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Research Article

Development and Evaluation of Clopidogrel Bisulphate Multi-Unit Floating Mini-Tablets

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ABSTRACT

The objective of the present work was to formulate and characterize multi-unit floating drug delivery system of Clopidogrel bisulphate to increase the bioavailability and sustain the drug release properties up to 8 h with more predictable drug release kinetics that avoids all or nothing emptying effect wherefore to improve patient compliance. Clopidogrel bisulphate floating mini-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 of prepared mini tablet formulations. 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 Clopidogrel bisulphate floating mini tablet formulations followed zero order kinetics. As per Korsmeyer-Peppas equation, the release exponent “n” ranged 0.561-0.758 indicating that drug release from all the formulations was by non-Fickian diffusion mechanism. Based on the results, Clopidogrel bisulphate floating mini tablets prepared by employing combination of 20% w/w HPMC K100M and 20% w/w Compritol 888 ATO offered desired *in-vitro* floating time and drug dissolution profile.

Keywords: Bioavailability, Clopidogrel bisulphate, floating mini-tablets, release kinetics, sustained release.

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INTRODUCTION

Oral controlled release drug delivery systems with ability to retain in the stomach are called gastro-retentive drug delivery system (GRDDS) which are aimed to enhance drug therapy with or without targeted action by prolonging the gastric residence time after oral administration [1].

The controlled gastric retention of the formulation may be achieved by the various approaches such as floatation, mucoadhesion, sedimentation, expansion and modified shape systems. 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 [2]. Most of the floating systems previously reported are single unit systems such as tablets and capsules. However, the problems such as all or nothing emptying of

single unit floating dosage forms made them unreliable and irreproducible in prolonging the gastric residence time, which led to the development of multiple unit floating systems [3].

Multiple unit floating drug delivery systems, such as mini-tablets with diameter of 3-6mm, show several advantages over single unit system, which include avoiding all or nothing emptying, more predictable drug release kinetics, less chance of localized mucosal damage and administration of units with different release profiles or containing incompatible substance. Mini tablet have the advantages of both tablets and pellets and shows more reliable dissolution profiles than single units, which means better bioavailability with more and even absorption of the drugs. In addition, they offer dosage forms of equal dimensions and weight with smooth regular surface that could be obtained in a reproducible and continuous way. Like other multiple unit systems, multiple mini-tablets can be filled into hard gelatin capsules that release these subunits after disintegration [4, 5].

Clopidogrel is a thienopyridine class inhibitor of P2Y₁₂ adenosine-5-diphosphate (ADP) platelet receptors and used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease. Clopidogrel is a pro-drug of carboxyl clopidogrel activated in the liver by cytochrome P450 and CYP2C19 enzyme. The active metabolite has elimination half-life of about 7-8 h and acts by forming a disulfide bridge with the platelet ADP receptor. Clopidogrel bisulphate is a BCS class II drug and exhibits pH dependent solubility and it is very soluble at pH value < 3. Following oral administration, it is well-absorbed with bioavailability of about only 50% due to poor water solubility. The main side effects of the drug are gastric bleeding and clopidogrel drug resistance during chronic treatment [6].

A sustained release floating clopidogrel formulation may be desired for a number of reasons, such as improving the bioavailability and to minimize the side effects of the drug such as gastric bleeding and to prevent the development of drug resistance wherefore to improve patient compliance [7]. Various single and multiple units of clopidogrel floating formulations has been reported in the literature, but very little work was carried in the field of multi-unit mini-tablets technology. The aim of the present study was to formulate and characterize clopidogrel bisulphate multi-unit floating mini-tablets to increase the bioavailability and sustain the drug release properties up to 8 h with more predictable drug release kinetics and avoiding all or nothing emptying effect using hydrophilic polymer, HPMC K100M and hydrophobic polymer, Compritol 888 ATO.

MATERIALS AND METHODS

Materials

Clopidogrel bisulphate Form-I (gift sample from Dr. Reddy's 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 [8].

Micromeritic properties

The pure drug and prepared formulation powder blends before compression were evaluated for the angle of repose, 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 plugged glass funnel and was then allowed to flow through the funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (h) formed as well as the radius of the heap (r) was noted. The angle of repose (θ) was calculated as: $\tan \theta = (h/r)$.

