. The optimized formulation F8 also showed satisfactory pH, drug content (97.12%),), ex vivo permeation (89.42%), effective in vitro drug release (98.99% in 10min), disintegration time of 24 seconds and satisfactory stability.

- **Buchi N. Nalluri et al., (2013)** formulating mouth dissolving films (MDFs) Sumatriptan Succinate (SUM) Film former, Hydroxy Propyl Methyl Cellulose along with film modifier/solubilizing agents, Polyvinyl pyrrolidone K30 (PVP K30) and Sodium Lauryl Sulphate (SLS) were used to formulate MDFs. The MDFs were prepared by wet film applicator technique and were evaluated for in- vitro dissolution characteristics, in vitro disintegration time, and their physico- mechanical properties. MDFs with 13% (w/w) of HPMC E5 gave better dissolution properties when compared to HPMC E15. MDFs with PVP K30and SLS gave superior dissolution properties when compared to MDFs without PVP K30 and SLS. The dissolution properties of MDFs with PVP K30 were superior when compared to MDFs with SLS.

- **H.D. Karen et al.,(2013)** developed Loratadine mouth dissolving films using HPMC E15 LV PREMIUM as film forming polymer, glycerin as am plasticizer and tween 80 as a surfactant. The strips were evaluated for thickness, tensile strength, % elongation, disintegration time and in vitro drug release. A trial and error approach

was used in present study for optimization. Oral strip containing HPMC E15 LV PREMIUM (190mg), tween 80 (15% of polymer) and glycerin (20% of polymer) has given the maximum in vitro drug release and imparts good transparency. A satisfactory result in the strip was exhibited in the way of in vitro release that came in 20 minutes. The drug excipients compatibility study showed that there were no interaction between drug and excipients. Stability study of the optimized formulation showed that the strips were stable at accelerated environmental conditions.

- **K. M. Mageshwari et al.., (2014)** formulated mouth dissolving films (MDFs) of Amlodipine Besylate(AMLO) using Film formers like hydroxy propyl methyl cellulose (HPMC) and methyl cellulose (MC) along with film modifiers like poly vinyl pyrrolidone K30(PVP K30), and sodium lauryl sulphate (SLS) as solubilizing agents were evaluated. The prepared MDFs were evaluated for in vitro dissolution characteristics, in vitro disintegration time, and their physico mechanical properties. All the prepared MDFs showed good mechanical properties like tensile strength, folding endurance, and % elongation. MDFs were evaluated by means of FTIR, SEM, and X-RD studies. MDFs with 7.5% (w/w) of HPMC E3 gave better dissolution properties when compared to HPMC E5, HPMC E15, and MC. Release kinetics data reveals diffusion is the release mechanism.

- **Ravi Kumar K and Mercy Sulochana M (2014**) formulated Lercanidipine hydrochloride fast dissolving films using polymers like HPMC E15, PVA as polymers and sodium starch glycolate, crospovidone as superdisintegrants by solvent casting method. Formulation HF2 with HPMC E15 and crospovidone is considered as the optimized formulation as it showed faster disintegration rate (28sec), maximum in vitro drug release i.e., 98.84% within 10mins. No significant changes were observed during stability studies for the optimized formulation. It was concluded that Lercanidipine hydrochloride fast dissolving oral films can be formulated as a potentially useful tool for an effective treatment of hypertension and management of angina pectoris with improved bioavailability, rapid onset of action and with increased patient compliance.

- **Desai V and Shah N (2014**) formulated mouth dissolving films of Olmesartan Medoxomil, prepared by solvent casting technique. Film made up of different polymers but combination of HPMC E15 and PVA was optimized as final formulation. The prepared films were evaluated for organoleptic evaluations, film weight, thickness, folding endurance, tensile strength, drug content uniformity of films, surface PH disintegration time and in-vitro dissolution studies.

- **Upreti K et al., (2014)** formulated mouth dissolving films of paracetamol were prepared by solvent casting method, using polymer like (hydroxy propyl methyl cellulose) and plasticizer (glycerol) concentrations. Sweetening and flavoring agents were also added to make the formulation palatable. The films were evaluated for thickness, folding endurance, weight variation, disintegration time, dissolution time and drug content. Thickness of the films was approximately 2 mm. The strips disintegrated completely within 4 minutes. In-vitro dissolution studies were carried out in distilled water as well as in simulated salivary fluid (pH 6.8).The optimized formulation showed 92% drug release within 30 min. The prepared strips seem to be an attractive alternative to conventional marketed formulations.

- **Padamwar P A et al.,(2015)** formulated Bisoprolol Fumarate film were prepared by using polymers such as hydroxy propyl methyl cellulose (HPMC) and Maltodextrin, plasticizer such as PEG 400, by a solvent casting method. They were evaluated for physical characteristics such as thickness, uniformity of weight, folding endurance, drug content, surface ph, percentage elongation and tensile strength and give satisfactory results. The formulations were subjected to disintegration, in-vitro drug release test. The in vitro disintegration time of the optimized batch F4 was found to be 20 sec. The optimized batch was found to be stable for 1 month underspecified stability conditions.

- **Kumar D N et al., (2015)** formulated metaprolol succinate fast dissolving films using polymers like HPMC E5 and HEC polymer by solvent casting method. The prepared films were evaluated for organoleptic evaluations, film weight, thickness,

folding endurance, tensile strength, drug content uniformity of films, surface PH disintegration time and in vitro dissolution studies. the formulation F5 has disintegration time of 7 seconds and is more promising and showed drug release of 98% after 5 minutes; hence formulation F5 was selected as best formulation.

- **Bhatt P and Patel M (2015**) formulated Rizatriptan benzoate mouth dissolving films using polymers like HPMC, PVA, PVP K30, Xanthan gum, Guar gum. Citric acid was used as a saliva stimulating agent and Propylene glycol as a plasticizer. The prepared oral films were evaluated for their physicochemical and mechanical parameters such as Physical appearance, surface pH, thickness uniformity, disintegration time, drug content uniformity, folding endurance, tensile strength, percentage elongation, in-vitro drug release. The polymer combination of HPMC E 15 & PVA was optimized. On applying factorial design to this combination, batch with polymer ratio of 1:7 (HPMC: PVA) was optimized. The formulation was found stable after 1 month.

- **Geedi V et al.,(2015)** formulated Fast Dissolving Oral Films of Zolmitriptan Films were prepared by solvent casting method using Natural Polymers Xanthan gum, Guar Gum, Sodium Alginate, Aloe vera Powder as the film forming polymer and PEG-400 as the plasticizer. Vanillin was used as taste masking agent in the formulation. The thickness, folding Endurance, disintegration time, % drug released and drug content were selected as dependent variables. The optimized formulation, F6 was found superior than remaining 7 batches. Among all the formulations, F6 has shown maximum drug release of 99.1±0.05% within 8 min and a very low disintegration time of 8.33±0.57sec due to super-disintegrant Sodium Starch Glycolate. Hence the films made of 2%w/v of Sodium Alginate and PEG-400 showed excellent film forming property with rapid drug release profile. FT-IR studies revealed that there was no physico-chemical interaction between polymer and drug. Stability studies revealed that optimized formulation was stable as the % drug release at the end of 3rd month was 99.1%.

- **Pawar S V and Junagade M S (2015)** formulated Risperidone fast dissolving films were formulated by solvent-casting method containing HPMC E5 as polymer and Propylene glycol as plasticizer. All films prepared were smooth and elegant in appearance and showed no visible cracks; were uniform in thickness, weight and drug content. Formulation A2 is considered as the optimized formulation as it showed good % elongation (120%), good folding endurance (185), faster disintegration rate (13 sec.) and maximum in vitro drug release (93.57%) within 10 mins. No significant changes were observed during stability studies for the optimized formulation. It was concluded that Risperidone fast dissolving oral films can be formulated as a potentially useful tool for an effective treatment of Schizophrenia with improved bioavailability, rapid onset of action and with increased patient compliance.

- **Kloner R A and Chaitman B (2016)** Angina pectoris is defined as substernal chest pain, pressure, or discomfort that is typically exacerbated by exertion and/or emotional stress, lasts greater than 30 to 60 seconds, and is relieved by rest and nitroglycerin. There are approximately 10 million people in the United States who have angina, and there are over 500 000 cases diagnosed per year. Several studies now show that angina itself is a predictor of major adverse cardiac events. In addition, angina is a serious morbidity that impedes quality of life and should be treated. In the United States, pharmacologic therapy for angina includes β-blockers, nitrates, calcium channel blockers, and the late sodium current blocker ranolazine. In other countries, additional pharmacologic agents include trimetazidine, ivabradine, nicorandil, fasudil, and others. Revascularization is indicated in certain high-risk individuals and also has been shown to improve angina. However, even after revascularization, a substantial percentage of patients return with recurrent or continued angina, requiring newer and better therapies. Treatment for refractory angina not amenable to usual pharmacologic therapies or revascularization procedures, includes enhanced external counterpulsation, transmyocardial revascularization, and stem cell therapy. Angina continues to be a significant cause of morbidity. Therapy should be geared not only to treating the risk factors for

atherosclerotic disease and improving survival but should also be aimed at eliminating or reducing the occurrence of angina and improving the ability of patients to be active.

- **Pathan A et al., (2016)** formulated and evaluate the Fast dissolving Oral film of Promethazine hydrochloride. The films were prepared Hydroxy propyl methyl cellulose E15 as a film base synthetic polymer and PEG400 (Poly Ethylene Glycol 400) as a plasticizer by solvent casting method. SLS (Sodium Lauryl Sulfate) and MCC (Micro Crystalline Cellulose) used as a surfactant in different concentration. Sucrose used as a sweetening agent and strawberry as a flavoring agent. Films were found to be satisfactory when evaluated for thickness, weight uniformity, in-vitro drug release, folding endurance, drug content and disintegration time. The in vitro drug release in optimized formulation F2 was found to be 14.36% in 2 min. The optimized formulation F2 also showed satisfactory pH, drug content (97.41±0.54%), effective in vitro drug release (96.03±0.68% in 16 min), disintegration time of 09 seconds and satisfactory stability.

- **Patel D M et al. 2016** The objective of the study was to designed and optimized fast dissolving film by casting method using HPMC E5 LV, polyethylene glycol 400, aspartame- neotam-tartaric acid- citric acid- mentholion exchange resins for taste masking of cetirizine and dextromethorphan. Films were formulated using plasticizers and also citric acid and tartaric acid as saliva stimulating agent along with, menthol as flavoring agent. Aspartame and Neotame were used as sweeteners and Kyron T111 as ion exchange resin to mask bitterness of drugs. Fast dissolving films contain more than 95% of drugs as per percent drug content study. Formulated film showed mouth dissolving time 17 seconds with more than 96% of drugs release occurs within 30 min. Films were prepared by solvent casting method without any organic solvent and found to satisfy the mouth dissolving time and other film parameters. Our results showed that all the four formulated films showed satisfactory film parameters. It can be concluded that, fast dissolving film containing Cetirizine

and Dextromethorphan can be casted by solvent casting method without any organic solvents.

- **Pawar and Kamat 2017** The was carried out with an objective to increase the bioavailability of the drug ondansetron hydrochloride by developing its mouth dissolving film using taro gum in combination with HPMC E5. Solvent precipitation method was used for extraction of polysaccharide. Polysaccharide (Taro gum) was extracted from tubers of Colocassia esculenta which was used as a polymer in film formulation. Films were formulated using solvent casting method. Xanthan gum, guar gum, sodium alginate, gum ghati and taro gum were used as polymer in film formulation. Concentration for taro gum was optimized. At this optimized concentration, films were formulated using other commercially available natural gums. These films were evaluated for various parameters like tensile strength, disintegration time, In vitro release and stability. All the formulated films showed disintegration time less than 60 s. The film formulated using taro gum showed better release profile, disintegration time and tensile strength than the films prepared using other commercially available gums. Taro film showed 90.64% release at the end of 5 min. Disintegration time of films prepared using taro gum was comparable to that of marketed film. Also, the film prepared using taro gum was more stable as compared to other films. Taro gum being extracted from edible tubers is non-toxic in nature. It can be extracted easily and successfully used in the developmented of mouth dissolving film of Ondansetron hydrochloride.

- **Thonte S S et al 2017** Aim of the present study was to develop the Fast Dissolving Oral Films of Glipizide. It is second-generation sulfonylurea that can acutely lower the blood glucose level. Fast dissolving oral films deliver drug directly in the vascular system and bypasses the hepatic first pass metabolism so dose of the drug may also reduce significantly. Fast dissolving films were prepared using solvent casting method, hydrophilic polymers (HPMC K-15, HPMC E-15, HPMC K- 100) were selected as film forming agents and PEG-400 was used as plasticizer to give flexibility to the films. In FT-IR study no interaction was observed between drug and

the excipients. Three blank films were selected for the incorporation of drug. After characterization the drug loaded films and studying their disintegration time & in-vitro drug release studies, among the formulations [F1 - F10] F3, F4, F6, F7 & F9 was selected the best formulation as its disintegration and dissolution time was less and it releases drug to a greater extent from 93% to more than 100% in ten minutes. Formulation F9 was selected best formulation as its disintegration and dissolution time was less and it released drug to a greater extent compared to other formulations. Therefore fast dissolving oral films can play an important role in oral drug delivery.Drug loaded films with both the polymers were stable under 40°C/75% RH conditions.

- **Ford T J et al. (2017)** The diagnostic management of patients with angina pectoris typically centres on the detection of obstructive epicardial CAD, which aligns with evidence-based treatment options that include medical therapy and myocardial revascularisation. This clinical paradigm fails to account for the considerable proportion (approximately one-third) of patients with angina in whom obstructive CAD is excluded. This common scenario presents a diagnostic conundrum whereby angina occurs but there is no obstructive CAD (ischaemia and no obstructive coronary artery disease—INOCA). We review new insights into the pathophysiology of angina whereby myocardial ischaemia results from a deficient supply of oxygenated blood to the myocardium, due to various combinations of focal or diffuse epicardial disease (macrovascular), microvascular dysfunction or both. Macrovascular disease may be due to the presence of obstructive CAD secondary to atherosclerosis, or may be dynamic due to a functional disorder (eg, coronary artery spasm, myocardial bridging). Pathophysiology of coronary microvascular disease may involve anatomical abnormalities resulting in increased coronary resistance, or functional abnormalities resulting in abnormal vasomotor tone. We consider novel clinical diagnostic techniques enabling new insights into the causes of angina and appraise the need for improved therapeutic options for patients with INOCA. We conclude that the taxonomy of stable CAD could improve to better reflect the heterogeneous pathophysiology of the coronary circulation. We propose the term

'stable coronary syndromes' (SCS), which aligns with the well-established terminology for 'acute coronary syndromes'. SCS subtends a clinically relevant classification that more fully encompasses the different diseases of the epicardial and microvascular coronary circulation.

- **Balla C et al (2018)** Ischaemic heart disease is a major cause of death and disability worldwide, while angina represents its most common symptom. It is estimated that approximately 9 million patients in the USA suffer from angina and its treatment is challenging, thus the strategy to improve the management of chronic stable angina is a priority. Angina might be the result of different pathologies, ranging from the ―classical‖ obstruction of a large coronary artery to alteration of the microcirculation or coronary artery spasm. Current clinical guidelines recommend antianginal therapy to control symptoms, before considering coronary artery revascularization. In the current guidelines, drugs are classified as being first-choice (beta-blockers, calcium channel blockers, and short-acting nitrates) or second-choice (ivabradine, nicorandil, ranolazine, trimetazidine) treatment, with the recommendation to reserve second-line modifications for patients who have contraindications to first-choice agents, do not tolerate them, or remain symptomatic. However, such a categorical approach is currently questioned. In addition, current guidelines provide few suggestions to guide the choice of drugs more suitable according to the underlying pathology or the patient comorbidities. Several other questions have recently emerged, such as: is there evidence-based data between first- and second-line treatments in terms of prognosis or symptom relief? Actually, it seems that newer antianginal drugs, which are classified as second choice, have more evidence-based clinical data that are more contemporary to support their use than what is available for the first-choice drugs. It follows that actual guidelines are based more on tradition than on evidence and there is a need for new algorithms that are more individualized to patients, their comorbidities, and pathophysiological mechanism of chronic stable angina.

3.1. AIM AND OBJECTIVE

The objective of the present study is to design a film of Nicorandil for delivery through oral cavity. Fast dissolving films are prepared when immediate onset of action is desired. The oral transmucosal drug delivery bypasses liver and avoids presystemic elimination in the gastro intestinal tract and liver.

Nicorandil is a niacinamide derivative that induces vasodilation of arterioles and large coronary arteries by activating potassium channels. It is often used for patients with angina who remain symptomatic despite optimal treatment it other antianginal drugs. Nicorandil is a dual-action potassium channel opener that relaxes vascular smooth muscle through membrane hyperpolarization via increased transmembrane potassium conductance and increased intracellular concentration of cyclic GMP. It is shown to dilate normal and stenotic coronary arteries and reduces both ventricular preload and afterload.

After oral (and i.v.) administration of the drug, the apparent volume of distribution is approximately 1.0-1.4 .L/kg body weight. Nicorandil is about 25% bound to human albumin and other plasma proteins. The main route of elimination is the kidney with more than 60% of the administered dose was eliminated in the urine 24 hours after dosing. In the present work an attempt was being made to develop and evaluate fast dissolving films as an alternative oral dosage form with following objectives.

- To provide quick onset of action.
- To bypass first pass metabolism.
- To avoid the problem of swallowing associated with the conventional dosage form.
- To decrease the dose size and reduction of adverse side effects.
- To enhance patient convenience and compliance.
- To provide more effective antispasmodic therapy.

The objective of the present study is to prepare fast dissolving films of Nicorandil with the purpose of developing a dosage form for very quick onset of action.

3.2. RATIONALE OF THE PROJECT

Amongst the various routes of drug delivery, oral route is most preferred by patients and clinicians. A renewed interest has been addressed to oral solid dosage forms designed for prompt availability of therapeutic dose. Of various solid dosage forms now a days the mouth dissolving products (tablets and films) have gained immense interest for drug delivery.

Fast dissolving film is offers many advantages as compared to other non-parenteral routes, such as rectal, transdermal and vaginal, fast dissolving oral film offers following advantages:-

- Prevent first pass metabolism
- Increase it bioavailability
- Impart patient compliance by avoiding intravenous administration drug cancer therapy
- Convenient dosing
- No water needed
- No risk of chocking
- Taste maskings
- Enhanced stability

Among the dosage forms developed to facilitate ease of medication, the orally disintegrating tablet is one of the most widely employed commercial product. The mouth dissolving tablet is placed in the oral cavity where in, saliva quickly penetrates into the pores causing rapid disintegration. Mouth dissolving tablets are useful in patients such as paediatric, geriatric, bedridden, developmentally disabled, mentally retarded and psychiatric patients. But the major drawbacks of MDT are fear of swallowing, chewing, or choking. As they are more friable or fragile, they require special and expensive packaging, special transportation and storing conditions. Above drawbacks of Mouth dissolving tablets can be overcome by the approach of developing fast dissolving films (**Borsadia 2003**).

Fast dissolving oral films (Mouth dissolving film) have become popular as a new drug delivery system because they are easy to administer and exhibit quick onset of action. As indicated earlier, a need exists for a fast-dissolving delivery system with the aforementioned capabilities for use within the pediatric and geriatric populations. This need has driven pharmaceutical scientists to develop a drug delivery system that will dissolve rapidly upon contact with the moist mucosal surfaces of the oral cavity and quickly release its components without mastication or water (**Mishra 2007; Borsadia 2003**).

The dissolution of the active ingredient is a prerequisite for absorption. Dissolution of fast dissolving film occurs in the oral cavity, which allows absorption via the oral mucosa. Therefore, target plasma levels are reached quicker. Small quantity of drug is also absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach which is an advantage of fast dissolving film. Drug is also retained at the site of application and rapidly releases the active agent for local or systemic absorption. Larger surface area of the film is also available for rapid dissolution in the oral cavity. (**Borsadia SB 2003**)

Nicorandil is chosen as drug candidate for the preparation of fast dissolving oral films, Nicorandil is an orally efficacious vasodilatory drug and antianginal agent. It is a niacinamide derivative that induces vasodilation of arterioles and large coronary arteries by activating potassium channels. It is often used for patients with angina who remain symptomatic despite optimal treatment it other antianginal drugs. The physico-chemical properties of Nicorandil, its suitable biological half life (1 hrs) and low molecular weight (211.177), its partly miscible water solubility make it suitable candidate for administration by buccal route.

Fast dissolving film were fabricated by solvent casting technique, it is very cost effective method. Polymer used for preparing the film is HPMC (hydroxyl propyl methyl cellulose) and Polyvinylalcohol (PVA). HPMC is an odorless and tasteless white or creamy-white fibrous or granular powder. Its pH is 5.5-8.0, suitable for buccal film. It is soluble in cold water and insoluble in chloroform, ethanol (95%) and ether. It is used as film former, coating agent stabilising agent. Polyvinyl alcohol (PVA) occurs as an

odorless, white to cream-colored granular powder. It is soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents. So both the polymer has all the desired characteristics which are necessary for the formulation of fast dissolving film. On the basis of these parameters both the polymer are selected for the formulation of fast dissolving oral film.

PLAN OF WORK

In an attempt to develop fast dissolving oral film of Nicorandil, the following plan of work was envisaged.

Stage-1: Preformulation Studies:-

1. Organoleptic properties

- Color
- Odor
- Taste
- State

2. Physical characterization of drug

- Solubility
- Melting point
- Partition coefficient
- Ultraviolet Visible spectroscopy
- Infra Red spectroscopy
- Moisture Content

3. Compatibility Studies of Drug and Excipients

- Differential scanning calorimetery
- Infra Red spectroscopy
- Analytical Methodology: Development and validation of Ultraviolet-visible method

Stage-2: Formulation and Evaluation of Oral Film

1. Fabrication of Film

I. Preparation of blank films:

- Selection of solvent

- Selection of plasticizer
- Selection of optimum polymer concentration

II. Study of drug-polymer-excipients compatibility

III. Formulation of optimized blank films

IV. Formulation of drug containing film.

2. Evaluation of Oral Films

I. Mechanical properties

- Tensile strength
- Elastic modulus
- % Elongation
- Folding endurance
- Morphology study
- Swelling property
- Texture and mouth feel

II. Uniformity of dosage units

III. Disintegration time

IV. Dissolution test

- In-vitro study
- E. Stability studies

3. In-vitro drug releases study

4. Result and Discussion

5. Conclusion

DRUG PROFILE

Introduction:

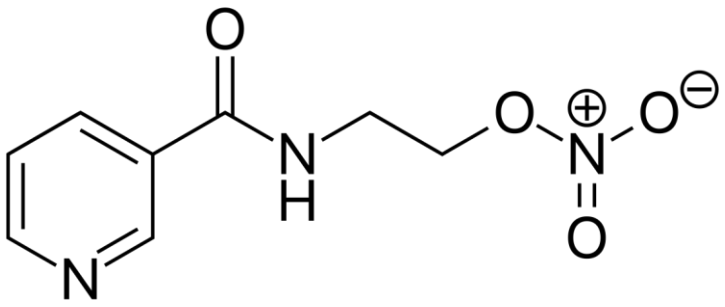
Nicorandil is a dual-action potassium channel opener that relaxes vascular smooth muscle through membrane hyperpolarization via increased transmembrane potassium conductance and increased intracellular concentration of cyclic GMP. It is shown to dilate normal and stenotic coronary arteries and reduces both ventricular preload and after load. Potassium channel openers are presently considered as an important class of drugs for hypertension and angina pectoris. Nicorandil is the first therapeutic molecule has an ability to hyperpolarize muscle cell membranes and a potent coronary vasodilator **Frydman MA et al. 1989**. Nicorandil appears to be effective in all types of angina pectoris, including advanced coronary artery lesion. Nicorandil may be of having particular effect in patients with impaired cardiac function, since it produces very few hemodynamic reactions and improve heart function. Since nicorandil does not produce a significant prolonged sinoatrial and atrioventricular conduction, it can be administered in patients with bradycardia and/or atrioventricular conduction disturbances **(Taira N et al. 1979, Sakai K et al. 1981, Habuchi Y et al. 1987)**.

Chemistry:

Nicorandil is a nicotinamide derivative, efficacious in the treatment of hypertension and angina pectoris. It is a potassium channel opener providing vasodilatation of arterioles and large coronary arteries. Its nitrate component produced venous vasodilatation **Sweetman SC 2005**. Nicorandil (N-[2-hydroxyethyl] nicotinamide nitrate [ester]}, (molecular formula {C8H9N3O4}, molecular weight {211.175}). Chemically nicorandil belongs to the organic nitrate groups, on the basis of the fact that nicorandil has a nitrate moiety, which has been reported to be essential for its pharmacologic activities. Organic nitrate produced a vasodilatation effect by stimulating the formation of cyclic GMP in smooth muscle cells **Holzmann S 1983, Kukovetz WR and Holzmann S 1983**. It opens the ATPsensitive K+ channels, thereby causing dilatation of peripheral and coronary resistant arterioles. In addition, it contains a NO2-moiety, which dilates systemic veins and epicardial coronary arteries14. N-nicotinoylethanolamine is widely used as the active moiety in the synthesis of nicorandil which is a new and higher efficient for antiangianal

therapy. The nicorandil has two nitrate groups in the structure which is shown in Figure 3.1. Nicorandil is a white to off, white needle crystalline powder. The drug is freely water soluble and melting point approximately 92 ºC.

Structural Formula:



Formula: C8H9N3O4

Molar mass: 211.175 g/mol

IUPAC Name: 2-[(pyridine-3—ylcarbonyl)amino]ethyl nitrate

Biological half-life: 1 hour

Metabolism: Hepatic

Bioavailability: 75 to 80 %

Dose: min 20 mg

Mode of Action:

Nicorandil has dual mechanism of action and its action differs significantly from currently available vasodilators by causing sustained dilation of both the venous capacitance and arterial resistant vessels, thus reducing preload and afterload. The vasodilating agent nicorandil produces marked coronary artery dilatation by a number of mechanisms including an increase in cyclic guanosine monophosphate (c-GMP), an effect, which is common to all organic nitrates and a novel potassium channel opening effect. Nicorandil has been shown to produce beneficial hemodynamic effects in patients with stable angina pectoris without significant deleterious effects on pulse rate, the cardiac conducting system, myocardial contractility or myocardial oxygen consumption

(Why HJF, Richardson PJ 1993). It has shown improvement in both functional and mechanism during recurrent myocardial ischemia which are independent of hemodynamic effects, as noted by the improvement in myocardial segment shortening during reperfusion, the reversal of a significant increase in free fatty acid uptake, an attenuation of increase in oxygen and CO2 production in the ischemic zone and the preservation of endocardial adenosine triphosphate (ATP) and total adenine nucleotides **(Endo T et al 1998)**.

It has definite cardioprotective properties in acute myocardial ischemia. At higher concentrations, nicorandil appears to act through the NO group-activated guanylate cyclase. While both pathways contribute to these effects, which are independent (**Hsieh GC et al. 2001)**. Investigation of nicorandil in angina (IONA) studies have classified the unique pharmacological effect of nicorandil not only improves symptoms but also reduces ischemia related cardiac events, e.g. death, non-fatal myocardial infarction and angina pectoris (**Hillis S 1999)**.

5.1 Pharmacokineticsa Pharmacodynamics:

Absorption:

Nicorandil is well absorbed from the gastrointestinal tract and maximum plasma concentration of nicorandil is linearly related to the administered dose. The urinary recovery data following oral administration of the drug indicated that more than 90% of the oral dose (20 mg) was absorbed. There is some evidence that consumption of food concurrently with the administration of nicorandil can prolong drug absorption resulting in a delayed and decreased maximum plasma concentration. The absolute bioavailability of nicorandil is 75±23%, indicating that no significant first pass effect exists **(Frydman MA et al. 1989)**. The different doses and its pharmacokinetic parameters of nicorandil.

