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PREPARATION AND *IN-VITRO* EVALUATION OF APREMILAST EFFERVESCENT FLOATING TABLETS

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ABSTRACT: Apremilast, the new PDE4 inhibitor drug, exhibits low solubility and low permeability; therefore, shows variable bioavailability. Effervescent floating tablets of apremilast were developed to sustain the drug release rate by increasing gastric retention time. These tablets were prepared by wet granulation technique, using different polymers like carbopol 934P, hydroxypropyl methylcellulose K4M, tragacanth and sodium alginate, either alone or in combination. Prepared tablets were characterized for physical parameters like floating capacity, hardness, % weight variation, friability, and content uniformity. Additionally, tablets were evaluated for in vitro release characteristics for 24 h. Results of this study exhibited good physical properties within the limit of acceptance. Batches prepared by carbopol 934P did not show any initial burst release as compared to other polymers. When polymer concentrations were increased drug release rate was decreased. Drug release from the tablets was followed by zero-order controlled release. Sodium alginate/ tragacanth and HPMC K4 in 1:3 ratio exhibited best drug release for 24 h. Carbopol batches (1:3 ratio) showed very first floating lag time (52 S) but less total floating time (only 8 hrs). However, formulations F5 and F6 (1:7) ratio showed total floating time more than 22 h. From this study we conclude that floating tablets enhance and sustained apremilast release time and would be considered for further *in-vivo* study.

INTRODUCTION: A new (approved by the FDA in 2014) small molecule apremilast (APM), an inhibitor of type-4 cyclic nucleotide phosphor di esterase (PDE-4) is a promising candidate in the treatment of active psoriatic arthritis and plaque psoriasis in adult. PDE-4 is predominantly found in inflammatory cells. Therefore the mechanism of this drug is to inhibit PDE-4 so that intracellular levels of cAMP increase and thereby inhibit the production of multiple pro-inflammatory mediators. Chemically it is a phthalimide derivative and non-hygroscopic in nature.

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This drug is practically insoluble in water, therefore, has low solubility and low permeability. For this reason, it is categorized as a BCS class IV type of drug [1]. Presently this drug is available as a oral tablet dosage form. However patents have been filed for its conventional topical formulation too. Due to its low solubility and permeability, its oral bioavailability is highly variable between different species (humans 73%, mice 20%–33%, rats 12%–63%, monkeys 78%, and rabbits ≤0.1%) [2].

The biological half-life of the drug is 8 h which recommends 2-3 times daily intake of this drug by oral route. Owing to the chronic nature of the disease (psoriatic arthritis and plaque psoriasis), a long-term treatment with apremilast is usually recommended. Conventional immediate-release formulation of apremilast possesses tolerability and dose regimen issues, which might impair patient compliance and therefore, the efficacy of the

treatment would be compromised [3, 4]. Therefore, an alternative drug-delivery system is urgently required to overcome the tolerability and the frequent daily dosing and to improve the bioavailability of APM. Recently, Tang *et al.* (2016) developed an extended-release formulation of APM to resolve the dosing and tolerability issue [5]. To overcome the problems of conventional oral dosage form, we tried to prepare a delivery system of apremilast to sustain the drug release rate by increasing gastric retention time so that half-life is increased and dosage frequency is decreased. With this object, we prepare a buoyant system of apremilast. These buoyant systems utilize matrices prepared with different swellable, biodegradable polymers like carbopol, tragacanth, sodium alginate, and HPMC and effervescent components (*e.g.,* sodium bicarbonate and citric acid). The system is so prepared that when it arrives in the stomach carbon dioxide is released, causing the formulation to float in the stomach. Classically effervescent systems are classified into two type's namely, gas generating systems and volatile liquid/ vacuum systems [6]. Gas generating systemsexploit effervescent reactions between citric/tartaric acid and carbonate/bicarbonate salts to liberate carbon dioxide, which gets entrapped in the jell like hydrocolloid layer of the systems, thus decreasing its specific gravity and making it float over gastric content. In this research work, we also explored this mechanism. However, volatile liquid/vacuum systems include two chambers having apressure responsive, impermeable, movable bladder separation. The former chamber contains drugs and the latter contains volatile liquid. To sustain the gastric residence time of a system an inflatable chamber is incorporated, which carries a liquid like ether.

