Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14,issue.32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Characterization and Development of Rapimelt Tablet for Anti Hypertensive Management.

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0Cite this paper as Mandapati Sreenivas Varma, Surendra Pratap Singh, Jitendra Kumar Malik, Sunil Kumar Shah.(2025) Characterization and Development of Rapimelt Tablet for Anti Hypertensive Management... .Journal of Neonatal Surgery, 14, (32s), 10120-10140

ABSTRACT

Rapimelt Tablets of Treprostinil Diolamine (TD) optimized by successfully prepared by direct compression method using selected superdisintegrants with Crosspovidone 1.5%, 3%, 6%, Crosscarmellose 1.5%, 3%, 6% and Sodium starch glycolate 1.5%, 3%, 6%, for the better patient compliance and effective therapy the relative efficiency of these superdisintegrant to improve the disintegration and dissolution rate of tablets were found in order. The disintegration of TF1, TF2, TF3 formulations to be as 8, 6, 5secs respectively and is almost better than TF4, TF5, TF6, TF7, TF8, TF9 formulations. Formulation TF3 In-vitro Dissolution studie 10 minutes almost total amount of the drug is released 6% crosspovidone (i.e. 96.96%). Crosspovidone shows good result as compare to other superdisintegrants.The drug release profiles of TD rapimelt tablets were fitted to various kinetic models such as Zero order, First order, Higuchi, Peppas and Hixson-Crowell. The dissolution parameters such as dissolution efficiency (DE) at 10 and 30 minutes were increased proportionately. Half-life of drug i.e., T50 was found to be 181,1.70, 1.53, 2.42, 1.94, 1.59, 2.81, 1.98 and 1.73 min for TF1, TF2, TF3, TF4, TF5, TF6, TF7, TF8 and TF9 formulations respectively. Shelf-life of the drug i.e.,T90 was found to be 9.75, 8.75, 8.24, 9.28 and 8.92 minutes for TF1, TF2, TF3, TF5 and TF6 formulations respectively. The drug release patterns of TD rapimelt tablets had followed the first order kinetic model. This release patterns are evident with the correlation coefficient 'r' values which are nearer to 1. The optimized formulation TF3 is kept for Accelerated stability stability studies. Studies, the results indicated that there was no significant change in evaluation of the tablets. In-vivo studies of TD rapimelt tablets. TD showed good linear relationship between the under peak areas and the concentrations. The lower limit of quantization was 0.05 mcg/ml for determination of TD in plasma. The limit had been sufficient for PK studies of TD Rapimelt tablets.

Keywords: Rapimelt Tablets, Treprostinil Diolamine(TD), dissolution efficiency (DE),.

1. INTRODUCTION

Worldwide hypertension is one of the common causes of cardiovascular disease. It is a disorder of major clinical, public health(1,2), and economic importance. It is a common cause for visiting physicians all over the world. One good thing about it is that if it is diagnosed at early stage, disease can be managed with lifestyle modifications(3,4). But negative thing about it is that person does not experience any obvious symptoms with this disease so most of the time diagnosis occurs at later stage of the disease. In India adolescent and young age population is more, it is a nation of youth(5). Today average age at which a person may experience a heart attack has come down from 40 years to 30 years. The justice for this scenario in Indian community is today's changing lifestyle.

The oral route of drug administration is popular, convenient and widely accepted method of administering the drugs because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient compliance. The major foucs of the formulation scientist is to develop formulations for oral application of newly synthesized drugs since they can be self- administered by the patient. The characteristics of drug, the application desired and the need for any special effects than dictates the type of oral dosage form to be developed (Roy, 1990). The monophasic liquids such as syrups, solutions, elixirs, biphasic liquids such as suspensions, emulsion etc. and solid dosage forms like tablets and capsules and liquid filled capsules are the common types of oral formulations.

Hypertension is an important public-health challenge worldwide(11,12).

In the Lancet literature was published from Jan 1, 1980, to Dec 31, 2002. The studies reported were sex-specific and age-specific prevalence of hypertension in representative population samples. All data were obtained with a standardized protocol and data-collection form(13). Overall, 26·4% (95% CI 26·0–26·8%) of the adult population in 2000 had hypertension (26·6% of men [26·0–27·2%] and 26·1% of women [25·5–26·6%]), and 29·2% (28·8–29·7%) were projected to have this condition by 2025 (29·0% of men [28·6–29·4%] and 29·5% of women [29·1–29·9%]). The estimated total number of adults with hypertension in 2000 was 972 million (957–987 million); 333 million (329–336 million) in economically developed countries and 639 million (625–654 million) in economically developing countries (14,15). The number of adults with hypertension in 2025 was predicted to increase by about 60% to a total of 1·56 billion (1·54–1·58 billion). Authentic data is needed about the prevalence of hypertension so that corrective measures are taken to prevent and control the disease. Under different circumstances an individua's blood pressure levels change but if it is consistently higher under same situations, the person is at risk of developing hypertension(16). But one blood pressure reading may not be enough to diagnose hypertension; at least two measurements with accuracy are needed to diagnose it. This disease has lifelong implications on person's life.

Hypertension (HTN) is considered one of the leading causes of increased cardiovascular disease. Lowering blood pressure does reduce cardiovascular risks; maintaining systolic blood pressure of less than 130 mm Hg demonstrably prevents complications in patients with heart failure, diabetes, coronary artery disease, stroke, and other cardiovascular diseases (17). This activity discusses the guidelines for selecting the appropriate antihypertensive medications. It presents the different classes for first, second, and third-line treatments for hypertension

and highlights the indications and side effects. It highlights the studies done to compare different classes of antihypertensive medications and indications for each class[18].

Material and Method

Preparation of Stock solution with Distilled water

100mg of the drug was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in sufficient quantity of methanol and volume was made up to the mark with methanol to get a 1000 µg/ml solution. This was the standard stock solution containing 1 mg/ml of model drug (Stock 1).

UV Absorption Maxima (λmax) of drug sample in water

One ml of the above solution was then further diluted to 100 ml with water to get a stock solution of 10 (µg/ml). UV scanning was done for 10 µg/ml drug solution from 200-400 nm using methanol as a blank in schimadzu, UV 1800 spectrophotometer. The wavelength maximum was found to be at 250 nm.

Preparation of the calibration curve

From the stock solution 2, 4, 6, 8, 10 and 12 ml were transferred to 10 ml volumetric flasks and were diluted with the water, up to the mark to obtain concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. Absorbance of each solution was measured at 226 nm. The Standard curve preparation was performed in triplicate. The absorbance was plotted against the concentrations and the graph with the straight line equation and r2 value were obtained[19].

Preparation of Stock solution with 6.8 pH Phosphate Buffer

100mg of the drug was accurately weighed and transferred into the 100 mlvolumetric flask. It was dissolved in sufficient quantity of phosphate buffer and volume was made up to the mark with methanol to get a 1000 µg/ml solution. This wasthe standard stock solution containing 1 mg/ml of model drug.(Stock 1).

UV Absorption Maxima (λmax) of drug sample in 6.8 pH Phosphate Buffer

One ml of the above solution was then further diluted to 100 ml with phosphate buffer to get a stock solution of 10 (µg/ml). UV scanning was done for 10 µg/ml drug solution from 200-400 nm using methanol as a blank in schimadzu, UV 1800 spectrophotometer. The wavelength maximum was found to be at 250 nm.

Preparation of the calibration curve

From the stock solution 2, 4, 6, 8, 10 and 12 ml were transferred to 10 ml volumetric flasks and were diluted with the phosphate buffer, up to the mark to obtain concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. Absorbance of each solution was measured at 250 nm. The Standard curve preparation was performed in triplicate. The absorbance was plotted against the concentrations and the graph with the straight line equation and r^2 value were obtained(20).

PREFORMULATION PARAMETERS(21)

Pre-formulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form.

Bulk Density:

Apparent bulk density was determined by pouring presieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is represent in gm/mL and is given by

D b = M/V0

Where, M mass of

powder, V0 Bulk

volume of the powder

Tapped Density:

It was determined by placing a graduated cylinder, containing a known mass of drug- excipient blend, on mechanical tapping apparatus. Take the powder to constant volume. The tapped volume was measured by tapping. It expressed in gm/mLand is given by

Dt = M / Vt

Where, M is the mass of powder,

Vt is the tapped volume of the powder.