Distribution:

After oral (and i.v.) administration of the drug, the apparent volume of distribution is approximately 1.0 L/kg body weight. The drug distribution in the body was reported that it follows two compartment model. Nicorandil is metabolized extensively

and the major route of elimination is through kidney: Less than 2% of the dose is excreted through the biliary route. As a consequence the parent drug is excreted poorly in urine (very low renal clearance), whereas 2-nicotinamidoethanol, a pharmacologically inactive denitrated metabolite, is the major nicorandil related compound excreted in urine. The nicotinamide/nicotinic acid biotransformation pathway contributes to the accumulation of nicorandil and 2-nicotinamidoethanol (denitrated metabolite) during repeated dosing because of the saturable merging of nicotinamide/nicotinic acid derivatives (from the nicorandil metabolism) into the NAD/NADP endogenous pool of coenzymes. While it is very weakly bound to albumin (19.4%) and protein binding is found to be (23.3 %) **(Frydman A 1992)**.

Metabolism and Excretion:

Nicorandil is eliminated by plasma with a half-life of approximately 1 hour. The total body clearance of nicorandil is equal to 52 ± 18 lit/hr, indicating that it is less than the liver blood flow. After metabolism the nicorandil is converted primarily to the denitrated compound, SG-86 (N-2-hydroxyethyl nicotinamide), which is pharmacologically inactive **(Shiraki Y et al. 1981)**. The urinary excretion and the alcohol metabolite accounted for 1% and 4% of the dose (single 20 mg dose) in 24 hours, respectively **(Frydman MA et al. 1989)**.

Dose, Dosing and Problems:

The therapeutic response is always associated with toxic effects. Nicorandil has a shorter half life and the usual oral dosage regimen is 5 to 40 mg taken daily 2 to 4 times. Nicorandil is hydrophilic; therefore it is available commercially in the form of injections and tablets such as, Nikoran IV 2 mg (Torrent Pharma) and conventional tablet Korandil 5 mg (Sun Pharma) and sustain release (SR) tablet Nikoran 20 mg (Torrent Pharma). Sublingual nitroglycerin may be co-administered with nicorandil to stop acute anginal attacks. Table 1 summarizes the therapeutic efficacy and toxicities encountered with nicorandil therapy. Intravenous injection of nicorandil (0.03-3 mg/Kg) decreased the systemic blood pressure dose dependently and the depression response reached a peak at about 1 min and retained to the basal value after 1 hour **(Shiraki Y et al. 1981)**.

The hypotension occurred in 4 of 10 patients with chest pain when 40 mg of nicorandil administered sublingually. Thus, an excessive high plasma concentration of nicorandil caused vasodilatation in the arteriolar resistant vessels, leading to general hypotension21. Adverse effects reported with nicorandil are headache, vasodilation, flushing, nausea, vomiting and weakness. An uncommon side effect includes angioneurtic oedema, photosensitivity as well as tachycardia **(Nick MA 1999)**.

Mouth ulceration has long been recognized as a major side effect of nicorandil treatment, but more recently it has been associated with ulceration of any region of the gastrointestinal tract including the perianal area. The ulceration is commonly severe, refractory to treatment and in a few patients, has led to perforation. Time of onset of ulceration may vary widely and ulcers only respond towithdrawal of nicorandil **(Sweetman SC 2005)**.

5.2 Drug Interaction:

A comparative study of nicorandil with nitroglycerin, nifedipine and propranolol in patients with coronary artery disease. Their investigated results showed that an increase in coronary sinus flow from 117 to 148 ml/min after intravenous (IV) administration 2 mg of nicorandil, but no change during the pacing stress, while nitroglycerine increased coronary sinus flow during pacing. Nifedipine showed a response similar to that of nicorandil. Propranolol did not changed coronary sinus flow. Since coronary sinus drains blood through the ischemic and nonischemic regions, the increase in the coronary sinus flow does not necessarily indicates an increase in the ischemic region **(Kobayashi K et al. 1986)**. Nicorandil revealed better results in case of vasospatic angina that was resistant to nifedipine therapy. Nicorandil showed decreased heart rate in patients those treated from last four to fifth weeks, but did not produce any change in blood pressure. In contrast, propranolol significantly decreased heart rate as well as blood pressure in patients and some adverse reactions like headache and gastrointestinal symptoms **(Masahiko K, Kazushige S 1990)**.

In another study, the possibility of drug interaction leading to decreased activity of Gliclazide **(Satyanrayana S et al 2006)**. The administration of diltiazem

hydrochloride in combination with nicorandil especially during therapy with beta blocking agents or other calcium antagonists affected atrioventricular nodal conduction and cardiac contractility. Moreover nicorandil does not produce an adverse reaction, even in combination with calcium antagonists or beta-blocking agents **(Ishikawa T et al. 1983)**.

Selection of Polymer:

Excipients for formulating fast dissolving oral film shall be selected on the Following basis:

- All the excipients used in the formulation should be hydrophilic in nature, So that it can readily dissolve or disintegrate in the oral cavity.
- It should be chemically inert.
- It should not show any drug excipients interactions or excipient-excipient interaction.
- Be non-toxic and pharmacologically inert.
- Be able to, preferable, increase the aqueous solubility of the drug.
- The ingredients used in formulation development should itself be stable on storage and during shelf life of the device.

5.3 EXCIPIENT PROFILE

Poly Vinyl Alcohol (PVA)

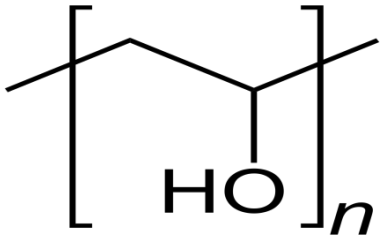
Synonyms: Alcotex; Gelvatol; Lemol; Mowiol; polyvinol; vinyl alcohol polymer.

Chemical Formula: $(C_2H_4O)_n$ 20000–200000

Polyvinyl alcohol is a water-soluble synthetic polymer represented by the formula $(C_2H_4O)_n$. The value of n for commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately 20000–200000.

Molecular Grade	Mol. Wt
High viscosity	200000
Medium viscosity	130000
Low viscosity	20000

Structural Formula:



Functional Category:

Used as Coating agent; lubricant; stabilizing agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

PVA is used primarily in topical pharmaceutical and ophthalmic formulations:

- It is used as a stabilizing agent for emulsions concentration (0.25–3.0% w/v).
- Polyvinyl alcohol is also used as a viscosity-increasing agent for viscous formulations such as ophthalmic product in concentration ranges from (0.25-3.00).
- It is used in artificial tears and contact lens solutions for lubrication purposes, in sustained release formulations for oral administration, and in transdermal patches.
- Polyvinyl alcohol may be made into microspheres when mixed with a glutaraldehyde solution.

Description:

Polyvinyl alcohol occurs as an odorless, white to cream-colored granular powder.

Typical Properties:

- Melting point: 228°C for fully hydrolyzed grades; 180–190°C for partially hydrolyzed grades.
- Specific gravity: 1.19–1.31 for solid at 25°C; 1.02 for 10% w/v aqueous solution at 25°C.
- Residue on ignition: It should not be more than 1%.
- pH: 4.5-6.5 (Europeian Pharmacopeia); 5.0-8.0(USP).
- Loss on drying: Loss on drying of the PVA should not be more than 5%.
- Particle size distribution: <30 µm.

Solubility:

It is soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents. Dissolution requires dispersion (wetting) of the solid in water at room temperature followed by heating the mixture to about 90°C for approximately 5 minutes. Mixing should be continued while the heated solution is cooled to room temperature.

Viscosity (dynamic):

Grades of viscosity	
Grade	**Dynamic viscosity of 4%w/v aqueous solution at 20°C (mPa s)**
High viscosity	40.0-65.0
Medium viscosity	21.0-33.0
Low viscosity	5.0-7.0

Stability and Storage Conditions:

Polyvinyl alcohol is stable when stored in a tightly sealed container in a cool, dry place. Aqueous solutions are stable in corrosion-resistant sealed containers. Preservatives may be added to the solution if extended storage is required. Polyvinyl alcohol undergoes slow degradation at 100°C and rapid degradation at 200°C; it is stable on exposure to light.

Incompatibilities:

Polyvinyl alcohol undergoes reactions typical of a compound with secondary hydroxyl groups, such as esterification. It decomposes in strong acids, and softens or dissolves in weak acids and alkalis. It is incompatible at high concentration with inorganic salts, especially sulfates and phosphates; precipitation of polyvinyl alcohol 5% w/v can be caused by phosphates. Gelling of polyvinyl alcohol solution may occur if borax is present.

Safety:

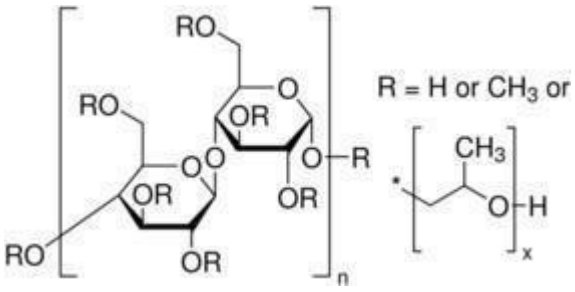
Polyvinyl alcohol is generally considered a nontoxic material. It is non- irritant to the skin and eyes at concentrations up to 10%; concentrations up to 7% are used in cosmetics. Studies in rats have shown that polyvinyl alcohol 5% w/v aqueous solution injected subcutaneously can cause anaemia and infiltrate various organs and tissues.

Hydroxypropyl Methyl Cellulose (HPMC): (Hand book of phar excipients1986)

Synonyms: Hydroxypropyl methylcellulose, HPMC, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose.

Chemical Name: Cellulose hydroxypropyl methyl ether.

Structural Formula:



Functional Category:

Used as Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

Primarily used as a tablet binder, concentrations of 2–20% w/w are used as film forming solutions to film-coat tablets, a suspending and thickening agent in topical formulations, also used as an emulsifier, suspending agent, and stabilizing agent.

Description:

HPMC is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Typical Properties:

- Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.
- Density (bulk): Bulk- 0.341 g/cm3, Tapped- 0.557 g/cm3, True- 1.326 g/cm3
- Melting point: Browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.
- Specific gravity: 1.26
- Moisture content: HPMC absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Solubility:

It is Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and water and alcohol.

Viscosity:

Typical viscosity values for 2% (w/v) aqueous solutions of Methocel measured at 20°C

Methocel Product	USP 28 Designation	Nominal Viscosity (mPa s)
Methocel E15 Premium LV	2906	15
Methocel E50 Premium LV	2906	50

Stability and Storage Conditions:

HPMC powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. HPMC undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90 °C. HPMC powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities:

HPMC is incompatible with some oxidizing agents. Since it is nonionic, HPMC will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety:

HPMC is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Polyethylene Glycol 400 (PEG-400)

PEG 400 is a low-molecular-weight grade of PEG. It is a clear, colourless, viscous liquid. Due in part to its low toxicity, PEG 400 is widely used in a variety of pharmaceutical formulations.

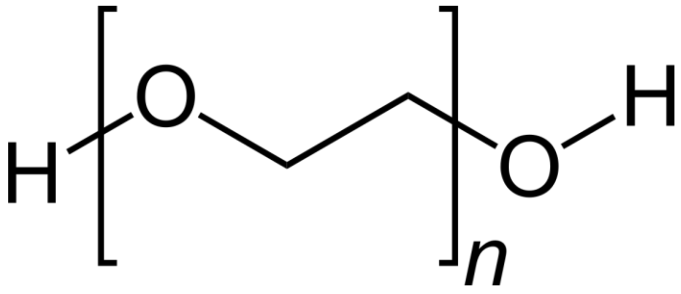
Chemical Name: α-hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)

Appearance: Clear liquid

Emperical Formula: $HOCH_2$ (CH_2OCH_2) mCH_2OH where m represents the average number of oxyethylene groups, where m = 8.7 for PEG

Molecular Weight: 380 – 420

Structural Formula:



Functional Category:

It is used as Ointment base; Plasticizer; solvent; suppository base; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations:

including Parentral, topical, ophthalmic, oral, and rectal preparations.

- It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.
- Polyethylene glycols are stable, hydrophilic substances that are essentially non irritant to the skin; they do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases. Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.
- Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids.
- Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, PEG also can act as emulsion stabilizers.

Disadvantages:

- They are chemically more reactive than fats; greater care is needed in processing to avoid in elegant contraction holes in the suppositories; the rate of release of water- soluble medications decreases with the increasing molecular weight of the PEG; and polyethylene glycols tend to be more irritating to mucous membranes than fats.
- Liquid PEGs are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell. In concentrations up to 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

Description:

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste.

Solubility:

All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher molecular- weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Typical Properties:

- pH: 5-7
- Density: 1.11–1.14 g/cm3 at 25°C for liquid PEGs
- Freezing Point: 4–8°C for PEG 400;
- Specific gravity: 1.12 - 1.13
- Viscosity: 90 cPs at 250Cs

Incompatibilities:

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation. The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols. Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Plastics, such as polyethylene, phenol formaldehyde, polyvinyl chloride, and cellulose-ester membranes may be softened or dissolved by PEGs. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

Stability and Storage condition:

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols should be stored

in well-closed containers in a cool, dry place. Stainless steel, aluminium, glass, or lined steel containers are preferred for the storage of liquid grades.

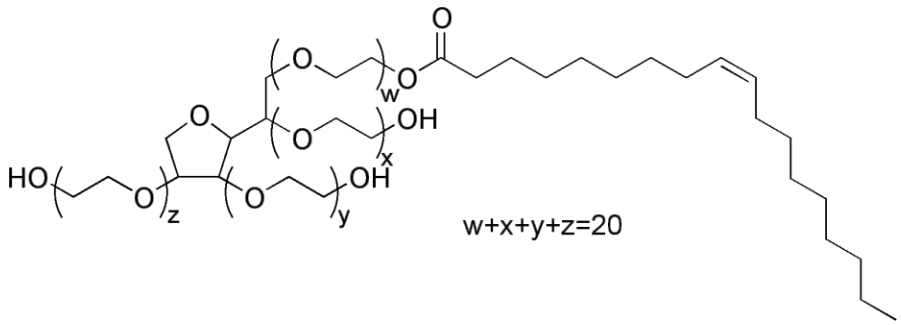
Tween 80 (Polysorbate 80)

Polysorbate 80 is a nonionic surfactant and emulsifier often used in foods and cosmetics. This synthetic compound is a viscous, water-soluble yellow liquid.

Synonyms: Polyoxyethylene 20 oleate, Tween 80, Polysorbate 80.

Chemical Name: Polyoxyethylene 20 sorbitan mono oleate

Structural Formula:



Chemical Formula: $C_{64}H_{124}O_26$

Molecular Weight: 1310

Functional Category:

Stabilizing agent, solubilizing agent, non-ionic surfactant, dispersing/ suspending agent, emulsifying agent, brain targeting agent.

Applications in Pharmaceutical Formulation or Technology:

Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a series of partial fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20, 5, or 4 moles of ethylene oxide for each mole of sorbitol and its anhydrides. The resulting product is therefore a mixture of molecules of varying sizes rather than a single uniform compound. Polysorbates containing 20 units of oxyethylene are hydrophilic nonionic surfactants that are used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions. They may also be used as solubilizing agents for a variety of

substances including essential oils and oil-soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions. They have been found to be useful in improving the oral bioavailability of drug molecules that are substrates for p-glycoprotein. Polysorbates are also widely used in cosmetics and food products.

- Emulsifying agent
- Used alone in oil-in-water emulsions
- Used in combination with hydrophilic emulsifiers in oil-in-water emulsions
- Used to increase the water-holding properties of ointments
- Solubilising agent
- For poorly soluble active constituents in lipophilic bases
- For insoluble active constituents in lipophilic bases

Description:

Polysobates have a characteristic odor and a warm, somewhat bitter taste, their color & physical form at 250C are yellow oily liquid.

Typical Properties:

- Acid value: 2%
- Moisture content: 3.0
- Saponification value: 45-55
- Acidity/alkalinity: pH = 6.0–8.0 for a 5% w/v aqueous solution.
- Flash point: 149°C
- HLB value: 15
- Specific gravity at 25 ºC: 1.08
- Viscosity: 425mPas

Solubility:

Soluble in water and ethanol, insoluble in mineral Oil and vegetable oil.

Stability and Storage Conditions:

Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid esters are sensitive to oxidation.

Polysorbates are hygroscopic and should be examined for water content prior to use and dried if necessary. Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

Incompatibilities:

Discoloration and/or precipitation occur with various substances, especially phenols, tannins, tars, and tarlike materials. The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.

Safety:

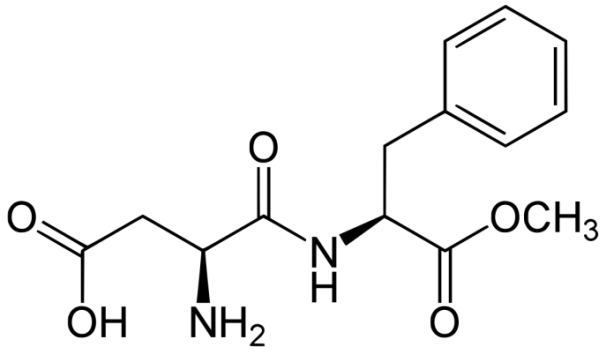
It is moderately toxic by IV route, mildly toxic by ingestion. Eye irritation may also occur. Experimental shows tumorigen, reproductive effects and mutagenic data.

Aspartame (Hand book of phar excipients1986)

Synonyms: 3-Amino-N-(aì-carboxyphenethyl) succinamic acid N-methyl ester, 3-amino-N-(aìmethoxycarbonylphenethyl) succinamic acid, APM, aspartyl phenylamine methyl ester, NutraSweet; Pal Sweet.

Chemical Name: N-aò-L-Aspartyl-L-phenylalanine 1- methyl ester.

Structural Formula:



Empirical Formula: $C_{14}H_{18}N_2O_5$

Molecular Weight: 294.31

Functional Category: Sweetening agent.

Application in Pharmaceutical Technology:

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics. Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.

Description:

Aspartame occurs as an off white, odorless crystalline powder with an intensely sweet taste.

Typical Properties:

- Acidity/alkalinity: pH = 4.5–6.0 (0.8% w/v aqueous solution).
- Flowability: 44% (Carr compressibility index)
- Density: Bulk- 0.5–0.7 g/cm3 for granular grade, 0.2–0.4 g/cm3 for powder grade, 0.17 g/cm3, tapped- 0.29 g/cm3, true- 1.347 g/cm3.
- Melting point: 246–247°C

Solubility:

It is slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20°C solubility is 10% w/v.

Stability and Storage Conditions:

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2, 5-diketopiperazine. Stability in aqueous solutions has been enhanced by the addition of cyclodextrins, and by the addition of polyethylene glycol 400 at pH 2. Aspartame degradation also occurs during prolonged heat treatment. The bulk material should be stored in a well-closed container, in a cool, dry place.

Incompatibilities:

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.

Safety:

The WHO has set an acceptable daily intake for aspartame at up to 40 mg/kg body-weight. A number of adverse effects which have been reported following the consumption of aspartame include: headaches, grand mal seizure, memory loss, gastrointestinal symptoms, and dermatological symptoms. The use of aspartame has been of some concern owing to the formation of the potentially toxic metabolites methanol, aspartic acid, and phenylalanine.

MATERIALS & EQUIPMENT

Table: 7 List of Chemicals

Sr. No.	Materials	Manufacturer
1	Nicorandil	Sigma labs ltd.
2	HPMC- E 15, E 50.	S.D fine chemicals.
3	Poly vinyl alcohol	S.D fine chemicals
4	Eudragid RL 100	Ranbaxy, New Delhi
5.	Glycerine	S.D fine chemicals
6	Propylene Glycol 400	Qualigens Fine Chemicals
7	Tween -80	Central Drug House (P) Ltd
8	Citric acid	Qualigens Fine Chemicals
9	Aspartame	Ranbaxy, New Delhi
10	Menthol	Central Drug House (P) Ltd.
11	Distilled Water	In House
12	Distilled Ethanol	In House

Table: 8 List of Instruments

Sr. No	Materials	Manufacturer
1	Petridish	Polylab Glass Petridishes
2	Beakers, Volumetric flasks	Qualigens,
3	Electrical Balance	Anamed instruments, Mumbai.
4	Screw guage	Mututoyo, Japan.
5	Sonicator	RC Systems, Bangalore.
6	Magnetic stirrer	Remi, Mumbai.
7	UV-Vis Spectrophotometer (UV- 1700)	Shimadzu Corporation, Japan.

8	Dissolution apparatus TDT- 8	Electro Lab, Mumbai.
9	Temperature controlled oven	Lab Control Equipment, Mumbai.
10	Digital pH meter	Eutech.
11	Melting point apparatus	Macro Scientific Works,Delhi-7
11	Stability Chamber	Jyoti Scientific Industries, Gwalior
12	FTIR Spectrophotometer (FT/IR- 5300)	FTIR – 8400S, Shimadzu
13	Differential Scanning Colorimetry	Shimadzu, Japan.
14	Distillation unit	Shimadzu, Japan.

PREFORMULATION STUDIES

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. Preformulation may be defined as a phase of the research and development process where the Preformulation scientist characterized the physical, chemical and medicinal properties of a new drug substance, alone and in combination with other excipients. Preformulation studies are developed for understanding the physicochemical properties of new drug entity, which may ultimately provide a rationale for formulation design or support the need for molecular modification or merely confirm that there are no significant barriers to the compounds development. The goals of the program therefore are:

- To gain knowledge about the physicochemical characteristics of the drug.
- To define the physical characteristics of the drug.
- To understand the stability characteristics of the drug.
- To determine the compatibility of excipients with the drug.

Hence, Preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies.

The following Preformulation Studies of the Drug were Carried Out-

- Identification of the drug.

(i) Organoleptic properties

(ii) U.V spectral Analysis

(iii) FTIR spectral analysis

(iv) DSC analysis of drug

- Solubility studies
- Melting point determination
- Loss on drying
- Partition coefficient

- Analytical method for Nicorandil
- Compatibility Studies

7.1 Identification Tests:

Organoleptic Properties:

Drug (Nicorandil) was Physically Characterized on the basis of colour, ordor and taste. All these parameter ware recorded and compared with standard

UV Spectral Analysis:

The ultraviolet absorbance of Nicorandil was scanned from 400 to 800 nm then the wavelength of maximum absorbance was compared with reported λ_{max}.

Procedure:

100 mg of Nicorandil was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved in 100 ml 6.8 phosphate buffer to get a solution of 1000 µg/ml (stock solution I). 10 ml of stock solution I was diluted to 100 ml with 6.8 pH phosphate buffer to get a solution of 100ug/ml (Stock solution II).

Further, 10 ml. of stock solution II was diluted up to 50ml with methyl orange solution (1%w/v) and extracted with chloroform (3x15 ml). Organic layers were separated and pooled. The volume of pooled organic layer was made up to 100 ml with sodium acetate solution (Stoke solution III). 1 ml of this stock solution was again diluted with water to 10 ml of 6.8 pH phosphate buffer to obtain a solution of 10µg/ml. The resulting solution was scanned between 400 nm to 800 nm in a double beam UV/ Visible spectrophotometer (Shimadzu, Japan) (**Jain and Singh 2010**). The spectrum obtained is shown in figure: 8.1.

Infra Red Spectral Analysis:

The infra Red Spectroscopy of the drug was carried out to ascertain identity of drugs. A pellet of approximately 1 mm diameter of each drug was prepared by compressing 3-5 mg of drug with 100-150 mg of potassium bromide in KBr press. The

pellet was mounted in IR compartment and scanned between wave number 4000-600 cm-1 using a shimadzu FTIR. The FTIR spectra of standard Nicorandil is shown in figure 8.2 and the FTIR spectra of sample drug is shown in figure 8.3 and interpretation is represented in table 8.1.

Differential Scanning Calorimetry Analysis

Differential scanning calorimetry was performed to determine the melting point of the dicyclomine. Accurately weighed samples (2mg) were transferred to aluminium pans and sealed. All samples were run at a heating rate of 5°C/min over a temperature range 45-200°C using PerkinElmer Thermal Analysis. Thermogram is represented in Figure: 8.4.

Solubility Analysis:

A solubility analysis was done to select a suitable solvent system to dissolve the drug properly and to test its solubility in the dissolution medium which was to be used. Nicorandil was Soluble 1 in 20 of water, 1 in 5 of ethanol and 1 in 2 of chloroform, and drug is very slightly soluble in ether.

Method:

An excess amount of drug was dissolved in 10 ml Buffer solution of different pH
6.8 and 7.4 in conical flask and was shaken for 24 hours with the Help of conical flask shaker. After 24 hrs the drug was filtered with what man filter paper NO.1, diluted appropriately and analyzed by U.V spectroscopy as given in table 8.2.

Melting Point Determination:

Melting point determination of the obtained drug sample was done because it is a good indication of purity of the sample since the presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range. Digital melting point apparatus is used for the determination of Melting point the result is represented in section 8.1.3.

Partition Coefficient Measurement:

The partition coefficient (P) is defined as the ratio of the equilibrium concentrations (ci) of a dissolved substance in a two-phase system consisting of two largely immiscible solvents. In the case n-octanol and water:

$$\mathbf{P_{o/w} = c_{octanol} / c_{water}}$$

The partition coefficient (P) therefore is the quotient of two concentrations and is usually given in the form of its logarithm to base 10 (log P). The partition coefficient is a ratio of concentrations of un-ionized compound between the two solutions. To measure the partition coefficient of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is un-ionized. The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is called log P:

$$log\ P_{oct/wat} = log\left(\frac{[solute]_{octanol}}{[solute]^{un-ionized}_{water}}\right)$$ Eqn(1)

Loss on Drying:

An empty Petridish was cleaned, dried and weighed accurately. About 1.0 gm of drug was placed in the petridish and weighed again. The accurate weight was noted. Now this petridish with drug was kept at 105°C temperature for 4 hrs. It was again weighed and the loss on drying was determined by using the formula as given below and the result is shown in table 8.4.

% Loss on drying = Weight of drug before drying - Weight of drug after drying / Weight of drug before drying × 100

Calibration Curves: Preparation of Calibration Curve of Nicorandil

7.2 Preparation of Reagents:

Preparation of 0.2M Potassium Dihydroxide Phosphate Solution:

Dissolved 27.218gm of potassium dihydrogen phosphate in distilled water and diluted the volume up to 1000ml with distilled water.

Preparation of 0.2M Sodium Hydroxide Solution:

Dissolved 8.0gm of Sodium hydroxide in distilled water and diluted the volume up to 1000ml with distilled water.

Preparation of pH 6.8 Phosphate Buffer (Simulated Saliva pH)

Place 50 ml of potassium dihydrogen phosphate buffer in a 200 ml volumetric flask. Add 22.4 ml of sodium hydroxide, mixed and volume was made up to 200 ml with distilled water.

Calibration Curve in 0.1N HCl

100 mg of Nicorandil was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved in 100ml of 0.1N hydrochloric acid to get a solution of 1000 µg/ml (stock solution I). 10 ml of stock solution I was diluted to 100 ml with 0.1N HCl to get a solution of 100 ug/ml (Stock solution II). Further, 10 ml. of stock solution II was diluted up to 50ml with methyl orange solution (1%w/v) and extracted with chloroform (3x15 ml). Organic layers were separated and pooled. The volume of pooled organic layer was made up to 100 ml with sodium acetate solution (Stoke solution III). This stock solution III was used to prepare a series of standard Nicorandil solutions as discussed below.

Procedure: From stock solution III aliquots of 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8, & 2ml were transferred to a series of 10 ml volumetric flasks. The volume was made upto 10ml with 0.1N HCl to give 2, 4, 6, 8, 10, 12, 14, 16, 18, & 20 µg/ml of Nicorandil. The absorbance of these solutions was measured at 508 nm against blank as shown in table 5.5. The standard plot obtained by the absorbance is shown in Figure 5.5 and the U.V graph is shown in Figure 8.6.

