Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2022, 14(8): 01-10
(http://www.derpharmachemica.com/archive.html)

Formulation Development and *In vitro* Evaluation of Apremilast Floating Tablet

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Received: 27-August-2020, Manuscript no: DPC-20-18166, **Editor assigned**: 01-September-2020, PreQC No: DPC-20-18166 (PQ), **Reviewed**: 15-September-2020, QC No: DPC-20-18166, **Revised**: 22-August-2022, QI No: DPC-20-18166, Manuscript No: DPC-20-18166 (R), **Published**: 19-September-2022, DOI: 10.4172/0975-413X.14.8.1-11

ABSTRACT

The objective of present work was to prepare a novel sustained release floating formulation of Apremilast for treatment of psoriatic arthritis. Pre-formulation study had carried out for possible drug and excipient interactions. Floating tablets were prepared using HPMC K4M and Carbopol 934 as polymer, Sodium bicarbonate and Citric Acid as gas generating agent, Starlac as diluents and PVPK 30 used as dry binder. Tablet was prepared by direct compression method. Initial formulation started with single polymers low to higher concentration and then combination of the polymers. It was found that combination of polymer gives good release retarding action in formulation and release the drug for 12 hr which is desire for formulation. Simultaneously gas generating agent was optimized by changing its concentration. Formulations were evaluated for Pre-compression parameter and post compression parameter like thickness, hardness, friability and floating lag time, floating time, swelling characteristics, In vitro dissolution studies, drug release kinetic study from the results it was concluded that F10 formulation was good release profile than the others. F10 formulation floated up to 12 hrs and floating time is within a min so F10 is optimized formulation.

Keywords: Floating tablet; Apremilast; Psoriasis; Sustain release

INTRODUCTION

Owing to tremendous curative benefits of the oral controlled release dosage forms are being preferred as the interesting topic of research over the past 3 decades. Primarily, the oral controlled release dosage forms have the potential to upkeep an effective concentration in system for a longer duration 1, 2 Apremilast is a novel, orally available small molecule inhibitor of type-4 cyclic nucleotide Phosphodiesterase (PDE-4). It is indicated in the treatment of active psoriatic arthritis in adults and moderate to severe plaque psoriasis. Apremilast had 10 mg/20 mg/30 mg dose two to three times in a day and bioavailability is 73% with pKa value of 4.83 in strong acid. So the drug remains in unionized condition in stomach. Hence, the attempt is made to develop a gastroretentive floating tablets of Apremilast which retain in gastric fluid up to 12 hours to improve the absorption of drug to reduce dosing frequency and improve patient compliance [1].

MATERIALS AND METHODS

Apremilast received as a gift sample from Zydus Research Centre, Ahmedabad. Starlac used as diluents, HPMC K4M, Carbopol 934 used as polymer, sodium bicarbonate and citric acid used as gas generating agent, PVP K30 used as binder and magnesium stearate as lubricant purchased from ACS Chemicals, Ahmedabad.

Pre formulation studies

Organoleptic characteristics: Colour and odour of drug were characterized and recorded using descriptive terminology.

Bulk density and tapped density

An accurately weighed quantity of the API (W), was carefully poured into the graduated cylinder and the Volume (V_o) was measured. Then the graduated cylinder was set for 100 taps and after that the Volume (V_f) was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas.

$$Bulk\ density = \frac{W}{V_0}$$

$$Tapped\ density = \frac{W}{V_f}$$

Compressibility Index (CI)/Carr's index

It was obtained from bulk and tapped densities. It was calculated by using the following formula.

$$\%\ Carr'sindex = \frac{(TD - BD)}{TD} \times 100$$

Hausner's ratio

Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

$$Hausner's\ ratio = \frac{Tapped\ Density}{Bulk\ density}$$

Angle of repose

Angle of repose of API powder was determined by the funnel method. Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$Tan\ \theta = \frac{h}{r}$$

Drug excipients compatibility study

FTIR study

The fourier transform infrared spectrum of moisture free powdered sample of Apremilast and final formulation was recorded on IR spectrophotometer by Potassium Bromide (KBr) pellet method. The range of spectra was found to be 600 cm^{-1} to 4000 cm^{-1}. The characteristics peaks of different functional group were compared with reported standard peak.

