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Research Article

FORMULATION AND IN VITRO EVALUATION OF APREMILAST PULSINCAP DRUG DELIVERY

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ABSTRACT:
The purpose of the present study was to design and evaluate an Oral, site specific, Pulsatile drug delivery system containing Apremilast as a model drug, which can be time dependent manner, to modulate the drug level in synchrony is a member of the drug class known as corticosteroid prodrug with an active metabolite. Apremilast is a non-steroidal medication used for the treatment of inflammatory conditions such as psoriasis and psoriatic arthritis. The basic design consists of an insoluble hard gelatin capsule body, filled with powder blend and sealed with a hydrogel plug. The powder blend containing Apremilast, Lactose. Karaya Gum, Lycoat, Ludiflash, Croscarmellose sodium, MCC and talc was prepared and evaluated for flow properties and FTIR studies. From the obtained results, F12 powder blend formulation was selected for further fabrication of pulsatile capsules. Hydrogel plug was formulated in a lone and in combination of hydrophobic polymer like ethyl cellulose with hydrophilic polymers like Ethyl Lactose and Karaya Gum in 1:1, 1:2, and 2:1 ratio to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. The prepared formulations were evaluated for drug content, weight variation and Invitro release studies. FTIR studies confirmed that there was no interaction between drug and polymers and Invitro release studies of pulsatile device revealed that increasing hydrophilic polymer content resulted in delayed release of Apremilast from the pulsincap after a predetermined lag time of 6hrs. Based on invitro studies performed, P3F12 was found to be optimized formulation.
Key words: Pulsatile system; time dependent delivery; Apremilast; Chrono pharmaceutics; In vitro release studies.

INTRODUCTION

Drug delivery refers to the method or process of administering a pharmacological substance to have a therapeutic effect in humans or animals. Drug delivery systems are technologies that enable the targeted delivery and/or controlled release of medical drugs. The oral method of administration for sustained release systems has received the most attention in terms of research into a variety of problems. This is because oral techniques provide more flexibility in dosing regimens than any other. The oral route gained popularity because of its ease of delivery and the common belief that medicine is well absorbed when administered orally[1]. Nowadays, the emphasis of pharmaceutical galenic research is moved towards the creation of more efficacious drug delivery methods with previously existing molecules rather than opting for new drug discovery due to the intrinsic difficulties provided by the drug discovery and development process[2]. However, for many medications, the adoption of such a system is inappropriate for a variety of reasons. There are several circumstances that necessitate pulsatile release. During the initial phase of dosage form administration, it may be necessary to prevent the medication from being released. This circumstance necessitates the release of a medication as a "pulse" after a time lag, and such a system must be constructed so that complete and fast drug release occurs

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following the lag period. These systems are called pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems[3-6].

Pulsatile drug delivery system provides medicine in a quick and burst way during a brief time period immediately following a programmed lag period[7]. A pulsatile-release profile is defined by a period of no release (lag time), followed by quick and full drug release. PDDS may be categorized into site-specific systems in which the medicine is delivered at the targeted location inside the digestive tract[8]. That is why pulsatile devices are gaining popularity since they deliver medicine to the exact site of action at the right time and dose, resulting in better spatial and temporal delivery and patient compliance. The medication's release as a pulse after a lag time must be developed such that the medicine is released quickly and completely after the lag. These technologies are meant to mimic the body's circadian rhythm. The potential benefits of pulsatile medication administration have been established in the treatment of certain disorders. PDDS is likely to be successful for diseases such as asthma, myocardial infarction, angina pectoris, peptic ulcer, arthritis, hypertension, and hypercholesterolemia since in these disorders specific rhythms in the onset and extent of symptoms are noted [9].

Apremilast, marketed as Otezla, is a phosphodiesterase 4 (PDE4) inhibitor that is extensively used to treat a variety of inflammatory autoimmune illnesses. It belongs to the same pharmacological class as Roflumilast and Crisaborole, both PDE4 inhibitors. Celgene distributes Apremilast, which was originally authorized in 2014. In July 2019, the FDA gave further clearance for its use in treating oral ulcers associated with Behçet's disease—an inflammatory illness characterized by recurrent inflammation affecting the skin, blood vessels, and central nervous system.[10]

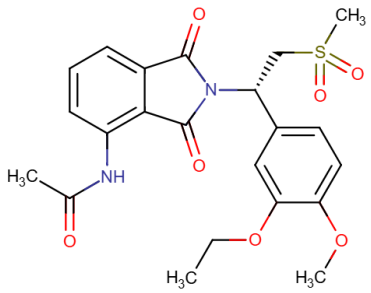

Figure.No.1 Structure of Apremilast

MATERIALS

Apremilast procured from Gathi Lifesciences, Ludiflash, Lycoat, Croscarmellose sodium from S D fine chemical Ltd, Mumbai, Microcrystalline cellulose, Talc from Loba chemie pvt.ltd, Lactose, Karaya Gum from Otto Chemicals, Mumbai, Magnesium stearate from Loba chemie pvt.ltd, Mumbai, Formaldehyde, Potassium permanganate from Qualigens fine chemicals, Mumbai, Potassium dihydrogen Phosphate from Qualigens fine chemicals, Mumbai.

METHODOLOGY

Solubility: Solubility is defined as the quantity of material that enters solution to form a saturated solution at a fixed temperature and pressure. The solvents utilized are water and methanol. Apremilast's solubility was assessed by adding modest increments to a test tube containing a set amount of various solvents. After each addition, the system was violently shook and visually inspected for any remaining solute particles.

Drug-Excipient compatibility studies:

To determine the chemical compatibility of the medication, spectroscopic techniques such as FTIR were utilized. The FTIR spectra were obtained with an IR spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The IR spectra for the samples were acquired using the KBr disk technique. The samples were created by grinding the pure drug, polymer, and physical combination with KBr separately. The drug and potassium bromide pellets were made by compressing the powders on a KBr-press at 20 pressure for 10 minutes, and the spectra were scanned in the 4000-600 cm-1 region. FTIR analysis was carried out on Apremilast, physical mixing of Apremilast, and the optimal formulation.

UV spectroscopy:

The key stage in pre-formulation is to develop a basic analytical procedure that will allow all subsequent measurements to be quantitative. Most medications absorb light at UV wavelengths (190-400nm) because they are aromatic or contain double bonds. Using an electronic balance, 10 mg of Apremilast was carefully weighed and dissolved in 2 mL of methanol. The volume was then increased to 10mL with buffer, yielding 1000µg/mL (stock solution-I). To get 100 µg/mL, 1 mL of stock solution I is pipetted into a 10mL volumetric flask and filled with pH 7.4 phosphate buffer. To get 10 µg/mL, 1mL was extracted from 100 µg/mL and diluted with buffer to a volume of 10 mL. The resulting volume was then scanned on a UV scanner at 2000-400nm. The graph's maxima were used to calculate the λmax for Apremilast in its corresponding buffers.

