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Development and Evaluation of Prasugrel Hydrochloride Floating Tablets

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ABSTRACT

The objective of the present work was to formulate and characterize floating drug delivery system of Prasugrel hydrochloride that releases the drug slowly up to 8 h in order to minimize its potential side effect bleeding and to improve the bioavailability with enhance patient compliance. Prasugrel floating tablets were prepared by effervescent approach with melt granulation and direct compression techniques alone and in combination using Hydroxypropyl methylcellulose (HPMC) K100M and Compritol 888 ATO at different concentrations (20%, 30% and 40% w/w) alone and in combination. Sodium bicarbonate at concentration 10% w/w was optimized as gas generating floating agent. Evaluations were carried out on physical parameters, floating behavior and influence of type of polymer on drug release rate. All the formulations were subjected to various quality control and *in-vitro* dissolution studies and corresponding dissolution data were fitted to popular release kinetic equations in order to evaluate release mechanisms and kinetics. All the prasugrel floating tablet formulations followed zero order kinetics. As per Korsmeyer-Peppas equation, the release exponent "n" ranged 0.550-0.776 indicating that drug release from all the formulations was by non-Fickian diffusion mechanism. Based on the results, prasugrel hydrochloride floating tablets prepared by employing combination of 15% w/w HPMC K100M and 15% w/w Compritol 888 ATO offered desired in-vitro floating time and drug dissolution profile.

Keywords: Prasugrel hydrochloride, floating tablets, side effects, bioavailability, sustained release.

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INTRODUCTION

Oral controlled drug delivery systems with ability to retain in gastric region for several hours and prolong the gastric residence time of drug are called gastro-retentive drug delivery system (GRDDS). These systems offer increased therapeutic efficacy of drugs by continuously releasing the drug for an extended period at the desired rate with targeted delivery in the stomach that improves drug absorption with improved patient compliance [1, 2].

Solubility of drugs those are less soluble in an elevated pH environment of the intestine can be improved by prolonging the gastric retention to increase bioavailability. Oral sustained-controlled release formulations with additional gastric retention property have a lower level of side effects by releasing the drug slowly in the stomach for an extended period of time and provide their therapeutic effects with better control of fluctuations in plasma drug concentration [3, 4].

The controlled gastric retention of the formulation may be achieved by the various approaches such as floatation, mucoadhesion, sedimentation, expansion and modified shape systems [3]. Among the various approaches, floating drug delivery system (FDDS) is one of the potential approach for prolonged gastric retention to improve solubility, reduces drug waste thereby improves bioavailability for the drugs that are less soluble in a high pH environment. FDDS offer the most effective and rational protection against early and random gastric emptying compared to the other methods proposed for prolonging the gastric residence time of solid dosage forms. However the gastric retention is influenced by many factors such as level of fluids in the stomach, gastric mobility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted [5, 6].

Prasugrel is a novel third-generation oral thienopyridine mainly used to reduce the risk of thrombotic cardiovascular events such as stent thrombosis or myocardial infarctions in patients with acute coronary syndrome (ACS). Prasugrel is a potent prodrug and inhibits platelet aggregation by an irreversible blockade of platelet adenosine diphosphate (ADP) P2Y12 receptor. Prasugrel is a BCS class II drug and exhibits pH dependent solubility and it is very soluble at low pH conditions. After oral adstration, prasugrel is rapidly absorbed and hydrolyzed by esterases located in the intestine and blood, to a thiolactone intermediate metabolite

which subsequently activated by cytochrome P450 (CYP) dependent step (predominantly CYP3A and CYP2B6) to sulfhydryl active metabolite. The active metabolite binds irreversibly to the platelet ADP P2Y12 receptor and inhibits platelet activation and aggregation. The active metabolite of prasugrel has an elimination half-life of 7 hours with an approximate bioavailability of 80%. It is more potent and has lower inter-individual variability in platelet response, and faster onset of activity compared with Clopidogrel. However, the potential side effect of the drug is bleeding, particularly gastrointestinal bleeding [7, 8].

A sustained release Prasugrel formulation that releases the drug slowly at the desired rate to avoid peak levels of the active metabolite for maintenance treatment may be desired mainly to minimize its potential side effect bleeding and to improve the bioavailability with enhance patient compliance. Further, hydrophilic polymer, HPMC K100M and hydrophobic polymer, Compritol 888 ATO have been reported to improve stability of drug in the formulations [9]. Therefore, an attempt has been made to develop gastro retentive floating tablets of prasugrel hydrochloride that release the drug locally where it is more soluble or absorbent in a sustained form that releases the drug slowly up to 8 h to minimize the potential side effect, bleeding and to improve the bioavailability by using the polymers HPMC K100M and Compritol 888 ATO.