7.3 Calibration curve in Phosphate Buffer pH

6.8 Procedure:

100 mg of Nicorandil was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved in phosphate buffer pH 6.8 to get a solution of 1000 µg/ml (stock solution I). 10 ml of stock solution I was diluted to 100 ml with phosphate buffer pH 6.8 (Stock solution II). Further, 10 ml. of stock solution II was diluted up to 50 ml with methyl orange solution (1%w/v) and extracted with chloroform (3x15 ml). Organic layers were separated and pooled. The volume of pooled organic layer was made up to 100 ml with sodium acetate solution (Stoke solution III). This stock solution III was used to prepare a series of standard Nicorandil solutions, concentration ranging from 10-20 ug/ml and the absorbance of these solutions was measured at 465 nm against blank as shown in table 5.6. The standard plot obtained by the absorbance is shown in figure 5.7 and the U.V graph is shown in Figure 8.8.

7.4 Calibration Curve in Phosphate Buffer pH

7.4 Procedure:

100 mg of dicyclomine was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved in 100ml phosphate buffer pH 7.4 to get a solution of 1000 µg/ml (stock solution I). 10 ml of stock solution I was diluted to 100 ml with phosphate buffer pH 7.4 to get a solution of 100ug/ml (Stock solution II). Further, 10 ml. of stock solution II was diluted up to 50ml with methyl orange solution (1%w/v) and extracted with chloroform (3x15 ml). Organic layers were separated and pooled. The volume of pooled organic layer was made up to 100 ml with sodium acetate solution (Stoke solution III). This stock solution III was used to prepare a series of standard Nicorandil solutions ranging from conc. 10-20ug/ml and the absorbance of these solutions was measured at 465 nm against blank as shown in table 5.7. The standard plot obtained by the absorbance is shown in figure 5.9 and the U.V graph is shown in figure 8.10.

Compatibility Studies:

The drug-polymer compatibility was observed visually as shown in table 5.6 and then the drug-polymer compatibility was further confirmed by taking IR spectrum and DSC thermogram of drug, polymer and physical mixture of drug and polymer proved that the excipients were compatible with the Nicorandil.

Compatibility Study by FTIR Spectroscopy:

Compatibility of the Nicorandil with film forming polymers and Sweetener used to formulate films was established by Infrared spectral analysis. I.R. Spectral analysis of Nicorandil, polymers and combination of the Nicorandil and polymers were carried out to investigate the changes in chemical composition of the drug after combination and the spectra of sample drug is compared with the standard spectrum (**Jain and Sigh 2010**). A pellet of approximately 1 mm diameter of each drug was prepared by compressing 3-5 mg of the drug with 100-150 mg of potassium bromide in KBr press (Model M-15, Techno Search Instruments). The pellet was mounted in IR compartment and scanned between wave number 4000^{-1} – 500 cm^{-1} using a Shimadzu FTIR as shown in Figure 8.11, 8.12, 8.13 and 8.14.

Compatibility Study by DSC Study:

DSC thermograms were also recorded to assess the compatibility of the drugs and Excipients. The DSC thermogram of drug, polymer (HPMC, PVA), Aspartame (sweetener) and physical mixture of drug and polymer in ratio of 1:1 were obtained using (PerkinElmer Thermal Analyzer) and endothermic peak of physical mixture was matched with the endothermic peak of the drug as represented in figure 8.17 and 8.18.

7.5 Formulation and Development of Fast Dissolving Oral

Film: Composition of the Placebo Film:

HPMC-5, HPMC 15cps, HPMC 50cps and PVA (poly vinyl alcohol), PVP, Eudragid RL-100 are well known polymers and have excellent film forming properties. Hence, these polymers were selected to prepare films separately and in combination with each other. Films were evaluated to compare efficiency of each polymer with other. The polymeric concentration was kept fixed at 2% in all the films. Compositions of films were shown in Table 8.9.

7.6 Method of Preparation:

HPMC-15cps Film:

The Placebo films were prepared by solvent-casting method. Hydroxy- propylmethyl cellulose (HPMC) is known for its good film forming properties & has excellent acceptability. Hence, Methocel E15 was used to develop the film. HPMC was soaked in water and then uniformly dispersed to obtain dispersion with continuously stirring on magnetic stirrer. Then the plasticizers and tween 80 were added in specific in the polymeric dispersion. Polymeric dispersion was mixed to obtain a homogenous dispersion with stirring on magnetic stirrer for 1hour. Then the solution was kept on the sonicator for 10min to remove the air bubbles. 10 ml of the dispersion was cast onto each Petri dish which was lubricated with olive oil. The dispersion was dried in a hot air oven at 30-40°C. The films were carefully removed from Petri dishes and cut into strips of dimensions 2×2 cm and stored in an air tight glass container (**Ivory et al. 2004**). The films were evaluated for imperfections and cuts, mechanical strength, thickness and dissolution time.

PVP (poly vinyl pyrrolidine) film:

PVP was soaked in water and then uniformly dispersed to obtain uniform dispersion with continuous stirring on magnetic stirrer. Films were fabricated as per the method described for the fabrication of HPMC films (**Ivory 2004**).

PVA (Poly Vinyl Alcohol) Films:

PVA was soaked in water and then uniformly dispersed to obtain uniform dispersion with continuous stirring on magnetic stirrer. Films were fabricated as per the method described for the fabrication of HPMC films.

All the films using different polymers and with the combination of polymers were prepared by the same method describe for the fabrication of HPMC films.

Optimization of the Polymer for Placebo Film Formulation:

The most important parameter that needs to be optimized in the development of fast dissolving oral film is the film forming capacity of the polymer, physical appearance, disintegration time, and mechanical properties of the films as shown in table.8.10 & 8.11.

Formulation of placebo fast dissolving film with different concentration of HPMC-15, PVA and combination of polymers:

Placebo films with varying concentration of HPMC-15 ranging from 1% to 3%, PVA films ranging from 1% to 3% and the combination of HPMC-15: PVA or HPMC-50

: Eudragid RL 100 were prepared as shown in table 5.12 & 5.13. All the films were evaluated for all the desired parameters. The polymer concentration and the combination of which showed best parameters was selected for the preparation of drug loaded film, evaluation parameters are shown in table 8.14, 8.15, 8.16 & 8.17.

Method Used: Solvent Casting

In Solvent Casting method water soluble ingredients were dissolved to form a clear viscous solution. The API and other agents were dissolved in smaller amounts of the solution, and combined with the bulk. This mixture was then added to the aqueous viscous solution. The entrapped air was removed by using sonicator. The resulting solution was cast as a film and allowed to dry, which was then cut into pieces of the desired size (**Mishra et al. 2007**).

Preparation of the Drug Loaded Films:

Drug (Nicorandil) containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of polymer was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of sweetener, and Plasticizer were dissolved in 95% ethanol and then added to the polymeric solution. Then optimized amount of drug was dissolved in 2ml of water and kept on sonication for proper dispersion. The drug solution was then added to the polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a plastic petridish having 68 cm^2 surface area and was dried at controlled room temperature (25° - 30 °C, 45% RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature (**Dinge et al 2008**). The dried film was carefully removed from the petridish and was cut into size required for testing. The films were stored in air tight plastic bags till further use. The composition of drug loaded film is shown in table 8.18.

7.8 Evaluation of Formulated Fast Dissolving Films:

Physicochemical Evaluation:

Film Thickness:

Thickness of films (after 4 folds) was measured using screw gauge. Five films were selected randomly and the average of five films was taken results are shown in table 8.21(**Dinge et al. 2008**).

Weight Variation:

The study was carried out for 10 films obtained from each formulation batch. The mean weight of film as well as the deviation from the mean was calculated and recorded as shown in table 8.21.

Hydration Study (Water Uptake/ Swelling Study):

The film sample was weighed and placed on a preweighed stainless steel wire mesh. The wire mesh was then submerged in a petridish containing 20 ml distilled water

(Sharma et al 2007; Yoo et al 2008). Increase in weight of the film was determined at regular time intervals until a constant weight was obtained as shown in table 8.21. The hydration ratio of the film was calculated using following formula-

$$\text{Hydration ratio} = W_t - W_0 / W_0$$

Where Wt = weight of film at time t and W0 = weight of film at zero time.

Moisture Loss and Percent Moisture Absorption:

The percent moisture loss was determined by placing prepared film in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed (**Tanwar et al. 2007**). The percent moisture loss was calculated using following formula mention below and the results are in table 8.21

$$\text{Moisture loss} = W_0 - W_t / W_0 \times 100$$

Where W0= initial weight Wt = final weight.

The percentage moisture absorption test was carried out to check the physical stability of the films at high humid conditions. Three 1cm diameter films were cut out and weighed accurately, and then the films were placed in desiccator containing saturated solution of sodium chloride keeping the humidity inside the desiccator at 75 %. After 3 days the films were removed, weighed and percentage moisture absorption was calculated. Average percentage moisture absorption is calculated by the formula given below.

$$\text{Percentage moisture absorption} = (\text{Final weight} - \text{Initial weight})/\text{Initial weight} \times 100$$

Measurement of Mechanical Properties:

The mechanical property gives an indication of the strength and elasticity of the film, reflected by the parameters- tensile strength, elastic modulus, % strain and load at yield (**Dahima et al. 2010; Bhise et al. 2010**). Characteristics of polymer are shown in table 8.21.

Table: 9. Mechanical Properties of Film

Type of polymer	Tensile Strength	Elastic Modulus	% Strain
Soft and Weak	Low	Low	Low
Hard and Brittle	Moderate	High	Low
Soft and Tough	Moderate	Low	High
Hard and Tough	High	High	High

The mechanical properties of the film gives idea about to what extent the film can withstand the force or stress during processing, packaging, transport and handling. The desirable characteristics of film are moderate tensile strength, low elastic modulus, high % strain and high load at yield. From the above table, the polymer should give soft but tough film.

Percent Elongation:

The prepared film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The elongation was determined by noting the distance travelled by pointer before break of film on the graph paper (**Peh et al. 2007; Ahmed et al. 2008**). The percent elongation was calculated by using formula-(mm-2) as shown in table 8.22.

$$\text{Percent elongation} = L1 / L0 \times 100$$

Where L1= increase in the length, L0 = Initial length.

Tensile Strength:

Film strip of dimension 2 X 2 cm^2 and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks (**Agarwal et al. 1985**). The force was measured when the films broke results is shown in table 8.22.

Tensile strength (kg/mm^2) = Force at Break / Initial cross sectional area of the film (mm^2)

Folding Endurance:

This parameter was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance as shown in table 8.21.

Drug Content:

The drug content and content uniformity test was performed to ensure uniform distribution of drug. Five film units (2 cm x 2 cm) were cut from the four corners and the central part of the film (n=3). Each film unit was placed in 100 ml of distilled water. Samples of 10 ml were withdrawn and diluted with 25 ml of methyl orange (1%w/v) and extracted with chloroform (3x7.5 ml), and then the volume of sample was made up to 50 ml with sodium acetate solution. The solutions were filtered and analyzed at 465nm in a UV-Visible Spectrophotometer (Shimadzu, Japan). The average of five films was taken as the content of drug in one film. The concentration of Dicyclomine HCL (in μg/ml) was calculated using standard calibration curve of dicyclomine and the drug content results are shown in table 8.21.

In vitro Disintegration and Dissolution Time

The disintegration time is the time when a film starts to break or disintegrate. The dissolution time is the time when the film completely dissolves. The in vitro disintegration and dissolution time of fast-dissolving films was determined visually in a glass dish of 25 ml distilled water with swirling every 10s (**Chen et al. 2006**). Disintegration and dissolution time was measure results are shown in table 8.22.

In Vitro Dissolution Study (Drug Release Rate Study):

The in vitro dissolution test was carried out in a USP II paddle dissolution apparatus. Samples of Dicyclomine-loaded films were equivalently containing 20 mg (4cm2) was cut and placed in dissolution media. The dissolution medium consisted of 300 ml freshly deionized simulated saliva (pH 6.8), maintained at 37 ± 1 0C and stirred at

100 rpm. Samples of 10 ml were withdrawn at predetermined time intervals & replaced with fresh medium. The samples was diluted with 25 ml of methyl orange (1%w/v) and extracted with chloroform (3x7.5 ml), and then the volume of sample was made up to 50 ml with sodium acetate solution. The solution was filtered using Whatman filter Paper. The absorbance was taken at 465 nm against blank UV spectrophotometer (UV1700, Shimadzu, Japans) results are shown in table 8.23, 8.24, 8.25 and 8.26.

Evaluation of Taste Masking:

Sensory analysis has been used by many pharmaceutical technicians for years to characterize flavors, odors, and fragrances.

Intensity of Bitterness Level:

For the taste masking evaluation in the present investigation, each formulation was given to healthy volunteers and was kept in mouth for specified time. Then conclusion was made based on the comparison of bitter level index (a numerical scale) and also their acceptability.

Bitter Level Index:

Arbitrary bitter level index was needed to be developed. A numerical value was assigned to various level of bitterness as given in table 5.20. This bitter level index was used further in the study for the taste evaluation of the film formulation.

Drug Release Kinetics:

The drug release kinetics were studied by various kinetic models such as Korsmeyer-peppas, Higuchi plot, first order plot and zero order plot. To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order as cumulative amount of drug released Vs time, first order as log cumulative percentage of drug remaining *vs.* time, and Higuchi‘s model as cumulative percentage of drug released *vs.* square root of time.

The best fit model was confirmed by the value of correlation coefficient near to 1. The data was presented for the most appropriate model. Zero order: Graph was plotted between cumulative amount of drug released *vs.* time

$$C = K0\ t \qquad \text{Eqn (2)}$$

Where, K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration Vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

First Order: Graph was plotted between log cumulative percentage of drug remaining Vs time

$$\text{Log } C = \text{Log } C0 - kt/2.303 \qquad \text{Eqn (3)}$$

Where, C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi's Model: Graph was plotted between cumulative percentage of drug released Vs square root of time.

$$Q = Kt1/2 \qquad \text{Eqn (4)}$$

Where, K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmeyer-Peppas: The dissolution data was also fitted to the well known Korsmeyer Peppas equation (as log cumulative percentage of drug released Vs log time), which is often used to describe the drug release behavior from polymeric systems and the exponent n was calculated through the slope of the straight line.

$$Mt/M\infty = Ktn \text{ Or } \log Mt/M\infty = \log K + n \log t \qquad \text{Eqn (5)}$$

Where, Mt /M∞ is the fractional solute release, Mt is the amount of drug released at time t, M∞ is the amount of drug release after infinite time, t is the release time, K is a kinetic release rate constant characteristic of the drug/polymer system, and n is the diffusional exponent that characterizes the mechanism of drug release.

If the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release. The result of drug release kinetics for X1-X4 formulation is shown in table 8.27 to 8.30.

Statistical Analysis:

Statistical analysis was conducted by using the software GraphPad InStat 3 results are shown in table 8.32.

Stability Studies:

Stability tests are the series of tests designed to obtain information on the stability of the pharmaceutical product in order to define its shelf life and utilization period under specified packaging and storage conditions.

Definition:

The stability of a product may be defined as the extent, to which a product retains, within specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packing. The characteristics include physical, chemical, microbiological, therapeutic and toxic properties and all are required to remain within acceptable limits till the time of use of the product by a patient.

The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. In addition, product-related factors influence the stability, e.g. the chemical and physical properties of the active substance and the pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system, and the properties of the packaging materials. Also, the stability of excipients that may contain or form reactive degradation products, have to be considered.

As a result of stability testing, a re- test period for the active substance or shelf life for the pharmaceutical product can be established, and storage conditions can be recommended.

A more comprehensive pharmacopoeial protocol (USP) prescribes the following criteria for acceptable levels of stability.

Stress testing of the active substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule. The nature of the stress testing will depend on the individual active substance and the type of pharmaceutical product involved (**Yoshio et al. 2006**).

Stress testing is likely to be carried out on a single batch of the active substance. It should include, the effect of temperatures in 100C increments (e.g., 500C, 600C, etc.) and above that for accelerated testing, humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the active substance. The testing should also evaluate the susceptibility of the active substance to hydrolysis across a wide range of pH values when in solution or suspension.

Accelerated Stability Studies:

The objective of accelerated stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably increasing the temperature. Accelerated stability studies are experimental designs.

- Many pharmaceutical preparations contain different adjuvant along with the drug. Ideally, drug degradation in the mixture has to be studied individually but it is time consuming and therefore, gross picture on the stability is evaluated.
- Some property of degradation, such as changes in the concentration of drug or the degraded substance, colour etc should be decided. Mechanism of the chemical reaction needs not to be explored, but such a study is always advantageous to predict stability.
- A stability indicating assay method is essential. Establish an analytical method which estimates the drugs but degraded substances should not interfere. Degradation product can also be estimated provided starting materials dose not interfere.
- The temperature dependency on the chemical degradation must be established, a linear relationship is desirable.

- Conclusion obtained by accelerated stability studies should be corroborated by results obtained at normal storage (temperature) conditions.
- A linear relationship with respect to time should be established as per kinetic principles. The order of reaction is determined.

Limitations:

Though accelerated stability studies have several advantages and widely used in pharmacy, it has a few limitations. The following aspects have to be considered in this study design.

- Accelerated stability studies are valid only when the breakdown depends on temperature.
- The results (shelf life etc.) obtained for one set of conditions for a preparation cannot be applied to other preparations of the same drug.
- Stability predictions at elevated temperatures are of little use when the degradation is due to

i. Diffusion

ii. Microbial contamination

iii. Photochemical reaction

iv. Excessive agitation

- Stability studies are meaningless, when the product loses its physical integrity at higher temperatures. For example

i. Coagulation of suspending agents

ii. Denaturation of proteins

iii. Breaking of as emulsion or change in the distribution coefficient of emulsifier at the high temperatures

iv. Loss of consistency of ointments

Predictions based on elevated temperature studies are generally satisfactory for solution dosage form.

In spite of these limitations, temperature is still considered as an important factor in the prediction of shelf life. However, use of excessively high temperature should be avoided.

Storage Condition and Sampling Plan:

Five Batches of the optimized formulation were wrapped in a butter paper followed by aluminium foil and placed in an aluminium pouch, which was heat-sealed at the end. The films were stored at 30 °C ± 0.5/ 60 ± 1 % RH and 45 °C ± 0.5/ 75 ± 1% RH in the stability chamber. Films were analyzed for various parameters.

General Protocol for Stability Studies of Films:

Stability studies for Film were conducted at two different storage conditions. From the batches of nicorandil films, optimized formulation was tested for stability studies. Films of optimized formula were stored at two different storage conditions namely 30 °C ± 0.5/ 60 ± 1 % RH and 45 °C ± 0.5/ 75 ± 1 % RH for one month. At periodic time intervals, the films were evaluated for weight variation, disintegration and dissolution time, drug content and in vitro drug release after storage for 5, 10, 15, 20, 25 and 30 days. The result of stability studies is shown in table 8.33, 8.34 and 8.35.

RESULTS AND DISSUSSION

Pre-formulation Studies:

Nicorandil was procure from Sigma Life Science. It was identified and characterized as per the identification test given in the Indian Pharmacopoeia (2010) and United State Pharmacopoeia.

Identification of the Drug:

Organoleptic Property:

- Colour: - White
- Odor: - Characteristic
- Taste: - Bitter
- Appearance: - white crystalline powder

UV Spectrophotometric Identification:

Estimation of Nicorandil by spectrometric method with simulated saliva buffer pH 6.8 media was done by the procedure mention in section 4.5.1.2 and compared with reference results. Maximum absorbance was observed at 845 nm shown in Figure 5.1.

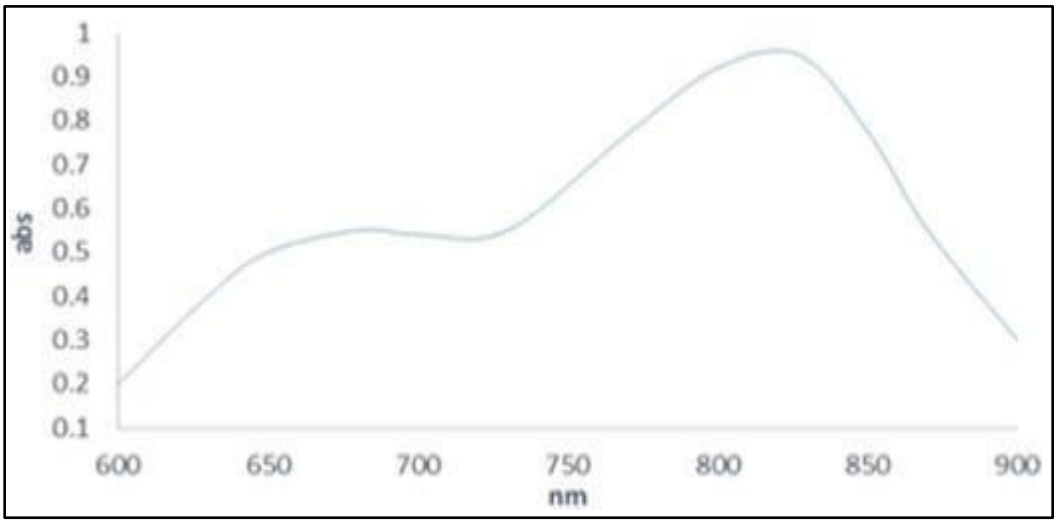


Figure: 7. U.V Spectroscopy of the Nicorandil

FTIR Spectroscopy

The IR spectrum of the obtained sample was done acc. to the procedure mention in section 4.5.1.3 and complied with the IR spectrum of reference standard of Nicorandil. IR spectra of sample drug show similar characteristic peaks. Figure 6.2 shows IR spectra analysis of standard drug Nicorandil and Figure 6.3 shows the IR spectra of sample drug and the interpretation is shown in table 5.1**.**

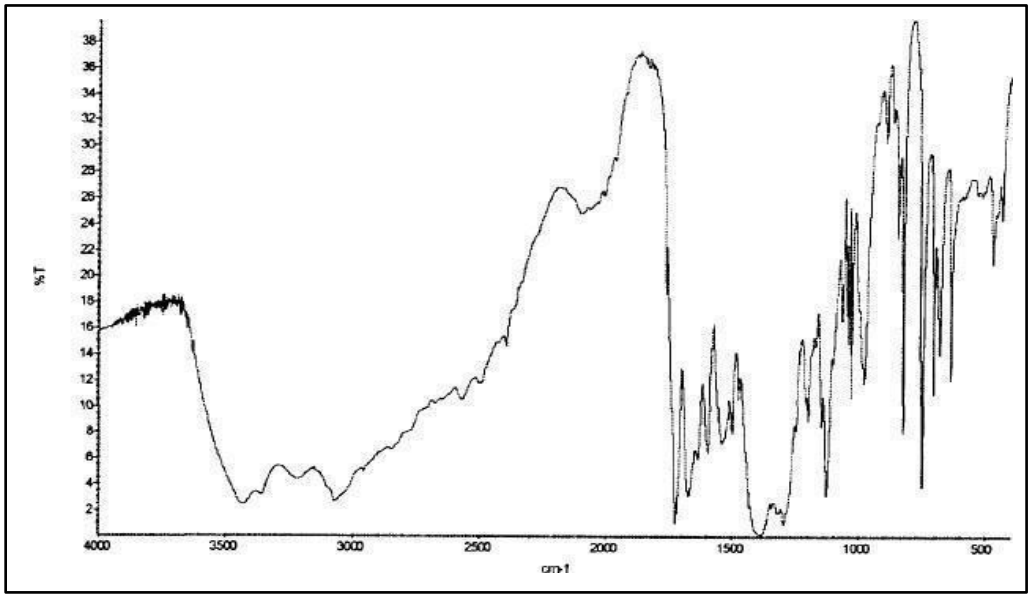


Figure: 8. IR spectra analysis of standard Nicorandil

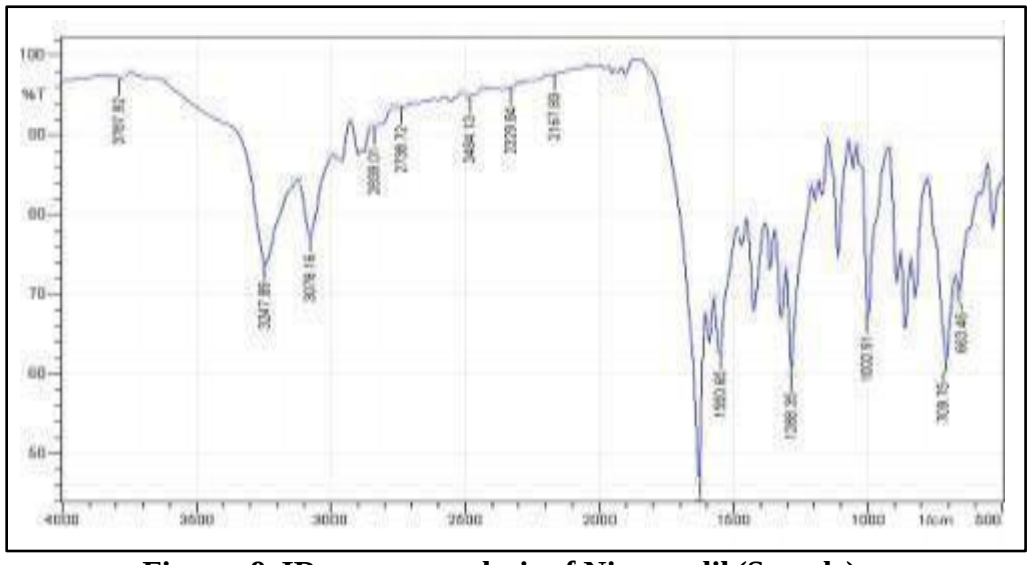


Figure: 9. IR spectra analysis of Nicorandil (Sample)

Table: 10. Interpretation of Nicorandil

Sr. no.	Reported peaks (cm^{-1}) in standard drug	Observed peak (cm^{-1}) of sample drug	Inference
1	1290 (1300)	1295	O-NO2 stretching
2	1060 (1075)	1002	C-0 stretching
3	1653 (1650)	1550	CO-NH
4	1371 (1310)	1388	Aromatic pyridine tertiary amine
5	3244 (3320)	3347	N-H stretching
6	1724 (1700)	1824	C=0 stretching

Inference:

The peaks of sample drug are very close to the peaks of standard drug so it indicates the sample of Nicorandil is authentic.

Differential Scanning Calorimetry:

The DCM was subjected to DSC acc. to the procedure mention in section 4.5.1.4 using (PerkinElmer Thermal Analyzer) and thermogram was obtained and enthdothermic peak was matched with the melting point of the drug.

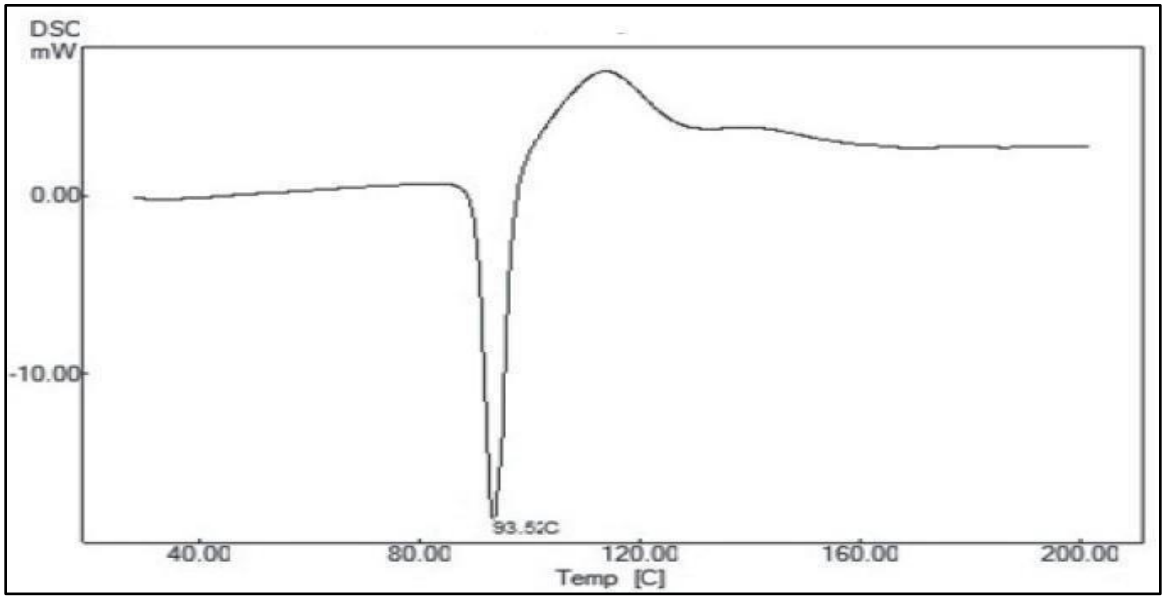


Figure: 10. DSC thermogram of Nicorandil

Inference:

The thermogram of differential scanning calorimetry showed sharp endothermic peaks of Nicorandil at 93.5 °C respectively corresponding to the melting range of Nicorandil (92-93 °C), Hence, complies with the standards.