Standard calibration curve for Apremilast:

The apremilast standard calibration curve was plotted in pH 7.4 phosphate buffer. An accurately weighed amount of 10 mg of medication was put into a 10 ml volumetric flask, and the primary stock solution was made by diluting the volume to 10 ml with pH 7.4 phosphate buffer. The resulting solution contains 1000 µg/mL of Apremilast in stock solution. From the primary stock solution, 1 ml was transferred to another 10 ml volumetric flask and made up to 10 ml with pH 7.4 phosphate buffer. From the secondary stock, 0.3, 0.6, 0.9, 1.2, 1.5, and 1.8ml was taken separately and made up to 10 ml with pH 1.2 buffer to produce 3, 6, 9, 12, 15, and 18µg/ml solutions, respectively. The absorbance was measured at 230 nm with a UV spectrophotometer. Similarly, Apremilast standard graphs were drawn in pH 7.4 phosphate buffer using the aforementioned approach.

FLOW PROPERTIES OF API:

Bulk Density (Db): It is the ratio of powder's total mass to its bulk volume. It was measured by pouring the weighed powder (passed through standard sieve#20) into a measuring cylinder and the initial volume was noted. This initial volume is known as the bulk volume. From this, the bulk density is computed using the method below. It is expressed in grams per cubic centimeter and given by:

$$Db = m/Vo$$

Tapped density (Dt): It is the ratio of the powder's total mass to its tapped volume. The volume was measured by tapping the powder 500 times. The tapping was then repeated 750 times, and the tapped volume was measured (the difference should be less than 2%). If it is greater than 2%, tapping is repeated 1250 times, and the tapped volume is logged. It is expressed in grams per cubic centimeter and given by:

$$Dt = m/Vi$$

Angle of Repose (θ): This is the greatest possible angle between the surface of a pile of powder or grains and the horizontal plane. The powders were allowed to flow through a funnel attached to a stand at a certain height (h). The angle of repose was then estimated by measuring the height and radius of the resulting granule heap.

$$\tan\theta = h/r$$

(Or)

$$\theta = \tan^{-1}(h/r)$$

Compressibility Index: The flow ability of powder may be determined by comparing its bulk density (Db) and tapped density (Dt) to the rate at which it packs down. Compressibility index is determined as follows:

$$\text{Compressibility index (\%)} = Dt - Db/Dt \times 100$$

Hausner's Ratio: It represents the ratio of tapped density to bulk density. It is supplied by:

$$\text{Hausner's ratio} = Dt / Db$$

PULSINCAP DESINGNING:

Pulsincap capsules are designed or prepared in three steps:

1. Prepare cross-linked gelatin capsules.
2. Create powder mixtures to fill capsules.
3. Formulate Apremilast Pulsincap.

PREPARATION OF CROSS-LINKED GELATIN CAPSULE:

Formaldehyde treatment:

Approximately 100 firm gelatin capsules, size '0', were taken. Their bodies were removed from their caps and put on a wire mesh. The corpses put on a wire mesh were spread out in a single layer. A desiccator was used to store 25 ml of a 15% v/v formaldehyde solution. To this, 5 g of potassium permanganate was added. The wire mesh containing the capsule bodies was placed on top of desiccators containing formaldehyde liquid at the bottom, in equilibrium with its vapor, and the desiccators were quickly closed and sealed.

The capsule bodies were exposed to formaldehyde fumes for varied durations of time, namely 2, 4, 6, 8, and 10 hours. The capsules were then removed, placed on filter paper, and dried for 24 hours to guarantee that the reaction between gelatin and formaldehyde vapors was complete. The capsules were then stored in an open atmosphere to ease the elimination of leftover formaldehyde. The capsule bodies were closed with an untreated cap and kept in a polythene bag.

Use of Formaldehyde treatment:

The primary goal of formaldehyde treatment was to improve the solubility of hard gelatin capsules. Exposure to formalin fumes caused gelatin molecules to cross-link. Cross-linking is the interaction of amino groups in gelatin molecular chains with aldehyde groups of formaldehyde via a "Schiff's base condensation," causing the gelatin to become water insoluble. Formaldehyde interacts with gelatin, generating an irreversible compound. The main amine group in gelatin interacts with formaldehyde, binding it permanently. Potassium permanganate was added to the formaldehyde solution to make formalin fumes. When the bodies of hard gelatin capsules were exposed to formaldehyde vapors for various amounts of time in a closed desiccator, the vapor became equilibrated with formaldehyde liquid, rendering the gelatin water insoluble.

EVALUATION OF FORMALDEHYDE TREATED CAPSULES:

PHYSICAL TESTS:

Identification characteristics: Capsules of appropriate size and lockability were chosen. When gelatin capsules are touched with a moist hand, they become sticky; however, after formaldehyde treatment, the capsules lose their stickiness.

Visual faults: 100 treated capsules were selected and physically inspected for visual defects; no more than 15-20 capsules were allowed to be deformed.

Dimensions: The differences in dimensions between formaldehyde-treated and untreated capsules were examined. The capsules' length and diameter were measured before and after formaldehyde treatment using Vernier calipers**.**

OPTIMIZATION OF FORMALDEHYDE TREATED CAPSULE BODIES EXPOSED AT VARIOUS TIME INTERVALS VIZ., 2, 4, 6, 8, 10 hrs :-

Formaldehyde-treated capsule bodies exposed at various time intervals (2, 4, 6, 8, 10 hours) were optimized using a disintegration test. The test was conducted on both untreated and treated capsules. Formaldehyde-treated bodies were combined with untreated caps and examined for disintegration. The disintegration test was performed using the Hiccon disintegration test device. The medium consisted of pH 1.2 and pH 7.4 phosphate buffers, which were kept at 37°C during the experiment. The time at which the capsules disintegrate is recorded.

PREPARATION OF APREMILAST TABLETS FOR FILLING INTO CAPSULES

All of the components were run through a #60 mesh sieve separately. The medication and MCC were combined together by adding a tiny amount of each at a time and mixing until a homogenous mixture was achieved, then set aside. The additional components were then combined in a geometric order and passed through a coarse filter (#44 mesh), before being compacted using a hydraulic press to form tablets. The machine's compression force was adjusted to ensure that all batches had a hardness of 4-5 kg/cm2. For all formulations F1 through F12, the pill weight remained consistent at 100 mg.

Table.1 Formulae for preparation of blend for filling of Apremilast Pulsincap

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Apremilast	10	10	10	10	10	10	10	10	10	10	10	**10**
Lycoat	5	10	15	20	--	--	--	--	--	--	--	**--**
Croscarmellose sodium	--	--	--	--	5	10	15	20	--	--	--	**--**
Ludiflash	--	--	--	--	--	--	--	--	5	10	15	**20**
MCC	81	76	71	66	81	76	71	66	81	76	71	**66**
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	**2**
Talc	2	2	2	2	2	2	2	2	2	2	2	**2**
Total	100	100	100	100	100	100	100	100	100	100	100	**100**

FORMULATION OF PULSINCAP OF APREMILAST:

The modified release pulsincaps containing 100mg of Apremilast were created by combining various excipients and polymers in varied proportion. The formaldehyde-treated capsule bodies that were subjected to 6 hours were optimized and selected for the pulsincap formulation based on disintegration time. The optimized formulation of Apremilast tablet was inserted into the capsule body. The hydrogel plug was made using a mixture of Lactose and Karaya Gum in different ratios. Initially, the total weight of the plug was 100 mg, and the hydrophobic/hydrophilic polymer ratios were 1:1, 1:2, and 2:1.