Carr's index:

It is expressed in percentage and is expressed by

Carr's Index = (ρtapped-ρbulk)/ρtapped*100

With ρ tapped: the tapped bulk density of the material (kg/m3) ρ bulk: the loose bulk density of the material (kg/m^3)

Hausner's ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula. H= Dt / Db

Where, Dt is the tapped density of the powder Db is the bulk density of the powder. Lower hausner ratio (< 1.25) indicate better flow properties than higher ones(>1.25).

Angle of Repose:

The frictional forces of a loose powder can be measured by using angle of repose. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

tan (θ) = h / r θ = tan-1 (h / r)

Where, θ is the angle of repose. h is the height in cms, r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). Angle of repose was calculated by measuring the tallness and radius of the heap of powder formed(21).

Rapimelt tablets containing 30 mg of model drug were prepared with a total table weight of 200mg. Considering the Preformulation studies and the literature survey conducted the excipients were selected and an attempt to produce Rapimelt tablets with ideal mouth feel maintaining the basic tablet properties was made.

Selection of Superdisintegrants:

Different superdisintegrants croscarmellose sodium, crosspovidone, Sodium starch glycol late in the concentration range of 1.5% to 6% were used which act as disintegrates used at various concentrations and a comparative study was carried out.

Selection of diluents

Since direct compression method was followed the choice of directly compressible diluents was important. Microcrystalline cellulose was selected as the filler or diluents owing to its multiple functionality as binder, disintegrants compressibility and flowability. Of the various grades available the granular form Avicel PH102 was selected as it had been already reported to provide lower crushing strengths and shorter disintegration times.

Mannitol was selected to produce a cooling and pleasant mouth feel, it was reported*that mannitol above the concentration of 33% gives good mouth feel, thus mannitol in all the batches was fixed at a concentration of 40-47%. Besides mannitol also possesses sweetening properties and reduces the gritty mouth feel effect due to microcrystalline cellulose. It also has good compressibility properties and solubility in water.

Selection of additional ingredients(22)

The flow property of the pure drug was found to be moderate (Hauser's ratio ~1.4) thus to still improve the flow of the blend magnesium stearate (2.5%to 4%) aslubricant were incorporated also magnesium stearate decreases the hardness of tablets

without affecting the disintegration time. Aspartame was used in the concentration of2.5%to 6% as the sweetener.

Formula

Rapimelt tablets of model drug was formulated using mannitol, Avicel pH102 (microcrystalline cellulose) as diluents. Rapimelt tablet was prepared by direct compression technique as it's a cost effective method. Superdisintegrants used are Crosspovidone, Crosscarmellose sodium, Sodium starch glycol late, disintegrantsodium CMC. Aspartame as sweetening agent. Magnesium stearate (3% to 4%) as lubricant.

Formulation of different batches

The main aim of the present study was to formulate different batches using three various superdisintegrants and other ingredients in varying concentrations. So different batches of formulations was planned accordingly. According to that F1, F2, F3 (with Crosspovidone 1.5%, 3%, 6%), F4, F5, F6 (with Crosscarmellose1.5%,3%, 6%) and F7, F8, F9 (with Sodium starch glycollate 1.5%, 3%, 6%).The slight bitter taste of the drug was masked using aspartame(2.5%to 6%)as the sweetening agent.

Method of formulation

Direct compression method.

The model drug (NMD) is thoroughly mixed with the superdisintegrants, and then other excipients are added to the mixer and passed through the sieve (#:40).Collect the powder mixer, blend with magnesium stearate (pre sieved), and subject the blend for tablet compression.

Representation of Direct Compression Technique for design of Rapimelt Tablets

The drug and the excipients were passed through sieve no: 40 except lubricant. The blend was further lubricated with Magnesium stearate (#:60)and the powder blend is subjected to drying for removal of moisture content and was compressed by direct compression method by using flat faced punches in CADMACH 16 punches tablet punching machine. Round punches measuring 8.7mm diameter were used for compression. Tablet of 200mg was prepared by adjusting hardness and volume screw of compression machine properly

Table 1: Formulations of different batches

Ingredients(mg)	Formulation Code								
	TF1	TF2	TF3	TF4	TF5	TF6	TF7	TF8	TF9
Treprostinil Diolamine	30	30	30	30	30	30	30	30	30
Crosspovidone	3	6	12	-	-	-	-	-	-
Crosscarmellose sodium	-	-	-	3	6	12	-		-
SSG	-	-	-	-	-	-	3	6	12
MCC102	66	64	58	66	64	58	66	64	58
Aspartame	10	10	10	10	10	10	10	10	10
Mannitol	80	80	80	80	80	80	80	80	80
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	4	4	4	4	4	4	4	4	4

Evaluation of tablets Hardness test:

Using a Monsanto hardness tester the rigidity (hardness) of the tablet was determined·

Friability:

The friability of a sample of 20 tablets was measured using a Roche friabilator (Electrolab). 20 previously weighed tablets were rotated at 25 rpm for 4 min. The weight loss of the tablets before and after

Measurement was calculated using the following formula

Percentage friability=Initial weight –Final weight x100

Initial weight

Weight Variation:

It was performed as per the method given in the united state pharmacopoeia. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and %variation of weight was calculated.

Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the identical thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded Vernier calipers using micrometer.

Drug Content Uniformity:

Selected twenty tablets randomly and powdered. A quantity of this powder corresponding to 200mg of model drug was dissolved in 100 ml of 6.8pH phosphate buffer, stirred for 15 min and filtered. The 1ml of filtrate was diluted with 100 ml with6.8pH phosphate buffer. Absorbance of this solution was measured at 250nm using 6.8 pH phosphate buffer as blank and content of drug was estimated.

In-vitro Disintegration Time:

Disintegration times for Rapimelt tablets were determined using USP tablet disintegration apparatus with saline phosphate buffer of pH6.8 as medium. Maintained the medium temp at 37±2°. The time in minute taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

Wetting Time:

A piece of tissue paper folded twice was placed in a small Petri dish (ID = 6.5cm) containing 6 mL of simulated saliva pH, a tablet was put on the amaranth powder containing paper the time required for upper surface of the tablet for formation of pink color was measured.

Water absorption ratio:

For measuring water absorption ratio, the weight of the tablet before keeping inthe petri dish is noted (W_b). The wetted form of tablet was taken from petridish and reweighed (W_a). The water absorption ratio (R) can be the determined according to the following equation.

$R=100 \times (W_a-W_b) / W_b$

In-vitro dispersion time:

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of pH6.8 (simulated saliva fluid).Tablets from each formulation werer and omly selected and *in vitro* dispersion time is expressed in seconds.

In-vitro Dissolution studies:

Dissolution of the tablet of each batch was carried out using USPXXIII dissolution type II apparatus (ELECTRO LAB) using paddles at 50 rpm. As per the official recommendation of IP 900ml of 6.8 pH of phosphate buffer used as dissolution medium and the temperature of the medium was set at 37 ± 0.5 ^{0}C. 5 ml of sample was withdrawn at predetermined time interval of 2 ,4, 6, 8 and 10 min. And same volume of fresh medium was replaced. The withdrawn samples were analyzed by an UV spectrophotometer at250 nm using buffer solution as blank solution.

Table 2: Summary of general dissolution conditions

S. No.	Parameter	Specifications
1	Dissolution medium	pH6.8phosphatebuffer +0.5%
2	Temperature	37ºC±0.5 ºC
3	Rotation speed	50rpm
4	USPType II	Paddle

5	Volume withdrawn	5 ml every2 minutes
6	λ max	250 nm

Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. The set wo situations exp and the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for Rapimelt but is used less frequently due to specific physical properties of tablets.

Drug release kinetics(22)

As a model independent approach, comparison of time taken for the given proportion of the active drug to be dissolved in the dissolution medium and figures such as T_{50} and T_{90} were calculated by taking the time points of 50% and 90% of the drug dissolved and another parameter dissolution efficiency (DE) .