MATERIALS AND METHODS:

Materials: Apremilast was obtained as a gift sample from Zydus Cadila Ltd, India and was used as such without further purification. HPMC K100M, carbopol, tragacanth, sodium alginate, sodium bicarbonate, citric acid, PVP, Mg. Stearate, talc are the other ingredients used for this study. All chemicals and reagents used were AR grade.

Methods:

Preparation of Apremilast Floating Tablets: All the ingredients were weighed accurately. At first, HPMC K_4M was mixed with sodium bicarbonate. After this PVP, other polymers and citric acid were added into this. Then the power was passed through a sieve no.40. In the next step, few drops of water were added to the mixture to prepare a coherent mass. The mass was passed through sieve no: 10 to form small granules. The granules were dried at 60-70 ºC for 20 min. Talc and magnesium stearate were finally added as glidant and lubricant respectively and compressed in 8-station rotary tablet press machine.

It was a modified method [7] described by Bahri-Najafi *et al.,* 2003. Three batches (F1, F2, F3) were prepared with 1:3 ratio of other polymer (carbopol/ tragacanth/sodium alginate) and HPMC K4M. Another three batches (F4, F5, F6) were prepared with 1:7 ratio of the same polymers, respectively. F7 batch is a combination of all four polymers. Refer to **Table 1** for the details of the composition.

TABLE 1: FORMULATION OF APREMILAST EFFERVESCENT FLOATING TABLETS

Ingredient	F1	F2	F3	F4	F5	F6	F7	Properties
HPMC K 4M	120	120	120	140	140	140	100	Hydrophilic polymer
Carbopol 934P	40			20			20	Release rate controller, help in floating
Tragacanth		40			20		20	
Sodium alginate			40			20	20	
Sodium bicarbonate	60	60	60	60	60	60	60	Help to produce effervescent
Citric acid	30	30	30	30	30	30	30	
PVP	10	10	10	10	10	10	10	Disintegrant
Mg. Stearate	5	5	5	5	5	5	5	Lubricant
Talc	5	5	5	5	5	5	5	Glidant

*All the formulations contain 20 mg drug. The average weight of a tablet is 270 mg.

Evaluation Parameters of Floating Tablets:

Weight Uniformity Test: If the tablet contains a drug in a small amount, then any variation in the tablet weight obviously indicates a variation in the active ingredient. Therefore weight uniformity test was carried out. For this purpose, 20 tablets were

selected at random and average weights were determined. Then individual tablets were weighed, and the individual weight was compared with the average. An electronic balance (Mettler Toledo, 3-MS-S/MS-L, Switzerland) was used to accurately weigh ten tablets which were randomly selected. The average weight of tablets was calculated by = Total weight of tablets/Number of tablets. The average weight of tablets

$$(X) = (X1+X2+X3+\ldots\ldots+X20) / 20$$

Hardness Uniformity Studies: The hardness of the prepared formulation was measured by using Monsanto Hardness tester. Six floating tablets were used for hardness uniformity studies. The hardness data used to calculate mean and standard deviation.

Thickness Uniformity Studies: The thickness uniformity studies were carried out by using Vernier Calipers. Six tablets were used for thickness uniformity studies and denoted in millimeters. The data obtained were used to calculate the mean and standard deviation.

Friability Test: The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%) 20 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm per min for 4 min (100 revolutions). The tablets were weighed again (W final). The was then calculated by the following formula

$$\% \text{ Friability} = (W1-W2) \times 100 / W1$$

Thickness and Diameter: Tablet thickness is important for tablet floating. The tablet thickness is varied by the diameter of the die, the amount of fill permitted to enter the die and the force or pressure applied during compression. The thickness of the tablet may be measured manually or by automatic equipment. The thickness and diameter of the tablets was measured by Vernier Caliper. It is expressed in mm.