Table.2 Pulsincap formulation

Ingredients	P1F12	P2F12	P3F12	P4F12	P5F12
Tablet	100mg	100mg	100mg	100mg	100mg
Lactose	100	100	200	100	-
Karaya Gum	100	200	100	-	100

Method of preparation of Pulsincap dosage form:

Preparation of powder blend:

The recipe used hard gelatin capsules of'size 0' that had been stiffened with formaldehyde for 6 hours. The bodies and caps were separated manually. The optimized formulation F12 was placed at the bottom of the capsule body.

Preparation of Hydrogel plug:

- A compressed pill was put at the capsule's entrance. The capsule body was sealed with a cap.
- Various polymers, including Lactose and Karaya Gum, were used to create a hydrogel plug at varying concentrations.

- A mixture of hydrophobic and hydrophilic polymers, Lactose and Karaya Gum, were utilized in various ratios, including 1:1, 1:2, and 2:1.
- Ensure a tight fit between the plug and capsule shell to prevent water penetration and medication release before the plug material erodes completely. Ideally, the plug should only dissolve on the surface exposed to the releasing media.
- Plugs can be ejected by swelling with aqueous fluids, increased internal pressure, erosion, or enzyme breakdown.

Capsule filling:

The 6th hour formaldehyde-treated capsule body was manually filled with a homogeneous combination of medication and excipients using the filling procedure. Then, a tablet-shaped hydrogel stopper is inserted above the mixture, at the capsule's aperture. The capsule body was sealed with a cap.

Capsule sealing:

A tiny amount of 1% ethanolic cellulose solution was used to seal the junction between the treated capsule body and the untreated capsule cap.

Evaluation of tablets:

Tablet Dimensions:

Thickness and diameter were measured using a calibrated vernier caliper. Three tablets of each formulation were selected at random, and their thickness was measured separately.

Hardness:

Hardness denotes a tablet's capacity to absorb mechanical shocks when handling. The hardness of the tablets was measured using a Monsanto hardness tester. It is stated in kilograms per square centimeter. Three tablets were selected at random, and their hardness was assessed.

Friability test:

The friability of tablets was tested using an electrolab Friabilator. It's given as a percentage (%). Ten pills were originally weighted (WI) and transferred to the Friabilator. The Friabilator was run at 25 rpm for 4 minutes, or up to 100 rotations. The pills were weighed again (WF). The percentage of friability was then computed as –

$$\%F = 100\ (1\text{-}WI/WF)$$

Tablets with a friability of less than 1% were regarded acceptable.

Weight Variation Test:

Ten pills were chosen at random from each batch and weighed separately to check for weight variance. According to the United States Pharmacopoeia, a little amount of variation in tablet weight is permitted. The following % variance in weight fluctuation was permitted.

Test for Content Uniformity:

A tablet containing 10mg of medication was dissolved in 50ml of pH 7.4 phosphate buffer in a volumetric flask. The medication was left to dissolve in the solvent. The solution was filtered, 2ml of filtrate was placed in a 10ml volumetric flask, diluted to the mark with distilled water, and evaluated spectrophotometrically at 230 nm. The concentration of Apremilast was determined using the drug's standard calibration curve. Drug content analyses were performed in triplicate for each formulation batch.

In vitro Disintegration Time:

The tablet was introduced to 900ml of distilled water at 37±0.5oC. The time it takes for a pill to completely disperse was measured.

In vitro Dissolution Study:

Apremilast tablet dissolving was investigated in vitro using a USP XXII dissolution test device. A 900ml pH 7.4 phosphate buffer (simulated fluid) was employed as the dissolution medium. The stirrer was set to revolve at 100 rpm. The dissolving medium's temperature was maintained at 37±0.5ºC throughout the experiment. Each test involved one pill. Samples of dissolving media (5ml) were withdrawn at predetermined intervals using a syringe equipped with a pre-filter and tested for drug release by detecting absorbance at 230 nm. The amount extracted at each time interval was replaced with a new quantity of dissolving medium. The cumulative percentage of apremilast released was computed and shown against time.

EVALUATION OF PULSINCAP DOSAGE FORM:101,102,103.

In vitro release studies:

A dissolution research was carried out to determine the drug's release rate from the pulsincap formulation. The in vitro dissolution profile of each formulation was assessed using the USP I equipment using the rotating basket technique. To promote pH shifts along the GI tract, two distinct dissolving medium with pH 1.2 and pH 7.4 phosphate buffer were employed successively, resulting in the "Sequential pH change method". During the experiment, the dissolving media were kept at 37 ± 0.5ºC and the basket rotated at 100 rpm. 900ml of dissolving medium was used each time. Apremilast Pulsincaps were put in a basket in each dissolving vessel to keep them from floating. During the trials, stimulated gastric fluid (SGF) pH 1.2 buffer was utilized for 2 hours (since the usual stomach emptying period is 2 hours) before being withdrawn and replaced with fresh stimulated intestinal

fluid (SIF) pH 7.4 phosphate buffer for the remaining hours. A syringe was used to extract 5 ml of dissolving fluid at predefined time intervals. The volume removed at each time interval was replaced with 5mL of new dissolving media kept at the same temperature. The filtered samples were diluted as needed and tested for Apremilast by measuring absorbance at 230 nm using UV absorption spectroscopy. The percentage CDR was determined throughout the sample periods.

Table.3 Dissolution specifications of Apremilast

Vessel temperature	37 ± 0.5oC
Bath temperature	38 ± 0.5oC
Dissolution media	pH 1.2, pH 7.4 phosphate buffer
Volume of dissolution media	900 ml
Aliquot withdrawn	5 ml
Aliquot replaced	5 ml of the fresh solution
Dissolution apparatus	USP type I (Basket)
Speed	100RPM

RELEASE KINETICS:

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient(R) value in various models. The models with high 'R-value is considered as the best fit on the release data.

Various mathematical models are:

1. Zero order release model
2. First order release model
3. Higuchi release model
4. Korsmeyer – peppas release model

Zero Order Release Equation: The equation for zero order release is

$$Qt = Qo + Kot$$

First Order Release Equation: The first order release equation is

$$Log\ Qt = Log\ Qo + Kt\ /2.303$$

Higuchi Release Equation: The Higuchi release equation is

$$Qt = KH\sqrt{t}$$

Korsmeyer -Peppas Release Equation: The Korsmeyer –Peppas equation is

$$F=Mt / M = Kmtn$$

RESULTS AND DISCUSSION

Solubility: It was determined as per standard procedure.

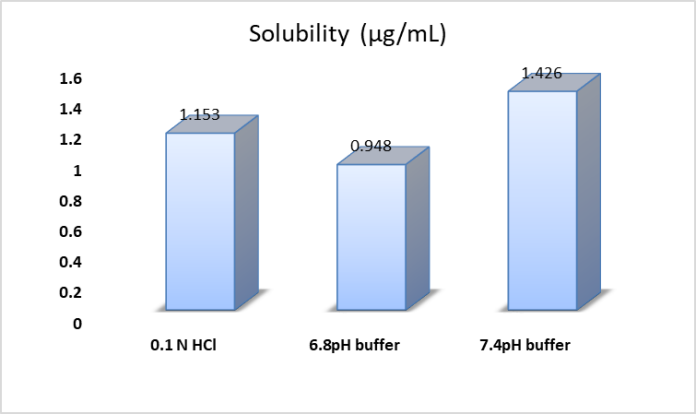

Figure.No.2 Solubility studies of Apremilast in various solvents

Discussion: From the above conducted solubility studies in various buffers we can say that pH 7.4 phosphate buffer has more solubility when compared to other buffer solutions.