MATERIALS AND METHODS

Materials

Prasugrel hydrochloride (Gift sample from MSN Laboratories, Hyderabad), Compritol ATO 888, HPMC K100M, Sodium bicarbonate, Microcrystalline cellulose, Magnesium stearate, Talc and all other ingredients are of laboratory grade.

Drug-excipient compatibility studies

Drug-excipient compatibility studies were performed for pure drug and physical mixture of optimized formulation of drug with polymers. The physical mixture samples were subjected to Fourier Transform infrared (FT-IR) studies. Spectra of drug and optimized formulation were taken and analyzed for any major interaction due to presence of polymers and other ingredients.

Micromeritic properties

The pure drug and prepared formulation powder blends were evaluated for micromeritic properties such as angle of repose (θ), bulk density (BD), tapped density (TD), Carr's index (CI) and Hausner's ratio (HR).

Angle of repose was determined by fixed funnel method by placing ten grams of powder blend in a cotton plugged glass funnel and then allowed to flow through the funnel orifice by removing the cotton plug. The height of the heap (h) formed and the radius of the heap (r) was noted. The angle of repose was calculated using the formula $\theta = \text{Tan}^{-1}(h/r)$.

BD and TD of 10 g of the powder blend were determined by using 50 ml graduated cylinder. Based on the initial volume occupied by the blend, BD was calculated in g/ml. The cylinder containing the blend was tapped until constant volume was obtained using bulk density apparatus from a height of 2 cm and the TD was calculated in g/ml. The percentage compressibility (CI) was calculated from the difference between the TD and the BD divided by the TD and the ratio expressed as a percentage. The HR is the ratio between the TD and BD [10].

Determination of lambda (λ) max by Ultraviolet–visible (UV) spectroscopy

The stock solution (1000 µg/ml) of prasugrel hydrochloride was prepared in 0.1N hydrochloric acid (HCl). This solution was appropriately diluted with 0.1N HCl to obtain a concentration of 10 µg/ ml. The UV spectrum was recorded in the range of 200-400 nm on double beam UV spectrophotometer. The spectrum and wavelength of maximum absorption were recorded.

Preparation of standard curve

The stock solution (1000 µg/ml) of prasugrel hydrochloride was prepared in 0.1 N HCl and from this 10 ml of solution was taken and the volume was adjusted to 100 ml with 0.1N hydrochloric acid (100µg/ml). The above solution was suitably diluted with 0.1N hydrochloric acid to get the series of dilutions containing 10, 20, 30, 40, 50µg/ml of prasugrel hydrochloride solutions. The absorbance of these solutions were measured at 258 nm against blank i.e. 0.1 N HCl. The coefficient of correlation and equation for the line are determined.

Preparation of prasugrel hydrochloride floating tablets

The prasugrel hydrochloride floating matrix tablets were prepared by effervescent approach with hydrophilic polymer, HPMC K100M and hydrophobic polymer, Compritol 888 ATO at varying concentrations (20%, 30%, 40% w/w) as shown in the Table 1 along with all other excipients. Sodium bicarbonate at concentration 10% w/w was optimized as gas generating floating agent and microcrystalline cellulose (MCC) was used as diluents. All the ingredients were passed through sieve 44. The formulation F1 to F3 were prepared by melt granulation method wherein Compritol 888 ATO was melted in a porcelain dish on hot plate and weighed drug was added to it. The resultant mixture was allowed to solidify at room temperature and passed through sieve 30 to form granules for compression. The formulations F4 to F6 were prepared by direct compression method using HPMC K100M. The formulations F7 to F9 were prepared by combination of Compritol 888 ATO and HPMC K100M wherein melt granulation was employed to incorporate the drug into Compritol polymer matrix then followed by direct compression method using HPMC K100M. The required quantities of other ingredients were added to the blend and mixed geometrically. The blend was lubricated with magnesium stearate and talc. The final blend was compressed into tablets using 5 mm size round concave single tip punch on multi station rotary compression machine.