Determination of λ_{max} and development of calibration curve of apremilast

Stock solution: Apremilast in pH 1.2 hydrochloric acid buffer solutions (100 µg/ml).

Scanning: From the stock solution, a suitable concentration (10 µg/ml) was prepared with pH 1.2 Hydrochloric acid buffer solutions and UV scan was taken between the wavelengths of 200 nm-400 nm and determining its λ_{max}.

Standard plot: From the stock solution 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml solutions of Apremilast were prepared in pH 1.2 hydrochloric acid buffer solutions. The absorbance was measured at 231 nm and a graph of concentration versus absorbance was plotted.

Dose calculation

The total dose of Apremilast for a sustained release formulation was calculated by following four equations using available pharmacokinetic data from a design of one compartment model with simultaneous release of loading dose and a zero order release maintenance dose, as described by Robison and Eriksen.

$k_0 = Dike$ (1)
$D_m = k_0T$ (2)
$D_l = D_i - k_0Tp$ (3)
$D_t = D_l + Dm$ (4)
$k_0 = D_ik_e = 10 \times 0.693/6 = 1.155$ mg (5)
$D_m = k0T = 1.155 \times 12 = 13.86$ mg (6)
$D_l = D_i - k_0T_p = 10 - (1.155 \times 2.5) = 7.1125$ mg (7)
$D_t = D_l + D_m = 7.1125 + 13.86 = 20.97 \equiv 21$ mg (8)

Where, k_0=zero order drug release;
k_e=0.693/t1/2;
D_i=Initial dose/conventional dose;
D_l=Loading Dose;
D_m=Maintenance Dose;
T=Time for sustained action;
T_p=Time to reach peak plasma concentration;
D_t=Total dose of drug.

Hence the tablet should contain a total dose of 21 mg for 12 h. sustained release dosage form and it should release 7.1125 mg in 1st hour like conventional dosage form and remaining dose (13.86 mg) in remaining 11 hours, Hence, the theoretical drug release profile can be generated using above value (Table 1).

Table 1: Theoretical drug release profile.

Time (hour)	Total amount of drug release from 21 mg tablet (mg)	% CPR
1	7.11	33.87
2	8.38	39.88
3	9.64	45.89
4	10.90	51.90
5	12.16	57.92
6	13.43	63.93
7	14.69	69.94
8	15.95	75.95
9	17.21	81.96
10	18.48	87.98
11	19.74	93.99
12	21.00	100.00

Method of preparation of floating tablets

Direct compression method

Apremilast, selected polymers and Starlac were taken in required quantities and passed through 40 meshes separately. In dry state, the drug with other ingredients was mixed for the period of 10 min in mortar to get uniform mixture power. The mixture was blended with Talc and Magnesium Stearate (60# pass) for 2 min-3 min to improve flow property. The powder was compressed into tablets using a rotary tablet press.

Formulation development of floating tablets

Various formulations of floating tablets were developed for Apremilast using various polymers like HPMC K4M, Carbopol 934; filler like Starlac. Magnesium Stearate and talc was used as lubricant (Table 2) [2-6].

Table 2: Formulation of floating tablets.

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Apremilast	21	21	21	21	21	21	21	21	21	21	21	21	21
HPMC K4M	40	50	60	70	-	-	-	-	20	25	30	35	40
Carbopol 934	-	-	-	-	40	50	60	70	20	25	30	35	40
Sodium Bicarbonate	20	30	15	40	40	40	40	40	40	40	40	40	40

Citric Acid	15	15	30	20	20	20	20	20	20	20	20	20	20
PVPK 30	10	10	10	10	10	10	10	10	10	10	10	10	10
Starlac	88	68	58	33	63	53	43	33	63	53	43	33	23
Mg. Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4
Total	200	200	200	200	200	200	200	200	200	200	200	200	200

Post compression parameters

Weight variation: Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation as per IP.