λmax Determination of Apremilast

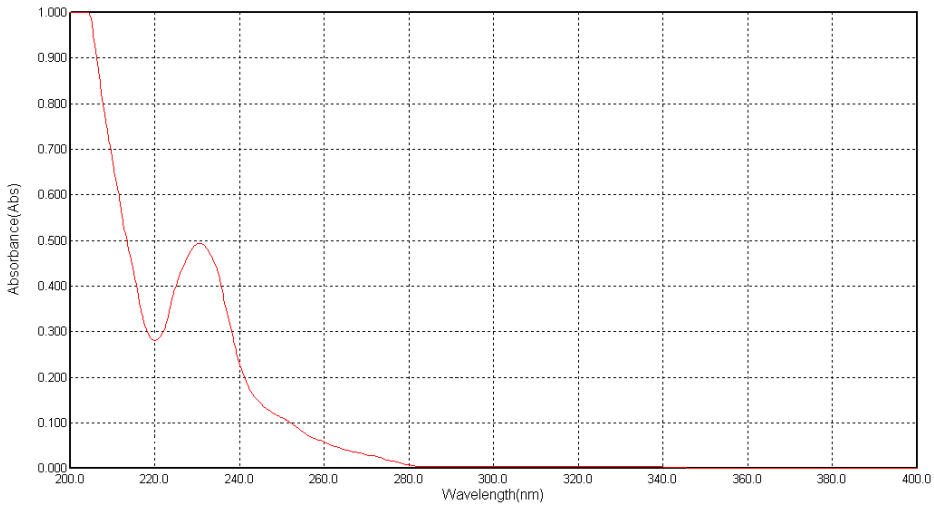

Figure.No.3 λmax Determination of Apremilast

Discussion: The λ-max of Apremilast of 100% solution i.e 12ppm (µg/ml) by using Single Beam Spectrophotometer (YIS-294) was found to be at 230 nm by using 7.4 pH Phosphate Buffer.

Standard Calibration Curve:

Standard Calibration Curve in 1.2 pH:

Table.4 Data for calibration curve of Apremilast in pH 1.2 HCl Buffer at 230 nm

Concentration (µg/mL)	Absorbance
0	0
3	0.065
6	0.134
9	0.226
12	0.312
15	0.386

18	0.458

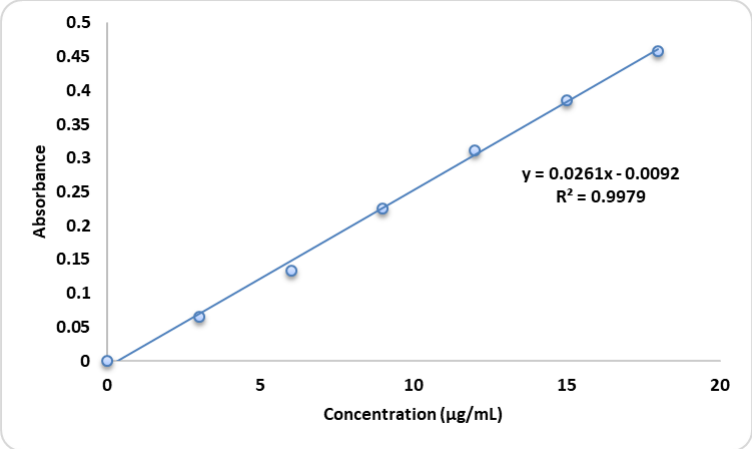

Figure.No.4 Standard Calibration Curve of Apremilast in pH 1.2 HCl Buffer at 230 nm

Discussion: The linearity was found to be in the range of 3-18µg/ml in acetone, pH 1.2 HCl buffer. The regression value was found to be 0.997 which less closer to 1 indicating the method obeyed Beer-lamberts' law.

Standard Calibration Curve in pH 7.4 Phosphate Buffer:

Table.5 Data for calibration curve of Apremilast in pH 7.4 Phosphate Buffer at 230 nm

Concentration (µg/mL)	Absorbance
0	0
3	0.086
6	0.175
9	0.256
12	0.332
15	0.416
18	0.498

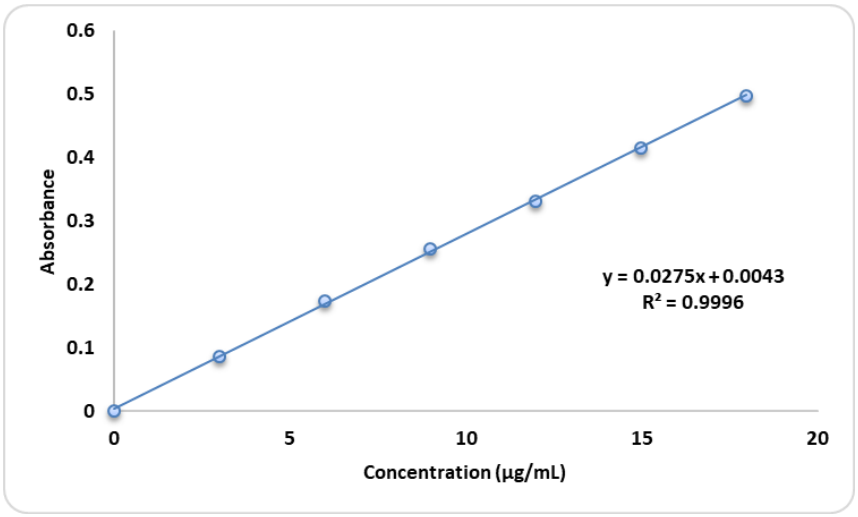

Figure.No.5 Standard Calibration Curve of Apremilast in pH 7.4 Phosphate Buffer at 230 nm

Discussion: The linearity was found to be in the range of 3-18µg/ml in acetone, pH 7.4 Phosphate Buffer. The regression value was found to be 0.999, which is more closer to 1 indicating the method obeyed Beer-lamberts' law.

Drug-Excipient compatibility studies: The IR spectrum of pure drug was found to be similar to the standard spectrum of Apremilast . The spectrum of Apremilast shows the following functional groups at their frequencies shown in Figure.