Zero order kinetics:

The zero order release has the ability to deliver a drug at a rate independent of time and drug concentration in a dosage form. Zero order ensures a steady amount of drug is released over time. This model represents the drug dissolution from dosage forms that do not disaggregate and release the drug slowly including transdermal systems or matrix tablets with low soluble drugs. The model is represented by the Equation below

$Q1=Q0+K0t$

Where (Q1) is the amount of drug dissolved; (t) is the time; (Q0) is the initial amount of drug in the solution; and (K0) is the zero order release constant.

First order kinetics(23)

This first order model is used to describe the absorption and elimination of some drugs. This model releases the drug proportionally to the amount of drug remaining in the interior of the dosage form, allowing for the amount of drug released per unit of time to diminish. The dosage forms which follow this dissolution profile include water soluble drugs in porous matrices.

$logQ1=logQ0+K1t2.303$

Where (Q1) is the amount of drug released; (Q0) is the initial amount of drug in solution; (t) is the time; and (K1) is the first order release constant.

Hixon-crowellcubth root model

Hixson-Crowell cube root la w describes the release from systems where there is a change in surface area and diameter of particle s or tablets. change in shape as a suspended solid dissolves, its surface decreases as the two-thirds power of its weight. This relation has been used by Hixson and Crowell in the derivation of the cube root **Qt1/3= Q01/3–KHCtQ01/3–Qt1/3= KHCt**

Higuchi model

The Higuchi model is used to study the release of water soluble and low soluble drugs incorporated in a semi-solid or solid matrix. This model describes drug release as a diffusion process based on Fick's law. The Higuchi model is used to describe drug dissolution from several types of modified release dosage forms such as transdermal systems or matrix tablets containing water soluble drugs.

$Q1=KH\sqrt{t}$

Where (Q1) is the amount of drug released (KH) is the Higuchi dissolution constant; and (t) is the time.

Korsmeyer-peppasmodel:

The Korsmeyer-Peppas model is a simple model relating, exponentially, the drug release to the elapsed time. The different release mechanisms are characterized by using an n-value, which differs depending on a slab or a cylinder. This model is used to analyze polymeric dosage forms that do not have a well-known release mechanism or more than one type of release is occurring simultaneously.

$F=MtM\infty=Kmtn$

Where (F) is the fraction of drug release at specific time; (Mt) is the amount of drug release; (M∞) is the total amount of drug in dosage form; (Km) is the structural and geometric constant; and (n) is the release exponent.

Stability Studies(24)

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

ICH specifies the length of study and storage conditions.

Long-Term Testing: 25^0 C $\pm 2^0$C/ 60%RH±5%for12 Months

Accelerated Testing: 40^0C± 2^0 C/75% RH±5%for6 Months

Stability studies were carried out at 40^0C±2^0C/75% RH±5% for all the formulations for a period of 3 months.

The selected formulations were closely packed in aluminium foils and then stored at 40^0 C ± 2^0 C/75% RH ± 5% in stability chamber for 3 months and evaluated for their physical appearance, drug content and *in-vitro* drug release studies at intervals of 1month. The shelf life period of the prepared buccal tablets is determined by using similarity factor.

In vivo studies

The bioavailability studies for pure TD, optimized formulation of TF3, and Marketed Formulation were carried out using male Wistar rats (200-250 g). The animals were maintained in a clean room at a temperature between 20°C ± 25°C with 12-h light and dark cycles and controlled RH. The animals were fasted for 12 h prior to commencement of the study as well as during the study and had access to water ad libitum(25). The experimental protocols were subjected to the securitization of the Institutional Animal Ethics Committee and were cleared by the same was obtained before conducting the studies. They were divided into four groups (six in each group); Group I served as a control group, whereas other three groups were treated with pure drug (suspended in normal saline with the help of Tween 80), tablet formulation containing SD of TD (TF1) and Marketed Formulation respectively. Tablets with a dose of 10 mg/kg body weight of rats were administered by dispersing in distilled water through oral feeding pipe.

2. RESULTS AND DISCUSSION

Objective of this study was to formulate directly compressible orally disintegrating tablets of Treprostinil Diolamine with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age group for easy administration for the treatment of Hypertension (Pulmonary Arterial Hypertension), nausea and vomiting, and motion sickness for rapid dissolution and absorption of drug which may produce rapid onset of action. It is also helpful for vestibular symptoms of other origins(26).

Treprostinil is a vasodilator that is used for the treatment of pulmonary arterial hypertension. Treprostinil is a chemically stable prostacyclin analog. Its principal pharmacologic action is direct vasodilation, which causes reduction of pulmonary and systemic arterial pressure, reducing right and left ventricular afterload; therefore improves the cardiac output. It also has an antiplatelet effect.

Preformulation Studies

General properties

Description : White to cream color crystalline powder.

Solubility Profile : Solubility in different pH buffers and solvents is given below.

Table: Solubility in different pH buffers is given below

Table 3: Preformulation Studies

pH Buffers	Solubility (mg/mL)	Solubility
1.2	Not soluble	Practically insoluble
2.4	Not soluble	Practically insoluble
4.5	Not soluble	Practically insoluble
6.8	100.34	Freely soluble
7.5	101.04	Freely soluble

Table 4: Solubility in different Solvent is given below

Name of the Solvent	Solubility
Methanol	Freely soluble
Ethanol	Freely soluble
N,N- Dimethyl formamide	Freely soluble
Water	Freely soluble

Melting Point by DSC: About 109°C.

Melting point by DSC has been performed for three production scale batches of Treprostinil Diolamine

Table 5: Melting Point by DSC

Batch#	Results
TD01	109.37°C
TD02	109.31°C
TD03	109.57°C

Hygroscopicity: Slightly Hygroscopic. Hygroscopicity report is provided in

Calibration curve of Treprostinil Diolamine

Preparation of Stock solution with Distilled water

100mg of the drug was accurately weighed and transferred into the 100 ml volumetric flask(27). It was dissolved in sufficient quantity of methanol and volume was made up to the mark with methanol to get a 1000 µg/ml solution. This was the standard stock solution containing 1 mg/ml of model drug (Stock 1).

UV Absorption Maxima (λmax) of drug sample in water

One ml of the above solution was then further diluted to 100 ml with water to get a stock solution of 10 (µg/ml). UV scanning was done for 10 µg/ml drug solution from 200-400 nm using methanol as a blank in schimadzu UV 1800 spectrophotometer. The wavelength maximum was found to be at 250 nm.

Preparation of the calibration curve

From the stock solution 2, 4, 6, 8, 10 and 12 ml were transferred to 10 ml volumetric flasks and were diluted with the water, up to the mark to obtain concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. Absorbance of each solution was measured at 226 nm. The Standard curve preparation was performed in triplicate. The absorbance was plotted against the concentrations and the graph with the straight line equation and r2 value were obtained.

Preparation of Stock solution with 6.8 pH Phosphate Buffer

100mg of the drug was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in sufficient quantity of phosphate buffer and volume was made up to the mark with methanol to get a 1000 µg/ml solution. This was the standard stock solution containing 1 mg/ml of model drug (Stock 1).

UV Absorption Maxima (λmax) of drug sample in 6.8 pH Phosphate Buffer

One ml of the above solution was then further diluted to 100 ml with phosphate buffer to get a stock solution of 10 (µg/ml). UV scanning was done for 10 µg/ml drug solution from 200-400 nm using methanol as a blank in schimadzu, UV 1800 spectrophotometer. The wavelength maximum was found to be at 250 nm.

Preparation of the calibration curve

From the stock solution 2, 4, 6, 8, 10 and 12 ml were transferred to 10 ml volumetric flasks and were diluted with the phosphate buffer, up to the mark to obtain concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. Absorbance of each

solution was measured at 250 nm. The Standard curve preparation was performed in triplicate. The absorbance was plotted against the concentrations and the graph with the straight line equation and r2 value were obtained.

