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Formulation and evaluation of floating tablets of clopidogrel bisulphate

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ABSTRACT

Clopidogrel bisulphate is a novel antiplatelet drug used in the treatment of coronary artery diseases. The main purpose of the present study was to develop a floating and sticking tablets of Clopidogrel bisulphate by using HPMC of different viscosity grades and carbopol 934P to improve the release profile of the drug for 24 hrs and target the drug to stomach via gastric retention with sodium bicarbonate as angas generation agent to promote floating. Pre compression and post compression parameters of floating tablets were evaluated for all the especially density, thickness, *in-vitro* buoyancy, swelling index and dissolution. The floating nature and *in vitro* dissolution studies were carried out in 0.1N Hcl (pH 1.2). All the prepared batches shown good in vitro buoyancy. It had been observed increase the polymer system viscosity ultimately drug release rate was decreased. The drug release from the tablets was Higuchi release model and Non-Fickian transport mechanism.

Keywords: Clopidogrel bisulphate, HPMC, Carbopol 934 P, floating tablets, *in vitro* buoyancy.

INTRODUCTION

Gastric emptying of the dosage forms is a virtually complex process and ability to sustain and control the gastric emptying is a valuable asset for dosage forms, which is situated in the stomach for a prolonged period of time than conventional dosage forms. For better absorption and enhance the bioavailability of dosage forms there are several factors are considered. The main difficulties are the inability of the dosage form to retention in the desired area of the stomach due to gastric emptying.

The drug absorption from gastro intestinal region is a complex procedure and it is subjected to lot of variables when administered orally. It is widely related that the drug absorption in GI tract is related to contact time with the upper part of small intestine due to higher absorption window.[1]

Gastroretentive dosage form retains in the stomach for prolonged period of time and it provide prolongation of the gastric residence time of narrow therapeutic indexed drugs. Prolonged gastric retention enhances the solubility of drugs that are poorly soluble in a higher pH environment and enhances the absorption, bioavailability and reduces the frequency of administration. Gastro retention offered enhanced bioavailability of dosage forms and improves the poor patients.[2,3,4,5]

The gastric retention of drug may be achieved by the mechanisms of mucoadhesivity, floating and addition of swelling agent that delay emptying of dosage form from the stomach their by enhance the therapeutic efficacy by increasing absorption.[6,7,8,9,10] The *In vivo/in vitro* evaluation of floating drug delivery system has been discussed by many researcher to assess the drug release characteristics and benefit of such delivery systems. Recent studies have been reported that offering the improvement of therapeutic efficiencyof such systems for drugs with low bioavailability.[11,12]

Development of oral controlled-release systems has been a difficult for formulation, scientists to formulate the dosage

form because of their inability to restrain and situated the system in the targeted area of the gastrointestinal tract. Controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains preferable. When the drug is formulated with a gel forming polymer such as semisynthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than one. It then remains buoyant and floats in the gastric fluid, affecting a prolonged gastric residence time. This floating dosage form is well known as a hydro dynamically balanced system.[13,14]

It has been recommended that an active material should be designed in the form of an gastro retentive system to enhance the bioavailability of dissolution and/or stability problem in the higher pH, drug locally act in the stomach, drug highly absorbed in the stomach and/or proximal of the small intestine.[15] Floating tablets, mucoadhesive system capsules, beads, microspheres, in situ gel and chambers have been reported in literature.[16]

Floating drug delivery systems has the density less than the gastric fluids (<1.004 g/cm^3 due to added low density polymer and thus remain floating in the gastric region for a longer period of time (>12 hrs).[17] System is floating on the gastric region and the drug is released slowly at a desired rate in sustained manner. Finally residual system is emptied from the body through elimination.

This results in an increase in the gastric retention time of narrow therapeutic indexed drug and a better control of drug fluctuations in the plasma. Floating tablets are matrix types of systems formulated with the help of low density and swellable polymers such as methylcellulose and chitosan with various effervescent compounds like sodium bicarbonate, tartaric acid and citric acid. Formulated dosage form when in contact with the stomach contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides floatation in to the stomach.