Thickness: Thickness of tablets is important for uniformity of tablet size. Thickness was measured using Vernier Calipers on 3 randomly selected samples.

Hardness: The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester.

Friability: Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \, loss = \frac{Initial \, wt. of \, tablets - Final \, wt. of \, tablets}{Initial \, wt. of \, tablets} \times 100$$

Assay: 10 tablets were weighed and average weight is calculated. All tablets were crushed and powder equivalent to 10 mg was dissolved in 250 ml 0.1 N HCl and shaken for 20 min. solution was filtered and after suitable dilution using 0.1 N HCL, absorbance was measured spectrophotometrically at 231 nm against reagent blank. Amount of drug present in one tablet was calculated [7-11].

Floating lag time: The lag time was carried out in beaker containing 100 ml of 0.1 N HCl as a testing medium maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Floating time: Floating time was the time, during which the tablet floats in 0.1 N HCL dissolution medium (including floating lag time).

Swelling characteristics: The swelling properties of matrix tablet containing drug were determined by placing the tablet matrices in the USP dissolution testing apparatus II, in 900 ml of 0.1 N HCl at 37°C ± 0.5°C, rotated at 50 rpm. The tablets were removed periodically from dissolution medium, blotted to remove excess water and weighed. Swelling characteristics were expressed in terms of percentage Water Uptake (WU%) according to the equation.

$$WU\% = \frac{Wt. of \, swollen \, tablets - Initial \, wt. of \, tablet}{Initial \, wt. of \, tablets} \times 100$$

Dissolution studies: The release rate of Apremilast from floating tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37° ± 0.5°C and 50 rpm. Aliquot volume was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. After filtration and suitable dilution the amount of drug release was determined from the calibration curve.

Drug release kinetic study

Data obtained form *in vitro* drug release studies were fitted to disso calculation software. The kinetic models used are zero order, first order, Korshmers and Papps, Hexon crowell, and Higuchi equation. The rate and mechanism of release of Apremilast from the prepared tablets were analyzed by fitting the dissolution data into the zero-order equation:

$$Q=k_0t$$

Where, Q is the amount of drug released at time t, k_0 is the release rate constant.
The dissolution data fitted to the first order equation

$$Ln\ (100-Q)=ln\ 100-K1\ t$$

Where, k1 is the release rate constant.
The dissolution data was fitted to the Higuchi's equation: $Q=K2\ t1/2$

Where, k2 is the diffusion rate constant.
The dissolution data was also fitted to Korsmeyer equation, which is often used to

Describe the drug release behavior from polymeric systems: Log (Mt/M∞)=log k+n log t

Where Mt is the amount of drug released at time t, M∞ is the amount of drug release. After infinite time, K is a release rate constant incorporating structural and geometric Characteristics of the tablet, n is the diffusional exponent indicative of the mechanism of drug release.

Stability study

The stability studies were carried out on the most satisfactory formulations as per ICH guidelines. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 40°C ± 2°C/75 ± 5% RH for 4 weeks. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, floating behavior and other physicochemical parameters.

RESULTS

Characterization of drug

Based on physical characterization of API it concluded that the API has a very poor flow itself so granular grade diluents need to be used for direct compression characteristics (Table 3).

Table 3: Characteristics of aprimlast.

Characteristic properties		Observation/result
Organoleptic characteristics	Colour	White crystalline Powder
	Odour	Odorless
Flow properties	Bulk density (g/ml)	0.302
	Tapped density (g/ml)	0.410
	Carr's index (%)	26.34
	Hausner's ratio	1.35
	Angle of repose (θ°)	28.14º
Solubility		Sparingly soluble in methanol, insoluble in water. Soluble in 0.1 N HCl

FTIR study

FTIR study of pure drug Apremilast and final formulation done. From the below results it concluded that no any interaction found between drug and excipients. Streching of Aromatic C-H stretch, Aromatic C=C stretch, Aromatic C-N stretch, C-O stretch was observed as 3228.38, 1504.52, 1253.38 and 1100.98 respectively.