Inference of Identification of Drug:

Organoleptic characters like color, odor and its nature, melting point of drug and UV spectrum of the drug were used for the identification of drug. The Organoleptic characters and melting point was observed and result was found similar to that given in official monographs. The drug was also observed for its UV spectrum. The scanning result showed the λmax for the drug is 465 nm. The spectrum was also super imposable to the official spectrum of Nicorandil. Thus on the basis of above result, the conclusion was drawn that the sample of Nicorandil was authentic.

Solubility Study of the Drug:

It is freely soluble in acetone, methanol, ethanol and acetonitrile; soluble in ethyl acetate and chloroform; sparingly soluble in water; slightly soluble in ether.

Determination of Melting Point:

Melting point range of the drug having from 92°C to 93 ºC and Melting point of the drug was found to be 92°C. So the drug was found to be suitable for the formulation.

Partition Coefficient of Nicorandil:

Partition coefficient of the drug was determined by the procedure mention under the section 7 and shown in table 8.2.

Table: 11 Partition coefficient of Nicorandi

Water: n-octanol (ml)	Conc. of drug in water (µg/ml)	Conc. of drug in n-octanol (µg/ml)	Log P
1:1	6.67	20.9	3.12
1:1	6.14	21.5	3.43

Inference:

The average value of log P was found out to be 3.12. The standard value of log P for the drug is 3.98.

Loss on Drying:

LOD of the sample drug was performed acc. to the procedure mention in section 4.5.5. According to USP monograph of Nicorandil, % loss of the drug should not be more than 1% of its weight and the result of LOD of Nicorandil is shown in Table 8.3.

Table: 12. % Loss on Drying of Nicorandil

S. No.	Wt. of drug before drying (gm)	Wt. of drug drying (gm)	LOD (%w/w)	Average LOD (%w/w)
1.	1.024	1.016	0.58	0.53
2.	1.026	1.019	0.48	

Analytical Method for Nicorandil:

Preparation of Calibration Curve of Nicorandil:

Calibration curve of Nicorandil were prepared as per the procedure mentioned in section 7.

Table: 13. Mean Absorbance ± S.D of Different Concentration of Nicorandil in 0.1N HCl

Sr. No.	Con. In µg/ml	Absorbance (at 508 nm)			Average Abs. with S.D.
		I	II	III	
1	2	0.106	0.12	0.107	0.261667
2	4	0.198	0.205	0.202	0.470333
3	6	0.294	0.287	0.275	0.672667
4	8	0.340	0.341	0.339	0.794
5	10	0.436	0.453	0.440	1.035667
6	12	0.543	0.547	0.545	1.271667
7	14	0.630	0.66	0.634	1.501333
8	16	0.757	0.758	0.755	1.766667
9	18	0.827	0.827	0.824	1.928667
10	20	0.913	0.901	0.909	2.117

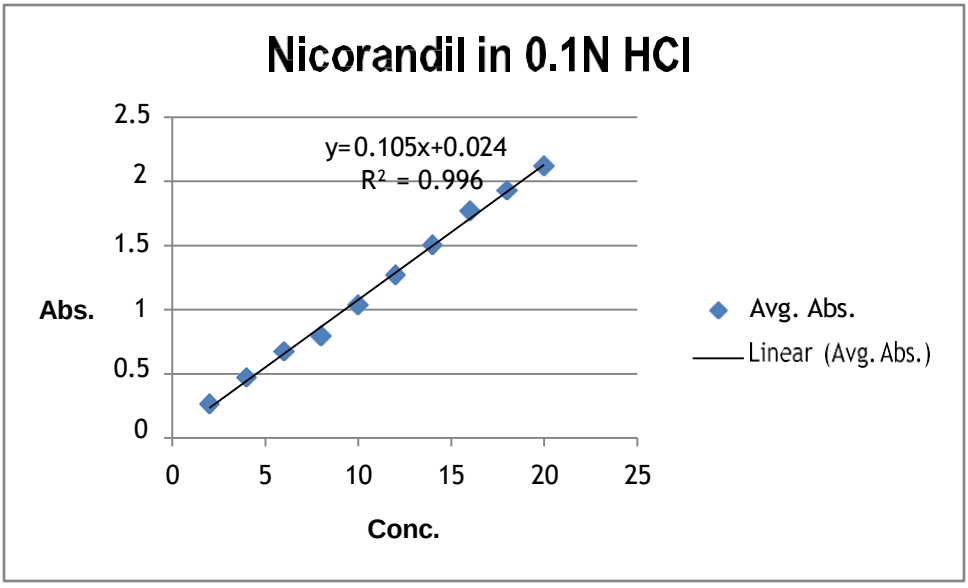


Figure: 11. Standard Plot of Nicorandil in 0.1N HCl at 508 nm

Table: 14 Mean absorbance ±S.D of different concentration of Nicorandil in phosphate buffer pH 6.8

Sr. No.	Con. In µg/ml	Absorbance (at 465 nm)			Average Abs. with S.D
		I	II	III	
1	10	0.083	0.094	0.090	0.207
2	20	0.195	0.201	0.195	0.461
3	30	0.273	0.274	0.281	0.640667
4	40	0.368	0.354	0.364	0.843333
5	50	0.457	0.455	0.450	1.062
6	60	0.539	0.540	0.545	1.260667
7	70	0.630	0.623	0.633	1.464
8	80	0.734	0.725	0.730	1.702333
9	90	0.801	0.810	0.820	1.884333
10	100	0.913	0.916	0.910	2.132333

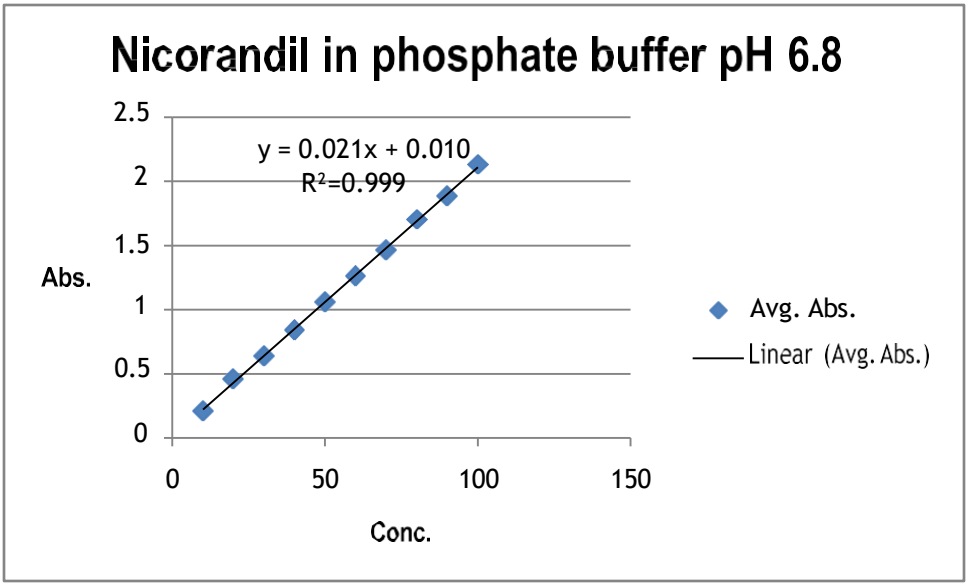


Figure: 12. Standard plot in phosphate buffer pH 6.8

Table: 15. Mean absorbance ±S.D of different concentration of Nicorandil in phosphate buffer pH 7.4

S. No.	Conc. (µg/ ml)	Absorbance at 465nm (at 465 nm)			Average Abs. with S.D
		I	II	III	
1.	10	0.137	0.141	0.143	0.325667
2.	20	0.199	0.200	0.201	0.466
3.	30	0.270	0.271	0.267	0.63
4.	40	0.341	0.340	0.339	0.794
5.	50	0.430	0.440	0.449	1.019667
6.	60	0.490	0.511	0.511	1.171333
7.	70	0.580	0.574	0.580	1.347333
8.	80	0.645	0.643	0.650	1.504667
9.	90	0.730	0.724	0.718	1.693333
10.	100	0.797	0.804	0.811	1.871333

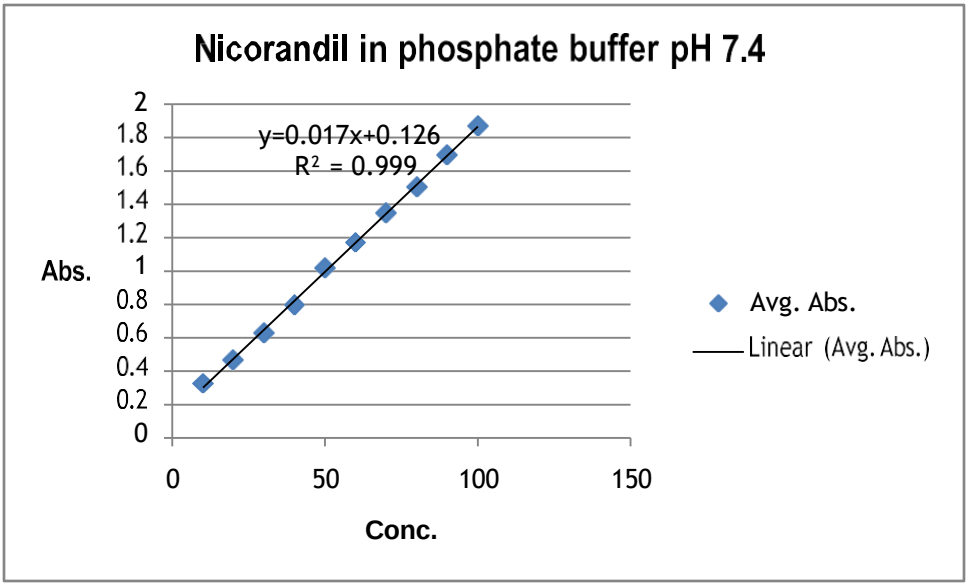


Figure: 13. Standard Plot of Nicorandil in phosphate buffer pH 7.4 Compatibility Study by FTIR:

FTIR spectra were recorded to assess the compatibility of the drugs and excipients. Study was performed acc. to the procedure mention under the section 4.5.7.1. The FTIR Spectra are represented in figure 5.8.

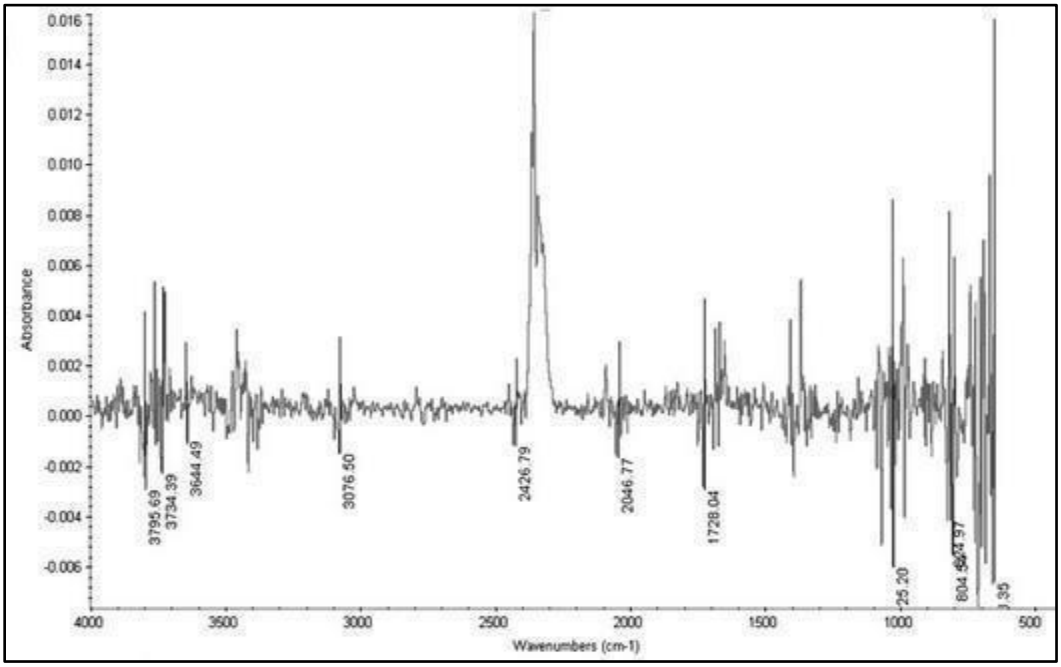


Figure: 14. FT-IR spectra of Nicorandil with excipients

Inference:

FTIR spectra of the dicyclomine, showed characteristic C-N, C-O, C-H, C=O(ester) stretching bands at 1134.07 cm-1, 1193.85 cm-1, 2929.67 cm-1, 1718.45 cm-1,respectively. The compatibility of drugs with physical mixture of drug (s) & PVA, physical mixture of drug and HPMC-15, and physical mixture of drug, and aspartame were recorded and examined. In FTIR spectra of dicyclomine, characteristic C=O stretching band was observed at 1718.45 cm-1 which are in agreement with the reported values. The results showed no chemical interaction and changes took place in FTIR spectra of the drug and various excipients alone or in combination exhibiting compatibility of the drug with all excipients.

Compatibility Study by DSC:

Study was performed acc. to the procedure mention under the section 7. The DSC thermograms of Nicorandil and physical mixture of Nicorandil, PVA and HPMC-15 are given in the figure 8.9.

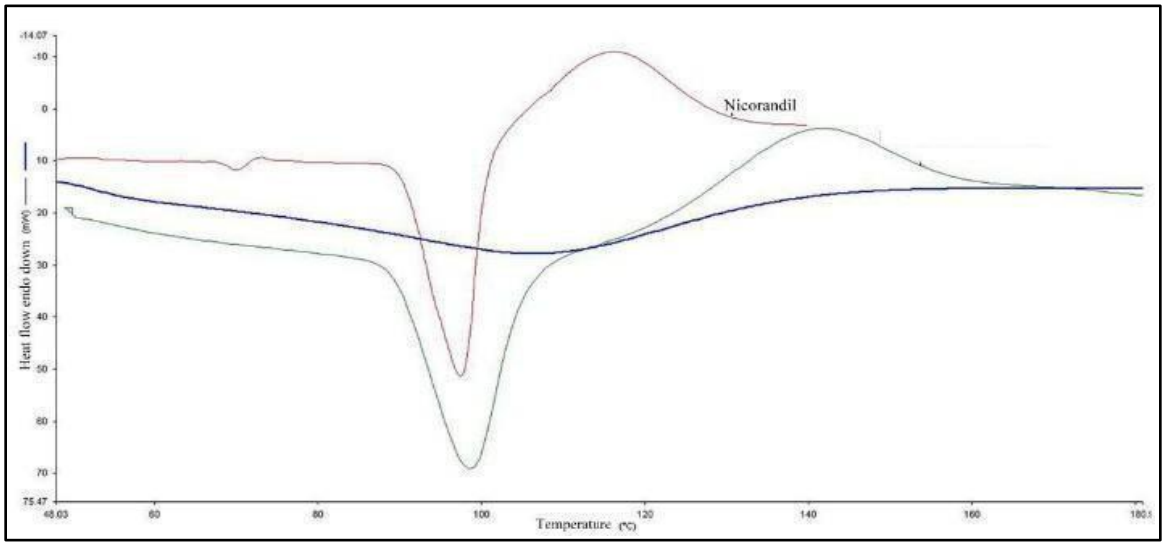


Figure: 15. DSC thermogram of drug and polymers

Inference:

It is observed that no any physical interaction was found between drug and polymers.

Optimization and Evaluation of Placebo Films

Composition of Polymeric Films:

In the Preformulation study the films were prepared using alone HPMC-15, HPMC-50, PVA, PVP, Eudragid RL-100 and in combination of HPMC-15/PVA, HPMC-50/Eudragid by the procedure mentioned under the section 4.6 and composition of placebo are shown in table 5.9. The prepared were evaluated for film flexibility, tensile strength, % elongation, dissolution time, and disintegration time. Results indicated that the films have variable film flexibility, tensile strength, % elongation, dissolution time, and disintegration time. So there is a need for optimization to get the film of desired properties.

Table: 16. Composition of Placebo Films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
HPMC-5	2%w/v	-	-	-	-	-	-	-
HPMC -15	-	2%w/v	-	-	-	-	-	-
HPMC-50	-	-	2%w/v	-	-	-	-	-
HPMC: Eudragid RL-100							1:1%	
PVA	-	-	-	2%w/v	-	-	-	-
PVP	-	-	-	-	2%w/v	-	-	-
HPMC:PVA	-	-	-	-	-	1:1%w/v	-	-
PEG-400	3%w/v	3%	3%w/v	3%w/v	3%w/v	3%w/v	3%w/v	3%w/v
Tween 80	0.2ml	-	-	-	-	-	-	-
Ethanol q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water q.s	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml

Table: 17. Evaluation of Film Forming Polymers and Combination of Polymers

Evaluation Parameters	**HPMC-50**	**PVP**	**HPMC-50/ Eudragid RL-100**	**HPMC-15/PVA**
Film forming capacity	Good	Very poor	Good	Good
Appearance	Transparent, No stickiness	-	Transparent	Transparent
Film flexibility	Moderate	-	moderate	Moderate

Tensile strength	Poor to moderate	-	Poor to moderate	Moderate
% elongation	Poor	-	moderate	Moderate to high
Disintegration time(sec)	49	-	30	32
Dissolution time (sec)	240	-	160	190
Thickness (mm)	0.150	-	0.280	0.260
Folding endurance	>800	-	600	500

Inference:

It was observed that the HPMC-15 and PVA, combination of HPMC-15: PVA and HPMC-50: Eudragid have good film forming capacity, optimum disintegration time and desired mechanical properties. HPMC-5 has average film forming capacity and mechanical properties but greater disintegration time. HPMC-50 has good film forming capacity and mechanical properties but greater disintegration time. Results indicated that the films have variable film flexibility, tensile strength, % elongation, dissolution time, and disintegration time shown in table 5.8. So on the basis of evaluation parameters PVA and HPMC -15and combination of HPMC-15: PVA and HPMC-50: Eudragid RL- 100 was selected for the preparation of fast dissolving film.

Table: 18. Formulation of placebo fast dissolving film with different concentration of HPMC-15 and PVA: **Films are prepared by the procedure mentioned under the section 7.**

Ingredients	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**
HPMC -15	1%w/v	1.5%w/v	2%w/v	3%w/v	-	-	-
PVA	-	-	-	-	2%w/v	2.5%w/v	3%w/v
PEG-400	3%w/v	3%	3%w/v	3%w/v	3%w/v	3%w/v	3%w/v
Tween 80	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml
Ethanol q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water q.s	100ml	100ml	100ml	100ml	100ml	100ml	100ml

Table: 19. Formulation of placebo fast dissolving film with different concentration of the combination of polymers

Ingredients	B1	B2	B3	B4	B5	B6	B7
HPMC- 15:PVA	1:1% w/v	1:1.5% w/v	1.5:1% w/v	-	-	-	-
HPMC-50:Eudragid				1:1%w/v	1.5:1% w/v	2:1% w/v	2.5:1% w/v
PEG-400	3%w/ v	3%w/v	3%w/v	3%w/v	3%w/v	3%w/v	3%w/v
Tween 80	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml
Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water q.s	100ml	100ml	100ml	100ml	100ml	100ml	100ml

Table: 20. Evaluation of Concentration of Film Forming Polymer (HPMC-15)

Evaluation Parameters	HPMC E 15 Conc.			
	1%	1.5%	2%	3%w/v
Physical appearence	Transparent, stickiness	Transparent, stickiness	Transparent, No stickiness	Transparent, No stickiness
Film flexibility	Less	Less	Moderate	Moderate
Tensile strength	Poor	poor	Moderate	Moderate
% elongation	Poor to moderate	Less	Moderate	Moderate
Disintegration time (sec)	30	35	37	52
Dissolution time (sec)	100	140	168	240
Folding endurance	200	300	400	300
Thickness (mm)	0.15	0.19	0.27	0.33

Table: 21. Evaluation of concentration of film forming polymer (PVA)

Evaluation parameters	PVA conc.		
Physical Appearence	2% w/v	2.5% w/v	3% w/v
Film Flexibility	Moderate	Good	Good
Tensile Strength	Moderate	High	High
% elongation	Less	Moderate	High

Disintegration time(sec)	12	14	26
Dissolution time	96	140	190
Folding endurance	>1000	>1000	>1000
Thickness	0.210	0.240	0.320

Table: 22. Evaluation of concentration of polymer used in combination:

Evaluation parameters	**HPMC-15: PVA.**		
	1:1% w/v	1:1.5% w/v	1.5:1% w/v
Physical Appearance	Transparent	Transparent	Transparent
Film Flexibility	Moderate	Moderate	Moderate
Tensile Strength	Low	Moderate	Moderate
% elongation	Poor to moderate	Moderate	Poor to moderate
Disintegration time(sec)	20	24	32
Dissolution time	140	129	160
Folding endurance	100	500	300
Thickness	0.154	0.170	0.172

Table: 23. Evaluation of Concentration of Polymer Used in Combination:

Evaluation parameters	**HPMC-50: Eudragid RL-100**			
Physical Appearance	1:1% w/v	1.5:1% w/v	2:1% w/v	2.5:1%w/v
	Transparent, Stickiness	Transparent , Stickiness	Transparent Stickiness	Transparent, No stickiness
Film Flexibility	Moderate	Moderate	Moderate	Moderate
Tensile Strength	Low	Moderate	Moderate	Moderate
% elongation	Poor to moderate	Moderate	Poor to moderate	Moderate
Disintegration time(sec)	20	25	27	24
Dissolution time	240	190	150	129
Folding endurance	>500	>800	>800	>800
Thickness	0.154	0.170	0.172	0.175

Optimization of Placebo Film on the Basis of Concentration:

The Prepared films were evaluated for various evaluation parameters as shown in table 5.14 and 5.15. Results indicated that the films have variable film flexibility, tensile strength, % elongation, dissolution time, and disintegration time .It was evaluated that the film formed by using HPMC-15(2%w/v), PVA (2.5%w/v), HPMC:PVA(1:1.5%w/v) and HPMC: Eudragid (2:1%) form transparent film without any stickiness, have optimum disintegration time and shows all the desired film forming parameters. So on the basis of evaluation parameters these were selected for the preparation of drug loaded film.

Formulation of Drug Loaded Film:

Dose calculation was done by the method mention in section 7 and formulation of drug loaded film was done as the procedure mentioned under the section 7.

Table: 24. Composition of Drug Loaded Fast Dissolving Film

Ingredients	X1	X2	X3	X4
Nicorandil (mg)	251	251	251	251
PVA(mg)	250	-	-	-
HPMC-15	-	200mg		-
HPMC- 50:Eudragid	-	-	200:100mg	-
HPMC-15:PVA	-	-	-	100:150mg
PEG-400	300	300	300	300
Aspartame	62.52	62.52	62.52	62.52
citric Acid	15	15	15	15
Menthol	0.029	0.029	0.029	0.029
Tween -80	0.2ml	0.2ml	0.2ml	0.2ml
Water(ml)	10	10	10	10
Ethanol	q.s	q.s	q.s	q.s

Optimization of Sweetener for the Fast Dissolving Films:

One of the approaches tried to mask the bitter taste of the formulation was addition of sweetener and flavor. Aspartame and was added in concentration: 5, 10, 15 and 20 % of

the polymer to mask the bitter taste of the drug by the procedure mentioned under the section 7.

Table: 25. Optimization of sweetener for the fast dissolving films:

Ingredients	Batch B1	Batch B2	BatchB3	Batch B4
Nicorandil (mg)	251	251	251	251
PVA (mg)	200	200	200	200
PEG-400 (% of Polymer)	15	15	15	15
Aspartame	5 (12.5mg)	10% (25.1mg)	15% (37.6mg)	25% (62.52mg)
citric acid	20mg	20mg	20mg	20mg
Menthol	0.029	0.029	0.029	0.029
Distilled Water (ml)	12	12	12	12
Bitter index level	2.5	2.0	1.5	1

Inference:

It was concluded that the bitterness of the drug was masked by addition of about 62.52 mg of aspartame (i.e. 25 % of drug). So batch B4 showed the best taste masking results.

Evaluation of Fast Dissolving Film:

All the evaluation parameters of fast dissolving film are performed according to the procedure mentioned under the section 7. The results are shown in table 8.21 and 8.22 and the X1-X4 formulations are shown in figure 8.19.