Table 1: Composition of prasugrel hydrochloride floating tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Prasugrel Hydrochloride	10.98	10.98	10.98	10.98	10.98	10.98	10.98	10.98	10.98
Sodium Bicarbonate	5	5	5	5	5	5	5	5	5
Compritol ATO 888	10	15	20	0	0	0	5	7.5	10
HPMC K100M	0	0	0	10	15	20	5	7.5	10
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MCC	23.02	18.02	13.02	23.02	18.02	13.02	23.02	18.02	13.02
Total weight	50	50	50	50	50	50	50	50	50

Evaluation of physical parameters of floating matrix tablets [5]

Tablet weight uniformity:

A total of twenty (20) tablets were weighed individually, average weight was calculated and the individual tablet weights were compared with the average weight. The tablets will meet the USP test if not more than two tablets are outside the percentage limit (± 10%) and if no tablets differ by more than two times the percentage limit.

Thickness test:

The thickness of three (3) randomly selected tablets from each formulation was measured with a Vernier calliper scale and their thickness was recorded and the average thickness along with the standard deviation is reported.

Hardness test:

Hardness of the tablet is the force applied across the diameter of the tablet to break the tablet. The hardness of three (3) tablets was determined using Monsanto hardness tester and the average is calculated and reported with the standard deviation and expressed in kg/cm^2.

Friability test:

Six tablets (6) were initially weighed (W_0) and transferred into Roche friabilator and the friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions and the tablets were again weighed (W). The percentage friability (%F) was then calculated by the following equation: $\%F = (1-W/W_0) \times 100$ and %F of tablets <1% are considered as acceptable.

Drug content:

A total of three (3) tablets were weighed and powdered. The quantity of powder equivalent to 10.98 mg of prasugrel hydrochloride was dissolved in 100 ml of 0.1 N HCl. Then the solution was filtered, diluted suitably and analyzed using an UV spectrophotometer at 258 nm.

In-vitro buoyancy studies

The in-vitro buoyancy was determined by floating lag-time method. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the total floating time respectively.

In vitro drug release studies

The in-vitro drug release study was performed for all the formulations using USP Type II dissolution apparatus at 75 rpm for 8 hours. Tablets were placed in 900 ml of dissolution medium i.e. 0.1 N HCl maintained at 37± 0.5°C. Aliquots of 5 ml were withdrawn at specified intervals of time, filtered and replenished with 5 ml fresh dissolution medium. Sample's absorbance was measured at λ_{max} 258 nm using UV spectrophotometer. The studies were performed in triplicate. The cumulative percentage drug released was calculated at each time interval using slope obtained from the standard curve.

Kinetic modeling of drug release: The data obtained from in vitro drug release studies were fitted to the following kinetic equations:

Zero order release kinetics equation: $Qt = Q_0 + K_0 t$; Where Qt is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time and graph was plotted for cumulative amount of drug released vs. time.

First order release kinetics equation: $\text{Log } C = \log C_0 - Kt/2.303$; where C_0 is the initial concentration of drug, k is the first order rate constant and t is the time and graph was plotted for log cumulative percentage of drug remaining vs. time.

Higuchi equation defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time and can be expressed as $Q = K_H t^{1/2}$; Where, K_H is the release rate constant. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent and graph was plotted for cumulative percentage of drug remaining vs. Square root time.

In order to define a model, which would represent a better fit for the formulation, dissolution data were further analyzed by Peppas and Korsmeyer equation: $Mt/M\infty = Ktn$; Where $Mt/M\infty$ is a fraction of drug released at time t, K is the release rate constant and n is the release exponent. In this model, the value of n characterizes the release mechanism of drug. For the case of cylindrical tablets, $n = 0.45$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxation) transport, and $n > 0.89$ to super Case II transport. Graph was plotted for log cumulative percentage of drug remaining vs. log time and first 60% drug release data were fitted in Peppas and Korsmeyer model.

RESULTS AND DISCUSSION

Calibration curve of prasugrel hydrochloride

An UV spectro-photometric method was used for estimation of prasugrel hydrochloride. A solution of prasugrel

hydrochloride (10µg/mL) was scanned in the wavelength range of 200-400 nm and found to have maximum absorption (λ_{max}) at 258 nm (Fig. 1) [11]. The standard plot of prasugrel hydrochloride was prepared in 0.1 N HCl (pH 1.2) and showed good linearity with R^2 value of 0.9998 (Fig. 2).