Table 6: Standard Calibration curve of Treprostinil Diolamine with Distilled water

S.No.	Concentration(mcg/ml)	Absorbance
1	0	0
2	2	0.208
3	4	0.435
4	6	0.646
5	8	0.808
6	10	0.996
7	12	1.234

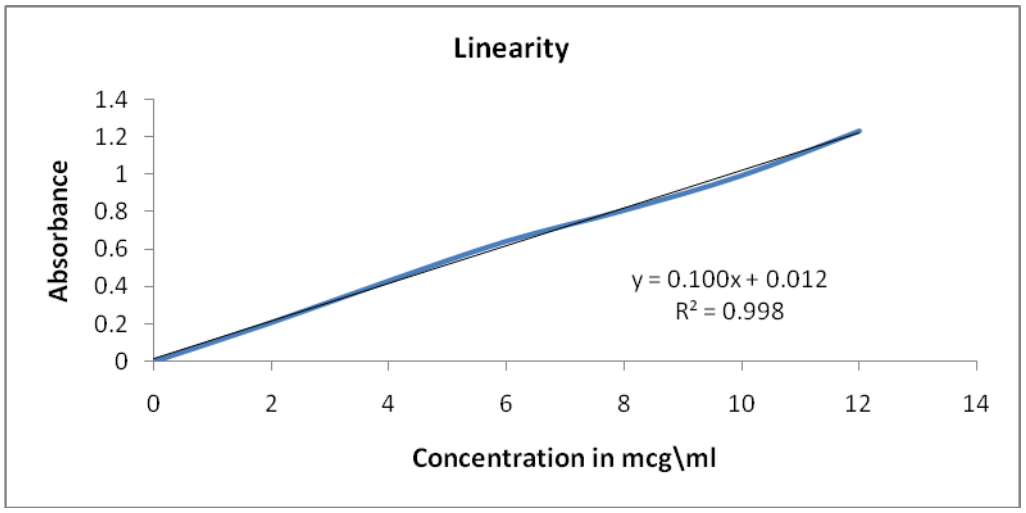

Figure1: Standard Calibration curve of Treprostinil Diolamine with Distilledwater

In the current investigation, analytical method obeyed beer-lamberts law in the concentration range of 2-12µg /ml and it was suitable for the estimation of Treprostinil Diolamine using Distilled water. The value of correlation coefficient(r) for the linear regression equation was found to be more than 0.99 which indicates a positive correlation between the concentration of drug and corresponding absorbance values.

Table 7: Standard Calibration curve of Treprostinil Diolamine with 6.8pH phosphate buffer

S.No.	Concentration(mcg/ml)	Absorbance
1	0	0
2	2	0.208
3	4	0.397
4	6	0.657
5	8	0.846

6	10	1.045
7	12	1.234

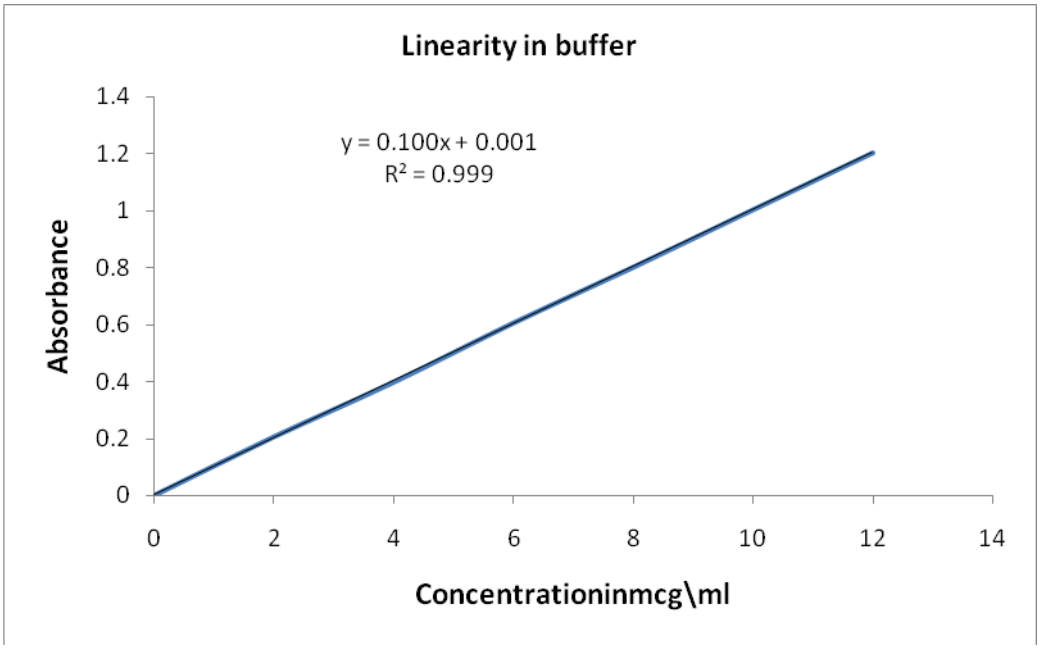

Figure 2: Standard Calibration curve of NMD with 6.8pH phosphate buffer

In the current investigation, analytical method obeyed beer-lamberts law in the concentration range of 2-12 µg/ml and it was suitable for the estimation of Treprostinil Diolamine using phosphate buffer of pH 6.8. The value of correlation coefficient (r) for the line arregression equation was found to be more than 0.99 which indicates positive correlation between the concentration of drug and corresponding absorbance values(28).

FT-IR studies

Table 8: FT-IR inter pretations of pured rug and physical mixtures

S.No	Functionalgroup	Characteristic peaks	Observed peaks						
			Treprostinil Diolamine	Treprostinil Diolamine: MCC	Treprostinil Diolamine: SSG	Treprostinil Diolamine: CCS	Treprostinil Diolamine: Crospovidone	Treprostinil Diolamine:Mannitol	Treprostinil Diolamine:Mg.stearate
1	C-H (Aromatic bending)	680-862cm^{-1}	782.18cm^{-1}	782.18cm^{-1}	781.30cm^{-1}	781.20cm^{-1}	782.18cm^{-1}	783.12cm^{-1}	782.13cm^{-1}
2	NO_2 (stretching)	1300-1600cm^{-1}	1369.54cm^{-1}	1368.56cm^{-1}	1369.53cm^{-1}	1369.53cm^{-1}	1369.523cm^{-1}	1369.523cm-1	1369.53cm-1
3	C=C (Aromaticstretching)	1400-1600cm^{-1}	1465.97cm^{-1}	1465.97cm^{-1}	1415.82cm^{-1}	1415.82cm^{-1}	1465.02cm^{-1}	1415.82cm-1	1426.43cm^{-1}

4	N-H (bending)	1580-1650cm^{-1}	1626.06cm^{-1}	1627.02cm^{-1}	1638.68cm^{-1}	1637.64cm^{-1}	1627.98cm^{-1}	1626.07cm-1	1624.14cm-1
5	C-H (stretching)	2850-3000cm^{-1}	2973.42cm^{-1}	2936.74cm^{-1}	2937.72cm^{-1}	2936.74cm^{-1}	2938.67cm^{-1}	2943.52cm-1	2934.83cm-1
6	O-H (stretching)	3200-3500cm^{-1}	3411.27cm^{-1}	3258.82cm^{-1}	3397.27cm^{-1}	3272.38cm^{-1}	3273.35cm^{-1}	3261.78cm-1	3271.42cm-1