Table: 26 Evaluation of mouth dissolving film of Nicorandil

Evaluation Parameters	Thickness (mm)	Mean weight (mg)	Drug content %	% moisture absorption	% Moisture loss	Swelling index
X1	0.149	118.3	98	1.50	1.426	67.20
X2	0.171	123.4	96	1.44	2.203	64.10
X3	0.173	128	98	2.30	2.879	66.32
X4	0.167	124.6	97	2.037	1.974	64.50

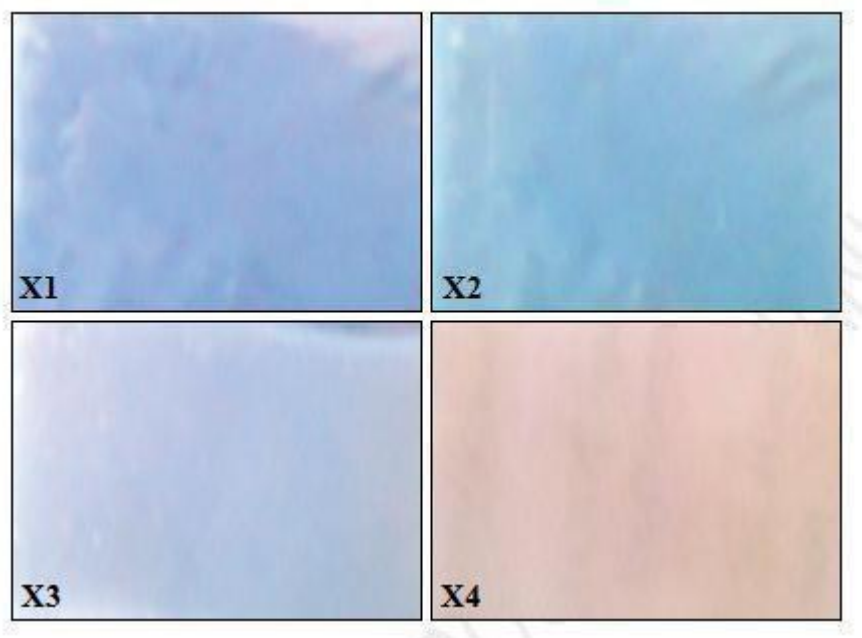


Figure: 16. Film formulation X1-X4

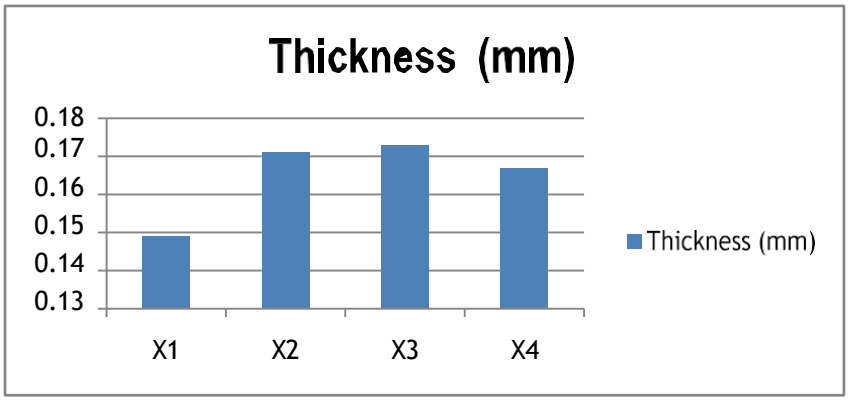


Figure: 17. Thickness study of X1-X4 film Formulations

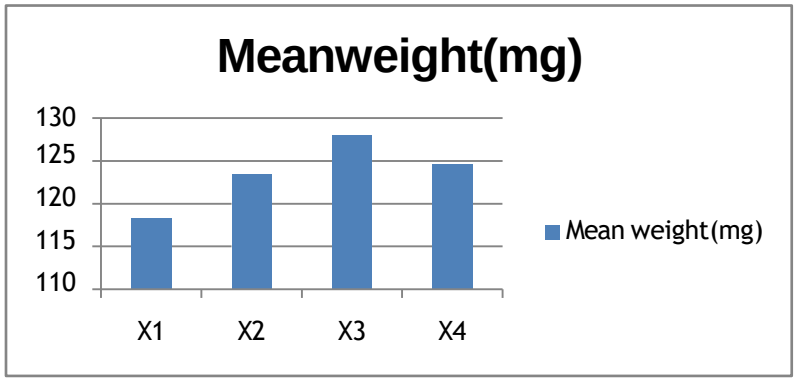


Figure: 18. Mean weight study of X1-X4 film Formulations

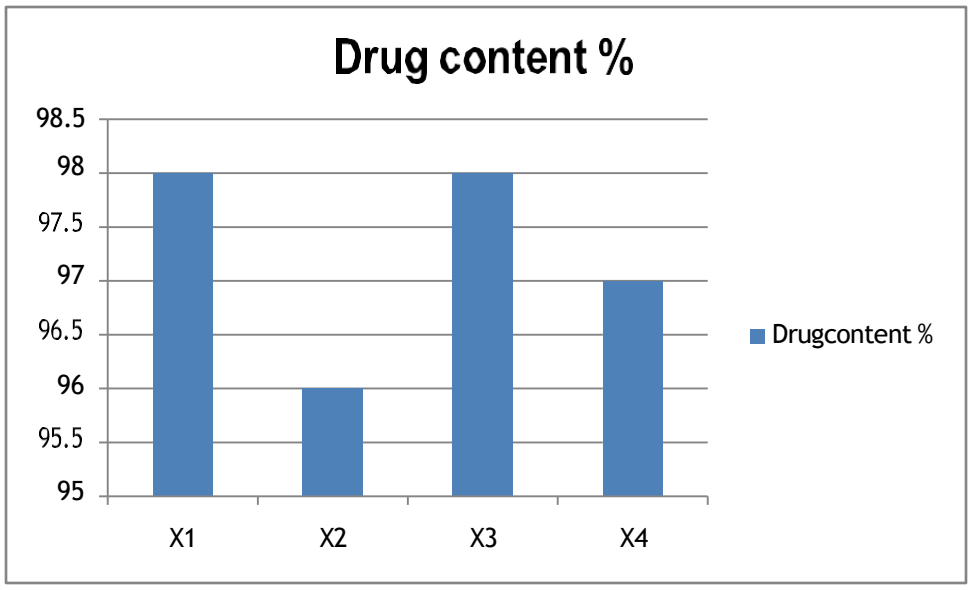


Figure: 19. Comparison of % drug content from X1-X4 formulations

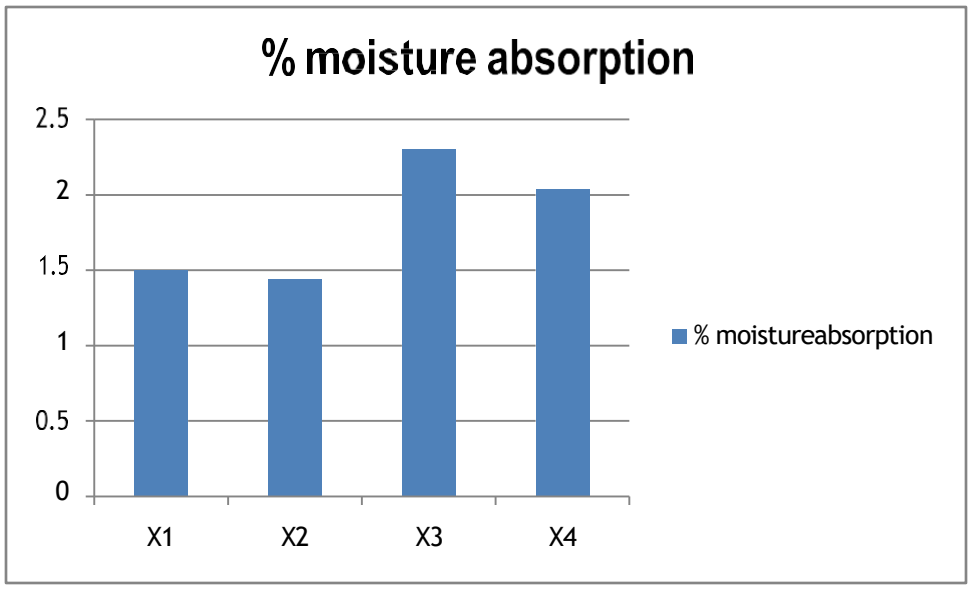


Figure: 20. % Moisture absorption study of X1-X4 film Formulations

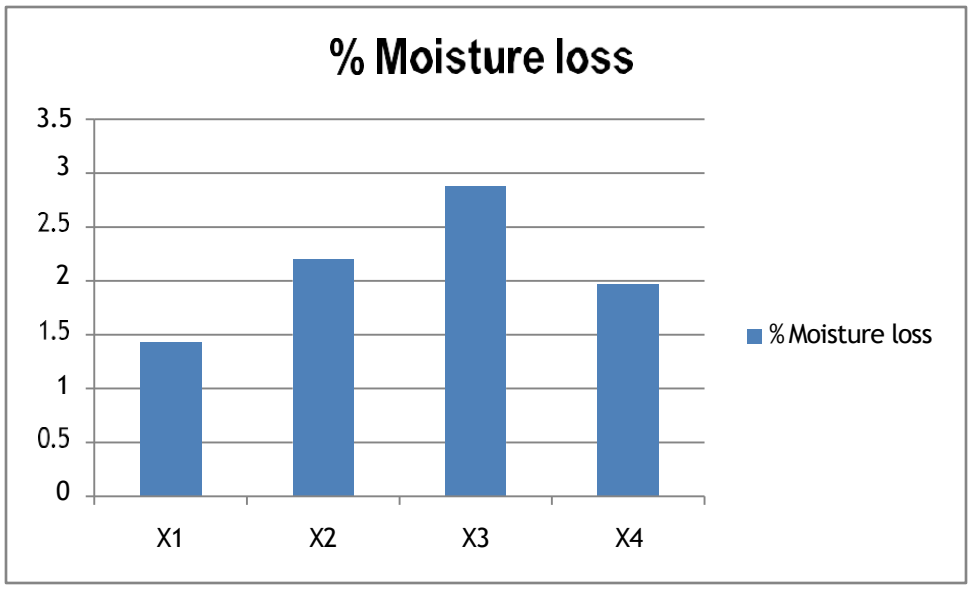


Figure: 21. % Moisture loss study of X1-X4 film Formulations

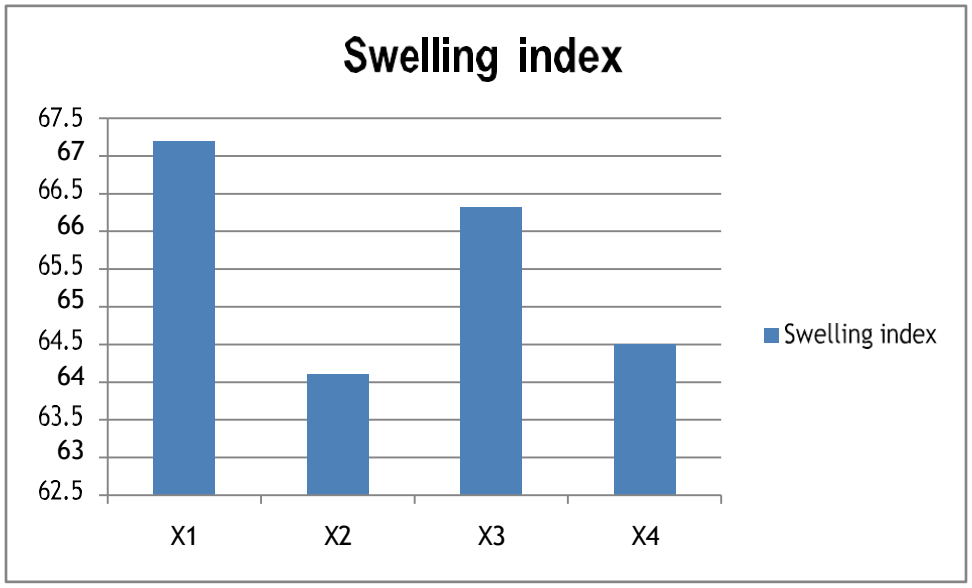


Figure: 22 Swelling index study of X1-X4 film Formulations

Table: 27. Evaluation of mouth dissolving film of Nicorandil

Evaluation Parameters	Tensile strength Kg/mm^2	% Elongation	Folding Endurance	Disintegration time (sec)	Dissolution time (sec)
X1	1.283±0.231	65.12±1.66	>800	15	134
X2	1.135±0.004	22.9±0.58	200	32	165
X3	1.286±0.037	36.27±1.67	>800	20	125
X4	1.393±0.091	40.72±1.42	600	23	122

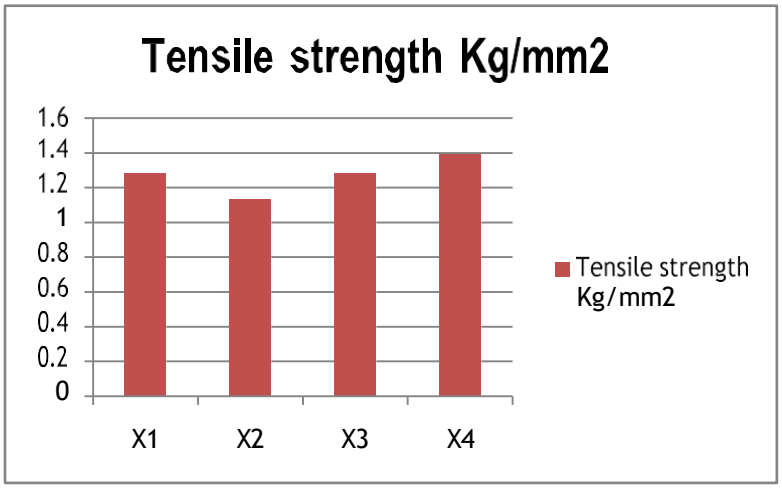


Figure: 23. Tensile strength study of X1-X4 film Formulations

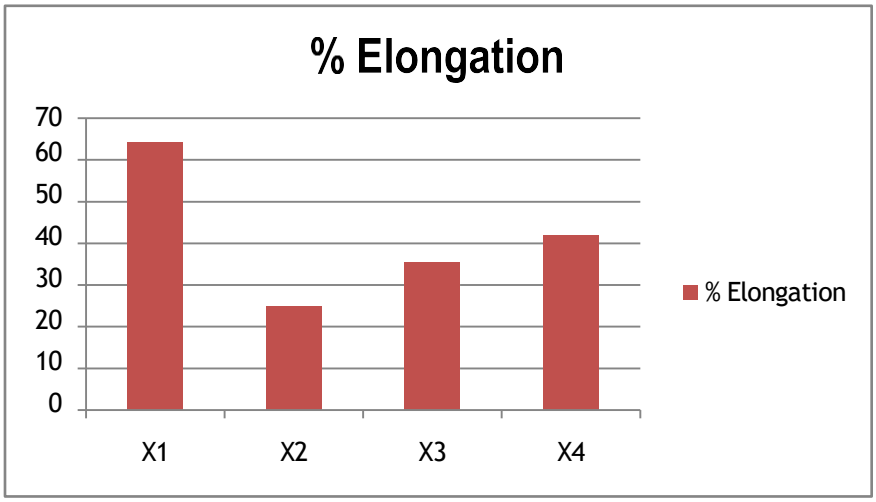


Figure: 24. % Elongation study of X1-X4 film Formulations

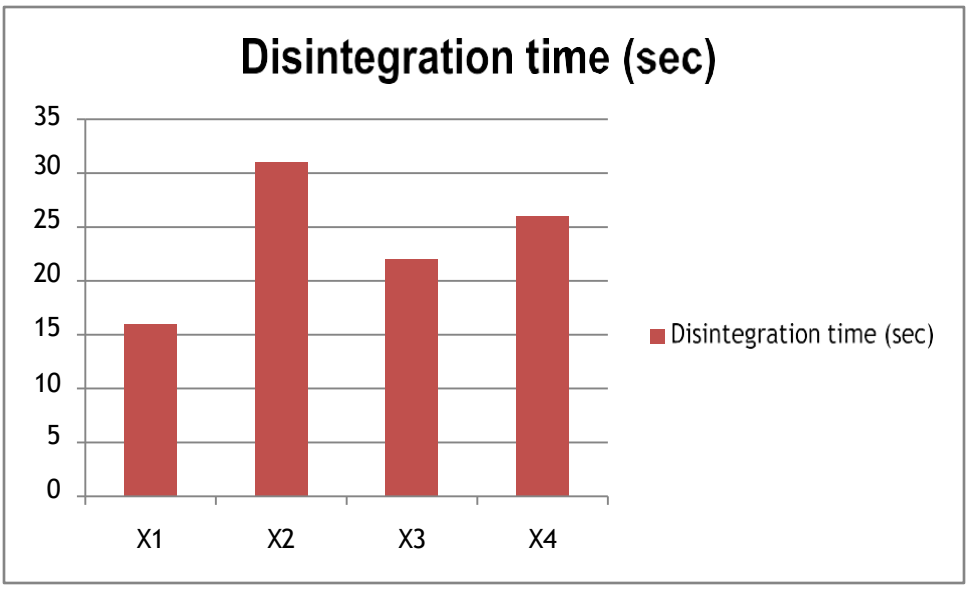


Figure: 25. Disintegration study of X1-X4 film Formulations

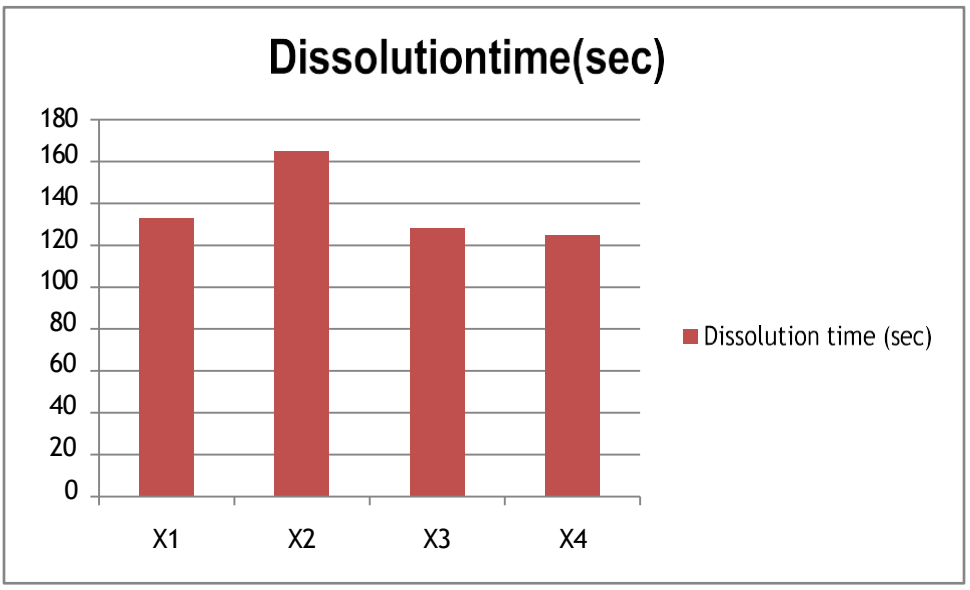


Figure: 26. Dissolution study of X1-X4 film Formulations

Inference:

It was observed that all the formulation posses desirable film forming parameters, but on the basis of thickness, swelling index, disintegration time and dissolution time X1 formulation was selected as optimized film. X1 film has minimum disintegration time about 15 sec and minimum dissolution time i.e. 134 sec. in comparison to other

formulation. The comparison graph between disintegration and dissolution time, % moisture absorption and % moisture loss, tensile strength, percent elongation.

Drug Content:

The percent drug content for all the formulations were calculated acc. to the procedure mention under the section 4.6.6.2 and the comparison between % drug content of all formulation batches is shown in figure 5.21.

In-vitro drug release of X1- X4 Formulation:

The in vitro dissolution test was carried out in a USP II paddle dissolution apparatus according to the procedure mentioned under the section: 4.6.6.4. the data obtained is shown in table 5.23 to 5.26.The in-vitro release graph of all the formulation is shown in figure 5.25.

Table: 28. In-vitro drug release of X1 Formulation

Time	Absor-bance	Concentration			Final conc.	CPDR	% DR	log of % DR	sq. root of (t)	Mt/m8	Ln	Ln of time
		Conc. in mg/10ml	Cum. Conc. in mg/10ml	Conc. in mg/300ml								
15	0.149	0.166	0.169	5.0335	5.043	26.16	76.98	1.876	3.809	0.455878	-0.78555	2.70905
30	0.201	0.235	0.40111	7.08	7.178	34.80	69.19	1.812	5.466	0.64910	-0.4326	3.401097
45	0.270	0.305	0.70890	9.21	9.622	49.03	50.97	1.798	6.717	0.869570	-0.13976	3.809662
60	0.320	0.346	1.05223	11.335	11.22	58.20	40.70	1.645	7.756	1.009	0.08	4.094945
90	0.355	0.380	1.43557	11.59	13.55	67.70	38.23	1.587	8.60	1.136898	0.128202	4.499081
120	0.399	0.445	1.87779	12.271	16.7	70.588	27.49	1.487	9.49	1.33189	0.286763	4.787092
150	0.445	0.480	2.36365	13.58	18.44	81.24	18.75	1.287	12.20	1.48989	0.398982	5.010035
180	0.443	0.468	2.85278	14.65	17.03	84.18	16.80	1.134	13.45	1.542417	0.439051	5.340108
210	0.449	0.493	3.34690	13.87	19.69	87.46	12.50	1.065	11.63	1.60190	0.498123	5.480039
240	0.447	0.498	3.84405	14.95	17.27	90.423	8.69	0.930	15.40	1.65098	0.507882	5.700782
300	0.449	0.494	4.34004	15.90	19.70	93.89	9.10	0.789	17.30	1.70079	0.534348	5.70382

Table: 29. *In- vitro* Drug Release of X2 Formulation

Time (sec)	Abs	Concentration			Final conc.	CPDR	% DR	Log of % DR	Sq. root of (t)	M0/M ∞	Ln	Ln of time
		Conc. in mg/10ml	Cum. Conc. in mg/10ml	Con. in mg/300 ml								
15	0.138	0.152	0.152	4.501	4.538	22.68	76.33	1.867	3.845	0.3835	-0.962	2.70845
30	0.190	0.223	0.376	6.643	6.752	33.70	65.24	1.834	5.467	0.5661	-0.563	3.401134
45	0.237	0.268	0.629	7.832	8.213	42.12	59.98	1.765	6.716	0.6221	-0.368	3.834662
60	0.281	0.330	0.948	9.637	11.29	53.30	47.67	1.667	7.741	0.8663	-0.143	4.095645
90	0.334	0.359	1.320	10.96	12.80	59.26	42.73	1.612	8.663	1.05	0.00	4.48881

120	0.387	0.429	1.734	12.93	13.20	71.26	29.75	1.46	9.485	1.223	0.1847	4.767492
150	0.404	0.439	2.193	13.37	15.18	74.40	25.59	1.380	16.221	1.276	0.2415	5.085635
180	0.405	0.446	2.639	13.48	16.29	77.94	26.03	1.343	19.344	1.32	0.2745	5.394108
210	0.4011	0.453	3.089	13.523	16.34	81.60	18.30	1.289	14.62	1.3690	0.3089	5.670639
240	0.413	0.459	3.542	13.50	17.66	83.23	17.72	1.245	19.49	1.413	0.3423	5.707572
300	0.427	0.454	3.989	13.52	17.12	85.54	15.46	1.162	19.32	1.467	0.3667	5.757782

Table: 30. *In- vitro* Drug Release of X3 Film

Time (sec)	**Abs**	**Concentration**			**Final conc.**	**CPDR**	**% DR**	**Log of % DR**	**Sq. root of (t)**	**M0/M8**	**Ln of M0/M∞**	Ln time
		Conc. in mg/10ml	Cum. Con in mg/10ml	Con. in mg/300ml								
15	0.143	0.157	0.1567	4.7356	4.73	23.69	75.33	1.873	3.873	0.398779	-0.931573	2.70
30	0.215	0.224	0.3896	6.878	6.994	34.99	64.04	1.843	5.477	0.555836	-0.541561	3.40
45	0.242	0.275	0.6546	8.232	8.586	42.73	56.07	1.796	6.708	0.714571	-0.33209	3.8
60	0.289	0.326	0.9822	9.745	11.346	51.09	49.21	1.673	7.746	0.866717	-0.145713	4.08
90	0.326	0.369	1.3523	11.13	12.322	60.18	78.92	1.631	8.66	1	0	4.4
120	0.391	0.439	1.7856	13.131	13.467	71.42	29.58	1.561	9.487	1.267191	0.1896456	4.78
150	0.425	0.462	2.255	13.998	15.56	79.07	28.23	1.887	10.25	1.39007	0.2720406	5.01
180	0.425	0.465	2.7289	14.17	15.498	82.13	16.9	1.283	13.42	1.366186	0.3122997	5.30
210	0.431	0.437	3.235	14.23	16.963	85.78	14.21	1.182	14.49	1.4987113	0.3440008	5.98
240	0.439	0.469	3.674	14.332	17.523	87.534	13.5	1.077	15.49	1.456935	0.3759774	5.79
300	0.449	0.497	4.1567	14.334	18.96	88.878	9.12	1.025	17.32	1.496875	0.4022514	5.79

Table: 31. *In-vitro* Drug Release of X4

Time	Abs	Concentration			Final Conc.	CPDR	%DR	Log of %DR	Sq. root of (t)	M0/M∞	Ln of M0/M∞	Ln time
		Conc. in mg/10 ml	Cum.con. in mg/10ml	Con. in mg/300 ml								
15	0.138	0.153	0.153	4.622	4.630	23.13	75.83	1.856	3.973	0.487442	-0.867362	2.7
30	0.199	0.222	0.377	6.61	6.764	33.77	67.23	1.891	5.477	0.609891	-0.5043438	3.40
45	0.251	0.27	0.655	8.338	8.708	43.56	55.46	1.852	6.798	0.765811	-0.234412	3.80
60	0.313	0.357	1.04	10.54	11.05	55.6	43.24	1.646	7.746	1	0	4.08
s90	0.388	0.449	1.41	13.206	14.57	71.94	29.66	1.497	8.06	1.2797	0.246928	4.4
120	0.426	0.479	1.913	14.12	15.55	77.02	32.28	1.308	10.95	1.393828	0.3980645	4.70
150	0.432	0.483	2.380	14.5	16.35	82.34	18.76	1.249	12.25	1.474651	0.4325516	5.0
180	0.43	0.480	2.898	14.97	17.0	84.99	16.01	1.106	13.42	1.524602	0.4765692	5.34
210	0.441	0.487	3.374	14.69	17.54	87.96	13.24	1.098	14.79	1.587867	0.4599418	5.48
240	0.42	0.491	3.894	14.7	18.02	90.07	9.828	0.994	15.89	1.698034	0.7628603	5.70
300	0.440	0.49	4.394	14.76	18.50	92.92	8.148	0.876	17.02	1.94408	0.5996094	5.70

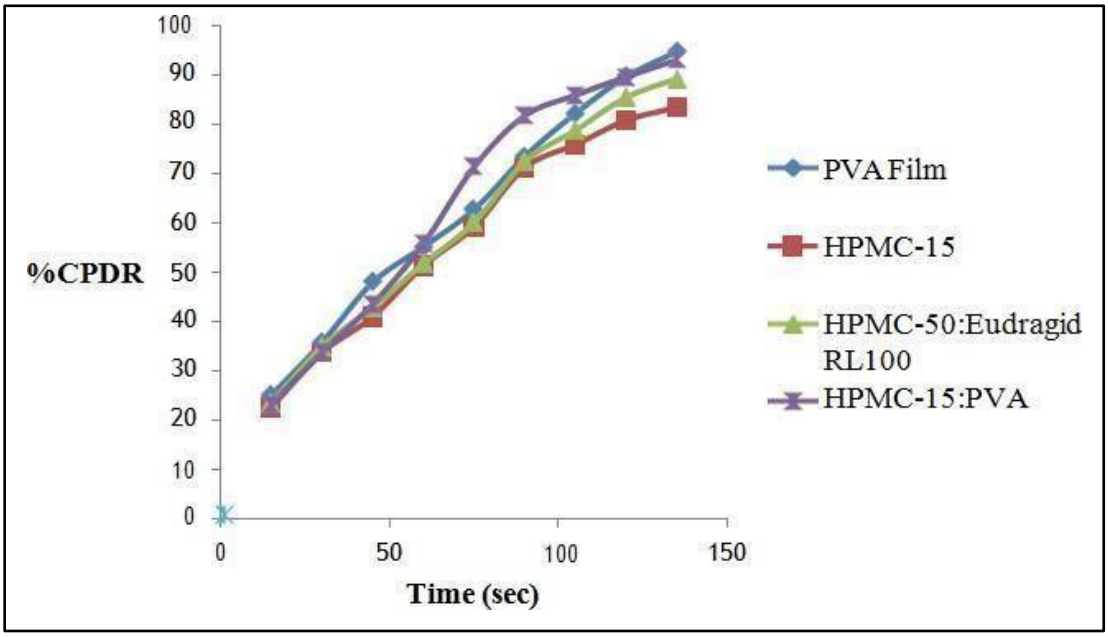


Figure: 27. *In-vitro* Release profile of Nicorandil film formulation X1-X4

Inference: It was observed that X1 formulation shows 93% release, X2 formulation shows 85.54% release, X3 formulation shows 89.88% release and X4 formulation shows 92.82 release. X4 formulation show maximum drug release so it was the optimized formulation.

Drug Release kinetics: Drug release kinetics study was done by the procedure mention under the section 7.