Floating systems provide the gastric retentive behavior that provide enhanced drug absorption, due to increased gastric retention time and solution form entered in to absorption site (upper small intestine), sustained delivery of drugs, drugs acting specifically in the stomach for treating gastrointestinal disorders such as gastro-esophageal reflux, simple and conventional equipment for manufacture and ease of administration and better patient compliance.

Clopidogrel has high therapeutic value in the prevention and treatment of pathologies induced by platelet aggregation. However, because clopidogrel is practically insoluble in water, significant bioavailability can be problematic. Clopidogrel bisulphate has a short biological half-life of 7 hrs and absolute bioavailability was only 50%, which is absorbed only in the stomach. It has been found that conventional dose of 75mg can inhibit platelet aggression up to 7 hrs but not up to 24 hrs.

In the present study gastro retentive drug delivery (floating tablets) of Clopidogrel bisulphate were prepared with effervescent agent by using different grades of HPMC K4M and HPMC K100LV as a semi synthetic and Carbopol 934P as a synthetic polymer. The present investigation aims to develop floating tablets of Clopidogrel bisulphate with a view of prolonging gastric residence time with a controlled release mechanism.

MATERIALS AND METHODS

Materials

Clopidogrel bisulphate was obtained as a gift sample from Intas pharma, Ahmedabad., India. HPMC K4M, K100LV and Carbopol 934 P were obtained from the Colorcon Asia Pvt. Ltd, India. All the polymers received were of pharmaceutical grade. Other materials and solvents used were of analytical grade. All the studies were carried in HPLC grade water.

Formulation of Floating Tablets

Floating matrix tablets of Clopidogrel bisulphate were prepared by using wet granulation method with different concentrations of HPMC K4M and K100LV, Carbopol 934p with sodium bicarbonate.

All the ingredients were mixed together using mortar in ascending order except magnesium stearate and talc. Blended mixture was passed through sieve no.60 to get uniformity distribution and coherent mass prepared with ethanolic PVP K 30 as a granulating agent and passed through sieve no.16 to make granules. The prepared granules dried in an oven for 60^{o}C about 30 minutes.

The dried granules were passed through the suitable sieve to get uniform size. Finally granules mixed with sodium bicarbonate as an effervescent agent and lubricated with magnesium stearate and talc. It was compressed into tablets by rotary tablet punching machine. Prior to compression, granules were evaluated for their flow and compressibility characteristics.[19, 20,21] The composition of floating tablets of Clopidogrel bisulphate was shown in Table 1

Table 1: Composition of floating tablets of Clopidogrel bisulphate

F. Code	Drug (mg)	HPMCK4M (mg)	HPMCK100LV (mg)	Carbopol l934p (mg)	SodiumBicarbonate (mg)	Talc (mg)	Magnesium stearate (mg)	PVP-K30 (mg)
F1	298	178	0	0	50	5	5	5
F2	298	178	0	60	50	5	5	5
F3	298	89	89	0	50	5	5	5
F4	298	89	89	60	50	5	5	5
F5	298	0	178	0	50	5	5	5
F6	298	0	178	60	50	5	5	5

Evaluation of granules properties

The angle of repose, Carr index and Hausner ratio was performed to determine the flow properties.[22] For determination of angle of repose (θ), the granules were passed through the funnel, which was fixed at a particular position. It was calculate by using the formula

$\tan^{-1}h/r$.

Granules were poured gently into a graduated cylinder. Initial weight of the cylinder with granules volume was calculated. The cylinder was tapped until the time no more decrease volume. Bulk density, tapped density, Hausner ratio and Carr's index were calculated according to the equations given below:

Bulk density = Mass / Untappedvolume

Tapped density = Mass / Tapped volume

Hausner ratio = Tapped density / Bulk density

Carr's Index = (Tapped density – Bulk density) x 100 / Tapped density

Evaluation of tablets properties

The prepared floating tablets were evaluated for their physical characteristics. The thickness and diameter of tablets were measured by calibrated dial caliper. Monsanto hardness tester was used to determine the tablet withstanding.[23] The friability of tablets was determined by using the Roche friabilator. The uniformity of prepared floating tablets were evaluated by using 20 tablets.[24]

The drug content was determined by using 20 tablets from each batch were weighed and powdered. Equivalent weight of drug was dissolved in 50 ml of 0.1 N Hcl and sonicated for 30 min and filtered through membrane filter, diluted suitably with buffer and the absorbance was measured spectrophotometrically at 240nm. Tablet density was determined by using 0.1N Hcl. When it contacts the test medium, tablet expanded and liberate CO_2 gas from sodium bicarbonate. The density was determined using following formula.