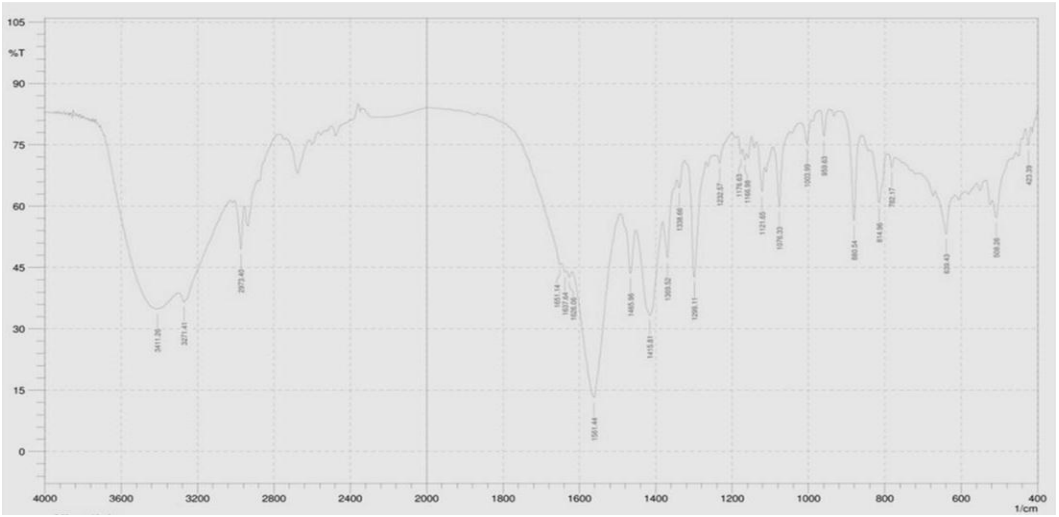

Figure 3: FT-IR spectra of Treprostinil Diolamine

FT-IR spectra of pure Treprostinil Diolamine and the physical mixtures of drug and excipients were given in Table 7.3 and Figure 7.3, 7.4, 7.5,7.6 7.7 and 7.9. Pure Treprostinil Diolamine showed principal absorption peaks at782.17cm^{-1}(C-H aromatic bending), 1368.54cm^{-1} (NO_2stretching), 1464.94 cm^{-1}(C=C aromatic stretching), 1626.06cm^{-1} (N-H bending), 2972.38 cm^{-1} (C-H stretching) and 3411.22cm^{-1} (O-H stretching).The identical peaks of C-H aromatic bending, NO_2 stretching, C=C aromatic stretching, N-H bending, C-H stretching and O-H stretching, vibrations were also noticed in the spectra of physical mixtures which contains drug and excipients. FT-IR spectra revealed that there was no interaction between the drug and the excipients used for fast dissolving tablets preparation.

Pre-compression parameters Treprostinil Diolamine fast dissolving tablets.

The angle of repose less than 31.82, which reveals good flow property it shown in for formulations TF1–TF9 .The loose bulk density and tapped bulk density for all formulation (TF1 – TF9) varied from 0.442 gm/cm^3 to 0.485gm/cm^3 and 0.502 gm/cm^{3}to 0.593 gm/cm^3 respectively. The results of carr's consolid at e index or % compressibility index for the entire formulation (TF1 – TF9) blend range from 15 to 19 shows fair flow properties.

Formulations of different batches

The rapimelt tablet of Treprostinil Diolamine will be prepared by direct compression method by adding various polymers and super disintegrants

Table 9: Formulations of different batches

Ingredients(mg)	**Formulation Code**								
	TF1	**TF2**	**TF3**	**TF4**	**TF5**	**TF6**	**TF7**	**TF8**	**TF9**
Treprostinil Diolamine	20	20	20	20	20	20	20	20	20

Crosspovidone	3	6	12	-	-	-	-	-	-
Crosscarmellose sodium	-	-	-	3	6	12	-		-
SSG	-	-	-	-	-	-	3	6	12
MCC102	76	74	68	76	74	68	76	74	68
Aspartame	10	10	10	10	10	10	10	10	10
Mannitol	80	80	80	80	80	80	80	80	80
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	4	4	4	4	4	4	4	4	4

Table 10: Evaluation of tablet blend for formulations(TF1-TF9)

Formulation	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose
TF1	0.463	0.573	1.22	19.2	29.46
TF2	0.422	0.504	1.17	15.6	27.64
TF3	0.457	0.543	1.23	15.7	25.55
TF4	0.468	0.558	1.26	16.5	26.24
TF5	0.486	0.592	1.12	18.23	27.22
TF6	0.462	0.557	1.22	17.3	30.37
TF7	0.476	0.574	1.23	16.7	28.47
TF8	0.452	0.555	1.27	18.8	25.72
TF9	0.441	0.538	1.28	17.7	31.83

Postcompression parameters Treprostinil Diolamine fast dissolving tablets.

Table 11: Evaluation of Rapimelt tablets for formulations(TF1– TF9)

Formulation	Hardness (kg/cm2)	Friability (%)	Weight (mg)	Thickness (mm)	Drug content (%)
TF1	3.0±0.16	0.24	201±0.58	3.9±0.0	97.4
TF2	2.8±0.22	0.22	198±0.62	4.2±0.02	97.7
TF3	3.1±0.17	0.27	201±0.46	3.7±0.07	98.3
TF4	2.9±0.14	0.23	202±0.87	3.8±0.10	97
TF5	3.2±0.17	0.29	204±0.45	3.9±0.03	98.43
TF6	2.8±0.23	0.33	198±0.64	3.9±0.06	100.7
TF7	3.2±0.25	0.27	201±0.78	3.8±0.15	97.2
TF8	2.9±0.22	0.28	201±0.87	3.9±0.03	98.2

TF9	2.8±0.18	0.23	203±0.75	4.1±0.01	95.34

The hardness values ranged from 2.8±0.17 kg/cm^{2}to 3.2±0.25 kg/cm^{2}for formulation (TF1-TF9) and were almost same. The friability values were found to be within the limit (0.5-1%).The above evaluation parameter showed no significant difference between TF1, TF2, TF3, TF4, TF5, TF6, TF7, TF8, TF9 formulations(28). The entire tablet passes weight variation test as the average % weight variation was within the Pharmacopeia limit of 7.5%. It was found to be 198±0.62 mg to 204±0.55 mg. The weight of all the tablets was found to be uniform with less deviation. The maximum concentration among all the formulations was found to be 100.8% and minimum % drug content from all formulation was found to be 95.34%.

Evaluation of Treprostinil Diolamine fast dissolving tablets.

Table 12: Evaluation of Rapimelt tablets for formulations (TF1–TF9)

Formulation	Disintegration time (sec)	Wetting time(sec)	Water absorption ratio(%)	*In vitro* dispersion time(sec)
TF1	8	20	19.42	8
TF2	6	15	22.47	5
TF3	5	12	19.78	5
TF4	10	16	16.13	15
TF5	9	14	17.27	11
TF6	8	19	12.17	9
TF7	18	27	15.32	14
TF8	10	20	12.047	12
TF9	9	20	13.92	8

Disintegration test carried out in modified dissolution apparatus, its hows the formulations with1.5%, 3%, 6% Sodium Starch Glycolate showed high value for disintegrating time as 18,10, 8 secs. The results showed that the disintegration time of TF1, TF2, TF3 with 1.5%, 3%, 6% CP formulations to be as 8, 6, 5secs respectively and is almost better than TF4, TF5, TF6, TF7, TF8, `TF9 formulations and comparative profile.

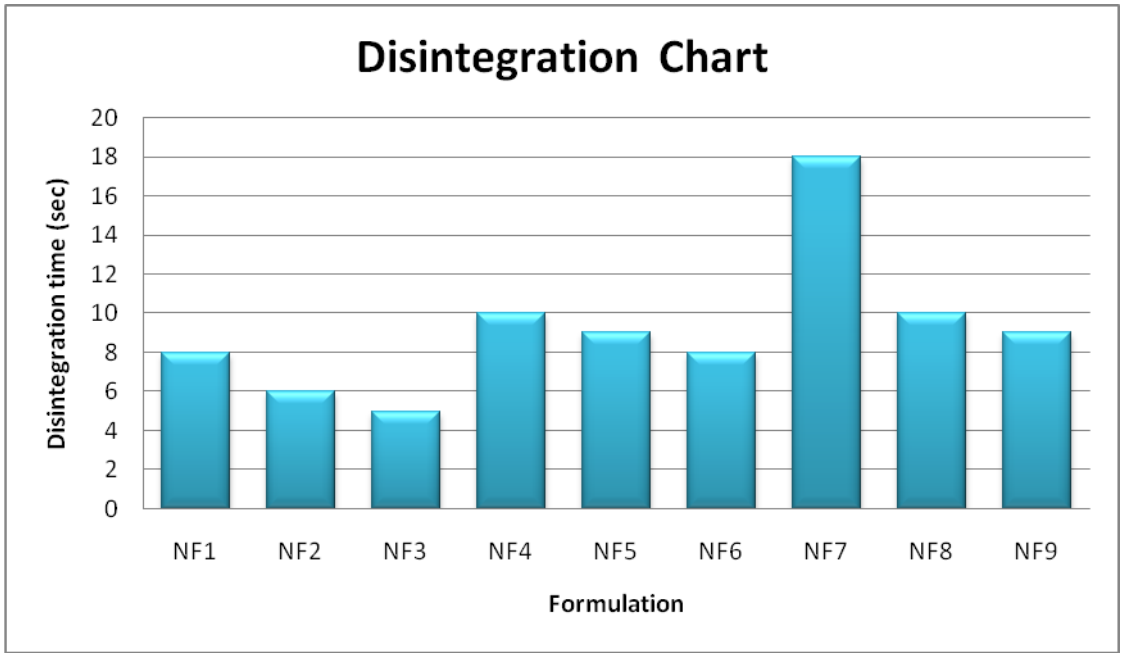

Figure 4: Bar graph comparison between disintegration times for formulations (TF1-TF9)