Release kinetics of X1 Formulation:

It includes the zero order plot, first order plot, higuchi plot, kosermeyer- peppas plot of X1 formulation as shown in figure 5.26 to 5.29 and the result is shown in table 8.27

Table: 32. Drug Release Kinetics of X1 Formulation

Release kinetics of X1 formulation	Zero order		1st order equation		Higuchi Equation		Korsmeyer Peppas's Equation	
	k	R^2	K	R^2	n		k	R^2
	0.2359	0.856	0.0039	0.987	5.3142		0.4483	0.96

R^2 =coefficient of determination: K=rate constant

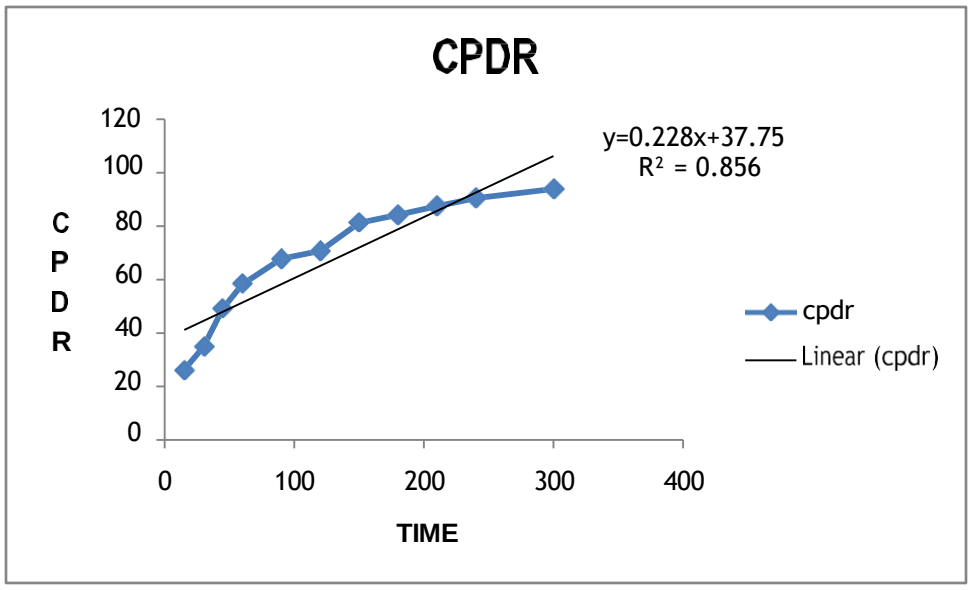


Figure: 28. Zero order Plot of X1 formulation

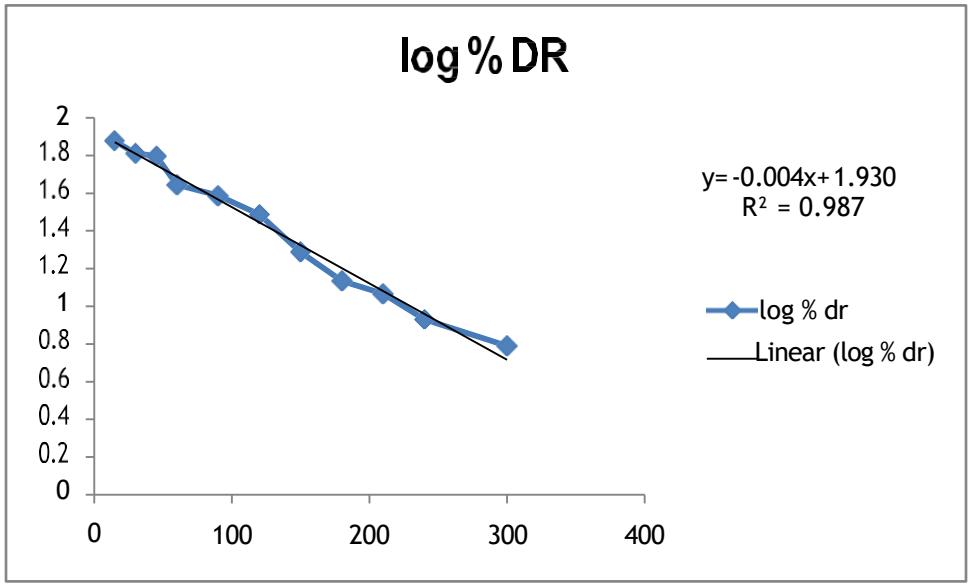


Figure: 29. First order plot of X1 formulation

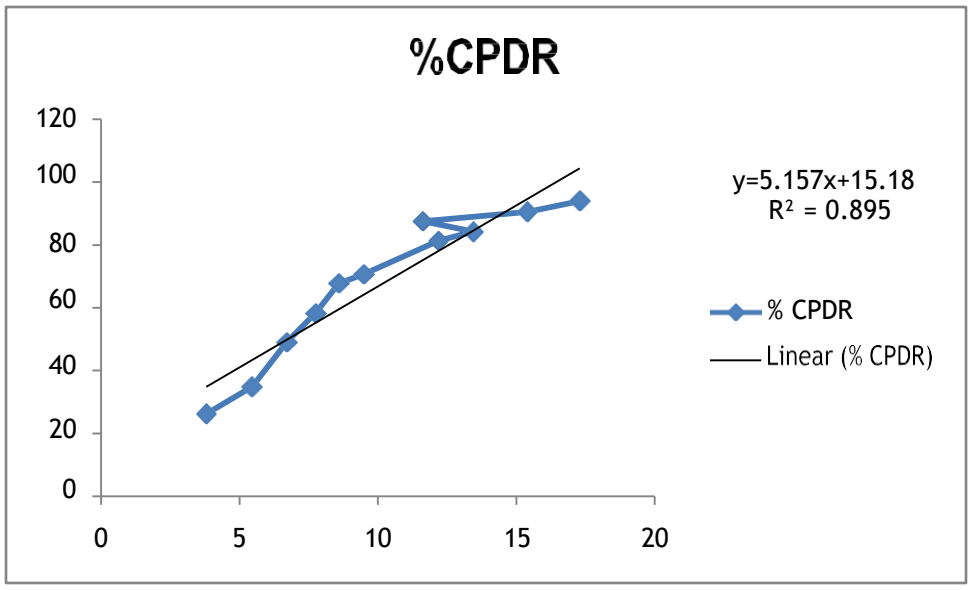


Figure: 30. Higuchi release plot of X1 formulation

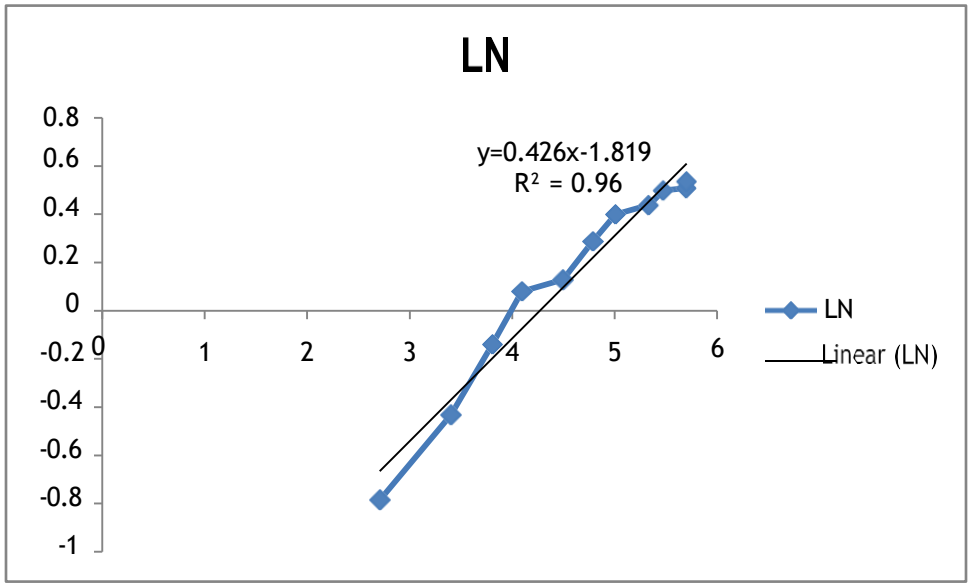


Figure: 31. Korsmeyer peppas Plot of X1 formulation

Release Kinetics of X2 Formulation:

It includes the zero order plot, first order plot, higuchi plot, kosermeyer-peppas plot of X2 formulation as shown in figure 8.26 to 8.29 and the result is shown in table 8.24.

Table: 33. Drug Release Kinetics of X2 Formulation

Release kinetics of X1 formulation	Zero order		1st order equation		Higuchi Equation		Korsmeyer Peppas's Equation	
	k	R^2	K	R^2	n	R^2	k	R^2
	0.2152	0.842	0.0027	0.853	4.8675	0.827	0.453	0.953

R^2 =coefficient of determination: K=rate constant

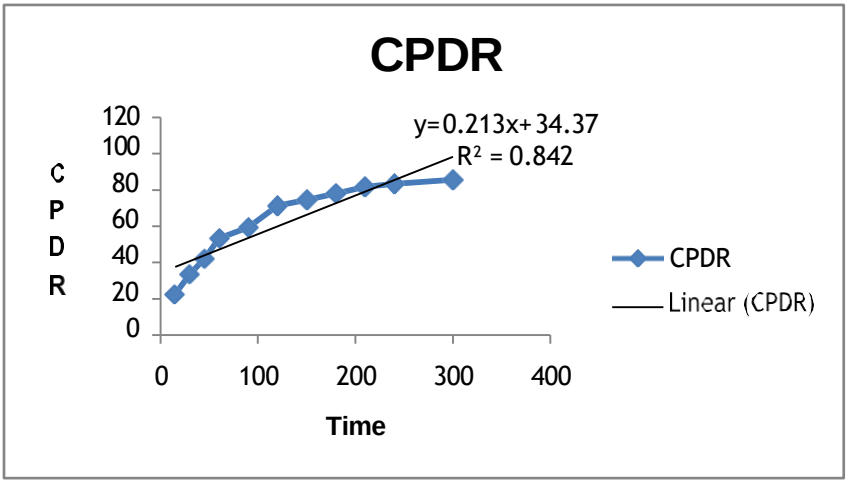


Figure: 32. zero order release plot of X2 formulation

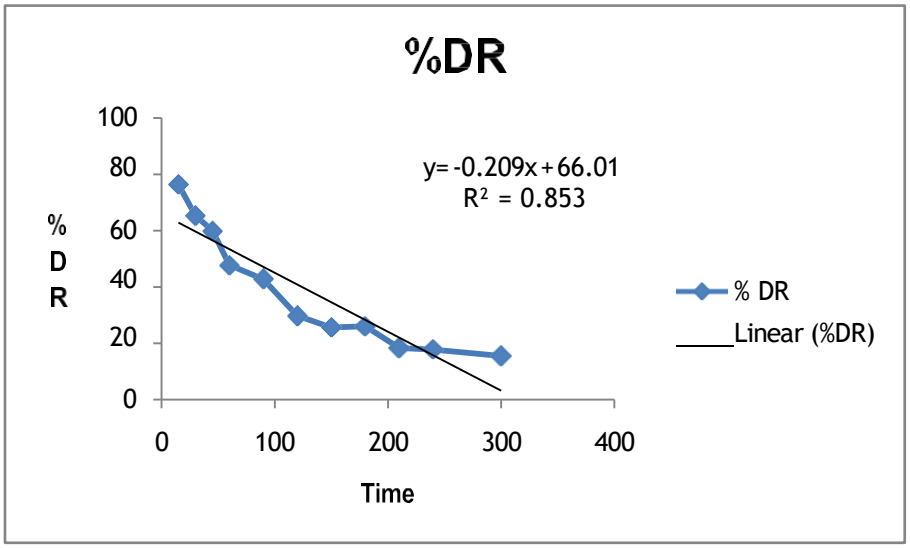


Figure: 33. First order release plot of X2 formulation

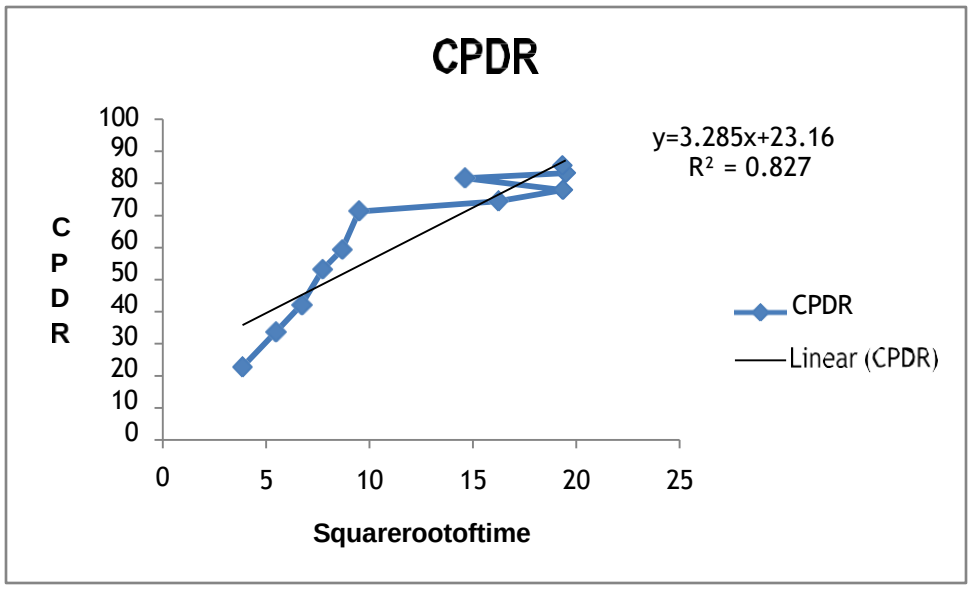


Figure: 34. Higuchi order release plot of X2 formulation

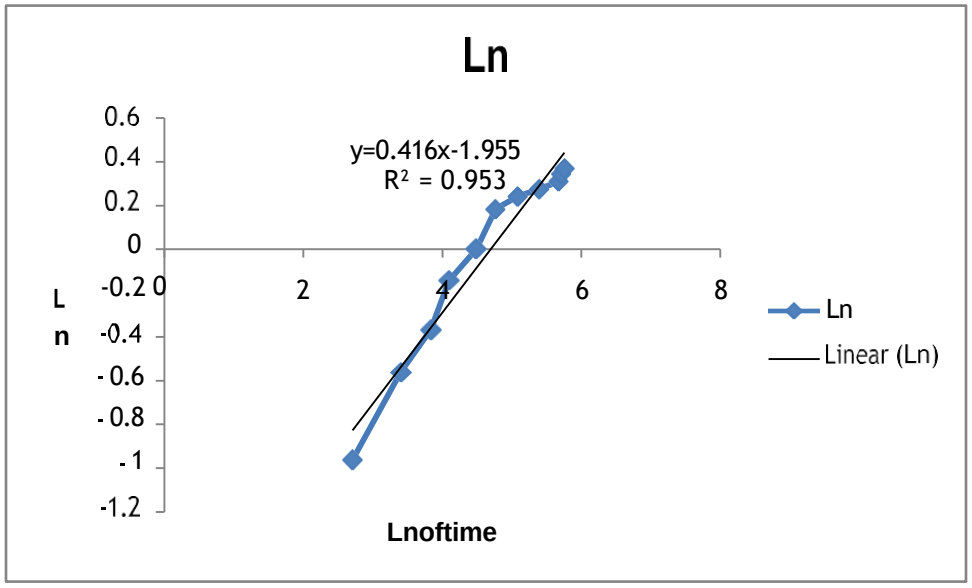


Figure: 35. Korsmeyer peppas release plot of X2 formulation

Release Kinetics of X3 Formulation:

It includes the zero order plot, first order plot, higuchi plot, kosermeyer- peppas plot of X3 formulation as shown in figure 8.30 to 8.33 and the result is shown in table 8.29.

Table: 34. Drug Release Kinetics of X3 Formulation

Release kinetics of X1 formulation	Zero order		1st order equation		Higuchi Equation		Korsmeyer Peppas's Equation	
	k	R^2	K	R^2	n	R^2	k	R^2
	3.61	0.862	-0.0032	0.804	5.1785	0.887	0.4577	0.983

R^2 =coefficient of determination: K=rate constant

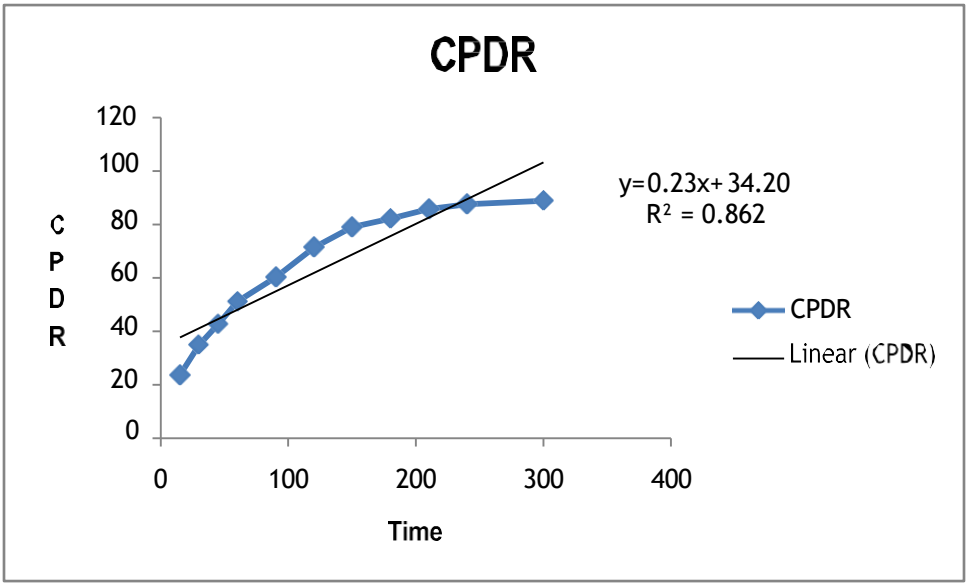


Figure: 36. 1ero order release plot of X3 formulation

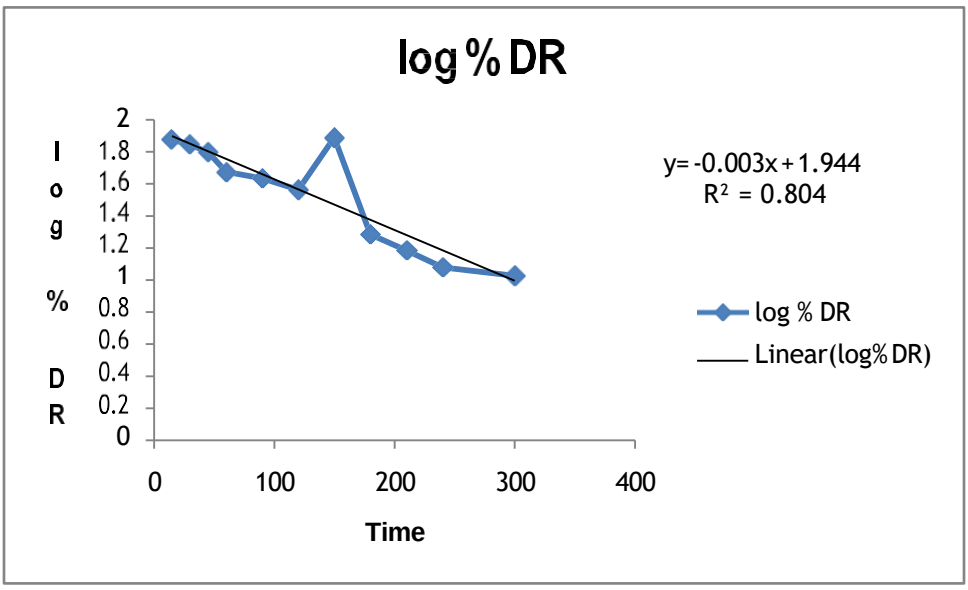


Figure: 37. First order release plot of X3 formulation

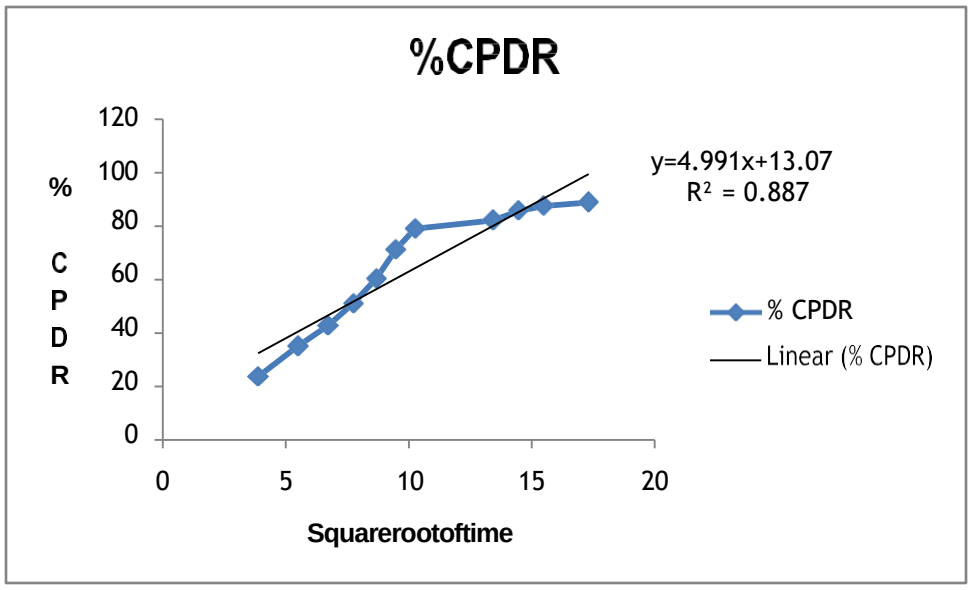


Figure: 38. Higuchi order release plot of X3 formulation

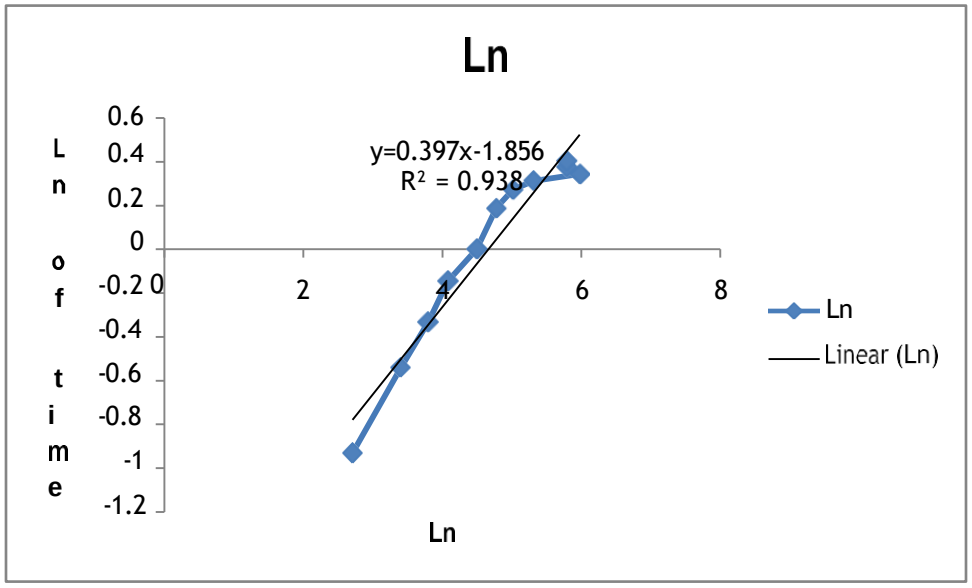


Figure: 39. Korsmeyer peppas release plot of X3 formulation

Release Kinetics of X4 Formulation

It includes the zero order plot, first order plot, higuchi plot, kosermeyer- peppas plot of X3 formulation as shown in figure 8.34 to 8.37 and the result is shown in table 8.30.

Table: 35. Drug Release Kinetics of X 4 Formulations

Release kinetics of X1 formulation	Zero order		1st order equation		Higuchi Equation		Korsmeyer Peppas's Equation	
	k	R^2	K	R^2	n	R^2	k	R^2
	0.2368	0.908	-0.0037	0.966	5.1759	0.887	0.4778	0.952

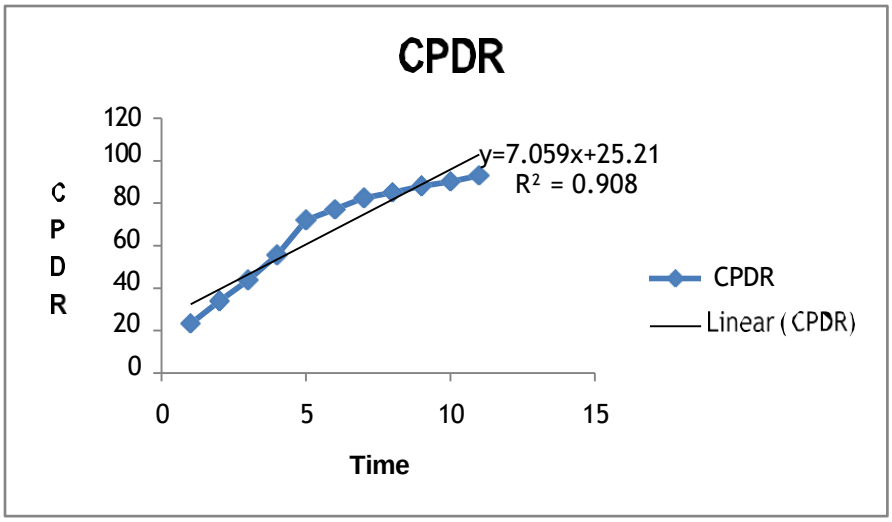


Figure: 40. zero order release plot of X4 formulation

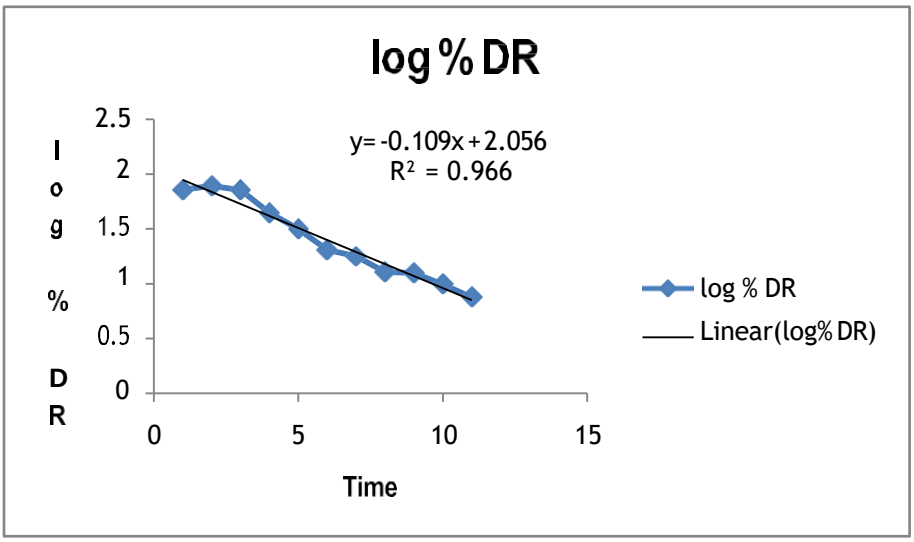


Figure: 41. First order release plot of X4 formulation

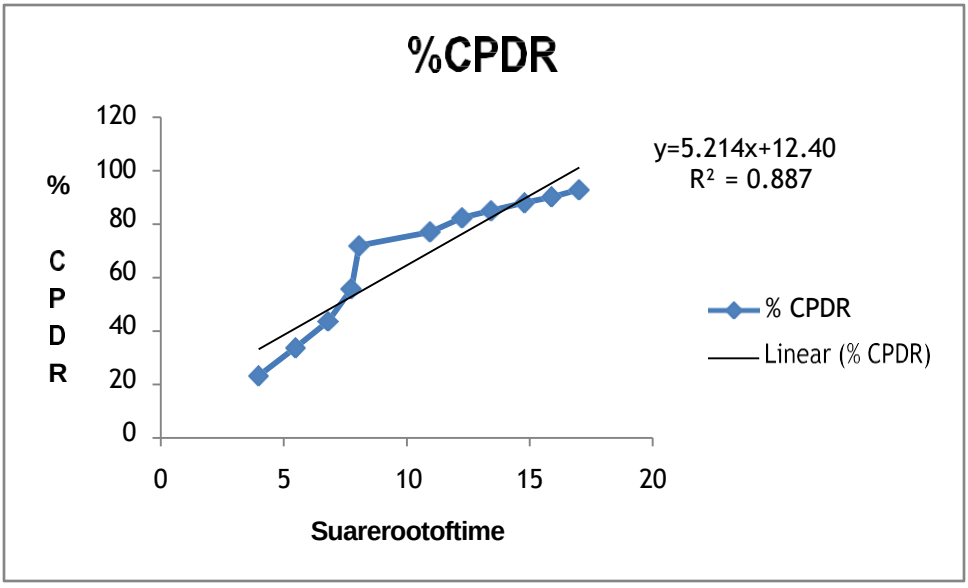


Figure: 42. Higuchi order release plot of X4 formulation

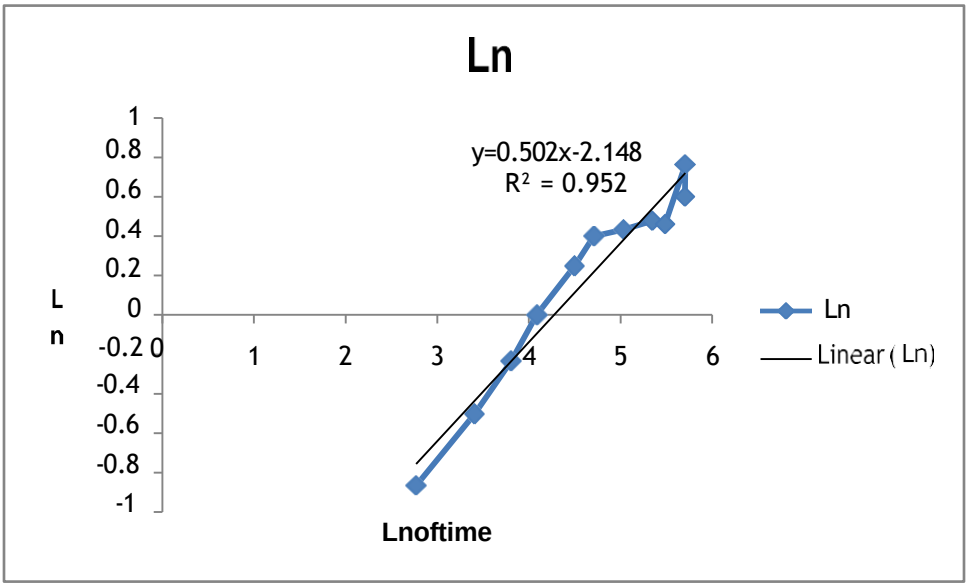


Figure: 43. Korsmeyer peppas release plot of X4 formulation

Analysis of the Drug Release Data

The zero-order rate describes the systems where the drug release rate is independent of its concentration; it shows the cumulative amount of drug release Vs time for zero-order kinetics. The first order rate describes the release from systems where the

release rate is concentration dependent; Higuchi‘s model describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. After undergoing the release model for all the formulations the in vitro drug release of the optimized formulation X1 was best explained by first order, as the plots showed the highest linearity (r2 = 0.9915), followed by Korsmeyer peppas (r2=0.9771), Higuchi (r2 = 0.9602) and then zero order (r2 = 0.8676).