Volume of tablet = $\pi r^2 h$

Density = m/v

The buoyancy of the floating tablet was determined when it placed in a beaker containing 0.1N Hcl. The time required for the tablets to float and duration of time that constantly remained on the surface of the medium was determined.[25]

The swelling ability of floating tablets was performed when the dosage form placed in in 0.1 N HCL at $37^0C \pm 0.5^0C$. Tablets were taken out carefully in specific time period and find out initial weight and final weight after remove the water present on the surface. Swelling ability of tablet were expressed in terms of percentage water uptake (WU %) between swelling index and time.[26]

WU % =100×(Wet weight of tablet–Dry weight of tablet/ Dry weight of tablet)

The dissolution behaviors of Clopidogrel bisulphate floating tablets were determined by using type-II Dissolution apparatus. Test was performed with 900ml of 0.1N Hcl (pH 1.2) as a medium and the temperature at $37^0C \pm 0.5^0C$ with 100 rpm. 1ml of sample was withdrawn at specific time intervals and analyzed spectrophotometrically at 240nm.[27, 28]

Kinetics of drug release

To determine the drug release mechanism from the dosage form were fitted with kinetic models like zero order, first order, Higuchi's, Peppas and correlation coefficient (r) values were calculated by regression analysis.

Stability studies

Accelerated stability studies were performed with optimized formulation (F2) according to ICH guidelines.[29] It was kept in the humidity chamber at 45°C and 75% RH for 3 months. The stability of dosage form was analyzed especially drug content, in vitro dissolution, floating behavior and it was compared with the same parameters in before the study

RESULTS AND DISCUSSION

It was observed from the study approached drug delivery provide low density than that of gastric fluids and thus remained floating in the stomach for a prolonged period of time and release the drug slowly from the dosage form at a desired rate due to added release retarding agent. Thus results in minimize fluctuations in the systemic circulation their by enhance absorption and bioavailability.

Flow Properties of Granules

Precompression parameters were performed to determine their suitability to tablet (Table 2). The angle of repose of all the formulations within the range of 28.06^0 to 31.32^0 and indicates granules were sufficient flow properties. The Bulk density and Tapped density ranged from 0.34±0.044 to 0.35±0.045 and 0.40 ± 0.07 to 0.42 ± 0.09 g/cm^3 respectively. Car's index was found to be between 12.23±0.6 to 17.48±0.6. The Hausner ratio ranged from 1.13±0.04 to 1.19±0.06. All the precompression parameters showed good flow characteristics.

Table 2: Physical characteristics of clopidogrel bisulphate granules

F.Code	Angle of repose (θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio
F1	28.06± 0.31	0.35±0.045	0.42 ± 0.09	15.60±0.2	1.18±0.02
F2	27.58± 0.15	0.35±0.045	0.40 ± 0.07	12.23±0.6	1.13±0.04
F3	28.44± 0.11	0.34±0.044	0.40 ± 0.09	12.58±0.8	1.14±0.08
F4	28.36± 0.13	0.35±0.045	0.42 ± 0.04	16.19±0.1	1.19±0.06
F5	28.52± 0.19	0.34±0.044	0.42± 0.01	17.48±0.6	1.18±0.08
F6	29.32± 0.19	0.35±0.045	0.41 ± 0.04	14.48±0.8	1.16±0.09

Evaluation of Floating Tablets

Post compression parameters were performed especially floating lag time, total floating time was performed and the results were shown in Table 3.