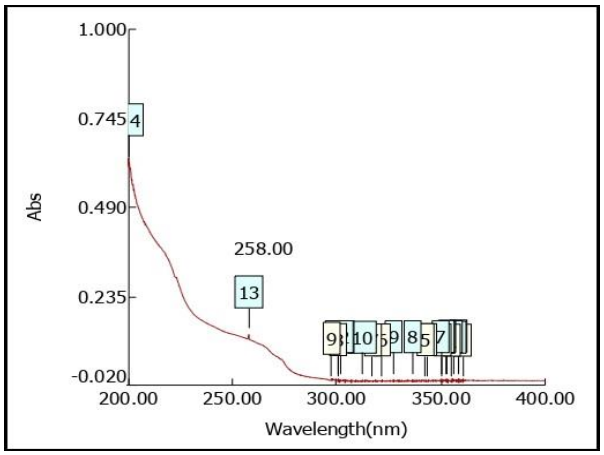

Fig. 1: UV scan spectrum curve of prasugrel hydrochloride

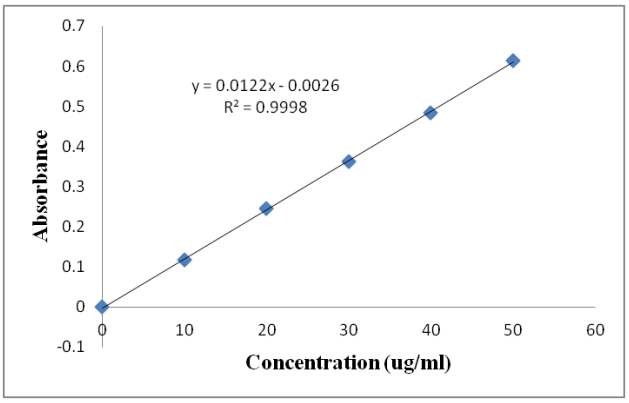

Fig. 2: Calibration curve of prasugrel hydrochloride at 258 nm

Drug-excipient compatibility studies [11]

The FT-IR spectrum of pure drug was compared with optimized formulation. The characteristic peaks which are observed for the pure drug in the FTIR spectra (Fig. 3a) were also observed for optimized formulation (Fig. 3b) with little shifting of peaks suggesting that there is no interaction between drug and excipients (Table 2).

Table 2: The Assignments of the FT-IR Absorption characteristic Bands of Prasugrel HCl and optimized formulation.

Functional group Assignment	Prasugrel Hydrochloride (Wavenumber (cm^{-1}))	Optimized formulation (F8) (Wavenumber (cm^{-1}))
($-NH^+$) stretching	2435.11	2435.17
(C=O); carboxylate stretching	1757.60	1757.17
(C=O); cyclopropylcarbonyl stretching	1688.72	1688.84
(C-H) bending	1492.64	1492.29
(C-F) stretching	1406.66	1406.61
(C-N) stretching	1352.61, 1325.02	1352.65, 1324.40
(C-O) stretching	1212.97, 1233.02	1213.31, 1233.36
(C-S) stretching	824.01, 757.36	824.25, 757.64