BD and TD of 10 g of powder blend were determined by using 50 ml graduated cylinder. The volume occupied by the blend was read and the BD 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 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 [9].

Determination of lambda (λ) max by Ultra Violet (UV) spectroscopy

The stock solution (1000 $\mu\text{g/ml}$) of Clopidogrel bisulphate was prepared in 0.1N hydrochloric acid (HCl). This solution was appropriately diluted with 0.1N HCl to obtain a concentration of 10 $\mu\text{g/ml}$. The UV spectrum was recorded in the range of 200-400 nm on double beam UV-visible spectrophotometer. The spectrum and wavelength of maximum absorption were recorded.

Preparation of standard curve

The stock solution (1000 $\mu\text{g/ml}$) of Clopidogrel bisulphate 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 (100 $\mu\text{g/ml}$). The above solution was suitably diluted with 0.1N hydrochloric acid to get the series of dilutions containing 10, 20, 30, 40, 50 $\mu\text{g/ml}$ of clopidogrel bisulfate solutions. The absorbance of these solutions were measured at 270.4 nm against blank i.e. 0.1 N HCl. The coefficient of correlation and equation for the line are determined [10].

Preparation of clopidogrel bisulfate floating mini tablets

The clopidogrel bisulfate floating mini 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. 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 mini tablets using 5 mm size round concave single tip punch on multi station rotary compression machine. In this work, each dose comprised 10 mini tablets which are equivalent to 98 mg clopidogrel bisulphate.

Table 1: Composition of clopidogrel bisulfate floating mini tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clopidogrel Bisulfate	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8
Sod 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
Microcrystalline cellulose	24.2	19.2	14.2	24.2	19.2	14.2	24.2	19.2	14.2
Total weight	50	50	50	50	50	50	50	50	50

Evaluation of physical parameters of floating mini matrix tablets [11]

Tablet weight uniformity:

A total of 20 mini 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 ($\pm 10\%$) and if no tablets differ by more than two times the percentage limit.

Thickness test:

The thickness of three randomly selected mini-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 10 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:

The friability of tablets was determined using Roche friabilator. Six mini tablets (6) were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by the following equation.

$$\%F = (1 - W/W_0) \times 100$$

% Friability of tablets $<1\%$ are considered as acceptable.

Drug content:

A total of 30 mini tablets were weighed and powdered. The quantity of powder equivalent to 98 mg of clopidogrel bisulfate was dissolved in 100 ml of 0.1 N HCl. Then the solution was filtered, diluted suitably and analyzed using an UV-visible spectrophotometer at 270.4 nm.

In-vitro buoyancy studies

The in-vitro buoyancy was determined using the USP dissolution apparatus II at 50 rpm containing 900 ml of 0.1 N HCl as the dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$. Ten mini-tablets were dropped in a basket and 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 50

rpm for 8 hours. Ten mini-tablets equivalent to 98 mg of clopidogrel bisulphate were placed in 900 ml of dissolution medium i.e. 0.1 N HCl maintained at $37 \pm 0.5^\circ\text{C}$. 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} 270.4 nm using UV-visible 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 [12]: The data obtained from in vitro drug release studies were fitted to the following kinetic equations:

Zero order release kinetics equation: $Q_t = Q_0 + K_0t$; Where Q_t 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: $\log C = \log C_0 - Kt/2.303$; 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.

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: $M_t/M_\infty = Kt^n$; Where M_t/M_∞ 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.

RESULTS AND DISCUSSION

Calibration curve of clopidogrel bisulphate

An UV spectro-photometric method was used for estimation of clopidogrel bisulphate. A solution of clopidogrel bisulphate ($10\mu\text{g}/\text{mL}$) was scanned in the wavelength range of 200-400 nm and found to have maximum absorption (λ_{max}) at 270.4 nm (Fig. 1). The standard plot of clopidogrel bisulphate was prepared in 0.1 N HCl (pH 1.2) and showed good linearity with R^2 value of 0.9999 (Fig. 2).