Table3: Evaluation of clopidogrel bisulphate floating Tablets

F.Code	*Diameter (mm)	*Thickness(mm)	Hardness (Kg/Cm^2)	Friability (%)	*Weight Variation (mg)	*Drug Content Uniformity (mg)
F1	13.09 ±0.040	5.2±0.20	5.7 ± 0.54	0.72	534.43±4.46	99.78± 0.56
F2	13.08 ±0.006	6.32 ±0.22	6.4 ±0 .75	0.37	593.81±4.02	99.70± 0.41
F3	13.09 ±0.067	5.28 ± 0.17	4.0 ±0.45	0.40	533.14±3.89	99.51± 0.72
F4	13.08 ±0.070	6.16±0.054	5.96 ±0.25	0.46	592.53±3.99	99.94± 0.19
F5	13.08 ±0.056	5.34±0.054	5.32±0.13	0.61	534.08±3.49	99.42± 0.35
F6	13.08 ±0.056	6.24±0.054	6.38±0.13	0.67	594.53±2.99	98.91± 0.35

Microscopic examinations of tablets from F1 to F6 were found to be circular shape with no cracks. Uniform thickness of tablets was observed in F1 to F6 formulations and it found to be with in the acceptable range(4.00mm to 6.38mm). The diameter and hardness of the tablets ranges between 13.08mm to 13.09mm and 5.2 to 6.32 kg/cm^2 respectively. The value of % Friability of each batch was found to be in the range of 0.37 to 0.72 and it was with in accepted criteria for all the formulations..

The weight of the tablet varied between 533.14±3.89 mg to 594.53±2.99mg for different formulations with low standard deviation values. Weight variation test was performed as per the USP monograph and it was observed with in the limit. The percentage of drug content for F1 to F6 was found to be 98.91% to 99.94 % indicating good content uniformity of clopidogrel bisulphate.

In vitro buoyancy studies was performed and the Floating lag time was in range of 70sec to 90sec results shown in photographs (Fig.1and Table.4). From the results it was observed that the formulation F2 with HPMC K4M showed satisfactory floating lag time (70 sec) while the formulation containing carbopol 934P and HPMC K4M and K 100LV showed highest floating lag time (90 sec).

Table 4: Tablet Density, Buoyancy Lag Time and Total Floating Time of clopidogrel bisulphate floating tablets

F.Code	Tablet Density (g/cc)	Buoyancy Lag Time (Sec)	Total Floating Time (hrs)
F1	0.82	78	22
F2	0.77	70	24
F3	0.87	80	22
F4	0.98	90	23
F5	0.90	83	21
F6	0.92	85	21

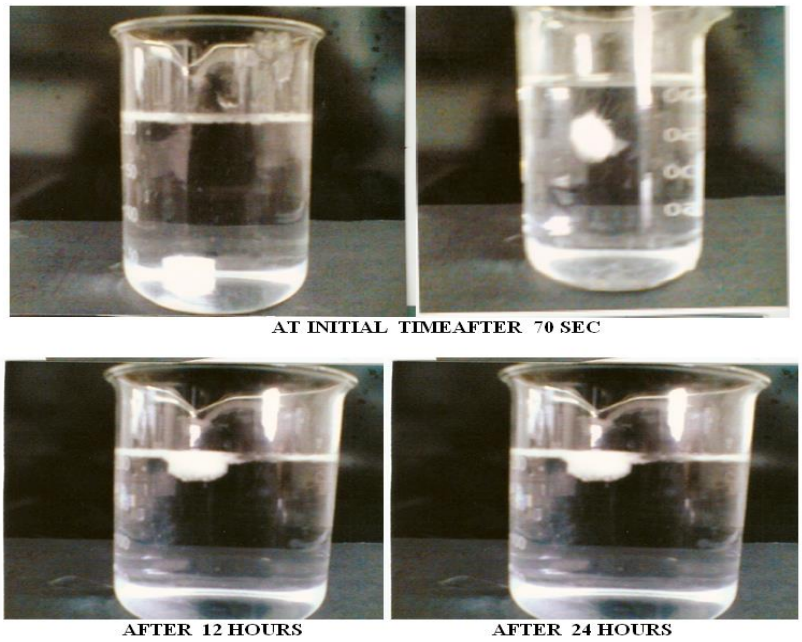

Fig 1: Photograph of *in vitro* buoyancy study of F2 batch

Swelling index was determined for all batches (F1 to F6) up to 5 hrs. The results were plotted in Fig.2. From the results it was observed that swelling increases as the time increases because the polymer gradually absorb water due to hydrophilic of polymer. In the present study, the less swelling index was found for tablets of batch F4 containing Carbopol 934P having nominal viscosity of 39,400 cps. Based on the results it was observed that linear relationship exists between swelling and the viscosity.