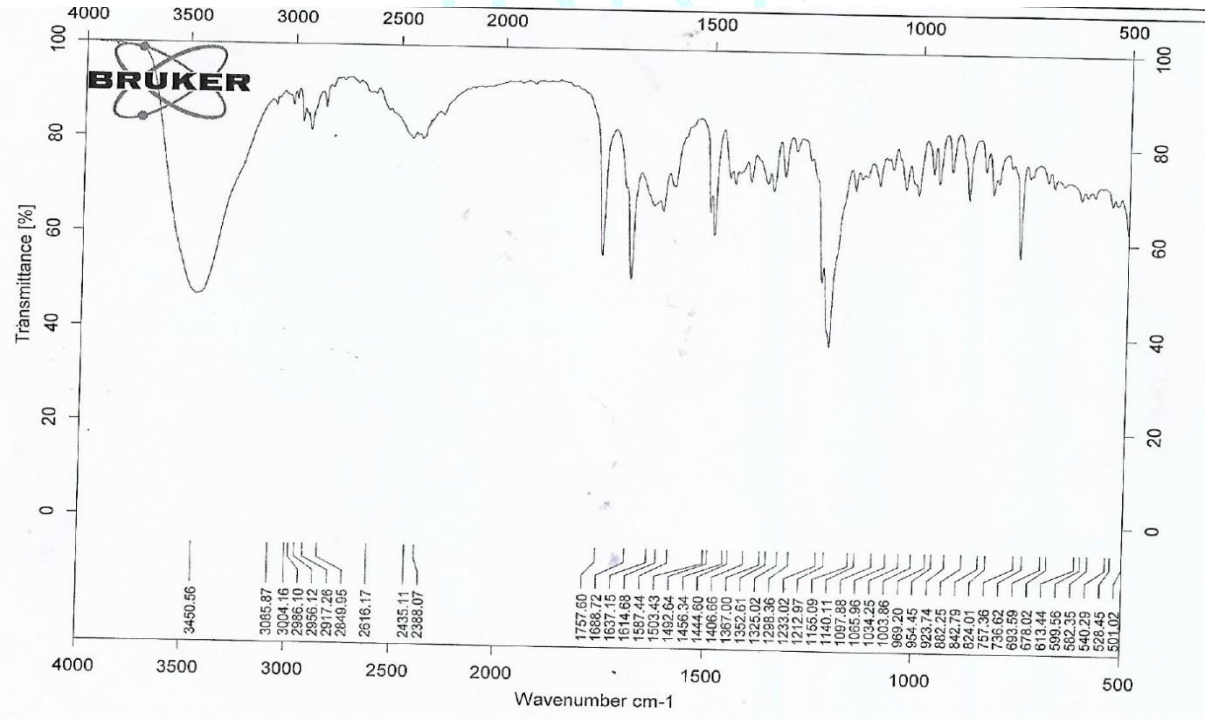

Fig. 3a: FT-IR spectra of pure prasugrel hydrochloride

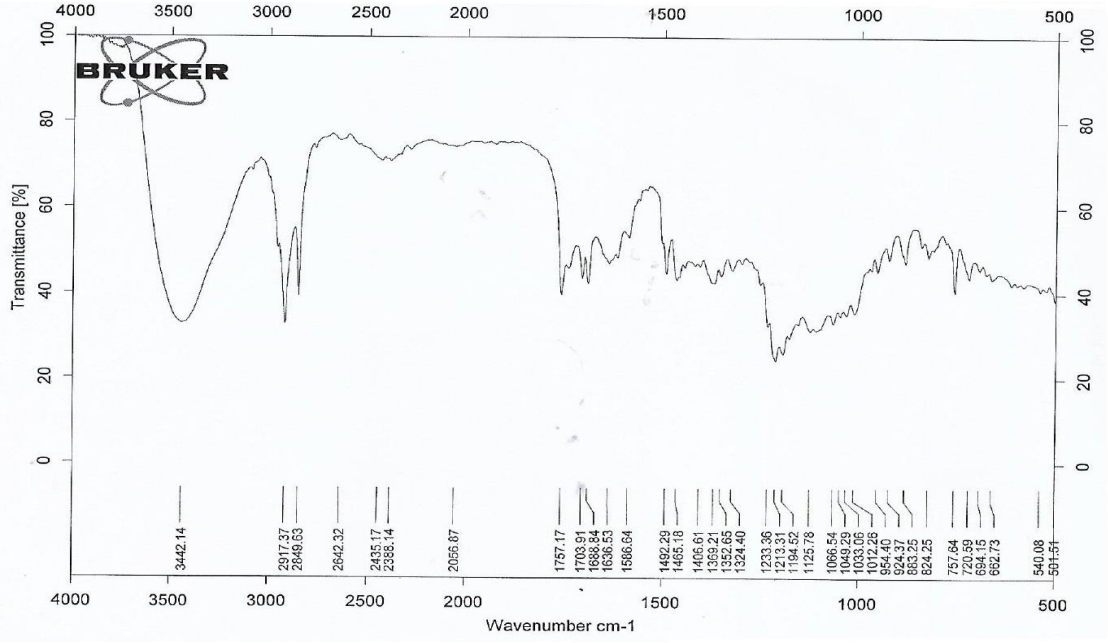

Fig. 3b: FT-IR spectra of physical mixture of prasugrel hydrochloride formulation F8 blend with HPMC K100M and Compritol 888 ATO.

Micromeritic properties

The micromeritic properties of prasugrel hydrochloride pure drug showed passable flow properties and the flow properties of the formulation powder blend with diluent, glidant and lubricant showed fair flow properties as it is observed from the values of CI and angle of repose. The micromeritic properties of drug and optimized bath of the formulation were shown in Table 3.