The corresponding plot (ln Mt/M∞ vs ln time) for the Korsmeyer-Peppas equation of the optimized formulation X1 indicated good linearity for X1 formulation. The release exponent ‗n‘ was found to be for X1 is 0.4487, which appears to indicate Fickian diffusion and may indicate that the drug release was controlled by first order release.

Statistical Analysis

In statistical analysis paired T-test of the formulations were performed according to the procedure mentioned under the section 7.

Table: 36. Paired Test of the Formulation

S. No.	Comparative Parameter	Test Applied	P Value	Level Of Significant	Passed Normality
1	X1 and X2	Paired Test	<0.0001	Extremly Significant	Passed
2	X1 and X3	Paired Test	<0.0001	Extremly Significant	Failed
3	X1 and X4	Paired Test	<0.0001	Extremly Significant	Failed
4	X2 and X3	Paired Test	<0.0001	Extremly Significant	Passed
5	X2 and X4	Paired Test	<0.0001	Extremly Significant	Passed
6	X3 and X4	Paired Test	<0.0001	Significant	Failed

Inference:

After undergoing statistical analysis of all the formulation it was concluded that on applying paired test no significant difference was found between the formulations (P=0.1420, r=0.9999.The data pass the normality test with P>0.05.

Table: 37 . Stability Studies – Drug Content, Weight Variation, Disintegration Time, and Dissolution time after 30 days storage of optimized formulation X1.

Storage condition	Tested after time (in days)	Weight variation (mg/4cm^2)	Disintegration time (sec)	Dissolution time (sec)	Drug content uniformity (n=3)
+30^{o}C/60 %RH	0	118±0.06	14	138± 2.15	100± 0.09
	5	117.5±0.04	14	135± 1.12	99.85±0.07
	10	118.2±0.1	14	138± 1.0	99.67±0.01
	15	119.4±0.05	16	136±1.57	99.37±0.02
	20	118.7±0.03	14	138±1.23	98.94±0.02
	25	118.6±0.06	15	139±1.56	98.58±0.01
	30	118.1±0.02	15	140±1.23	98.13±0.04
45^{o}C/75 % RH	0	119.6±1.52	15	140±1.13	101±0.03
	5	116.4±0.01	15	142±2.34	100.23±0.05
	10	117.9±0.05	16	140±1.18	99.71±0.03
	15	118.4±0.07	14	139±1.84	99.31±0.012
	20	118.2±0.1	14	137±1.0	99.05±0.01
	25	117.8±0.06	13	138±1.42	98.75±0.03
	30	118.1±0.02	13	137±1.0	98.41±0.023

Table: 38. Stability studies – In vitro release profile of film X1 at 30^{o}C/60% RH.

Time	Abs	Concentration			final conc.	CPDR	%DR
		conc.In mg/10ml	Cum. Conc. In mg/10ml	Conc. In mg/300 ml			
30	0.145	0.161111	0.161111	4.833333	4.833333	24.16667	75.83333
60	0.198	0.22	0.381111	6.6	6.761111	33.80556	66.19444
90	0.235	0.261111	0.642222	7.833333	8.214444	41.07222	58.92778
120	0.294	0.326667	0.968889	9.8	10.44222	52.21111	47.78889
150	0.348	0.386667	1.355556	11.6	12.56889	62.84444	37.15556
180	0.376	0.417778	1.773333	12.53333	13.88889	69.44444	30.55556
210	0.421	0.467778	2.241111	14.03333	15.80667	79.03333	20.96667
230	0.454	0.504444	2.745556	15.13333	17.37444	86.87222	13.12778
300	0.461	0.512222	3.257778	15.36667	18.11222	90.56111	9.438889

Table: 39. Stability studies – In vitro release profile of film X1 at 45°C and 75% RH.

Time	Abs	Concentration			final conc.	CPDR	%DR
		conc. In mg/10ml	Cum. Conc. In mg/10ml	Conc. In mg/300 ml			
30	0.146	0.162222	0.162222	4.86666	4.86666	24.3333	75.66667
60	0.2	0.222222	0.384444	6.66666	6.82888	34.1444	65.85556
90	0.239	0.265556	0.65	7.96666	8.35111	41.7555	58.24444
120	0.297	0.33	0.98	9.9	10.55	52.75	47.25
150	0.351	0.39	1.37	11.7	12.68	63.4	36.6
180	0.378	0.42	1.79	12.6	13.97	69.85	30.15
210	0.425	0.472222	2.262222	14.1666	15.9566	79.7833	20.21667
230	0.455	0.505556	2.767778	15.1666	17.4288	87.1444	12.85556
300	0.459	0.51	3.277778	15.3	18.0677	90.3388	9.661111

Inference: It was observed that during the stability studies the weight variation, drug content, disintegration time and dissolution time of the film all were in the desirable range without any uncertainty which indicates degradation of the film. The in-vitro release profile of X1 film after 30 days storage at 30oC/ 60% RH and at 45oC/ 75% RH shows 99.56% and 90.33% drug release. So, Stability studies revealed that optimized X1 film was found to be stable at different environmental conditions with no much variation or change in any parameters.

SUMMARY

Fast dissolving oral film is consist of a very thin oral strips, it is an oral drug delivery system, which is simply placed on the patient‘s tongue or any oral mucosal tissue, instantly wet by saliva; releasing the drug, which dissolve or disperses in the saliva.

In this research work fast dissolving oral film of Nicorandil was prepared and evaluated for various film parameters to obtain quick effect in the treatment. The coronary vasodilating activity of nicorandil is considered to be the consequence of the increasing cyclic GMP production by stimulating guanylyl cyclase in the coronary vascular smooth muscle, similar to other nitrates/nitrites (in vitro).

Nicorandil is an antianginal drug, the drug caused an increase in the cGMP content in isolated blood vessels. These facts suggest that the vasodilating effect of the drug is related to the effect of opening the ATP-sensitive K channel, as well as to the effect of increasing production of cGMP.

Identification of the drug sample was carried by U.V spectroscopy, FTIR and DSC to obtain the purity of drug sample. Preformulation studies were also carried out by UV, FTIR and DSC to confirm compatibility of drug with polymers and other excipients. It was observed that FTIR spectra of the Nicorandil, showed characteristic C-N, C-O, C- H, C=O(ester) stretching bands at 1134.07 cm-1, 1193.85 cm-1, 2929.67 cm-1, 1718.45 cm-1, respectively. The compatibility of drugs with physical mixture of drug (s) & PVA, physical mixture of drug and HPMC-15, and physical mixture of drug, and aspartame were recorded and examined.

In FTIR spectra of Nicorandil, characteristic C=O stretching band was observed at 1718.45 cm-1 which are in agreement with the reported values. The results showed no chemical interaction and changes took place in FTIR spectra of the drug and various excipients alone or in combination exhibiting compatibility of the drug with all excipients.

In the present work optimization studies have been carried for selection of suitable film forming polymers. Optimization studies were also carried out for the selection of appropriate concentration of the optimized polymer and combinations, for the selection of plasticizer and sweetener.

The optimized components for formulation of fast dissolving dissolving films composed HPMC-15, PVA, combination of HPMC-15 : PVA and combination of HPMC-50:Eudragid RL-100 in concentration range of 2%; 2.5%; 1:1.5%; 2:0.5% w/v respectively. Dicyclomine FDOF were prepared by solvent casting method using these components. Four batches of the film were prepared designated as X1 to X4.

Formulated films were evaluated for parameters like drug content and content uniformity, tensile strength, percent elongation, thickness, folding endurance, hydration ratio, Differential scanning calorimetry, % in vitro release studies, and stability studies.

The results indicate that all formulations appear as elegant transparent to opaque films with good tensile strength, percent elongation, folding endurance. Weight variation and thickness test of all the formulations shows satisfactory results. Tensile strength test, % elongation test & folding endurance test revealed that all formulations have good mechanical properties. It was observed that X1 and X4 formulation showed high tensile strength, folding endurance and moderate per cent elongation as compared to other formulations. Drug content of all formulations revealed that drug was uniformly distributed in polymer matrices with good reproducibility. Hydration ratio study has revealed that X1 formulation shows higher hydration ratio than all formulation.

All formulations show less disintegration and dissolution time, but on the basis of thickness, swelling index, disintegration time and dissolution time X1 formulation was selected as optimized film. X1 film has minimum disintegration time about 14sec and minimum dissolution time i.e. 135 sec. in comparison to other formulation. In vitro dissolution results showed that maximum cumulative % drug release was more in formulation X1(93.88) and X4 (92.82) when compared to formulation X2(85.54) and X3(89.88).

All the formulations showed almost complete drug release in less than 15 minutes. Release kinetic study of all formulations follows first order kinetics, which indicates that FDOF obeys rapid dissolution due to diffusion or self erosion of polymer matrix.

Stability studies revealed that optimized X1 film was found to be stable at different environmental conditions with no much variation or change in any parameters.

Future Plan

1. **Optimization of Formulation**
   - Further optimization of the fast dissolving oral film will be carried out using advanced formulation techniques to achieve rapid disintegration, improved drug release, and enhanced patient compliance.
2. **Stability Studies**
   - Accelerated and long-term stability studies will be conducted according to ICH guidelines to evaluate the physical, chemical, and mechanical stability of the developed formulation.
3. **In-Vitro and Ex-Vivo Evaluation**
   - Additional in-vitro and ex-vivo studies will be performed to assess drug permeation, dissolution behavior, and mucosal compatibility of the oral film.
4. **Pharmacokinetic Studies**
   - Pharmacokinetic investigations will be undertaken to determine bioavailability, onset of action, and absorption characteristics compared with conventional dosage forms.
5. **Scale-Up and Manufacturing Studies**
   - Efforts will be made to establish a scalable manufacturing process suitable for commercial production while maintaining product quality and uniformity.
6. **Clinical Evaluation**
   - Clinical studies will be planned to evaluate the safety, efficacy, and patient acceptability of the developed fast dissolving oral film in the treatment of angina pectoris.
7. **Regulatory and Commercial Development**
   - Regulatory requirements will be addressed to facilitate product approval and future commercialization as a patient-friendly dosage form.

Expected Outcomes

- Development of a stable and effective fast dissolving oral film for the management of angina pectoris.
- Rapid onset of therapeutic action due to quick disintegration and absorption of the drug through the oral mucosa.
- Improved patient compliance, particularly among geriatric and dysphagic patients.
- Enhanced bioavailability by minimizing first-pass metabolism.
- Establishment of a cost-effective and scalable formulation suitable for industrial production.
- Generation of scientific data supporting the use of fast dissolving oral films as an alternative to conventional dosage forms for angina treatment.

CONCLUSION

Fast dissolving films of Nicorandil was formulated with available low viscosity film formers viz. HPMC E15, Polyvinylalcohol and combination of HPMC-15: PVA and HPMC-50: Eudragid RL-100.

The Optimized fast dissolving films comprising of drug and HPMC E15, Polyvinylalcohol and combination of HPMC-15:PVA and HPMC-50: Eudragid RL-50 in concentration range of : 2%, 2.5%, 1:1.5%, 2:0.5%w/v were successfully prepared by solvent casting method.

PEG 400 used as Plasticizer resulted in better films in respect to physicochemical parameter like, tensile strength, % elongation, folding endurance and flexibility. Aspartame was used as a sweetener, will successfully mask the bitter taste of the drug Nicorandil.

It was concluded that from all the Formulation batches X1 batch shows minimum disintegration and dissolution time in comparison to other formulation. In vitro drug release studies shows that X1 was the best formulation showed 93.88% drug release in 5 min.

Data obtained from release kinetics revealed that drug release from all formulations batches followed by first order kinetics. The drug release of X1 formulation follow first order release indicates fician diffusion mechanism.

In vitro stability evaluation of optimized formulation batch X1 with different environmental conditions, confirms the potential of films for longer storage.

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FORMULATION AND EVALUATION OF NICORANDIL MOUTH DISSOLVING FILMS FOR ENHANCED PATIENT COMPLIANCE

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Abstract:
The present study aimed to formulate and evaluate Nicorandil mouth dissolving films to enhance patient compliance and provide a rapid onset of therapeutic action. Films were prepared using the solvent casting method with HPMC grades, polyvinyl alcohol, plasticizers, and suitable excipients. The prepared formulations (X1–X4) were evaluated for thickness, weight variation, drug content, moisture uptake, moisture loss, swelling index, mechanical strength, disintegration, and dissolution behavior. All films exhibited uniform thickness and weight distribution, with drug content ranging between 96–98%, confirming uniform drug dispersion. Moisture absorption and loss remained low, indicating stability toward environmental humidity. Among all formulations, X1 demonstrated superior mechanical properties, the highest folding endurance (>800), the shortest disintegration time (15 seconds), and the highest cumulative drug release (93.89% at 300 minutes). Stability studies conducted at 30°C/60% RH and 45°C/75% RH for 30 days indicated no significant variations in physicochemical parameters or drug release behavior, confirming the stability of the optimized formulation. Overall, the results suggest that Nicorandil mouth dissolving films, particularly formulation X1, offer an effective and patient-friendly drug delivery system with rapid disintegration, favorable mechanical strength, and efficient drug release, making them a promising alternative to conventional dosage forms.

Keywords: *Nicorandil, Mouth Dissolving Films, Solvent Casting Method, Rapid Disintegration, Patient Compliance, HPMC, Polyvinyl Alcohol, Mechanical Properties, Drug Release, Stability Studies.*

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INTRODUCTION:

Nicorandil is a potent vasodilatory anti-anginal agent with a dual mechanism of action, functioning both as a nitrate donor and as an opener of ATP-sensitive potassium channels. Despite its proven therapeutic efficacy in the management of ischemic heart diseases, its oral administration is often associated with limitations such as variable bioavailability, delayed onset of action, and difficulties in swallowing among geriatric and pediatric populations [1]. Dysphagia, which affects nearly 35–40% of elderly patients, significantly reduces adherence to conventional solid dosage forms and thereby compromises therapeutic outcomes. These challenges highlight the need for an alternative dosage form that ensures rapid onset of action, improved bioavailability, and better patient acceptability [2].

Mouth Dissolving Films (MDFs) have emerged as a novel drug delivery technology designed to disintegrate or dissolve rapidly in the oral cavity without the requirement for water. This approach offers distinct advantages including ease of administration, improved dosing accuracy compared to liquid formulations, and enhanced patient compliance, especially in populations with swallowing difficulties. MDFs also allow partial pre-gastric absorption through the oral mucosa, leading to reduced first-pass metabolism and a potentially faster onset of therapeutic action attributes particularly beneficial for drugs used in acute angina episodes [3].

Nicorandil's physicochemical properties, including moderate water solubility and susceptibility to hepatic first-pass metabolism, make it a suitable candidate for MDF formulation. Incorporation of Nicorandil into a polymeric film matrix composed of safe, fast-dissolving materials such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), or pullulan can enhance its dissolution rate and hasten absorption through the oral mucosa. Additionally, the use of plasticizers, sweeteners, and stabilizers can improve film flexibility, palatability, and patient acceptability [4].

Previous studies on fast-dissolving oral drug delivery systems have demonstrated significant improvements in onset of action and patient compliance. However, limited literature is available on systematically developed and optimized mouth dissolving films of Nicorandil. Therefore, the development of a robust, stable, and patient-friendly Nicorandil MDF formulation has the potential to address existing therapeutic challenges and enhance clinical utility [5].

The present study aims to formulate and evaluate Nicorandil mouth dissolving films with optimized mechanical strength, rapid disintegration, enhanced dissolution profile, and satisfactory drug content uniformity. By employing suitable film-forming polymers and excipients, this research seeks to develop an effective alternative dosage form that promotes rapid relief, improved compliance, and better therapeutic management of angina pectoris.

MATERIAL AND METHODS:

Material

The materials used for the formulation of Nicorandil fast dissolving oral films (FDOFs) included Nicorandil as the active pharmaceutical ingredient, obtained from Sigma Labs Ltd. Hydrophilic film-forming polymers such as HPMC E15 and E50 and polyvinyl alcohol (PVA) were sourced from S.D. Fine Chemicals, while Eudragit RL 100 was procured from Ranbaxy, New Delhi. Plasticizers like glycerine (S.D. Fine Chemicals) and propylene glycol 400 (Qualigens Fine Chemicals) were used to enhance film flexibility. Surfactant Tween-80 (Central Drug House Pvt. Ltd.) was incorporated to aid drug solubilization, whereas citric acid (Qualigens Fine Chemicals) acted as a saliva-stimulating agent. Aspartame (Ranbaxy, New Delhi) and menthol (Central Drug House Pvt. Ltd.) were used as sweetener and flavoring agent, respectively, to improve palatability. Distilled water and ethanol, prepared in-house, served as solvents for polymer dissolution and film casting.

Methods

Formulation and Development of Fast Dissolving Oral Film

Placebo Film Composition

The development of placebo fast dissolving oral films (FDOFs) involved the use of well-known film-forming polymers such as HPMC-5, HPMC 15cps, HPMC 50cps, PVA (polyvinyl alcohol), PVP, and Eudragit RL-100. These polymers were selected based on their excellent film-forming properties and were evaluated individually as well as in combination with each other to compare their efficiency. The polymer concentration in all films was maintained at 2% to ensure consistent evaluation across formulations [6].

Table 1: Composition of Placebo Films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
HPMC-5 (% w/v)	2%	–	–	–	–	–	–	–
HPMC-15 (% w/v)	–	2%	–	–	–	–	–	–
HPMC-50 (% w/v)	–	–	2%	–	–	–	–	–
HPMC : Eudragit RL-100 (% w/v)	–	–	–	–	–	–	1:1 %	–
PVA (% w/v)	–	–	–	2%	–	–	–	–
PVP (% w/v)	–	–	–	–	2%	–	–	–
HPMC : PVA (% w/v)	–	–	–	–	–	1:1 %	–	–
PEG-400 (% w/v)	3%	3%	3%	3%	3%	3%	3%	3%
Tween-80 (mL)	0.2	–	–	–	–	–	–	–
Ethanol (q.s.)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Distilled Water (mL)	100	100	100	100	100	100	100	100

Table 2: Formulation of Placebo Fast Dissolving Films with Different Concentrations of HPMC-15 and PVA

Ingredients	A1	A2	A3	A4	A5	A6	A7
HPMC-15 (% w/v)	1	1.5	2	3	–	–	–
PVA (% w/v)	–	–	–	–	2	2.5	3
PEG-400 (% w/v)	3	3	3	3	3	3	3
Tween 80 (mL)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water (mL)	100	100	100	100	100	100	100

Table 3: Formulation of placebo fast dissolving film with different concentration of the combination of polymers

Ingredients	B1	B2	B3	B4	B5	B6	B7
HPMC-15 : PVA (% w/v)	1 : 1	1 : 1.5	1.5 : 1	–	–	–	–
HPMC-50 : Eudragid RL-100 (% w/v)	–	–	–	1 : 1	1.5 : 1	2 : 1	2.5 : 1
PEG-400 (% w/v)	3	3	3	3	3	3	3
Tween 80 (mL)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water (mL)	100	100	100	100	100	100	100

Table 4: Evaluation of Concentration of Film Forming Polymer (HPMC-15)

Evaluation Parameter	1% w/v	1.5% w/v	2% w/v	3% w/v
Physical appearance	Transparent, sticky	Transparent, sticky	Transparent, non-sticky	Transparent, non-sticky
Film flexibility	Less	Less	Moderate	Moderate
Tensile strength	Poor	Poor	Moderate	Moderate
% Elongation	Poor–Moderate	Less	Moderate	Moderate
Disintegration time (sec)	30	35	37	52
Dissolution time (sec)	100	140	168	240
Folding endurance	200	300	400	300
Thickness (mm)	0.15	0.19	0.27	0.33

Table 5: Evaluation of concentration of film forming polymer (PVA)

Evaluation Parameter	2% w/v	2.5% w/v	3% w/v
Physical appearance	Transparent	Transparent	Transparent
Film flexibility	Moderate	Good	Good
Tensile strength	Moderate	High	High
% Elongation	Less	Moderate	High
Disintegration time(sec)	12	14	26

Dissolution time	96	140	190
Folding endurance	>1000	>1000	>1000
Thickness	0.210	0.240	0.320

Table 6: Evaluation of concentration of polymer used in combination:

Evaluation parameters	HPMC-15: PVA		
	1:1% w/v	1:1.5% w/v	1.5:1% w/v
Physical Appearance	Transparent	Transparent	Transparent
Film Flexibility	Moderate	Moderate	Moderate
Tensile Strength	Low	Moderate	Moderate
% elongation	Poor to moderate	Moderate	Poor to moderate
Disintegration time(sec)	20	24	32
Dissolution time	140	129	160
Folding endurance	100	500	300
Thickness	0.154	0.170	0.172

Table 7: Evaluation of concentration of polymer used in combination

Method of Preparation

Evaluation parameters	HPMC-50: Eudragid RL-100			
Physical Appearance	1:1% w/v	1.5:1% w/v	2:1% w/v	2.5:1%w/v
	Transparent, Stickiness	Transparent, Stickiness	Transparent Stickiness	Transparent, No stickiness
Film Flexibility	Moderate	Moderate	Moderate	Moderate
Tensile Strength	Low	Moderate	Moderate	Moderate
% elongation	Poor to moderate	Moderate	Poor to moderate	Moderate
Disintegration time(sec)	20	25	27	24
Dissolution time	240	190	150	129
Folding endurance	>500	>800	>800	>800
Thickness	0.154	0.170	0.172	0.175

The placebo films were prepared using the solvent casting method. For HPMC-15cps films, the polymer was first soaked in water and dispersed uniformly under continuous stirring on a magnetic stirrer. Plasticizers and Tween-80 were then added to the polymeric dispersion, followed by further stirring for one hour to achieve a homogenous mixture. The dispersion was sonicated for 10 minutes to remove entrapped air bubbles. Approximately 10 ml of the dispersion was cast onto olive oil-lubricated Petri dishes and dried in a hot air oven at 30–40°C. Once dried, films were carefully removed, cut into 2×2 cm strips, and stored in airtight containers.

The preparation of PVP and PVA films followed the same procedure as described for HPMC films, ensuring uniform dispersion and consistent casting. Films using combinations of polymers were also prepared similarly to evaluate the synergistic effects of polymer blends on film properties [7].

Optimization of the Polymer for Placebo Film Formulation

Key parameters in FDOF development, including film-forming capacity, physical appearance, disintegration time, and mechanical properties, were systematically evaluated. Placebo films with varying concentrations of HPMC-15 (1–3%), PVA (1–3%), and combinations of HPMC-15:PVA or HPMC-50:Eudragit RL-100 were prepared. Each formulation was assessed for disintegration, flexibility, tensile strength, and overall appearance, with the optimal polymer type and concentration selected for drug-loaded films [8].

Preparation of Drug-Loaded Films

Nicorandil-loaded FDOFs were prepared using the solvent casting technique. The optimized polymer was dissolved in water with continuous stirring for one hour. Sweeteners and plasticizers were dissolved in 95% ethanol and added to the polymeric solution. Nicorandil was dissolved separately in water, sonicated to ensure uniform dispersion, and then incorporated into the polymeric solution. The final mixture was stirred for an additional 30 minutes, left undisturbed to

remove entrapped air, and cast onto a plastic Petri dish with a 68 cm² surface area. The films were dried at controlled room temperature (25–30°C, 45% RH) or using a microwave oven. Once dried, films were carefully removed, cut to the required size, and stored in airtight plastic bags until further evaluation [8].

Table 8: Composition of Drug Loaded Fast Dissolving Film

Ingredients	X1	X2	X3	X4
Nicorandil (mg)	251	251	251	251
PVA(mg)	250	-	-	-
HPMC-15	-	200mg		-
HPMC- 50:Eudragid	-	-	200:100mg	-
HPMC-15:PVA	-	-	-	100:150mg
PEG-400	300	300	300	300
Aspartame	62.52	62.52	62.52	62.52
citric Acid	15	15	15	15
Menthol	0.029	0.029	0.029	0.029
Tween -80	0.2ml	0.2ml	0.2ml	0.2ml
Water(ml)	10	10	10	10
Ethanol	q.s	q.s	q.s	q.s

Table 9: Optimization of sweetener for the fast dissolving films:

Ingredients	Batch B1	Batch B2	BatchB3	Batch B4
Nicorandil (mg)	251	251	251	251
PVA (mg)	200	200	200	200
PEG-400 (% of Polymer)	15	15	15	15
Aspartame	5 (12.5mg)	10% (25.1mg)	15% (37.6mg)	25% (62.52mg)
citric acid	20mg	20mg	20mg	20mg
Menthol	0.029	0.029	0.029	0.029
Distilled Water (ml)	12	12	12	12
Bitter index level	2.5	2.0	1.5	1

Physicochemical Evaluation of Formulated Films

The prepared films were evaluated for several physicochemical parameters to ensure quality and consistency. Film thickness was measured using a screw gauge, and weight variation studies were performed on ten films per batch. Hydration studies, or water uptake/swelling studies, were carried out by immersing films on a pre-weighed stainless steel mesh in distilled water and monitoring weight changes over time to determine the hydration ratio. Moisture loss and percentage moisture absorption were also evaluated by storing films in desiccators with anhydrous calcium chloride or saturated sodium chloride solution to assess stability under dry and humid conditions [9].

Mechanical Properties

Mechanical characteristics of the films, including tensile strength, elastic modulus, percent elongation, and load at yield, were determined to assess film strength and flexibility. Tensile strength was measured by applying weights to a film strip until it broke, and percent elongation was calculated based on the distance stretched before breaking. Folding endurance was assessed by repeatedly folding the film at the same point until it fractured, providing an indication of the film's durability during handling, packaging, and transport. Desirable mechanical properties included moderate tensile strength, low elastic modulus, high percent elongation, and high folding endurance, indicating a soft yet tough film suitable for practical use [10].