Calibration curve of apremilast

The calibration curve of Apremilast was found to over a concentration range 2 µg/ml-10 µg/ml. (R^2=0.998) (Table 4) (Figure 1).

Table 4: Calibration curve of apremilast in 0.1 N Hcl at 231 Nm.

Sr. No	Concentration (µg/ml)	Absorbance ± SD (n=3)
1	0	0
2	2	0.156 ± 0.005
3	4	0.305 ± 0.007
4	6	0.448 ± 0.003
5	8	0.621 ± 0.005
6	10	0.745 ± 0.003

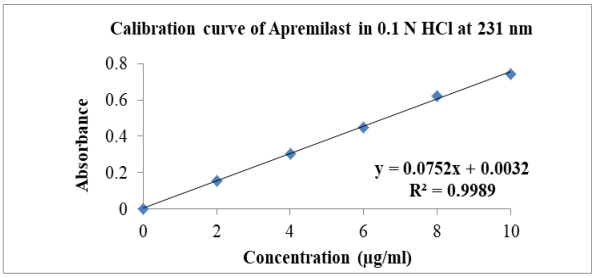

Figure 1: Calibration curve of apremilast in 0.1 N HCl at 231 nm.

Pre compression parameters

Powder blend of formulation F1-F13 checked for pre compression parameters like, Bulk density, Tapped density, Compressibility index (CI) / Carr's index, Hausner's ratio, Angle of repose. Observed results are mentioned in following Table 5. From the below Table 5 it concluded that all the formulation have a good flow property because of Hausner's ratio value is less than 1.23 for all. So the rational for using of Starlac as flow improving agent is fulfilled (Table 5) [12,13].

Table 5: Pre compression parameters of formulation F1-F13.

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ°)
F1	0.51 ± 0.08	0.56 ± 0.05	8.93 ± 0.04	1.10 ± 0.01	19.56 ± 0.04
F2	0.52 ± 0.02	0.58 ± 0.04	10.34 ± 0.05	1.12 ± 0.01	18.75 ± 0.03
F3	0.47 ± 0.04	0.54 ± 0.02	12.96 ± 0.05	1.15 ± 0.01	17.84 ± 0.03
F4	0.58 ± 0.03	0.65 ± 0.03	10.77 ± 0.02	1.12 ± 0.01	19.29 ± 0.05
F5	0.49 ± 0.04	0.58 ± 0.08	15.52 ± 0.03	1.18 ± 0.02	22.14 ± 0.08
F6	0.47 ± 0.05	0.54 ± 0.08	12.96 ± 0.04	1.15 ± 0.02	21.04 ± 0.07
F7	0.48 ± 0.06	0.59 ± 0.07	18.64 ± 0.02	1.23 ± 0.01	18.56 ± 0.05
F8	0.58 ± 0.05	0.64 ± 0.05	9.38 ± 0.03	1.10 ± 0.01	17.45 ± 0.06
F9	0.48 ± 0.04	0.53 ± 0.06	9.43 ± 0.05	1.10 ± 0.02	16.84 ± 0.04
F10	0.43 ± 0.03	0.49 ± 0.04	12.24 ± 0.06	1.14 ± 0.01	19.84 ± 0.06
F11	0.46 ± 0.07	0.52 ± 0.07	11.54 ± 0.02	1.13 ± 0.01	21.54 ± 0.04
F12	0.51 ± 0.03	0.57 ± 0.05	10.53 ± 0.04	1.12 ± 0.02	23.45 ± 0.05
F13	0.52 ± 0.02	0.59 ± 0.07	15.25 ± 0.08	1.18 ± 0.01	21.15 ± 0.02

Weight variation: The average weight of all formulation is 200 mg and no any formulation deviate from its weight variation test. All formulations are found between 197 mg to 203 mg.