Table 3: Micromeritic properties of drug and optimized batch of prasugrel blend

Parameters	Pure drug	F8
Angle of repose	42.61	33.42
Carr's index (%)	22.44	18.36
Hausner's ratio	1.28	1.22

Evaluation of physical parameters of floating tablets

All the prepared tablet formulations were tested as per official methods for various physical parameters such as thickness, weight variation, hardness and friability. Results of the physical tests were shown in Table 4. All the formulation of tablets showed uniform thickness. The hardness of all the formulations was found to be in the range of 4-5 kg/cm². The weight variation of tablet formulations was found to be within USP specification. The friability of all the tablet formulations was found to be <1% which is an indication of satisfactory mechanical resistance of the tablets. The tablet formulations showed no evidence of capping, cracking, cleavage or breaking after being removed from the friabilator. The drug content of the formulations was in between 98% and 102%. Hence, all the prasugrel floating tablet formulations were of good quality and fulfilled the official pharmacopoeial specifications with regard to drug content, hardness and friability.

Table 4: Physical characteristics of prasugrel floating tablet formulations

Formulation code	Thickness(mm)-(n=3)	Weight Variation (n=20)	Hardness (kg/cm2) (n=3)	Friability (%) (n=6)	Assay (%) (n=3)
F1	2.65±0.02	51.18±1.10	4.16±0.28	0.14	100.50±1.32
F2	2.63±0.02	50.11±1.06	4.50±0.50	0.13	99.93±1.40
F3	2.62±0.01	49.94±1.15	4.33±0.28	0.14	100.36±1.92
F4	2.61±0.02	51.17±1.12	4.66±0.28	0.17	101.00±0.65
F5	2.61±0.02	50.12±1.11	4.66±0.28	0.16	98.73±0.60
F6	2.62±0.02	49.22±1.03	4.66±0.57	0.18	101.30±0.75
F7	2.61±0.01	49.29±1.15	4.33±0.28	0.19	99.46±1.10
F8	2.62±0.02	50.39±1.14	4.83±0.28	0.16	100.50±1.10
F9	2.64±0.03	49.76±1.15	4.83±0.28	0.17	100.53±1.10

Floating properties of prasugrel floating matrix tablets

All the tablet formulations were tested for floating properties such as floating lag and total floating time. The results of *in-vitro* buoyancy study are shown in the Table 5. Sodium bicarbonate was used as gas generating agent at 10% w/w concentration. The sodium bicarbonate induces CO_2 generation in the presence of acidic dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/ml, and the tablet becomes buoyant. tablet formulations prepared with Compritol 888 ATO (F1 to F3) did not show floating behaviour because the formulations did not swell and hence failed to form a gel and the CO_2 generated did not get entrapped, thus these formulations failed to float the tablet. The total floating time of other formulations (F4 to F9) was observed in between 10 to 12 h with floating lag time <1 min and showed better and desired floating characteristics. Pictorial presentation of in-vitro buoyancy study results of optimized formulation (F8) was shown in Figure 4.

Table 5: In-vitro buoyancy data of prasugrel floating tablets

Formulation code	Floating Lag Time* (Seconds) (n=3)	Floating time (Hours)*
F1	NF	NF
F2	NF	NF
F3	NF	NF
F4	19.66±0.57	10
F5	20.33±1.52	>12
F6	20.66±1.15	>12
F7	25.66±0.57	10
F8	26.66±0.57	>12
F9	27.33±0.57	>12