Wetting time is closely related to the inner structure of tablet. The experiment mimics the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of tablet. This shows the wetting process was very rapid in almost all formulations. This may be due to the ability of swelling followed by breaking and also capacity of water absorption and causes swelling. It was found to be in the range of 14 secs to 27secs.It shows crosspovidone formulations TF1, TF2, TF3 (1.5 – 6%) have better wetting time comparing with that of croscarmellose sodium starch glycolate, and comparative profile(29). Water absorption ratio which is important criteria for understanding the capacity of disintegrates to swell in the presence of little amount of water, was calculated. It was found to be in the range of 12.17 to 22.47%. This shows that all the formulations have good water absorption capacity.

The in-vitro dispersion time is measured by time taken to uniform dispersion, the rapid dispersion. It was found to be in the range of 5secs to 15secs (Graph). The result showed that the in vitro dispersion time of TF1, TF2, and TF3 formulations is almost equal and better than TF4, TF5, TF6, TF7, TF8, TF9 formulations.

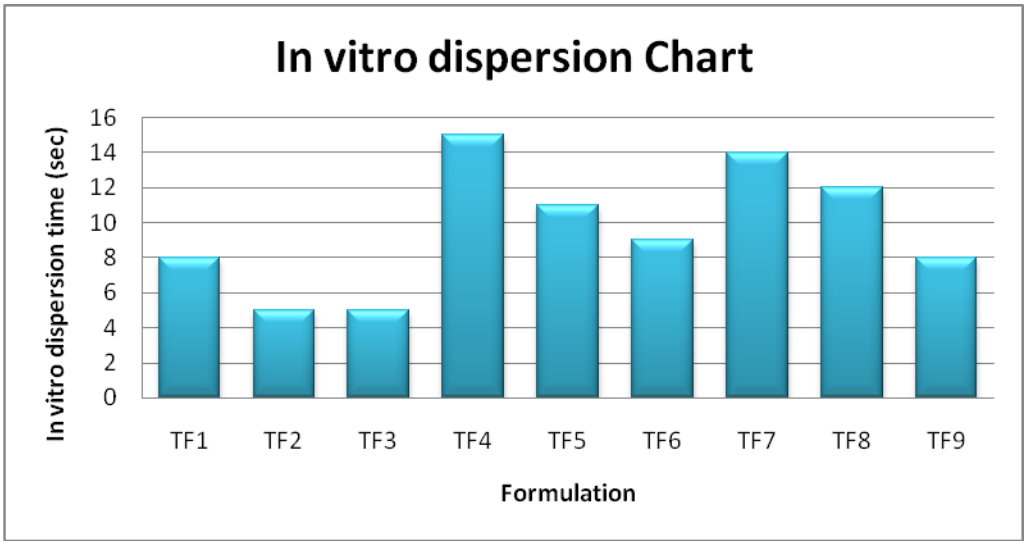

Figure 5: Bar graph comparison between In-vitro dispersion times for formulations (TF1-TF9)

In-vitro **dissolution studies of Treprostinil Diolamine fast dissolving tablets.**

Table 13: Cumulative % drug release for formulations (TF1-TF9)

Cumulative % drug release									
Time	**TF1**	**F2**	**TF3**	**TF4**	**TF5**	**TF6**	**TF7**	**TF8**	**TF9**
2Min	55.14	58.9	65.5	48.07	51.42	62.7	45.93	50.54	57.98
4Min	68.7	72.1	74.9	57.28	61.54	71.12	55.97	61.72	61.07
6Min	71.13	80	82.64	72.92	76.55	81.16	71.44	73.22	77.24
8Min	81.8	87.07	89.06	79.68	84.61	86.57	76.05	81.83	84.12
10Min	91.17	94.83	96.96	88.42	93.32	94.18	85.2	87.07	89.24

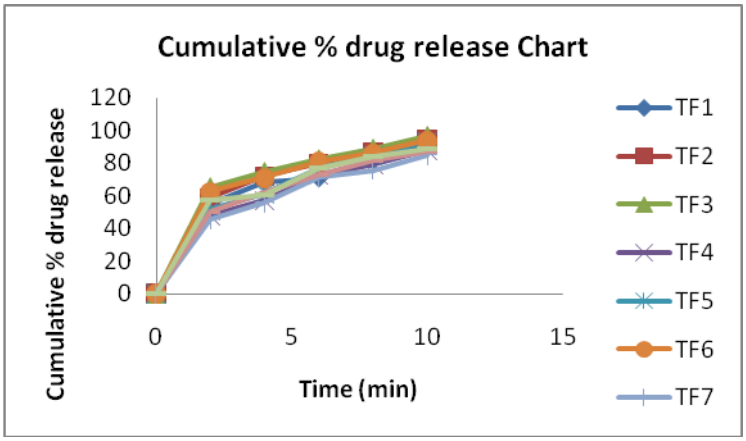

Figure 6: Comparison between cumulative % drug releases for formulations (TF1-TF9)

Dissolution is carried out in USP-2 type apparatus at 50rpm in the volume of 500mldissolution media (phosphate buffer pH 6.8) for 10 minutes. At the end of 10 minutes almost total amount of the drug is released (i.e. 96.96%), from the formulation prepared by the direct compression method with 6% crosspovidone.

Drug release kinetics of Treprostinil Diolamine fast dissolving tablets.

Correlation coefficient (r) & rate constant (k) Values of Treprostinil Diolamine Rapimelt tablets containing Crospovidone, croscarmellose sodium, sodium starch glycolate(30).

Table 14: Drug release kinetics

Kinetic model		TF1	TF2	TF3	TF4	TF5	TF6	TF7	TF8	TF9
Zero order	r	0.94367	0.9392	0.9179	0.9365	0.9318	0.9155	0.9423	0.8382	0.8978
	k	17.14	18.26	18.72	14.32	15.37	17.78	13.99	15.42	15.42
Higuchi	r	0.9943	0.9913	0.9647	0.9942	0.9737	0.9832	0.9954	0.9927	0.9797
	k	35.18	37.09	39.08	29.63	31.80	37.17	28.83	31.76	32.72
First order	r	0.9962	0.9938	0.9992	0.9981	0.9994	0.9902	0.9989	0.9992	0.9823
	k	0.2698	0.3192	0.3456	0.2127	0.2466	0.3105	0.2057	0.241	0.24
Peppas	r	0.9796	0.9996	0.9985	0.9893	0.9914	0.9127	0.9913	0.9972	0.9614
	k	0.293	0.2894	0.2388	0.3878	0.3758	0.2512	0.3894	0.3489	0.28823
Hixson-crowell	r	0.9658	0.9703	0.9627	0.9815	0.9855	0.858	0.9762	0.9742	0.9602
	k	0.3717	0.4023	0.4284	0.2865	0.3162	0.3932	0.2776	0.3177	0.3177
DE10		44.72	47.47	51.48	38.36	41.13	49.12	36.96	40.47	44.37
DE30		58.97	63.63	66.89	54.53	57.96	64.55	52.84	56.59	59.72
T50		1.82	1.70	1.53	2.43	1.93	1.58	2.82	1.97	1.72
T90		9.74	8.74	8.23	0	9.27	8.93	0	0	0