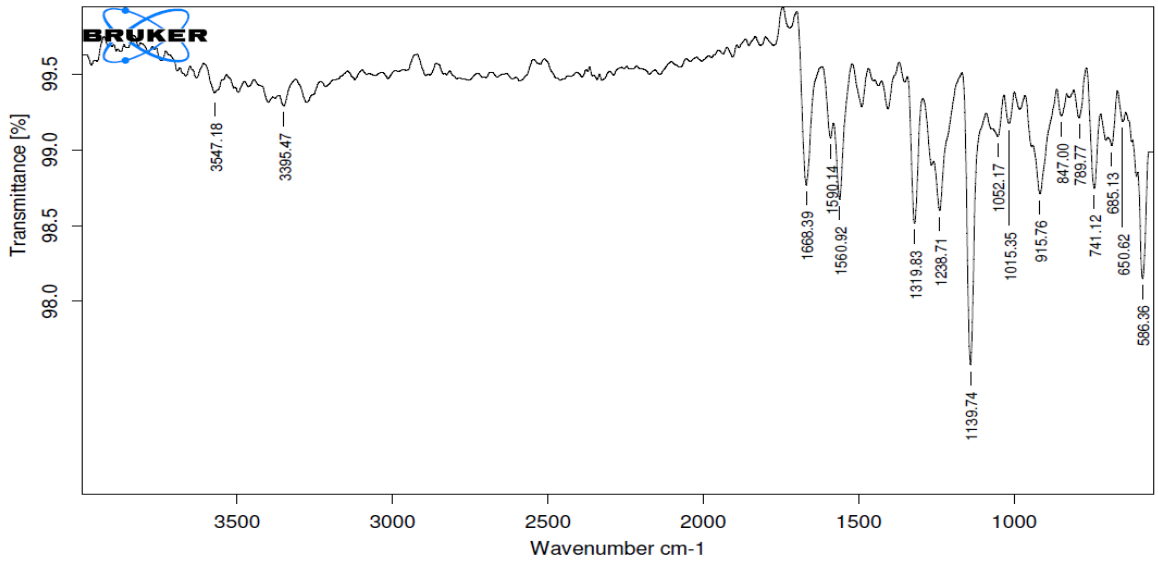

Figure.No.6 FTIR spectrum of Apremilast

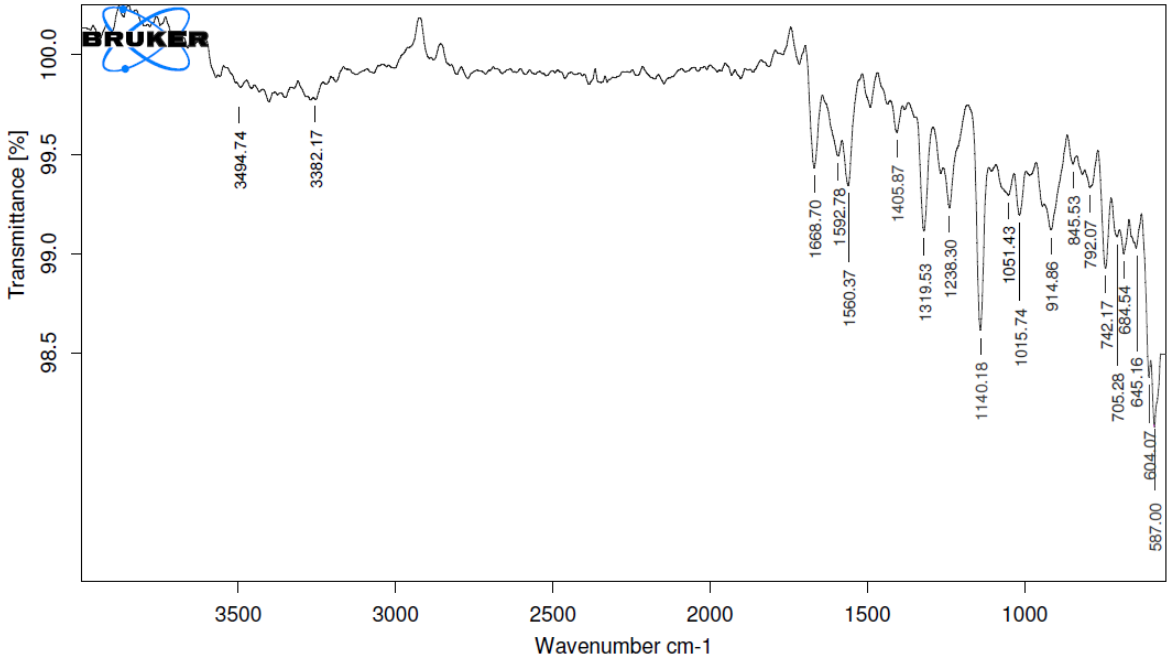

Figure.No.7 FTIR Spectrum of optimized formulation

Discussion: The FTIR spectrum of pure Apremilast , prepared colon Targeted Pulsincap of Apremilast formulation are shown in Figure respectively. The units are represented as cm^{-1}. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Apremilast) and optimized formulation (Apremilast + Excipients) which indicates there are no physical changes.

Flow properties of powder blend:

Table.6 Flow properties of powder blend

Formulation Code	Angle of Repose±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
F1	28.78±1.14	0.204±0.002	0.315±0.001	19.57±1.17	1.19±0.02
F2	27.54±1.20	0.210±0.001	0.323±0.003	18.61±1.26	1.17±0.01
F3	25.14±1.34	0.217±0.003	0.329±0.004	16.23±1.45	1.16±0.01
F4	25.46±1.19	0.226±0.004	0.335±0.002	15.51±1.38	1.16±0.02
F5	29.26±1.02	0.210±0.002	0.321±0.001	17.48±1.20	1.17±0.01

F6	27.84±1.14	0.219±0.003	0.328±0.002	15.20±1.45	1.15±0.01
F7	28.75±1.45	0.228±0.002	0.333±0.002	14.38±1.05	1.15±0.02
F8	26.02±1.17	0.237±0.002	0.341±0.003	13.51±1.75	1.14±0.01
F9	26.45±1.20	0.215±0.005	0.318±0.002	16.19±1.10	1.16±0.01
F10	25.37±1.34	0.224±0.001	0.327±0.001	14.20±1.25	1.14±0.01
F11	26.78±1.57	0.236±0.001	0.336±0.002	12.54±1.69	1.13±0.01
F12	24.68±1.12	0.247±0.002	0.348±0.003	11.36±1.45	1.12±0.02

Discussion: The angle of repose of different formulations was ≤ 29.26±1.02, which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.204±0.002 g/cm^3 to 0.247±0.002 g/cm^3.Tapped density was found between 0.315±0.001 g/cm^3 to 0.348±0.003 g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.36±1.45-19.57±1.17and Hausner's ratio from 1.12±0.02-1.19±0.02 which reveals that the blends have good flow character.

Characterization of Tablets

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.