Thickness: Thickness of all formulations F1 to F13 have thickness between 3.2 mm to 3.7 mm.

Hardness: Hardness of all F1 to F13 having hardness 5.1 kg/cm^2 to 6.3 kg/cm^2. All formulations have a good hardness.

Friability: All formulation tablets pass the Friability test and no any formulation has deviate from friability test. So it concluded that the formulation have a good mechanical strength (Table 6).

Table 6: Post compression parameters of formulation F1-F13.

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	201 ± 1.9	3.7 ± 0.3	6.3 ± 0.28	0.47
F2	203 ± 3.2	3.2 ± 0.2	6.3 ± 0.28	0.38
F3	198 ± 2.5	3.6 ± 0.4	5.1 ± 0.16	0.29
F4	197 ± 3.1	3.5 ± 0.3	5.3 ± 0.16	0.14
F5	199 ± 2.4	3.4 ± 0.2	5.5 ± 0.28	0.26
F6	201 ± 3.9	3.3 ± 0.3	5.3 ± 0.16	0.39
F7	198 ± 2.6	3.3 ± 0.4	5.6 ± 0.16	0.52
F8	199 ± 2.7	3.4 ± 0.3	5.7 ± 0.28	0.31
F9	199 ± 3.9	3.3 ± 0.4	5.3 ± 0.28	0.39
F10	201 ± 2.8	3.3 ± 0.5	5.8 ± 0.16	0.28
F11	199 ± 2.7	3.4 ± 0.3	5.7 ± 0.28	0.31
F12	198 ± 3.9	3.0 ± 0.4	5.3 ± 0.28	0.39
F13	201 ± 2.8	2.3 ± 0.5	5.8 ± 0.16	0.28

Assay: Assay of all formulations was found that it was within 98% to 99%.

Floating lag time: Time taken to float on a medium by tablet was checked for all formulations F1-F13. It was found that the ration of sodium bicarbonate to citric acid in formulation is very important to float a tablet in the medium. With single polymer F1 to F4 formulation have a different ration of effervescent agent in which equal proportion of both take more time to float a table where in F4 formulation 50 mg sodium bicarbonate and 20 mg citric acid float a table within a min (Table 7).

Table 7: Post compression parameters of formulation F1-F13.

Formulation code	Assay (%)	Floating lag time (sec)	Floating time (hour)
F1	99.66 ± 1.60	550 ± 27	6 ± 1
F2	99.56 ± 2.39	480 ± 35	8 ± 1
F3	98.77 ± 2.30	387 ± 19	8 ± 1
F4	99.19 ± 2.92	45 ± 8	8 ± 1
F5	98.06 ± 1.57	50 ± 10	5 ± 1
F6	98.63 ± 2.57	44 ± 6	7 ± 1
F7	99.36 ± 2.69	42 ± 7	8 ± 1
F8	98.48 ± 2.37	51 ± 13	8 ± 1
F9	99.82 ± 2.71	48 ± 15	12 ± 1
F10	99.89 ± 2.72	42 ± 6	12 ± 1
F11	99.32 ± 2.37	49 ± 3	12 ± 1
F12	98.75 ± 1.68	56 ± 6	12 ± 1
F13	99.56 ± 2.50	58 ± 2	12 ± 1

Floating time: The time up to which tablet was remain floated called floating time. In F1 to F4 tablets floated up to 8 hr only in presence of HPMC. After that F6 to F8 formulation gives better floating time up to 8 hours but not sufficient. Finally combination of both polymers gives floating up to 12 hr which requires in formulation.

Swelling characteristics

All the formulations show good swelling behavior (Table 8).

Table 8: Swelling characteristics of floating tablets F1-F13.