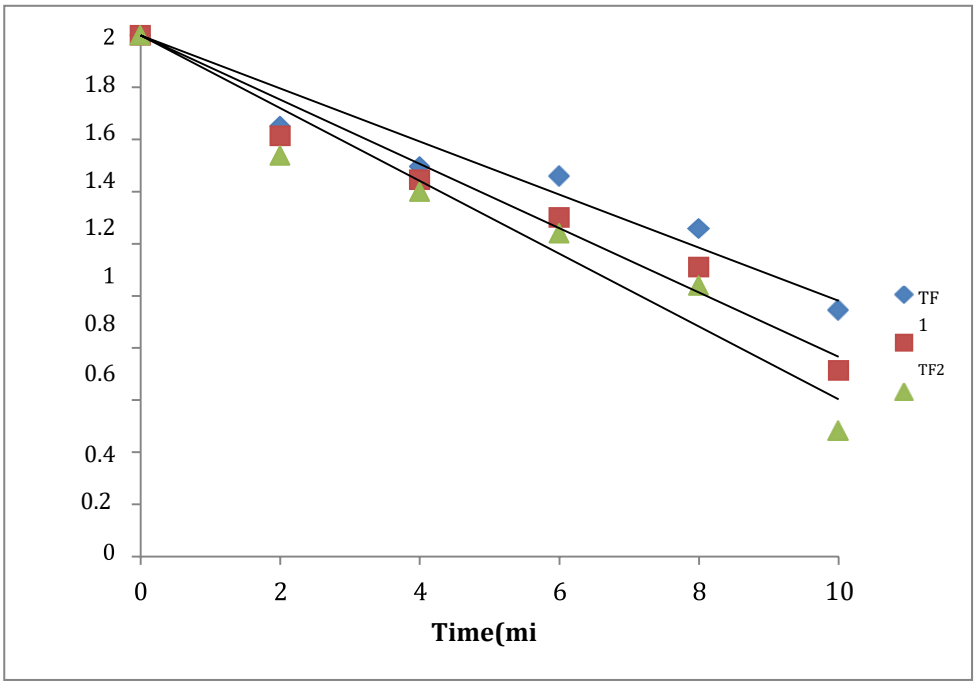

Figure 7: First order plots of Treprostinil Diolamine Rapimelt tablets containing crosspovidone

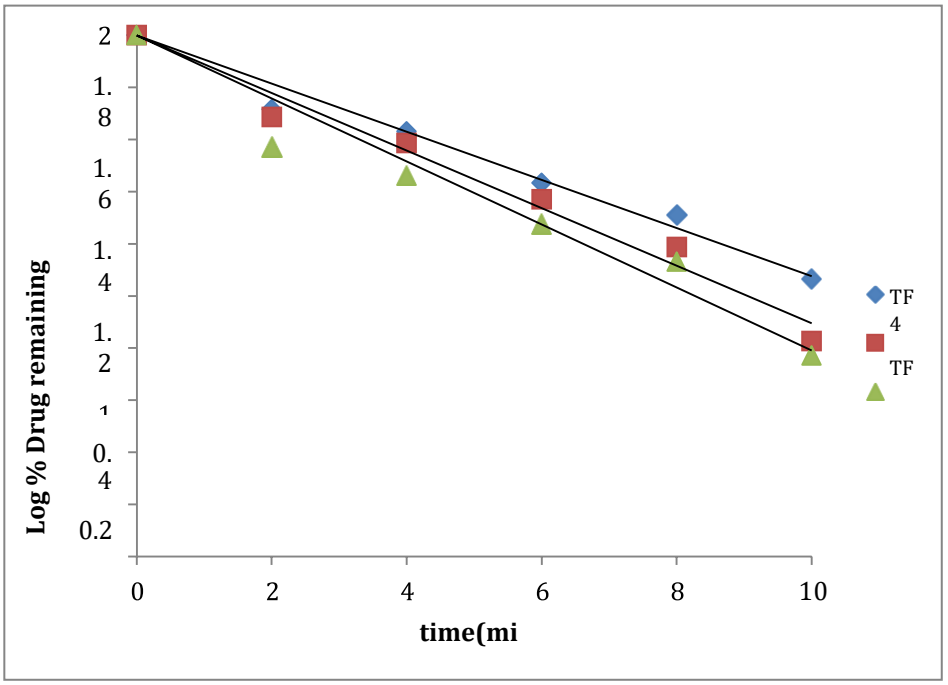

Figure 8: First order plots of Treprostinil Diolamine Rapimelt tablets containingCroscarmellosesodium

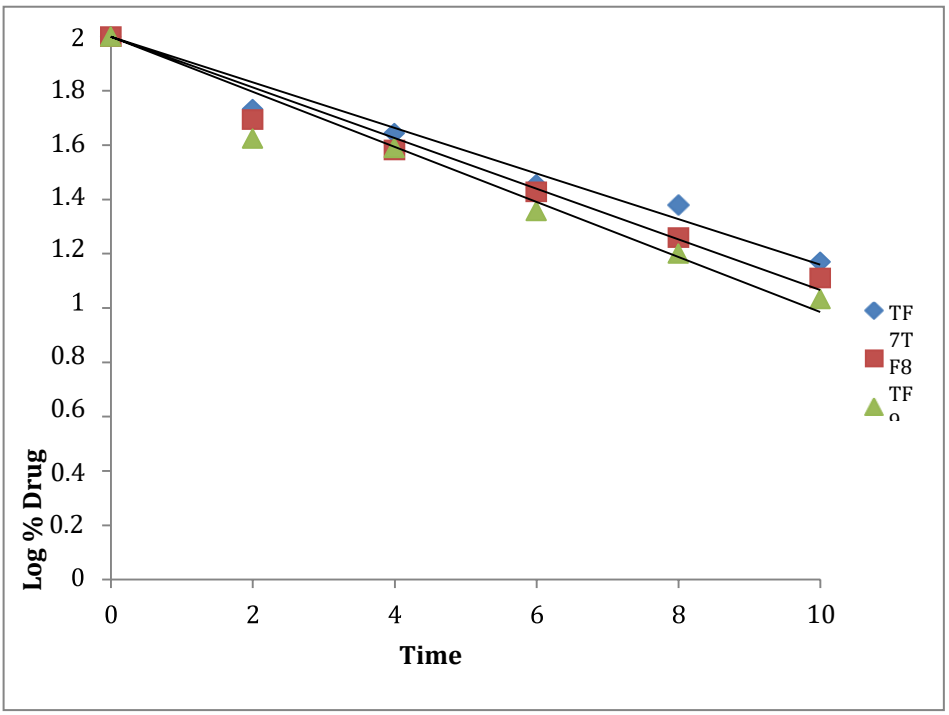

Figure 9: First order plots of Treprostinil Diolamine Rapimelt tablets containing sodium starch glycolate

The drug release profiles of Treprostinil Diolamine Rapimelt tablets were fitted to various kinetic models such as Zero order, First order, Higuchi, Peppas and Hixson-Crowell. The dissolution parameters such as dissolution efficiency (DE) at 10 and 30minutes were increased proportionately. Half-life of drug *i.e.,* T_{50} was found to be181,1.70, 1.53, 2.42, 1.94, 1.59, 2.81, 1.98 and 1.73 min for TF1, TF2, TF3, TF4, TF5, TF6, TF7, TF8 and TF9 formulations respectively. Shelf-lifeofthedrug*i.e.,*T_{90}wasfoundtobe 9.75, 8.75, 8.24, 9.28 and 8.92 minutes for TF1, TF2, TF3, TF5 and TF6 formulations respectively. The drug release data of Treprostinil Diolamine fast dissolving tablets have treated with different kinetic models are shown in Table 7.7. The drug release patterns of Treprostinil Diolamine fast dissolving tablets had followed the first order kinetic model. This release patterns are evident with the correlation coefficient 'r' values which are nearerto 1.

Stability Study of Treprostinil Diolamine fast dissolving tablets.