Table.7 Characterization Apremilast Tablets

Formulation code	%Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness	Friability (%)	Disintegrating time(sec)	Drug content (%)
F1	101.17 ±1.45	1.98 ±0.02	6.75 ±0.10	7.28 ±1.57	0.87 ±0.02	28±1.00	93.48 ±1.14
F2	100.68 ±1.20	2.14 ±0.03	6.29 ±0.11	7.46 ±1.45	0.69 ±0.05	25±1.00	96.67 ±1.51
F3	102.45 ±1.69	2.09 ±0.02	6.68 ±0.10	7.68 ±1.25	0.75 ±0.08	21±2.00	97.24 ±1.37
F4	100.12 ±1.24	2.21 ±0.01	6.45 ±0.09	8.51 ±1.42	0.68 ±0.03	18±1.00	98.28 ±1.65
F5	101.30 ±1.45	1.97 ±0.01	6.29 ±0.08	7.49 ±1.97	0.79 ±0.09	22±1.00	94.36 ±1.67
F6	98.84 ±1.15	1.99 ±0.02	6.76 ±0.07	7.68 ±1.48	0.72 ±0.02	18±2.00	95.35 ±1.26
F7	99.37 ±1.19	2.18 ±0.02	6.55 ±0.05	8.35 ±1.25	0.65 ±0.08	16±1.00	96.15 ±1.17
F8	100.27 ±1.45	2.21 ±0.01	6.75 ±0.04	8.49 ±1.45	0.59 ±0.05	14±1.00	97.85 ±1.65
F9	101.15 ±1.38	1.98 ±0.02	6.42 ±0.02	7.57 ±1.45	0.67 ±0.07	17±2.00	95.22 ±1.48
F10	102.45 ±1.12	2.14 ±0.01	6.59 ±0.05	8.26 ±1.45	0.59 ±0.03	15±1.00	96.36 ±1.29
F11	99.57 ±1.16	2.02 ±0.02	6.74 ±0.05	8.54 ±1.84	0.52 ±0.05	13±2.00	97.37 ±1.28
F12	100.20 ±1.46	2.25 ±0.01	6.89 ±0.02	8.78 ±1.22	0.45 ±0.01	12±1.00	99.15 ±1.15

Discussion:

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 7.28±1.57-8.78±1.22 kg/cm^2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeia limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 –F12 and considered to be satisfactory ensuring that all the formulations are mechanically stable.

The drug content values for all the formulations (F1-F12) was found to be in the range of 93.48±1.14-99.15±1.15%.

Dissolution studies of the tablets:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release.

Table.8 % Cumulative drug release of formulations F1-F6

Time (mins)	F1	F2	F3	F4
0	0	0	0	0
5	19.12±1.45%	23.67±1.45	39.57±1.48%	45.58±1.45%
10	26.17±1.45%	35.12±1.37%	55.14±1.20%	63.57±1.14%
15	39.29±1.06%	42.17±1.45%	69.46±1.27%	79.57±1.57%
20	57.36±1.24%	59.20±1.45%	75.41±1.59%	87.78±1.51%
30	66.57±1.14%	68.39±1.14%	83.66±1.14%	92.97±1.27%
40	75.26±1.34%	74.65±1.20%	90.37±1.45%	98.58±1.37%
50	87.48±1.18%	90.48±1.45%	98.27±1.20%	
60	98.54±1.78%	98.17±1.21%		

Table.9 % Cumulative drug release of formulations F7-F12

Time (mins)	F5	F6	F7	F8
0	0	0	0	0
5	20.48±1.05%	29.17±1.21%	39.14±1.42%	56.45±1.02%
10	35.25±1.45%	43.27±1.37%	50.67±1.35%	69.29±1.75%
15	48.48±1.67%	59.38±1.16%	65.12±1.46%	77.57±1.06%
20	57.65±1.20%	67.46±1.16%	77.39±1.12%	85.48±1.49%
30	69.82±1.74%	76.12±1.12%	89.45±1.17%	93.26±1.20%
40	76.45±1.02%	88.47±1.43%	95.37±1.12%	98.67±1.37%
50	84.28±1.34%	95.20±1.12%	98.42±1.37%	
60	97.14±1.45%	98.64±1.45%		

Table.10 % Cumulative drug release of formulations F7-F12

Time (mins)	F9	F10	F11	F12
0	0	0	0	0
5	32.19±1.45%	36.85±1.25%	43.42±1.42%	71.57±1.43%
10	39.27±1.18%	47.42±1.57%	55.21±1.32%	79.68±1.12%
15	48.34±1.27%	55.35±1.24%	68.36±1.12%	88.85±1.37%
20	54.18±1.12%	69.63±1.49%	79.75±1.45%	94.45±1.45%
30	67.43±1.24%	78.49±1.75%	88.15±1.37%	99.27±1.15%
40	75.16±1.27%	84.31±1.02%	93.28±1.14%	
50	89.43±1.20%	90.53±1.34%	99.57±1.10%	
60	98.49±1.24%	98.76±1.45%		

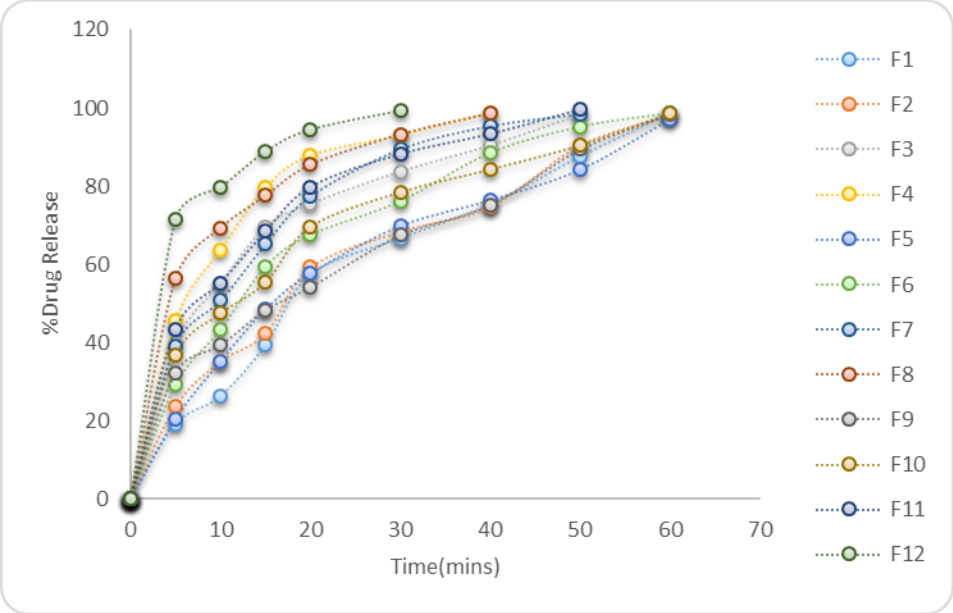

Figure.No.8 In vitro drug release of formulations F1-F12

Discussion: From the in vitro drug release in studies, it was observed that the formulations containing Croscarmellose sodium as a super disintegrant in different concentrations like 5mg, 10mg, 15mg, 20mg, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F12 formulation containing **Ludiflash** 20 mg concentration shows maximum amount of drug release (99.27±1.15%) at the end of 40mins. So, F12 formulation containing 20mg in concentration of ludiflash shows max. Release 99.27±1.15% within 40mins so that it is chosen as optimized formulation.

EVALUATION OF FORMALDEHYDE TREATED CAPSULES:

Physical tests:

Identification attributes: The size '0' capsules chosen were opaque, with white colored body and red cap. The normal capsule bodies were soft and sticky when touched with wet hand. After treating with formaldehyde, there were no significant changes in the physical appearance of the capsules except for the stickiness. The body of capsule was hard and non-sticking even when touched with wet hand due to treatment with the formaldehyde.

Visual defects: Among 100 capsules body which were treated with formaldehyde, about 15 to 20 capsule bodies showed visual defects. They were found to be shrunk and distortion into different shapes due to the complete loss of moisture.