Formulation code	% Swelling index			
	2 hr	4 hr	6 hr	12 hr
F1	35	74	81	-
F2	47	78	92	97
F3	84	104	141	185
F4	54	94	115	140
F5	47	68	-	-
F6	57	84	110	-
F7	24	42	98	142
F8	35	48	68	147
F9	84	110	125	165
F10	65	84	113	145
F11	45	68	98	116
F12	24	54	87	121
F13	25	39	69	125

***In vitro* dissolution studies**

The percentages of drug release of all formulations are performed. Here initial trials initiated with taking HPMC K4M in low amount and the drug release of F1 is gives 99% within 6 hr. So the amounts of polymer increase in F1-F4 formulation. It seems that no any formulation from F1-F4 gives release more than 8 hr. Further trials taken with carbopol 934 and maximum drug release found up to 9 hr only in F8 formulation. So carbopol 934 alone is not able to retard the drug release up to 12 hr. Further trials with both polymers in different ratio taken and found that it gives drug release up to 12 hr. here both the polymer gives good release retarding action in formulation and release the drug for 12 hr which is desire for formulation (Figure 2). Addition of higher amount in F11, F12 and F13 formulation retard the drug release (Table 9) [14].

Table 9: Perecentage drug release of F1 to F13 formulations.

Time (hr)	F1	F2	F2	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	30.3 ± 1.5	25.4 ± 1.9	32.2 ± 1.7	25.9 ± 1.5	39.1 ± 1.6	23.5 ± 1.3	27.0 ± 1.7	18.5 ± 1.9	40.7 ± 1.3	31.1 ± 1.5	6.7 ± 1.7	5.6 ± 1.2	2.8 ± 1.5
2	49.7 ± 1.3	39.5 ± 1.8	45.1 ± 1.6	36.5 ± 1.0	45.9 ± 1.7	36.5 ± 1.5	39.7 ± 1.5	30.6 ± 1.7	49.7 ± 1.8	40.5 ± 1.8	10.3 ± 1.6	9.9 ± 1.3	9.4 ± 1.2
3	65.4 ± 1.5	47.1 ± 1.3	54.1 ± 1.9	48.7 ± 1.6	65.1 ± 1.5	48.1 ± 1.8	49.2 ± 1.7	35.9 ± 1.8	52.0 ± 1.6	47.2 ± 1.7	15.0 ± 1.5	16.5 ± 1.2	13.5 ± 1.4
4	78.8 ± 1.7	58.2 ± 1.2	65.1 ± 1.8	59.0 ± 1.4	78.4 ± 1.4	54.3 ± 1.7	55.9 ± 1.6	45.9 ± 1.5	59.1 ± 1.8	51.5 ± 1.6	24.0 ± 1.5	19.4 ± 1.2	24.7 ± 1.6
5	87.6 ± 1.8	69.1 ± 1.4	74.1 ± 1.5	69.9 ± 1.5	98.5 ± 1.2	59.7 ± 1.5	69.0 ± 1.8	54.9 ± 1.4	70.3 ± 1.5	58.5 ± 1.7	35.9 ± 1.4	26.5 ± 1.4	29.9 ± 1.2
6	99.1 ± 1.9	78.2 ± 1.3	79.0 ± 1.4	72.1 ± 1.3	-	78.1 ± 1.4	79.8 ± 1.7	68.5 ± 1.6	73.3 ± 1.8	64.5 ± 1.4	43.2 ± 1.2	38.1 ± 1.2	33.5 ± 1.1
7	-	97.5 ± 1.4	84.2 ± 1.2	89.5 ± 1.7	-	97.2 ± 1.0	85.4 ± 1.4	81.6 ± 1.2	76.3 ± 1.7	70.7 ± 1.2	50.3 ± 1.8	46.3 ± 1.5	39.4 ± 1.8
8	-	100 ± 1.0	97.1 ± 1.0	98.1 ± 1.4	-	-	99.2 ± 1.0	95.3 ± 1.1	79.2 ± 1.3	76.2 ± 1.5	61.0 ± 1.5	54.3 ± 1.7	46.5 ± 1.7
9	-	-	-	-	-	-	-	99.2 ± 1.5	85.2 ± 1.5	82.0 ± 1.4	67.0 ± 1.7	61.5 ± 1.7	52.3 ± 1.5
10	-	-	-	-	-	-	-	-	94.5 ± 1.8	88.5 ± 1.7	82.1 ± 1.8	71.3 ± 1.9	59.1 ± 1.8
11	-	-	-	-	-	-	-	-	99.7 ± 1.7	94.1 ± 1.8	85.0 ± 1.7	79.4 ± 1.5	63.4 ± 1.7
12	-	-	-	-	-	-	-	-	99.9 ± 1.5	99.9 ± 1.9	89.8 ± 1.9	85.4 ± 1.0	78.9 ± 1.9