Drug Content and Uniformity

Drug content uniformity was analyzed to ensure consistent Nicorandil distribution throughout the films. Sections of the film were dissolved in distilled water, treated with methyl orange, and extracted with chloroform, followed by dilution with sodium acetate solution. The absorbance was measured using a UV-Visible spectrophotometer, and the average drug content per film was calculated [11].

In Vitro Disintegration and Dissolution Studies
The disintegration time, defined as the time taken for the film to start breaking, and the dissolution time, representing complete film dissolution, were determined visually in distilled water with gentle swirling. In vitro dissolution studies were performed using a USP II paddle apparatus in simulated saliva (pH 6.8) at 37 ± 1°C and 100 rpm. Samples were withdrawn at predetermined intervals, processed with methyl orange and chloroform, filtered, and analyzed spectrophotometrically. These studies provided critical data on the drug release profile and onset of action [12].

Taste-Masking Evaluation
Taste masking was assessed using sensory analysis in healthy volunteers. The bitterness intensity was scored using a predefined numerical scale, and formulations were compared to ensure optimal palatability for patient acceptability [13].

Drug Release Kinetics
The release of Nicorandil from the FDOFs was analyzed using kinetic models including zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations to determine the mechanism of drug release and predict in vivo performance [14].

Stability Studies
Stability studies were conducted to assess the performance of the films under specified storage conditions. Parameters such as drug content, mechanical properties, disintegration time, and dissolution profile were monitored over time to define the shelf life and ensure the reliability of the dosage form under real-world conditions [15].

RESULTS AND DISCUSSION:

The results of the present investigation on Nicorandil mouth dissolving films indicate that all formulations developed using the solvent casting method exhibited satisfactory physicochemical and mechanical properties. The uniform thickness and weight variation observed among formulations X1 to X4 confirm the consistency and reproducibility of the preparation method. Drug content values remained within the acceptable pharmacopeial range, demonstrating uniform dispersion of Nicorandil throughout the polymeric matrix. The low moisture absorption and moisture loss values suggest that the films are relatively stable and resistant to environmental humidity, which is essential for maintaining film integrity during storage. The swelling indices of all formulations indicate their capacity to hydrate upon contact with saliva, a necessary characteristic for ensuring quick disintegration and release of the drug in the oral cavity.

Mechanical characterization showed variation among the formulations, with X1 and X3 demonstrating higher tensile strength and superior folding endurance compared to X2 and X4. This suggests that formulations with optimal polymer ratios yield more flexible and durable films. The disintegration time was significantly shorter for X1 (15 seconds), confirming its potential as an effective fast-dissolving film suitable for patients who require immediate drug action or those who experience difficulty in swallowing conventional dosage forms. Dissolution studies further supported these findings, as formulation X1 exhibited the highest cumulative drug release, reaching 93.89% within 300 minutes. The drug release pattern suggests a diffusion-controlled mechanism, indicating that the polymer matrix facilitates a consistent release of Nicorandil.

Stability studies conducted at 30°C/60% RH and 45°C/75% RH revealed no significant changes in weight, disintegration time, dissolution time, or drug content over 30 days. This confirms that formulation X1 is physically and chemically stable under both intermediate and accelerated conditions. The in-vitro drug release profiles obtained during stability testing also maintained high release percentages, comparable to the initial fresh formulation, emphasizing that the optimized film retains its performance characteristics even after prolonged storage. Overall, formulation X1 demonstrated the most favorable balance of mechanical strength, rapid disintegration, and efficient drug release. These results collectively indicate that Nicorandil mouth dissolving films, particularly formulation X1, can serve as a promising alternative dosage form offering improved patient compliance, rapid onset of action, and enhanced therapeutic efficiency.

Table 10: Evaluation of Mouth Dissolving Film of Nicorandil

Formulation Code	Thickness (mm)	Mean Weight (mg)	Drug Content (%)	% Moisture Absorption	% Moisture Loss	Swelling Index (%)
X1	0.149	118.3	98	1.50	1.426	67.20
X2	0.171	123.4	96	1.44	2.203	64.10
X3	0.173	128.0	98	2.30	2.879	66.32
X4	0.167	124.6	97	2.037	1.974	64.50

Table 11: Evaluation of Mechanical and Disintegration Properties of Nicorandil Films

Formulation Code	Tensile Strength (kg/mm²)	% Elongation	Folding Endurance	Disintegration Time (sec)	Dissolution Time (sec)
X1	1.283 ± 0.231	65.12 ± 1.66	>800	15	134
X2	1.135 ± 0.004	22.90 ± 0.58	200	32	165
X3	1.286 ± 0.037	36.27 ± 1.67	>800	20	125
X4	1.393 ± 0.091	40.72 ± 1.42	600	23	122

Table 12: In-vitro Drug Release Profile of Nicorandil Mouth Dissolving Film (Formulation X1)

Time (min)	Absorbance	Concentration (mg/10 ml)	Final Conc. (mg/10 ml)	Cumulative Conc. (mg/300 ml)	% DR	% CPR	Log (% DR)	√t	Mt/M∞	Ln (Mt/M∞)	Ln t
15	0.149	0.166	0.169	5.033	26.16	76.98	1.876	3.809	0.455	-0.785	2.709
30	0.201	0.235	0.401	7.178	34.80	69.19	1.812	5.466	0.649	-0.432	3.401
45	0.270	0.305	0.708	9.622	49.03	50.97	1.798	6.717	0.869	-0.139	3.809
60	0.320	0.346	1.052	11.22	58.20	40.70	1.645	7.756	1.009	0.080	4.094
90	0.355	0.380	1.435	13.55	67.70	38.23	1.587	8.600	1.136	0.128	4.499
120	0.399	0.445	1.877	16.70	70.588	27.49	1.487	9.490	1.331	0.286	4.787
150	0.445	0.480	2.363	18.44	81.24	18.75	1.287	12.20	1.489	0.398	5.010
180	0.443	0.468	2.852	17.03	84.18	16.80	1.134	13.45	1.542	0.439	5.340
210	0.449	0.493	3.346	19.69	87.46	12.50	1.065	11.63	1.601	0.498	5.480
240	0.447	0.498	3.844	17.27	90.423	8.69	0.930	15.40	1.650	0.507	5.700
300	0.449	0.494	4.340	19.70	93.89	9.10	0.789	17.30	1.700	0.534	5.703

Table 13: Stability Studies of Optimized Formulation (X1) – Drug Content, Weight Variation, Disintegration Time & Dissolution Time After 30 Days (Storage Condition: 30°C / 60% RH)

Days	Weight Variation (mg/4 cm²)	Disintegration Time (sec)	Dissolution Time (sec)	Drug Content (%)
0	118 ± 0.06	14	138 ± 2.15	100 ± 0.09
5	117.5 ± 0.04	14	135 ± 1.12	99.85 ± 0.07
10	118.2 ± 0.10	14	138 ± 1.00	99.67 ± 0.01
15	119.4 ± 0.05	16	136 ± 1.57	99.37 ± 0.02
20	118.7 ± 0.03	14	138 ± 1.23	98.94 ± 0.02
25	118.6 ± 0.06	15	139 ± 1.56	98.58 ± 0.01
30	118.1 ± 0.02	15	140 ± 1.23	98.13 ± 0.04

Storage Condition: 45°C / 75% RH

Days	Weight Variation (mg/4 cm^2)	Disintegration Time (sec)	Dissolution Time (sec)	Drug Content (%)
0	119.6 ± 1.52	15	140 ± 1.13	101 ± 0.03
5	116.4 ± 0.01	15	142 ± 2.34	100.23 ± 0.05
10	117.9 ± 0.05	16	140 ± 1.18	99.71 ± 0.03
15	118.4 ± 0.07	14	139 ± 1.84	99.31 ± 0.012
20	118.2 ± 0.10	14	137 ± 1.00	99.05 ± 0.01
25	117.8 ± 0.06	13	138 ± 1.42	98.75 ± 0.03
30	118.1 ± 0.02	13	137 ± 1.00	98.41 ± 0.023

Table 14: In-Vitro Drug Release Profile of Film X1 at 30°C / 60% RH

Time (min)	Abs	Conc. (mg/10 ml)	Final Conc.	CPDR	%DR
30	0.145	0.161	0.161	4.833	24.166
60	0.198	0.220	0.381	6.600	33.805
90	0.235	0.261	0.642	7.833	41.072
120	0.294	0.326	0.968	9.800	52.211
150	0.348	0.386	1.355	11.600	62.844
180	0.376	0.417	1.773	12.533	69.444
210	0.421	0.467	2.241	14.033	79.033
230	0.454	0.504	2.745	15.133	86.872
300	0.461	0.512	3.257	15.366	90.561

Table 15: In-Vitro Drug Release Profile of Film X1 at 45°C / 75% RH

Time (min)	Abs	Conc. (mg/10 ml)	Final Conc.	CPDR	%DR
30	0.146	0.162	0.162	4.866	24.33
60	0.200	0.222	0.384	6.666	34.14
90	0.239	0.265	0.650	7.966	41.75
120	0.297	0.330	0.980	9.900	52.75
150	0.351	0.390	1.370	11.700	63.40
180	0.378	0.420	1.790	12.600	69.85
210	0.425	0.472	2.262	14.166	79.78
230	0.455	0.505	2.767	15.166	87.14
300	0.459	0.510	3.277	15.300	90.33

CONCLUSION:

Nicorandil mouth dissolving films were successfully developed with acceptable physicochemical properties and rapid disintegration. Among all formulations, X1 showed the best performance, with the shortest disintegration time, excellent mechanical strength, and highest drug release. Stability studies confirmed its robustness. Nicorandil MDFs especially X1 offer a stable, fast-acting, and patient-friendly alternative to conventional dosage forms.

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Review Article

FAST DISSOLVING ORAL FILMS OF NICORANDIL: INNOVATIONS IN ACUTE ANGINA MANAGEMENT

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ABSTRACT

Angina pectoris is a prevalent cardiovascular condition characterized by transient episodes of chest pain due to myocardial ischemia. Nicorandil, a potassium channel opener with dual nitrate-like and ATP-sensitive potassium channel activity, is widely used for its anti-anginal efficacy. Conventional oral dosage forms of Nicorandil often face limitations such as delayed onset, variable bioavailability due to first-pass metabolism, and poor patient compliance. Fast dissolving oral films (FDOFs) have emerged as an innovative dosage form to overcome these challenges, offering rapid disintegration in the oral cavity, enhanced bioavailability, ease of administration, and improved patient compliance. This review comprehensively discusses the formulation strategies, excipient selection, drug release mechanisms, evaluation parameters, and comparative advantages of Nicorandil FDOFs. Furthermore, it explores recent advancements, including nanotechnology integration, mucoadhesive films, and 3D printing approaches for personalized therapy. FDOFs represent a promising patient-centric platform for the rapid and effective management of acute and chronic angina, with potential to transform therapeutic outcomes and adherence in cardiovascular care.

Keywords: Nicorandil, Angina Pectoris, Fast Dissolving Oral Films (FDOFs), Buccal Drug Delivery, Polymer Matrix, Rapid Drug Release, Patient Compliance, Sustained Bioavailability, Formulation Strategies.

INTRODUCTION

Angina pectoris is a clinical manifestation of myocardial ischemia, characterized by transient episodes of chest pain, discomfort, or pressure due to an imbalance between myocardial oxygen demand and supply (Ford and Berry, 2020). It is most commonly caused by atherosclerotic narrowing of the coronary arteries, leading to reduced blood flow to the heart muscle. The prevalence of angina is increasing globally, particularly in aging populations, highlighting the need for effective and rapid therapeutic interventions. Conventional treatment strategies include nitrates, beta-blockers, calcium channel blockers, and potassium channel openers, among which Nicorandil has emerged as a potent anti-anginal agent (Schoenhagen *et al.*, 2001). Nicorandil is a unique dual-acting compound that combines nitrate-like vasodilation with ATP-sensitive potassium channel activation. This dual mechanism allows it to dilate both large coronary arteries and arterioles, reducing cardiac preload and afterload, thereby improving myocardial oxygen delivery and alleviating

anginal symptoms. Nicorandil has demonstrated significant efficacy in chronic stable angina, unstable angina, and even acute ischemic events. However, conventional oral dosage forms, such as immediate- and sustained-release tablets, face challenges including delayed onset of action, variable bioavailability due to first-pass metabolism, and reduced patient compliance, particularly among pediatric, geriatric, or dysphagic patients (Baldwin and Sweet; 1988).

Fast dissolving oral films (FDOFs) represent an innovative drug delivery approach designed to overcome these limitations. FDOFs are thin, flexible polymeric films that rapidly disintegrate and release the drug upon contact with saliva, without the need for water. The drug is either absorbed via the oral mucosa for partial systemic delivery or swallowed for gastrointestinal absorption. FDOFs offer several advantages over conventional tablets and capsules: they provide rapid onset of action, improved bioavailability, ease of administration, enhanced patient compliance, and potential for taste masking. Moreover, these films are portable, convenient, and suitable for emergency use during acute anginal attacks, where rapid relief is significant (Saxena and Singh; 2022).

Formulating Nicorandil into an FDOF requires careful consideration of various factors including polymer selection, plasticizer concentration, drug loading, and film thickness. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP) are commonly employed to achieve rapid disintegration, while plasticizers such as glycerin, propylene glycol, or polyethylene glycol improve film flexibility and prevent brittleness. Taste-masking agents and sweeteners are also incorporated to enhance patient acceptability, as Nicorandil has a naturally bitter taste (Jacob *et al.*, 2023).

2. Advantages of Nicorandil FDOFs in Angina Management

Advantage	Explanation
Rapid Onset	Immediate dissolution in saliva allows faster absorption and quicker relief during angina attacks.
Enhanced Bioavailability	Partial avoidance of first-pass metabolism improves systemic drug levels.
Patient Compliance	Ease of administration without water benefits pediatric, geriatric, and bedridden patients.
Portability and Convenience	Thin films can be carried easily, suitable for emergency use.
Taste Masking	Formulation allows masking of Nicorandil's bitter taste.

Formulation Components and Strategies

The formulation of Nicorandil fast dissolving oral films (FDOFs) requires careful selection of excipients and optimization of processing techniques to achieve rapid disintegration, acceptable mechanical properties, and effective drug release. The primary components of FDOFs include film-forming polymers, plasticizers, sweeteners and flavoring agents, solubilizers, and sometimes permeation enhancers or taste-masking agents. Each of these components plays a critical role in

determining the performance, stability, and patient acceptability of the final dosage form (Akhtar *et al.*, 2020).

Film-Forming Polymers

Film-forming polymers constitute the backbone of FDOFs, providing structural integrity and controlling the disintegration and dissolution behavior. Hydrophilic polymers are preferred for fast dissolving films as they readily hydrate upon contact with saliva, leading to rapid disintegration. Commonly used polymers include hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), sodium alginate, and polyvinylpyrrolidone (PVP). The choice of polymer and its concentration significantly influence film thickness, tensile strength, folding endurance, and the rate at which the film releases Nicorandil. Often, combinations of polymers are used to balance mechanical strength with rapid disintegration (Kumar *et al.*, 2025).

Plasticizers

Plasticizers are incorporated to enhance the flexibility, elasticity, and handling properties of the films, preventing brittleness and cracking during storage and administration. Commonly employed plasticizers include glycerin, propylene glycol, polyethylene glycol (PEG), and sorbitol. The concentration of plasticizer must be optimized, as excessive amounts can lead to sticky films, while insufficient amounts may produce brittle films that are difficult to handle (Kuveskar and Wani; 2025).

Sweeteners and Flavoring Agents

Nicorandil is inherently bitter, which can affect patient compliance, particularly in pediatric or geriatric populations. Therefore, taste-masking is a essential aspect of FDOF formulation. Sweeteners such as aspartame, sucralose, or saccharin, along with natural or synthetic flavoring agents (mint, orange, or strawberry), are incorporated to improve palatability and enhance the acceptability of the film. Some strategies also involve complexing Nicorandil with ion-exchange resins or cyclodextrins to mask bitterness (Amer *et al.*, 2025).

Solubilizers and Permeation Enhancers

To improve the solubility and bioavailability of Nicorandil, solubilizing agents such as poloxamers, sodium lauryl sulfate, or cyclodextrins can be included in the formulation. Additionally, permeation enhancers may be used to facilitate transmucosal absorption through the oral cavity, providing faster systemic drug levels, which is particularly advantageous for acute angina management (Jacob *et al.*, 2023).

Strategies for Film Preparation

Several formulation strategies are employed to prepare Nicorandil FDOFs, with solvent casting being the most widely used method. In this technique, the polymer and excipients are dissolved or dispersed in a suitable solvent system, and the drug is uniformly incorporated. The solution is then cast onto a flat surface and dried to form a thin film. Other approaches such as hot-melt extrusion, electrospinning, or rolling methods have also been explored to achieve uniform thickness, rapid disintegration, and reproducible drug loading. Optimization of drying conditions, polymer concentration, and drug-polymer interactions is essential to achieve films with suitable mechanical strength, rapid in vitro disintegration, and predictable drug release.

Evaluation of Fast Dissolving Oral Films (FDOFs)

Evaluation of FDOFs is important to ensure the films meet quality, efficacy, and patient acceptability standards. Since these films are intended for rapid disintegration and drug release in the oral cavity, their physicochemical, mechanical, and pharmacotechnical properties must be systematically assessed (Preis *et al.,* 2013).

Physical Appearance and Organoleptic Properties

The first step in evaluation is the visual and tactile assessment of the films. Films should be smooth, uniform in thickness, flexible, and free from air bubbles, cracks, or irregularities. Organoleptic properties such as taste, odor, and color are important for patient compliance, especially since Nicorandil has a bitter taste. Incorporation of suitable flavoring and sweetening agents should ensure that the films are palatable and acceptable for both adult and pediatric patients (Krampe *et al.,* 2016).

Thickness, Weight Uniformity, and Drug Content

Uniformity in thickness and weight is essential for consistent dosing. Thickness is typically measured using a micrometer at multiple points of the film, while weight uniformity ensures that each strip contains a reproducible amount of Nicorandil. Drug content analysis is performed to confirm accurate drug loading**,** typically using UV spectrophotometry or HPLC. These evaluations guarantee that the patient receives the intended dose with each film and that therapeutic efficacy is maintained (Panda *et al.,* 2012).

Mechanical Properties

Mechanical strength is assessed through parameters such as tensile strength, percent elongation, and folding endurance**.** Tensile strength indicates the film's ability to resist breaking under stress, while percent elongation measures flexibility. Folding endurance evaluates the number of times a film can be folded at the same point without breaking. These properties are influenced by polymer type, plasticizer concentration, and film thickness. Adequate mechanical strength ensures easy handling, packaging, and transport without compromising drug release (Alaei *et al.,* 2021).

Surface pH and Moisture Content

Surface pH is measured to ensure the films are non-irritant to the oral mucosa. Nicorandil FDOFs should have a neutral or near-neutral pH to prevent irritation or discomfort upon administration. Moisture content and moisture absorption studies are performed to assess film stability**,** as excessive moisture can lead to swelling, stickiness, or microbial growth (Joshi and Petereit; 2013)

In Vitro Disintegration and Dissolution Studies

A critical parameter for FDOFs is the in vitro disintegration time, which should be rapid, usually within a few seconds to a minute. Dissolution studies determine the rate and extent of from the film under simulated saliva conditions (pH 6.8–7.4). Rapid drug release is essential to achieve fast onset of action, particularly in acute angina management. Kinetic modeling of dissolution data also helps to understand the mechanism of drug release**,** such as diffusion-controlled or erosion-assisted release (Nishimura *et al.,* 2009).

Surface Morphology and Compatibility Studies

Surface morphology is often evaluated using scanning electron microscopy (SEM) to examine film uniformity and drug distribution. Compatibility between Nicorandil and excipients is assessed using FTIR or DSC studies**,** which ensures there are no chemical interactions that could compromise stability or efficacy.

Stability Studies

Finally, accelerated stability studies are conducted to assess the films' performance over time under stress conditions of temperature and humidity. Parameters such as drug content, disintegration time, mechanical properties, and dissolution profile are monitored. Stable formulations maintain consistent drug release, mechanical integrity, and palatability throughout their shelf life, ensuring reliable therapeutic outcomes.

Mechanism of Drug Release from FDOFs

The mechanism of drug release from fast dissolving oral films (FDOFs) is primarily governed by the composition of the polymer matrix, drug solubility, and interaction with saliva. In FDOFs, water-soluble polymers such as hydroxypropyl methylcellulose (HPMC), pullulan, or polyvinyl alcohol (PVA) dissolve rapidly upon contact with saliva, forming a gel-like layer. Nicorandil, being highly water-soluble, diffuses quickly from this hydrated matrix into the saliva, enabling rapid absorption through the oral mucosa.

Upon administration, the film rapidly hydrates, increasing in volume and softening to facilitate disintegration. The disintegration process is accelerated by the presence of superdisintegrants (e.g., croscarmellose sodium, sodium starch glycolate), which absorb water and swell, creating hydrodynamic forces that break the polymer matrix apart. This ensures that Nicorandil is released almost immediately, typically within seconds to a few minutes, which is significant for the fast onset of action required in angina management**.**

Drug release from FDOFs is usually controlled by a combination of diffusion and erosion mechanisms**.** In diffusion-controlled release, Nicorandil molecules migrate from the hydrated polymer network into the surrounding saliva due to the concentration gradient**.** Erosion-controlled release occurs when the polymer matrix gradually dissolves or erodes in the oral cavity, allowing continuous liberation of the drug. In most Nicorandil FDOFs, rapid disintegration and high water solubility favor diffusion-dominated release**,** whereas the presence of slowly dissolving polymers or plasticizers can impart a slight erosion-controlled component.

Furthermore, formulation factors such as polymer type, polymer concentration, plasticizer content, and film thickness significantly influence the release kinetics. For instance, higher polymer concentrations can form a more viscous gel barrier, slightly delaying drug diffusion, while thinner films disintegrate faster, enhancing immediate release. Additives like sweeteners, flavoring agents, or saliva stimulants can also modify the hydration rate, indirectly affecting the drug release rate (Bhatt *et al.*, 2019).

Future Directions

The development of Nicorandil fast dissolving oral films (FDOFs) holds significant promise for improving patient compliance and providing rapid relief in angina pectoris, yet there remain multiple avenues for innovation and optimization. One key direction is the use of novel polymers and excipients that can further enhance film flexibility, mechanical strength, and rapid disintegration while maintaining drug stability. Natural and biodegradable polymers, such as pullulan, chitosan, and modified starch derivatives, can be explored to improve biocompatibility and reduce potential mucosal irritation.

Another promising area is nanotechnology-assisted FDOFs**,** where Nicorandil can be incorporated into nanocarriers such as nanoparticles, nanocrystals, or liposomes within the film matrix. This approach can enhance drug solubility, provide controlled release, and improve mucosal permeation, potentially leading to faster onset of action and better bioavailability. Additionally, orodispersible films with mucoadhesive properties can be designed to prolong drug residence time in the oral cavity, allowing more efficient absorption through the buccal mucosa and minimizing first-pass metabolism.

Advances in 3D printing and solvent-casting technologies offer another avenue for precision manufacturing of FDOFs. 3D printing enables customization of drug load, film thickness, and release profiles, allowing personalized therapy based on patient-specific needs, such as age, weight, or severity of angina episodes. Integration of multidrug FDOFs is another area of research, where Nicorandil could be combined with other cardiovascular drugs in a single film to provide synergistic therapy in angina management, potentially improving adherence to polypharmacy regimens.

Finally, future research must focus on in vivo pharmacokinetic and clinical studies to validate the efficacy and safety of Nicorandil FDOFs. Correlating in vitro dissolution data with plasma drug levels (IVIVC) will be essential for optimizing formulation design and regulatory approval. In parallel, patient-centric studies assessing taste masking, mouthfeel, and ease of administration will ensure that these films are not only effective but also acceptable to patients, especially the elderly and those with swallowing difficulties.

Advantages over conventional dosage forms

Dosage Form	**Limitation**	**FDOF Advantage**
Tablets	Swallowing difficulty, delayed onset	Rapid disintegration, easy administration
Chewing gum	Requires mastication, slower absorption	Faster dissolution, dose accuracy
Sustained-release tablets	Not suitable for acute attacks	Immediate onset possible, flexible dosing
Extended-release tablets	Slow absorption	Immediate release for acute pain, option for combination FDOFs

CONCLUSION

Fast dissolving oral films of Nicorandil offer a promising, patient-centric solution for effective angina management. They provide rapid drug release, bypass first-pass metabolism, and improve patient compliance. Careful selection of polymers, plasticizers, and solubilizers ensures mechanical stability, palatability, and rapid dissolution. FDOFs represent the next-generation dosage form, potentially transforming acute and chronic angina therapy.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

Table 1: Comparative formulations of Nicorandil Formulations

Author (Year)	Work Done / Key Contribution	Reference
Reddy et al. (2003)	Developed once-daily sustained-release matrix tablets using HPMC + ethylcellulose; optimized F-IX formulation showed diffusion–erosion controlled release over 24 h.	Reddy KR, Mutalik S, Reddy S. *AAPS PharmSciTech*. 2003;4(4):E61.
Yashaswini et al. (2010)	Formulated nicorandil medicated chewing gum using direct compression; F4–F6 showed better mechanical strength & buccal release profile.	Yashaswini PM et al. *Res J Pharma Dosage Forms Tech*. 2010;2(4):301–306.
Pahade et al. (2010)	Developed sustained-release matrix tablets using hydrophilic + hydrophobic polymers; F16 achieved 24-hour controlled release.	Pahade A, Jadhav VM, Kadam VJ. *J Pharm Res Dev*. 2010;4(1):107–111.
Kim et al. (2015)	Designed extended-release tablets; established IVIVR; ER tablets provided up to 24 h release and predictable plasma levels.	Kim JY et al. *Asian J Pharm Sci*. 2015;10(2):108–113.
Iffat et al. (2017)	Used central composite design to optimize hydrophilic (Polyox) + hydrophobic (EC) polymers; F6 was best formulation with 12-month shelf-life.	Iffat W, Shoaib M, Yousuf R. *Latin Am J Pharm*. 2017;36:907–917.
Lakshmiprasanna et al. (2022)	Developed compressed-coated pulsatile tablets; Eudragit RS100 achieved effective lag-time based release.	Lakshmiprasanna M et al. *IJRPC*. 2022;12(2):84–94.
Srivastava et al. (2023)	Formulated floating tablets using natural polymers (alginate, xanthan, guar gum); achieved 24-hour sustained gastric-retentive release.	Srivastava AK et al. *Asian J Pharm Res Dev*. 2023;11(2):74–82.

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16th March 2024

ICERIPLST/PH/2024/1405

Certificate of Appreciation

This is to certify that Dr/ Mr/ Ms

Ratnesh Kumar Mishra

of **Faculty of Pharmacy,P.K. University Shivpuri M.P.**

has presented a poster / oral presentation on **Formulation Development and Evaluation of Fast Dissolving Oral Film for The Treatment of Angina Pectoris**

in the Conference organized by Career Point School of Pharmacy, CPU Kota, Rajasthan.

Prof (Dr) M. K. Gupta	Mr. Kamal Arora	Mr. Lav Sharma	Dr. Yogesh Kumar	Dr. Rajkumari Thagele
Vice Chancellor (Off.) Dean Pharmacy, CPU, Kota	Registrar CPU, Kota	Sr. General Manager, Amneal Pharmaceuticals Ltd., Ahmedabad Gujarat.	Senior PDF Scientist Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.	H.O.D, CP School of Pharmacy, CPU, Kota

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Certificate of Participation

This is to certify that Dr./Mr./Ms. **Ratnesh Kumar Mishra** affiliated to **Faculty of Pharmacy, PK University Shivpuri (M.P)** has presented titled **Fast Dissolving Oral Films of Nicorandil: Innovations in Acute Angina Management** in the 2nd International Conference on Sustainability and Green Technology (ICSGT - 2025) organized by FS University, Shikohabad, Uttar Pradesh, India, held during 10th & 11th October 2025.

Organising Secretary
ICSGT - 2025, FS University

Conference Chair &
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