*NF- Not Floated

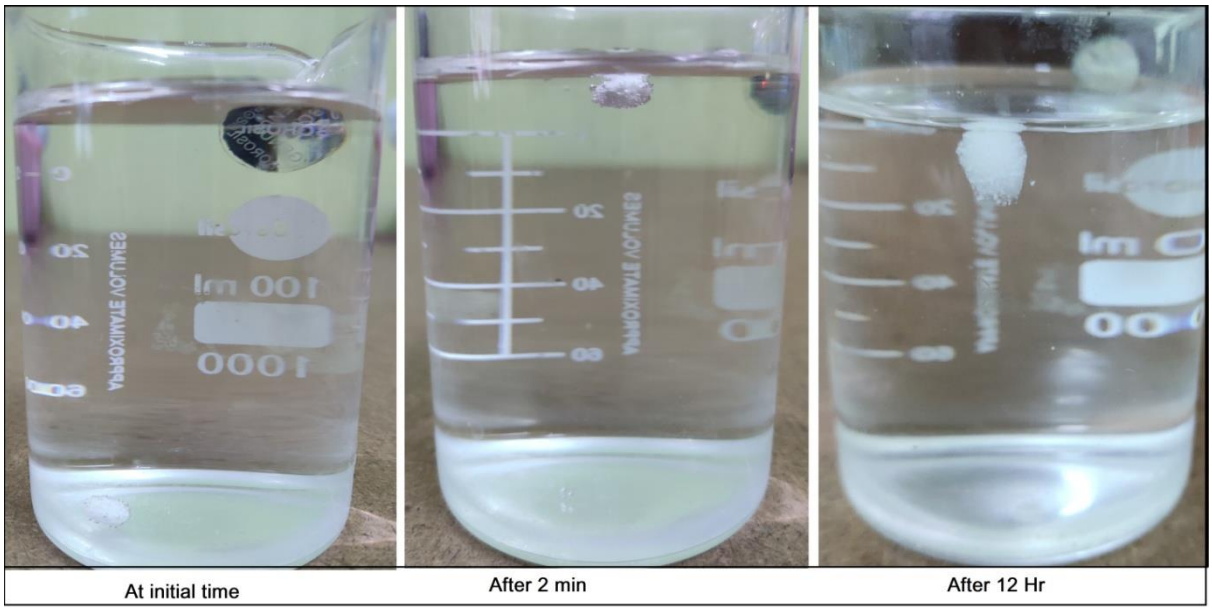

Fig. 4: Pictorial presentation of in-vitro buoyancy study of optimized formulation (F8)

In-vitro drug release studies

In-vitro drug release studies of floating formulations revealed that the release of prasugrel hydrochloride from different formulations varies with type and composition of matrix forming polymers.

The in-vitro drug release profiles of the F1, F2 and F3 formulations each had hydrophobic retardant, compritol are shown in Figure 5a. The initial 1 h drug release was 39%, 26% and 16% for F1, F2 and F3 formulations respectively. Formulation F1 showed rapid/bust drug release pattern in initial hours due to insufficient polymer concentration, in which compritol was only 10 mg (20% w/w) and almost 85% drug was released within 4 h. F2 and F3 formulations containing 15 mg (30% w/w) and 20 mg (40% w/w) of compritol showed controlled drug release wherein 98 % in 8 h and 83 % in 8h was released from the respective formulations. However, these formulations did not show any floating characteristics as the tablet formulations did not swell.

The in-vitro drug release profiles of the F4, F5 and F6 formulations each had hydrophilic retardant, HPMC K100M are shown in Figure 5b. The initial 1 h drug release was 30%, 16% and 13% for F1, F2 and F3 formulations respectively. F4 formulation showed less sustained effect may be as it has only 10 mg (20% w/w) polymer concentration and sustained the drug release up to 6 h only. F5 formulation containing 15 mg (30% w/w) sustained the drug release up to 8 h and released 87 % of drug. The drug release from F6 formulation containing 20 mg (40% w/w) was slow and failed to release the complete drug at 8 h and released 74 % only. The formulations (F1, F2, F3) prepared with hydrophilic polymer HPMC K100M showed better controlled retardation of drug release than the hydrophobic polymer compritol 888 ATO formulations (F4, F5, F6) at their defined respective concentrations as 83% drug was released in 8 h from matrix tablets containing 30% compritol but matrix tablets containing 30% HPMC only released 74 % drug at the same time.

The in-vitro drug release profiles of the F7, F8 and F9 formulations each had combination of HPMC K100M and compritol 888 ATO are shown in Figure 5c. The initial 1 h drug release was 34%, 22% and 14% for F7, F8 and F9 formulations respectively. F7 formulation showed rapid drug release as it has only 5 mg (10% w/w) of compritol and 5 mg (10% w/w) of HPMC K100M polymer concentration and more than 85 % drug was released within 5 h which may be due to insufficient polymer concentrations. F8 formulation released 97% of drug at 8 h whereas the drug release from F9 formulation was slow and released only 84 % of drug in 8 h. Formulation F8 with 7.5 mg (15% w/w) of compritol and 7.5 mg (15% w/w) of HPMC K100M polymer concentration showed better and desirable complete drug release within 8 h with required floating characteristics, hence it was considered as an optimized formulation. It was noted that incorporation of compritol with HPMC at defined respective concentrations, increases the drug release from the formulations as compared to HPMC K100M alone formulations.