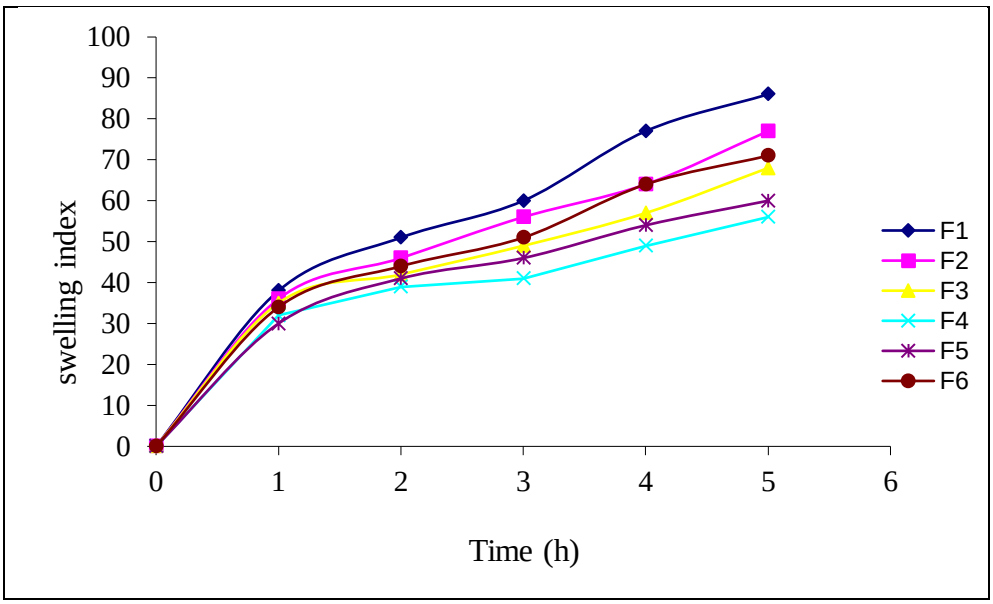

Fig 2: Swelling index of formulations F1-F6

There has been considerable interest in using different grades of HPMC in controlled release drug delivery system due to their hydrophilic nature and fast hydration. The *in vitro* studies showed the cumulative percentage of 96.05%,95.56 %, 94.35 %, 92.69%, 97.51% and 95.57% in 24 hours for the formulations F1, F2, F3, F4,F5 and F6 respectively. From the study F2 had better sustained release than the other formulations and considered as an optimized one. The comparative graphs were shown in Fig.3.