Content Uniformity: Twenty tablets were taken, and the amount of drug present in each tablet was determined. The tablets were crushed in a mortar, and the powder equivalent to 100 mg of drug was transferred to 100 ml standard flask. The powder was dissolved in methanol and make up the final volume. The sample was mixed thoroughly and filtered through a 0.45 µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at 230 nm, using methanol as a blank [8].

***In-vitro* Floating Study:** *In-vitro* buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing simulated gastric fluid, pH1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as Floating Lag Time (FLT). The duration of time the dosage form constantly remained on the surface of the medium was determined as the Total Floating Time (TFT).

***In-vitro* Dissolution Studies:** The release rate of floating tablets was determined using United States Pharmacopoeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl for 24 hrs. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly, and the samples were replaced with a fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1N HCl for 24 h. The absorbance of these solutions was measured at 230 nm using a UV/ Visible spectrophotometer.

Kinetics Modeling of Drug Dissolution Profiles [9]: The dissolution profile of all the batches was fitted to Zero order, First order, Higuchi model, and Korsmeyer to ascertain the kinetic modeling of the drug release. Korsmeyer-Peppas model explains a simple relationship that described drug release from a polymeric system equation to find out the mechanism of drug release. $Mt/M\infty = kt^n$ Where Mt is the amount of drug release at time t, $M\infty$ is total amount of drug present in the formulation, k is release rate constant depends on geometry of dosage form and n is diffusion exponent indicating the mechanism of drug release.

Preparation of Standard Curve of Apremilast: Standard stock solution of Apremilast was prepared by dissolving 0.025 mg of Apremilast in a 25 ml volumetric flask with Methanol. The final volume was made up to 25 ml with methanol to get a working standard stock solution containing 1000

µg/ml of Apremilast, and further dilutions were made by using methanol. From the standard stock solution, appropriate dilutions were made with methanol to obtain a concentration in the range 2-10 µg/ml. The spectrum was recorded, absorbance was measured at 230nm, and a calibration curve was plotted [8].

RESULT AND DISCUSSION:

Physical Characterization: The results showed that the weight variation and thickness of all the batches were lying within limits. Because of variation in the compressional forces, there is a slight variation in the hardness of tablets. As the proportion of polymers increases, the hardness of the tablets was found to increase. The friability loss was found to be within limits in all the formulations. As the amount of polymer increased, the friability of the floating tablet was found to decrease. The evaluation result of different tablet batches was listed in **Table 2**. The thickness of tablets varied between 2.68- 2.97 mm. The weight of all tablets varied between 268 mg and 292 mg with a low standard deviation. The hardness of the tablet ranges from 3.29 to 3.88 Kg/cm^3. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

TABLE 2: CHARACTERIZATION OF EFFERVESCENT FLOATING TABLETS

Formulation Code	Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (nm)	Floating Lag time(s)	Total time (h)	Drug Content (%)
F1	268±2.0	3.29±0.8	0.07±0.3	2.68±0.21	52±0.5	>8	98.09±0.51
F2	291±1.3	3.88±0.5	0.04±0.4	2.70±0.33	79±0.7	>12	99.12±0.32
F3	286±1.5	3.34±0.9	0.13±08	2.52±0.54	66±0.5	>15	99.4±0.88
F4	273±1.4	3.17±0.6	0.11±0.6	2.00±0.32	72±0.7	>18	98.89±0.89
F5	296±2.1	3.65±0.9	0.06±0.5	2.13±0.45	90±0.6	>22	98.63±0.65
F6	279±1.8	3.58±1.0	0.08±0.7	1.98±0.54	88±0.8	>24	99.45±0.45
F7	278±1.6	3.80±0.5	0.05±0.3	2.50±0.45	80±0.6	>20	99.12±0.86

*Data are presented in triplicate as their standard deviation

Analysis of Standard Curve: The UV spectra of Apremilast were scanned in the region between 200-400 nm. The overlay spectra of Apremilast at different concentrations were taken, absorbance maximum at 230 nm, which was selected as the detection wavelength. The response of the Apremilast was found to be linear in the ranges from 2-20 µg/mL with a good correlation coefficient of $r^2 = 0.969$.