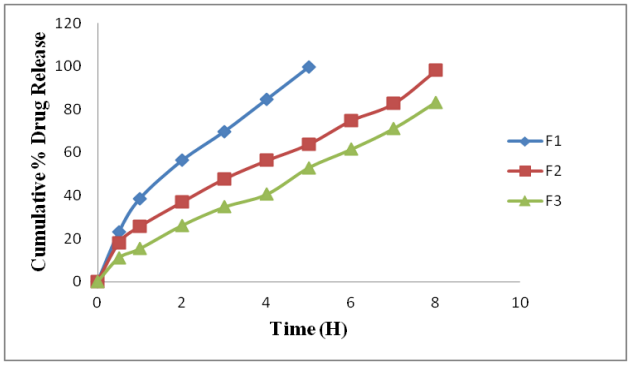

Fig. 5a: Cumulative percentage drug release of formulations with Compritol 888 ATO

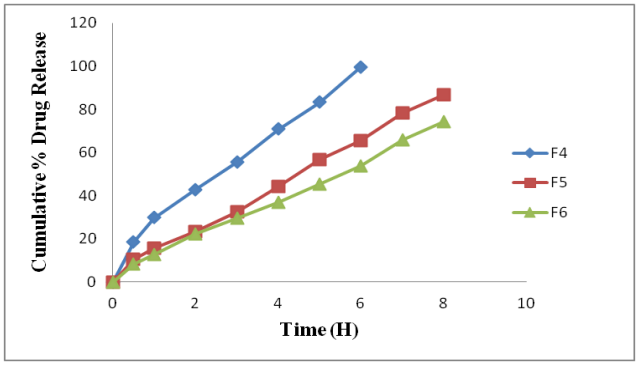

Fig. 5b: Cumulative percentage drug release of formulations with HPMC K100M

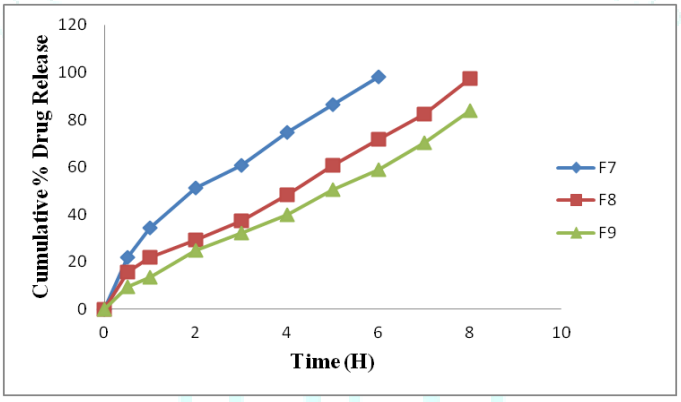

Fig. 5c: Cumulative percentage drug release of formulations with combination of Compritol 888 ATO and HPMC K100M

Kinetic modelling of drug release

Analysis of the drug release data as per zero order and first order kinetic models indicated that all the formulations followed zero order kinetics and dissolution rate constant (K) values were presented in Table 6. In the analysis of release data as per Korsmeyer-Peppas equation, the release exponent "n" was in the range 0.550-0.776 indicating non-fickian diffusion as the release mechanism from all the prasugrel floating tablets. The drug release rate of prasugrel was found to be affected by the type and concentration of the polymer used in the formulation. As the concentration of the polymer was increased, the drug release was found to be retarded.

Table 6: Regression coefficient (R^2) values of floating tablet formulations for different kinetic models

Formulation code	R2				Peppas (n)	Zero order rate constant (K)
	Zero	First	Higuchi	Korsmeyer–Peppas		
F1	0.9574	0.8208	0.9911	0.9916	0.649	18.16
F2	0.9768	0.7644	0.9755	0.9987	0.550	10.81
F3	0.9938	0.9335	0.9445	0.9902	0.698	9.687
F4	0.9835	0.698	0.9706	0.9971	0.602	15.30
F5	0.9965	0.931	0.9329	0.9811	0.722	10.60
F6	0.9958	0.9556	0.9361	0.994	0.776	8.86
F7	0.9899	0.8505	0.9915	0.9947	0.575	14.94
F8	0.9902	0.8148	0.9384	0.9735	0.563	11.15
F9	0.9925	0.8903	0.9261	0.9939	0.748	9.87

CONCLUSION

In this research work, an attempt has been made to develop floating tablets of prasugrel hydrochloride by effervescent approach using the polymers HPMC K100M and Compritol 888 ATO to sustain the drug release properties up to 8 h to minimize the potential side effect bleeding and to improve the bioavailability. According to the above results, optimised floating tablet formulation (F8) prepared by employing combination of 15% w/w HPMC K100M and 15% w/w Compritol 888 ATO with 10% w/w sodium bicarbonate offered desired in-vitro floating time and drug dissolution profile and the adopted method yielded uniform and reproducible floating matrix tablets.

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