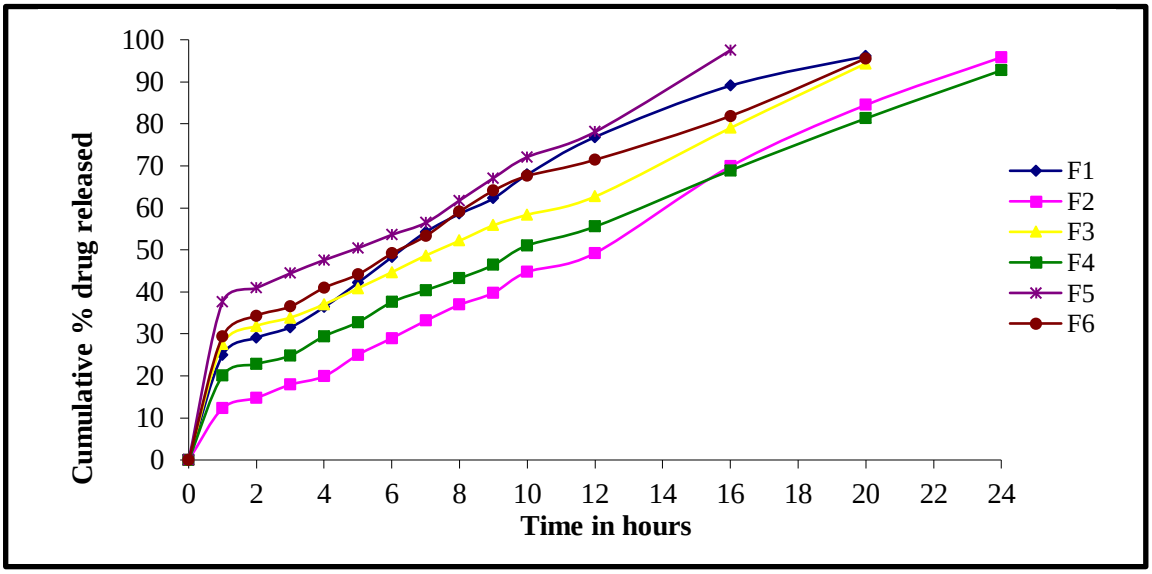

Fig 3: Comparative in vitro dissolution profiles of formulation F1-F6

The release profiles appear to be initial burst effect followed by slower release in the second phase due to added polymer. This biphasic pattern of drug release is characteristic of matrix diffusion kinetics.[30] The viscosity of HPMC K4M, K100LV is 4000 and 100 cps respectively. In this study the viscosity of a mixture of HPMC K4M and K100LV is determined to be 780 cps. Polymeric system with low viscosity polymer (HPMC K100LV) provides a faster initial burst effect.

Incorporation of carbopol 934P decreases the release of clopidogrel from the gastric drug delivery system. Carbopol is insoluble in water and 0.1N Hcl (pH=1.2). Formulation without carbopol showed a much higher burst effect, likely due to the fact that carbopol is a cross-linked polymer with high molecular weight when contact with water swell and hold water inside the network. These may partially be responsible for the retarded release of clopidogrel from the gastro floating drug delivery systems.[33]

Initial burst effect decreased and the final release increased with the Carbopol 934p concentration. This was because of the fact that Carbopol934p which has pKa of 6.0, remains unionized in the acidic environment of dissolution medium. Therefore the release rate was controlled by HPMC-K15M and PVP-K30 with the particles of Carbopol 934P acting as a physical barrier to drug release.[34]

Kinetic models were performed to determine the release behaviors with first order, zero order, Higuchi and Korsmeyer and Peppas.[35,36,37] The release exponent values thus obtained were from 0.50 to 0.79. Based on these values formulations F1 to F6 exhibited non-fickian transport. The drug release was diffusion controlled as the plot of Higuchi's model was found to be linear (r>0.9291).

The formulations F1, F5 and F6 showed higher R^2 values for first order plot indicating that the drug release from these formulations was concentration dependent and followed first order kinetics. While the formulations F2, F3 and F4 showed higher R^2 values for zero order plot indicating that drug release followed zero order kinetics and drug release from these floating tablets were by both diffusion and erosion (Table .5).

Table 5: Kinetics of *In Vitro* Clopidogrel bisulphate Release from Floating Tablets

F.Code	Zero order		First order		Higuchi	Peppa's	Mechanism of drug release
	R^2	K_0	R^2	K_1	R^2	n	
F1	0.9344	4.45	0.9507	0.1467	0.9803	0.5752	First order non fickian difussion
F2	0.9936	3.87	0.8974	0.1181	0.9279	0.7929	Zero order non fickian difussion
F3	0.9316	3.87	0.8753	0.1142	0.9528	0.5784	Zero order non fickian difussion
F4	0.9692	3.42	0.9253	0.0918	0.9697	0.580	Zero order non fickian difussion
F5	0.8785	4.74	0.9773	0.1543	0.9291	0.5091	First order non fickian difussion
F6	0.9068	4.00	0.9122	0.1266	0.9794	0.5709	First order non fickian difussion

In view of the potential utility of the formulation, stability studies were carried out on F2 formulations at 45°C and 75% RH for three months to assess their long-term stability. The protocols of stability studies were incompliance with the guidelines in the WHO document for stability testing of products intended for the global market. After storage, the formulation was subjected to a drug assay, floating behavior and invitro dissolution studies. The stability studies indicate that did not show any chances in the drug content, floating behavior and drug release over the period of stability studies.

CONCLUSION

The present study was concluded that the developed Clopidogrel bisulphate floating tablets following oral administration improves the absorption and bioavailability. Based on the study it was concluded that the delivery of Clopidogrel bisulphate from the dosage form was sustained due to added low density polymer and provide enhanced absorption and oral bioavailability. However further radiographic and pharmacokinetic studies are need to performed to confirm the presence of dosage form and enhancement of bioavailability in systemic circulation in animal/healthy volunteers.

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