Table 15: Comparison of Various Parameters for Stability Study

Evaluation Parameter	Initial	1 month	2 month	3month
Hardness(kg/cm^2)	3.1 ± 0.17	3.2 ± 0.36=7	3.3 ± 0.04	3.3 ± 0.92
% Friability	0.26	0.25	0.23	0.23
Disintegration Time(sec)	5	7sec	8sec	9 sec
Drug Content	98.3	99.5	99.3	99.70

The optimized formulation TF3 is kept for stability studies. Accelerated stability studies were carried out at 40^{0}C / 75% RH for 3 months. The tablets were then evaluated for hardness, friability, disintegration and drug content at 1st month, 2ndmonth

and 3rd month. The results indicated that there was no significant change in evaluation of the tablets.

Table 16: Comparison of Drug Release Profile of Batch TF3

Time(min)	Initial	1 month	2 month	3 month
2	65.4	64.92	63.54	62.43
4	74.8	73.70	72.24	71.65
6	82.65	81.08	80.03	79.65
9	89.05	88.92	87.24	86.08
10	96.97	95.98	94.83	94.02

The optimized formulation TF3 is evaluated for *in-vitro* drug release studies after keeping the table that accelerated stability conditions (40^0C/75% RH) for 3months. It is evaluated initially, 1st month, 2nd month and 3rd month. *In-vitro* drug release studies were performed in phosphate buffer pH 6.8 by using USP dissolution test apparatus-Type II, Rotating Paddle method. The results indicated that there was no significant change in i*n-vitro* drug release studies.

In-vivo studies of Treprostinil Diolamine fast dissolving tablets.

The linear regression analysis of Treprostinil Diolamine (TF3) was constructed by plotting the peak–area ratio of drug versus analyte concentration (mcg/ml) in spiked plasma samples. The average regression equation and correlation coefficients were calculated. r^2 = 0.999 for TD showed good linear relationship between the under peak areas and the concentrations. The lower limit of quantization was 0.05 mcg/ml for determination of TD in plasma. The limit had been sufficient for PK studies of Treprostinil Diolamine. From the pharmacokinetic analysis, it can be concluded that the In-vivo studies mimic the in vitro results. In vitro results demonstrated considerable difference in the percentage drug release between pure drug and Optimized formulation, similarly differences were observed in C_{max}, T_{max} and AUC_{0-t} between pure drug and optimized formulations (Figure 7.12).

The average peak plasma concentration obtained for the drug and fast-dissolving tablet, indicated an increase in the extent of absorption (AUC_{0-t}). The decrease in the T_{max} values indicated faster absorption from the optimized formulation and increase in the C_{max} values indicated higher attainable plasma drug concentrations with the same dose of the drug. The higher values of PK parameters (AUC_{0-t}, C_{max}, T_{max} and $t_{½}$) showed enhancement in bioavailability of TD by formulating fast-dissolving tablet.

Table 17: In vivo cumulative percentage drug release at 40±2°C, 75±5% RH for Treprostinil Diolamine

Time in minutes	Cumulative percentage drug release		
	Initial *N* = 3 mean ± SD	After 3 months *N* = 3 mean ± SD	After 6 months *N* = 3 mean ± SD
2	61.6±0.3	61.2±0.3	61.7±0.4
4	70.6±0.42	70.8±0.12	70±0.12
6	81.1±0.08	81.6±0.31	81.9±0.14
8	88.48±0.02	88.2±0.12	88±0.6
10	93.8±0.63	93.7±0.37	93.2±0.54

Table 18: Pharmacokinetic parameters of fast dissolving tablets of Treprostinil Diolamine

Pharmacokinetic parameters	Pure drug	Prepared formulation	Marketed formulation
Peak plasma concentration Cmax (µg/mL)	80.34	200.88	94.67
Time to reach peak plasma concentration Tmax (h)	1.0 h	0.5 h	1 h
Biological half-life t ½ (h)	24.53	24.54	24.57
Elimination rate constant Ke (h−1)	0.0282	0.027	0.0282
Area under the curve (0-t)(total) (µg/mL)h*)	251.44	740	321.58

3. CONCLUSION

Rapimelt Tablets of The optimized can be successfully prepared by direct compression method using selected superdisintegrants with Crosspovidone 1.5%, 3%, 6%, Crosscarmellose 1.5%, 3%, 6% and Sodium starch glycolate 1.5%, 3%, 6%, for the better patient compliance and effective therapy the relative efficiency of these superdisintegrant to improve the disintegration and dissolution rate of tablets were found in order.

The disintegration of TF1, TF2, TF3 with 1.5%, 3%, 6% Crosspovidone formulations to be as 8, 6, 5secs respectively and is almost better than TF4, TF5, TF6, TF7, TF8, TF9 formulations. Formulation TF3 In-vitro Dissolution studie 10 minutes almost total amount of the drug is released 6% crosspovidone (i.e. 96.96%). Crosspovidone shows good result as compare to other superdisintegrants.

Dissolution is carried out in USP-2 type apparatus at 50rpm in the volume of 500 ml dissolution media (phosphate buffer pH 6.8) for 10 minutes. At the end of 10 minutes almost total amount of the drug is released (i.e. 96.96%), from the formulation prepared by the direct compression method with 6% crosspovidone. Drug release kinetics of Treprostinil Diolamine fast dissolving tablets. Correlation coefficient (r) & rate constant (k) Values of Treprostinil Diolamine Rapimelt tablets containing Crospovidone, croscarmellose sodium, sodium starch glycolate.

The drug release profiles of Treprostinil Diolamine Rapimelt tablets were fitted to various kinetic models such as Zero order, First order, Higuchi, Peppas and Hixson-Crowell. The dissolution parameters such as dissolution efficiency (DE) at 10 and 30minutes were increased proportionately. Half-life of drug i.e., T50 was found to be181,1.70, 1.53, 2.42, 1.94, 1.59, 2.81, 1.98 and 1.73 min for TF1, TF2, TF3, TF4, TF5, TF6, TF7, TF8 and TF9 formulations respectively. Shelf-life of the drug i.e.,T90 was found to be 9.75, 8.75, 8.24, 9.28 and 8.92 minutes for TF1, TF2, TF3, TF5 and TF6 formulations respectively. The drug release patterns of Treprostinil Diolamine fast dissolving tablets had followed the first order kinetic model. This release patterns are evident with the correlation coefficient 'r' values which are nearer to 1.

The optimized formulation TF3 is kept for stability studies. Accelerated stability studies were carried out at 400C / 75% RH for 3 months. The tablets were then evaluated for hardness, friability, disintegration and drug content at 1st month, 2nd month and 3rd month. The results indicated that there was no significant change in evaluation of the tablets.

In-vivo studies of Treprostinil Diolamine fast dissolving tablets.

The linear regression analysis of Treprostinil Diolamine (TF3) was constructed by plotting the peak–area ratio of drug versus analyte concentration (mcg/ml) in spiked plasma samples. The average regression equation and correlation coefficients were calculated. r2 = 0.999 for Treprostinil Diolamine showed good linear relationship between the under peak areas and the concentrations. The lower limit of quantization was 0.05 mcg/ml for determination of Treprostinil Diolamine in plasma. The limit had been sufficient for PK studies of Treprostinil Diolamine. From the pharmacokinetic analysis, it can be concluded that the In-vivo studies mimic the in-vitro results. In vitro results demonstrated considerable difference in the percentage drug release between pure drug and Optimized formulation, similarly differences were observed in Cmax, Tmax and AUC0-t between pure drug and optimized formulations (Figure 7.12).

The average peak plasma concentration obtained for the drug and fast-dissolving tablet, indicated an increase in the extent of absorption (AUC0-t). The decrease in the Tmax values indicated faster absorption from the optimized formulation and increase in the Cmax values indicated higher attainable plasma drug concentrations with the same dose of the drug. The higher values of PK parameters (AUC0-t, Cmax, Tmax and t½) showed enhancement in bioavailability of Treprostinil Diolamine by formulating fast-dissolving tablet.

These phytochemicals compounds of AaEE have been found to induce a wide spectrum of activities such as reduction in oxidative stress, suppression of inflammation, and cell proliferation and modulating numerous signal transduction pathways. The findings of this study suggest that the extract of A. adstringens ("cuachalalate") has substantial potential for the treatment of inflammatory colitis.

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