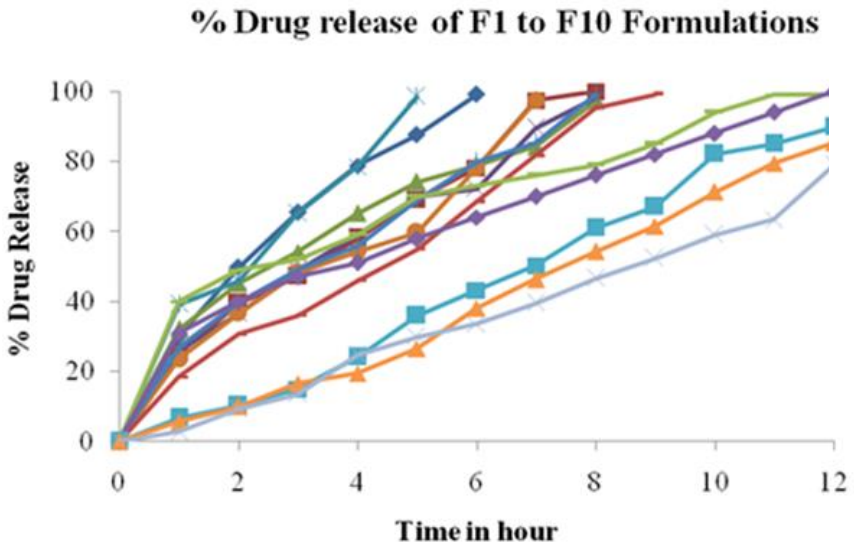

Figure 2: 1% Drug release comparison of F1 to F13 formulations. **Note:** : F1; : F2; : F3; : F4; : F5; : F6; : F7; : F8; : F9; : F10; : F11; : F12; : F13

Drug release kinetic study

The results of dissolution data were fitted to various drug release kinetic equations. The zero order drug release graph is plotted between the time taken on x-axis and the cumulative % of drug release on Y-axis. First order drug release graph is plotted between the time taken on X-axis and the log cumulative % of drug remaining on y axis. Higuchi's square root graph is plotted between the square root of time taken on X-axis and the cumulative % of drug release on Y-axis (Table 10). Korsmeyer-Peppas drug release graph is plotted between the log time taken on X-axis and the log cumulative % of drug release on Y-axis (Figures 3 to 6). The result of kinetic drug release of formulation F10 in the R2 values was highest for korsmeyer-peppas model. The 'n' value is 0.521 indicates the non Fickian diffusion [15].

Table 10: Drug release kinetic study of optimized batch F10.

Batch No	Zero order kinetics	First order kinetics	Higuchi model	Korsmeyer-peppas model	n (release exponent)
F10	0.9842	0.8551	0.7669	0.9912	0.521

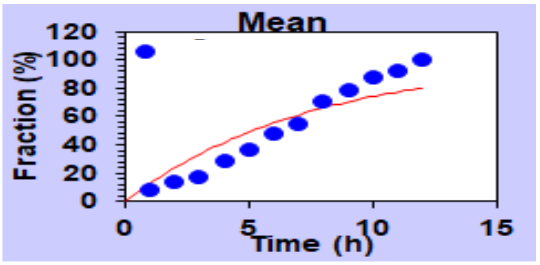

Figure 3: 2 Drug release zero order kinetic modeling graph of batch F10.