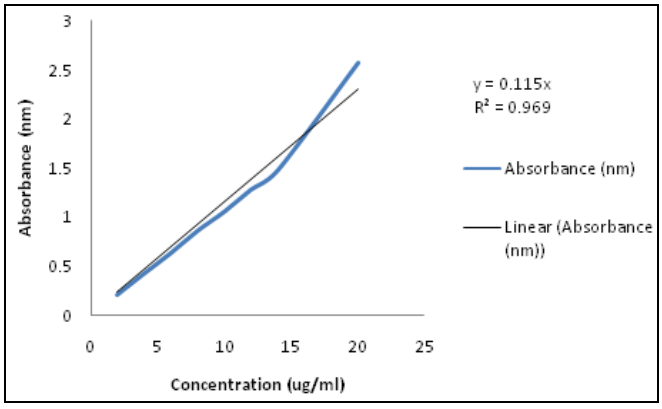

FIG. 1: STANDARD CURVE OF APREMILAST

***In-vitro* Buoyancy Study:** Floating capacity of fabricated tablets was determined in 0.1N HCl, and the results are presented in **Table 2**. The tablets of all batches exhibited floating lag time less than 90s. The tablets of carbopol 934P batches exhibited less time to float as compared to other batches. The combination of three polymers showed no significant effect on floating lag time. Tablets formulated from carbopol 934P (CP934) exhibited a total floating time less than 9 h. This might be due to the high affinity of carbopol toward the water that promotes water penetration in tablet matrices leading to increased density [10, 11]. As the amount of CP934P increased, TFT decreased; this could be due to the high affinity of carbomer towards the water. CP934 has a negative effect on the floating behavior of the delivery system.

This can be explained by the moisture isotherm of CP934. The moisture gain for CP934 is significantly higher compared to moisture gain for HPMC (55% weight gain for CP934 versus ~33% for HPMC at RH of 95%); this results in a dramatic increase in the density of the GFDDS, which, in turn, shows a corresponding decrease in the floating capacity of GFDDS. CP934, a polyacrylic acid-based system, appears to have a much stronger solid water interaction compared with HPMC, a cellulose-based polymer [7]. Further, the investigated gastric floating systems employed sodium bicarbonate

($NaHCO_3$) as a gas-forming agent, which is trapped in a hydrogel matrix (HPMC K_4M and Na alginate). As the amount of HPMC K_4M increased, the total floating time increased this is because of the increased gel strength of the matrices, which prevents the escape of involved CO_2 from the matrices, leading to decreased density.

The *in-vitro* study also revealed that formulations contained less carbopol, but high HPMC K_4 was able to keep the drug buoyant for more than 18 h **Table 2.** A similar result was obtained from the other two batches prepared with a low amount of tragacanth/ Na alginate and high HPMC K4M. They showed TFT more than 24 h. As the amount of Na alginate increased, TFT decreased; this is because of the poor gelling strength of Na alginate compared to HPMC K4M that was previously reported [12, 13].

***In-vitro* Dissolution Studies:** It is evident from the in vitro dissolution studies that tablets of all batches sustained the drug release for more than 12 h **Fig. 2**. However, the drug release rate was dependent on the type and concentration of the collaborated polymers. A higher concentration of HPMC K4M would promote the formation of highly viscous gels upon contact with aqueous fluids. This would promote retardation of the drug release rates. Siepmann and Peppas [14] suggested that drug release from HPMC matrices is sequentially governed as follows: at the initial time, when the tablet contacts the media, water can penetrate into the polymeric complex, and due to water absorption, HPMC will swell and increase the dimensions of the complex. Then, the drug will dissolve and diffuse out due to the concentration of the polymers.