Dimensions: Dimensional examination was done by using vernier calipers.

Average capsule length:

Before formaldehyde treatment (untreated cap and body) : 25.8 mm
After formaldehyde treatment (treated body and untreated cap) : 24.5 mm

Average diameter of capsule body:

Before formaldehyde treatment : 8.9 mm
After formaldehyde treatment : 7.7 mm

Average length of capsule body:

Before formaldehyde treatment : 20.4 mm
After formaldehyde treatment : 18.6 mm

Discussion: On formaldehyde treatment, the "0" size capsules bodies showed a significant decrease in length and diameter and attained hardness.

Chemical test:

Qualitative test for free formaldehyde: The formaldehyde treated capsules were tested for the presence of free formaldehyde by comparing color of sample solution with standard solution. It was found that the sample solution was not more intensity colored than the standard solution inferring that less than 20µg/ml of free formaldehyde was present in 25 capsule bodies.

Discussion: Limit test for the presence of residual formaldehyde, indicated that the amount of formaldehyde present in treated capsules was well within limits.

Optimization of formaldehyde treated capsule bodies exposed at various time intervals viz., 2, 4, 6, 8, 10hrs:

Table.11 Disintegration test for Treated Capsules

Capsule Code	Disintegration Time (hrs)	
	1.2 pH (2hrs)	7.4 pH (up to 24hrs)
(2rd hr)	2	_
(4th hr)	2	1
(6th hr)	2	7
(8th hr)	2	9
(10th hr)	2	12

Discussion: Basing on the disintegration studies, it was observed that the 3rd capsule 6th hr treated capsule remained intact for 7 hrs so lag time was maintained. 4th and 5th remain intact for 9, 12 hrs respectively and therefore they were not selected for the formulation because the required lag time was 6hrs. As the required lag time is 6hrs, (6th hr treated capsule) was selected as optimized time for formaldehyde treatment for further studies.

In vitro release studies:

Dissolution study was carried out to measure the release rate of drug from prepared pulsincap formulation using USP I dissolution apparatus at 37^0C using 2 different dissolution media of pH 1.2, pH 7.4 phosphate buffer in order to mimic in vivo GIT conditions. Initially first 2hrs of dissolution was conducted in pH 1.2 buffer, followed by 10hrs of dissolution study in pH 7.4 phosphate buffer.

Table.12 In vitro dissolution data of formulations P1F12 to P5F12

Time (hrs)	P1F12	P2F12	P3F12	P4F12	P5F12
0	0	0	**0**	0	0
1	0	0	**0**	0	0
2	0	0	**0**	0	0
3	0	0	**0**	0	0
4	0	0	**0**	45.26	0
5	0	0	**0**	63.16	49.95
6	51.24	67.24	**0**	88.21	73.36
7	83.19	88.48	**86.14**	99.58	88.48
8	98.45	98.85	**90.28**		98.85
9			**99.46**		
10					

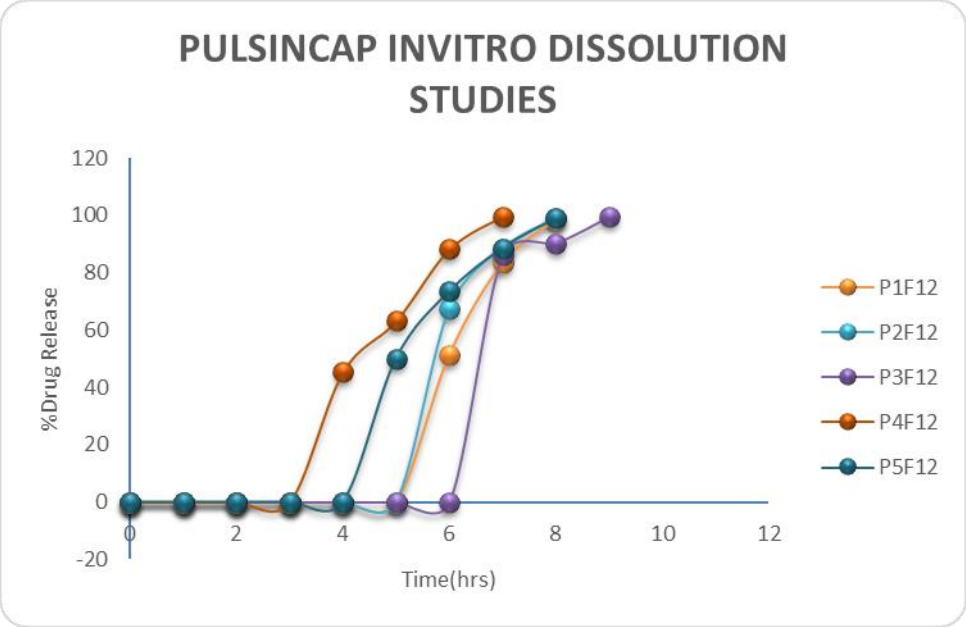

Figure.No.9 Dissolution plots for formulations P1F12 to P5F12

Discussion:

All the 5 formulations of Apremilast pulsincaps were subjected to dissolution studies. Formulations P1F12, P2F12, P3F12, P4F12 & P5F12, contain the hydrogel plug with alone and combination of hydrophobic polymer and Hydrophilic polymer i.e Ethyl Cellulose: HPMC K15M in the ratio of 1:1, 2:1 & 1:2 of total 100mg weight of the plug. It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Ethyl Cellulose and HPMC K15M hydrogel plug in the 2:1. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So, basing on these observations, of all the 5 pulsincap formulations, P3F12 formulation containing hydrogel plug of Ethyl Cellulose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

RELEASE KINETICS:

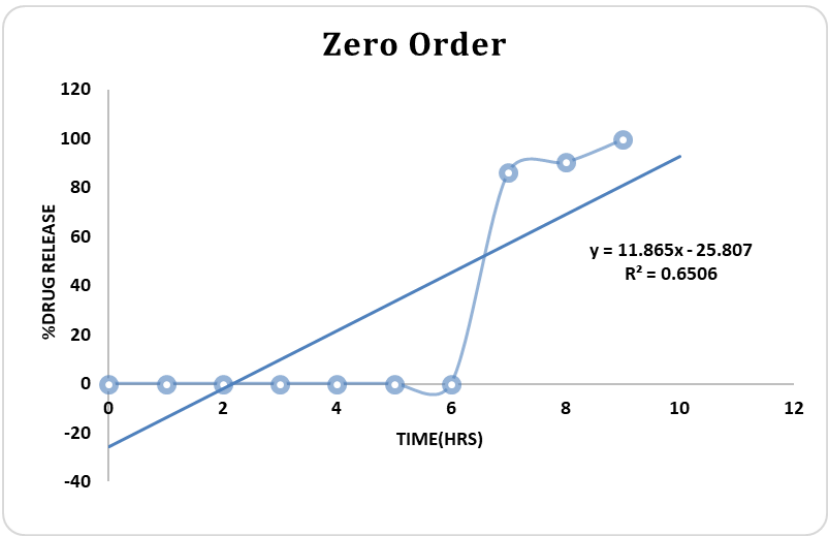

Figure.No.10 Zero order plot for optimized formulation P3F12

Figure.No.11 First order plot for optimized formulation P3F12

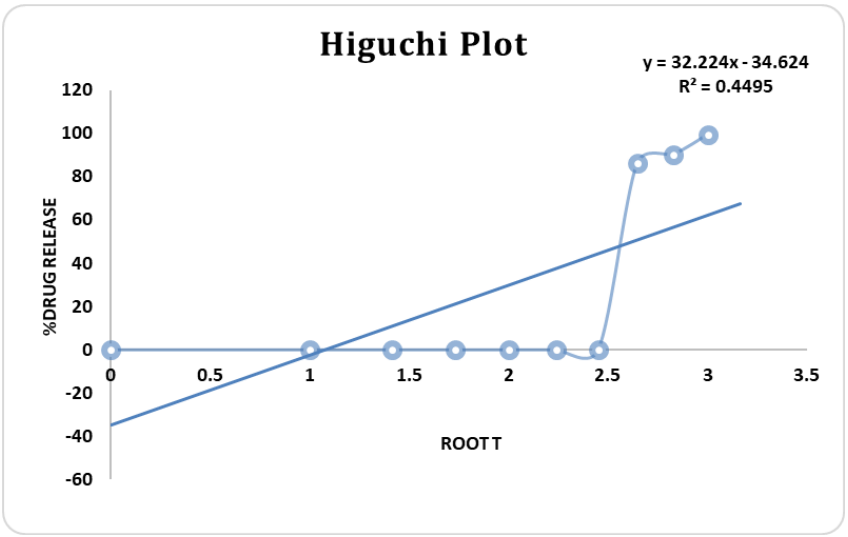

Figure.No.12 Higuchi's order plot for optimized formulation P3F12

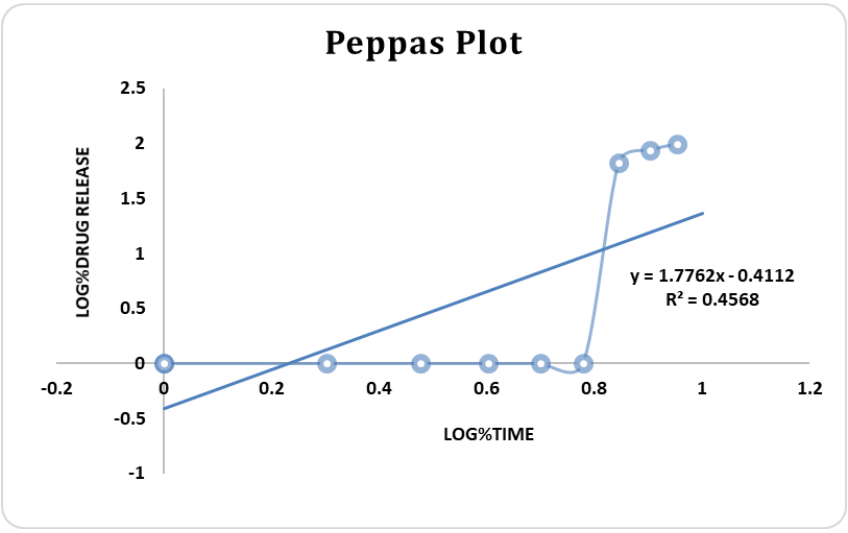

Figure.No.13 Koresmayer peppas order plot for optimized formulation P3F12

Discussion:

To analyze the mechanism of drug release from optimized P3F12 pulsincap formulation, data obtained from the drug release studies was subjected to different kinetic treatments. The correlation coefficient (R) was used as

indicator of the best fitting for each of the models considered. The drug release kinetics for the optimized formulation P3F12 followed the Zero order and Peppas follows super case II transport mechanism.

SUMMARY:

Over the past two decades there has been a growing appreciation on the importance of circadian rhythms on GIT physiology and on disease states, together with the realization of the significance of the drug administration on resultant pharmacodynamic and pharmacokinetics parameters. The significance of these day-night variations has not been over looked from the drug delivery perspective and pharmaceutical scientists have displayed considerable ingenuity in development of time delayed drug delivery systems to address emerging Chronotherapeutic formulations. Prior to formulation, Pre formulation studies were carried out in order to establish compatibility between Apremilast and excipients by FTIR spectroscopy. The results revealed that the drug and polymers were satisfactorily compatible, without any significant changes in the chemical nature of Apremilast. The capsule bodies were made insoluble by formaldehyde treatment by exposing at various time intervals viz., 2, 4, 6, 8, 10 hrs and then optimized by using disintegration studies and finally the optimized treated capsule bodies were then subjected to various physical and chemical tests such as identification attributes, visual defects, dimensional studies and qualitative test for free formaldehyde.

Total 12 formulations were formulated by using super disintegrant in different ratios by direct compression method. The formulations were subjected to flow properties and FTIR study. Based on the results obtained F12 containing 20mg Ludiflash was considered as the optimum powder blend for fabrication of pulsincap capsule.

Different concentration of the polymers like Lactose and Karaya Gum alone and in combination were used for the preparation of hydrogel plug to maintain the suitable lag period and it was found that the drug release was controlled by the proportion of polymers used.

The powder blend F6 was filled into the 6th hr formaldehyde treated capsule bodies and plugged with hydrogel polymers, 100mg hydrogel plug. The ratios of hydrophobic polymer like Lactose and HPMC were taken in alone and 1:1, 1:2 and 2:1,. Finally after arranging the plug, the joint of the capsule body and cap was sealed with a small amount of 1% lactose ethanolic solution. The prepared pulsincaps were evaluated for Invitro studies. All the 5 formulations of Apremilast pulsincaps were subjected to dissolution studies. Formulations P1F12, P2F12, P3F12, P4F12 and P5F12, contain the hydrogel plug with alone and in combination of hydrophobic polymer and Hydrophilic polymer i.e., Lactose: Karaya Gum in the ratio of 1:1, 1:2 and 2:1 of total 100mg weight of the plug.

It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Lactose and Karaya Gum hydrogel plug in the 2:1. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So, basing on these observations, of all the 5 pulsincap formulations P3F12 formulation containing hydrogel plug of Lactose and Karaya Gum in 2:1 ratio was selected as optimized pulsincap formulation.

CONCLUSION

The aim of this study was to explore the feasibility of time specific pulsatile drug delivery system of Apremilast to treat short-term treatment.

From the results obtained from executed experiments it can be concluded that:

The Pre formulation studies like pH, solubility and UV-analysis of Apremilast were compiling with BP standards.

The FTIR Spectra revealed that, there was no interaction between polymer and drug.

The solubility studies of empty gelatin capsule bodies, which were cross linked with formaldehyde treatment, revealed that they are intact for 24 hrs, and hence suitable for colon targeting.

The polymers like Lactose and Karaya Gum can be used as hydrogel plugs to delay the release of Apremilast.

The result of micromeritic properties showed good flow property of the powder blend indicating uniform distribution of drug within the various batches of capsule with negligible loss during the formulation stage.

In conclusion, this system can be considered as one of the promising formulation technique for preparing time specific drug delivery systems and in Chronotherapeutic management. From the preliminary trials it was concluded that it is possible to formulate the pulsatile drug delivery system by the design of time modified chrono pharmaceutical formulation.

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