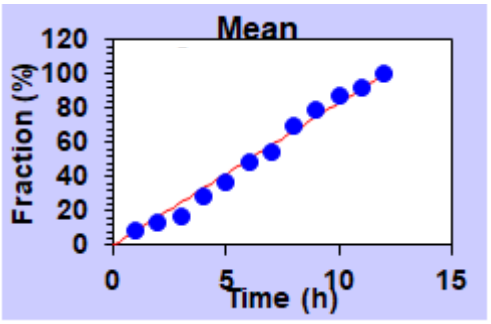

Figure 4: 3 Drug release first order kinetic modeling graph of batch F10.

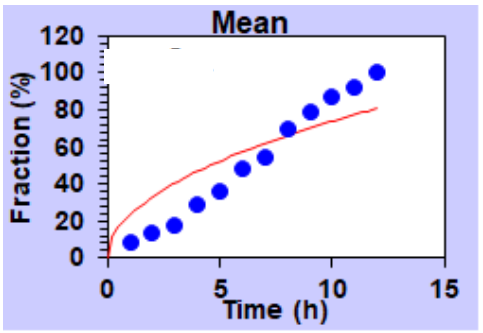

Figure 5: 4 Drug release Higuchi modeling graph of batch F10.

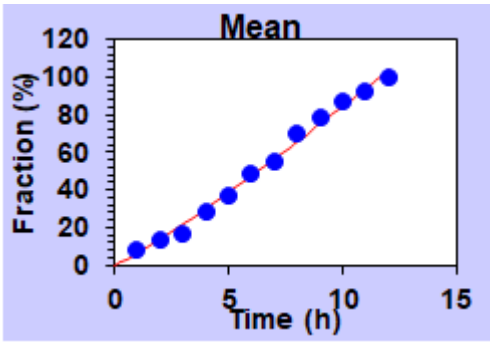

Figure 6: 5 Drug release korsmeyer-peppas modeling graph of batch F10.

CONCLUSION

The objective of the present work was to develop a stable sustained release floating formulation which gives drug release up to 12 hr, twice a daily formulation of Apremilast with an aim to reduce the dosing frequency and improves the patience compliance with the help of natural polymer with newer excipient. In preformulation study drug shows passable flow property and good compressibility. From the drug Excipient compatibility study it was observed that there was no physical and chemical change in the drug properties. Direct compression method adopted by using Starlac new direct compressible diluents. PVPK 30 used as dry binder. During precompression parameters checking it observed that all the formulation have a good flow property because of Hausner's ratio value is less than 1.23 for all. So the rational for using of Starlac as flow improving agent is fulfilled. Initial trials

initiated with taking HMPC K4 M in low amount and the drug release of F1 is gives 99% within 6 hr. So the amount of polymer increases in F1-F4 formulation. It seems that no any formulation from F1-F4 gives release more than 8 hr. Further with Carbopol 934, maximum drug release found up to 9 hr only in F8 formulation. So HMPC K4 M and carbopol 934 alone is not able to retard the drug release up to 12 hr. Both polymers in different ratio taken and found that it gives drug release up to 12 hr here both the polymer gives good release retarding action in formulation and release the drug for 12 hr which is desire for formulation. From the results it was concluded that F10 formulation was good release profile than the others. F10 formulation floated up to 12 hrs and floating time is within a min so F10 is optimized formulation.

ACKNOWLEDGEMENT

The author and co-author, Saraswati Institute of Pharmaceutical Sciences, for providing the necessary facility to accomplish the work we also humble gratitude to our colleague and non-teaching staff for their support during the work.

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