As the concentration of carbopol 934P was increased drug release rate was decreased, this might be due to the higher affinity of carbopol to the water produce layer over tablet, which prevents the dissolution of drug. Therefore, tablets of batch F1 not showed a good dissolution profile. It released 8% drug in first one hour, and about 66% of the drug was released in 12 h, while tablets of batch F4 released the drug in a controlled manner at the minimum level of carbopol content (7.4% w/w of tablet weight). Formulations without CP934 exhibited a much higher burst effect, likely due to the fact that CP934 is a cross-linked polymer with high molecular weight (~2 × 106 Da) and viscosity and when contacted with water, it would swell and hold water inside its microgel network. This particular property may partially be responsible for the retarded release of apremilast from the GFDDS. An initial burst release was found in the first one hour for the batches F2 (30%) and F3 (25%) prepared with tragacanth and alginate in combination with HPMC (1:3 ratio). After 3 h a controlled release pattern was found, and it was sustained upto 24 hrs. Almost 98 and 95 % of the drug was released from the respective formulations in 24 hrs. However, for the formulations contain 1:7 ratio of polymer and HPMC (F4, F5, F6) drug release pattern was slow and decreased. In 24 h 70, 86, and 80% of the drug was released from the respective formulations. Amongst these three formulations, an initial burst release was found for F5 and F6 prepared by tragacanth and SA alginate, respectively. But formulation with CP934 (F4) did not show initial burst release but a steady sustained release pattern like F1. Formulation F7, prepared by a combination of all the four polymers, followed a controlled release of apremilast till 24 h.

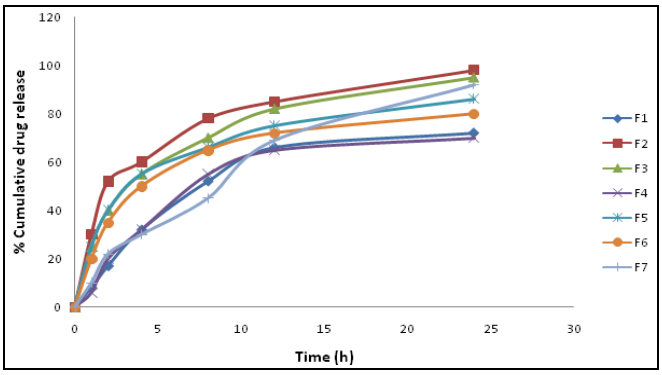

FIG. 2: RELEASE PROFILE OF EFFERVESCENT FLOATING TABLETS CONTAINING APREMILAST

Kinetic Results: To establish the mechanism of drug release, all data from the dissolution studies of floating tablets were obtained and fitted in kinetic models **Table 3**. The correlation coefficient was used as an indicator for best fitting, in which all formulation regression values were between 0.413 to 0.996. By comparing the regression values of different models, the zero-order models were found to be the best model (0.996 for F4 and F7). According to the results, it could be predicted that the drug release model of the prepared tablet was of the diffusion type.

TABLE 3: RESULT OF KINETICS FOR DRUG RELEASE

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)
F1	0.964	0.959	0.970	0.576
F2	0.989	0.818	0.983	0.482
F3	0.992	0.972	0.977	0.564
F4	0.996	0.968	0.988	0.413
F5	0.871	0.974	0.988	0.606
F6	0.989	0.851	0.962	0.558
F7	0.996	0.926	0.954	0.596

CONCLUSION: The research was undertaken with the aim to formulate and evaluate the sustained release effervescent floating tablets of Apremilast. Apremilast is a new drug, and very less number of researches have been carried out with its delivery system. For this purpose, various polymers, such as HPMC K_4M, sodium alginate, CP943, and tragacanth, were tested. From the results obtained, it was found that the formulations showed sustained drug release pattern and total floating time for 24 h. This result complies with the rationale of gastro retentive systems. Comparisons of all release studies showed that the drug release mechanism was diffusion mediated. From this study, it can be concluded that the floating dosage form of this novel drug would be a good option to sustain its biological activity and to reduce its dosage frequency. Further *in vivo* study should be carried out to establish its efficacy.

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CONFLICTS OF INTEREST: There are no conflicts of interest during this research.

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