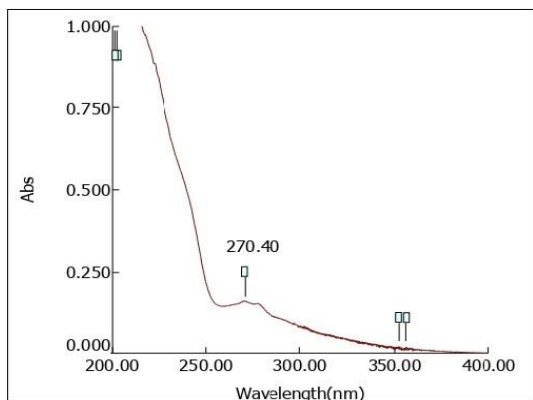


Fig. 1: UV scan spectrum curve of clopidogrel bisulfate

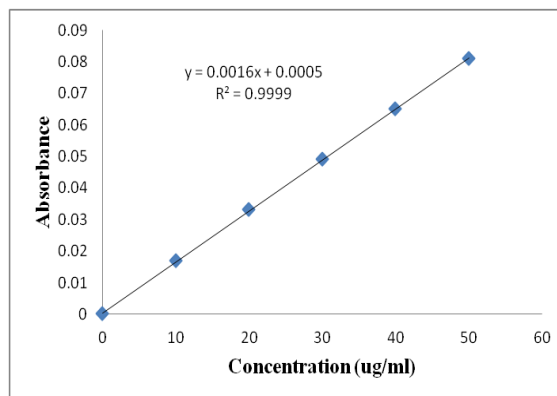


Fig. 2: Calibration curve of clopidogrel bisulfate at 270.4 nm

Drug-excipient compatibility studies

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: Functional groups and range for Clopidogrel bisulphate and optimized formulation

Functional groups	Clopidogrel bisulphate (Form I)	Optimized formulation (F9)
O-H Carboxylic	3450.10	3440.27
C-H Stretching	2917.69	2917.31
C=O Stretching	1750.42	1737.54
C-O Stretching	1129.12	1110.24
Form I unique band	839.04	839.04

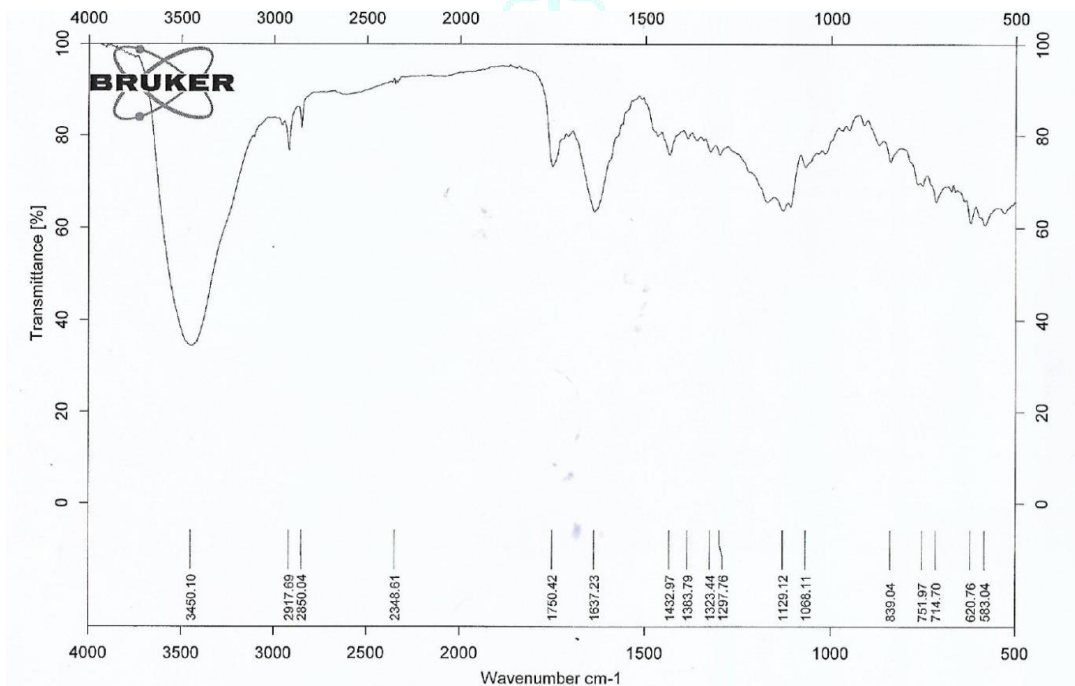


Fig. 3a: FT-IR spectra of pure clopidogrel bisulfate

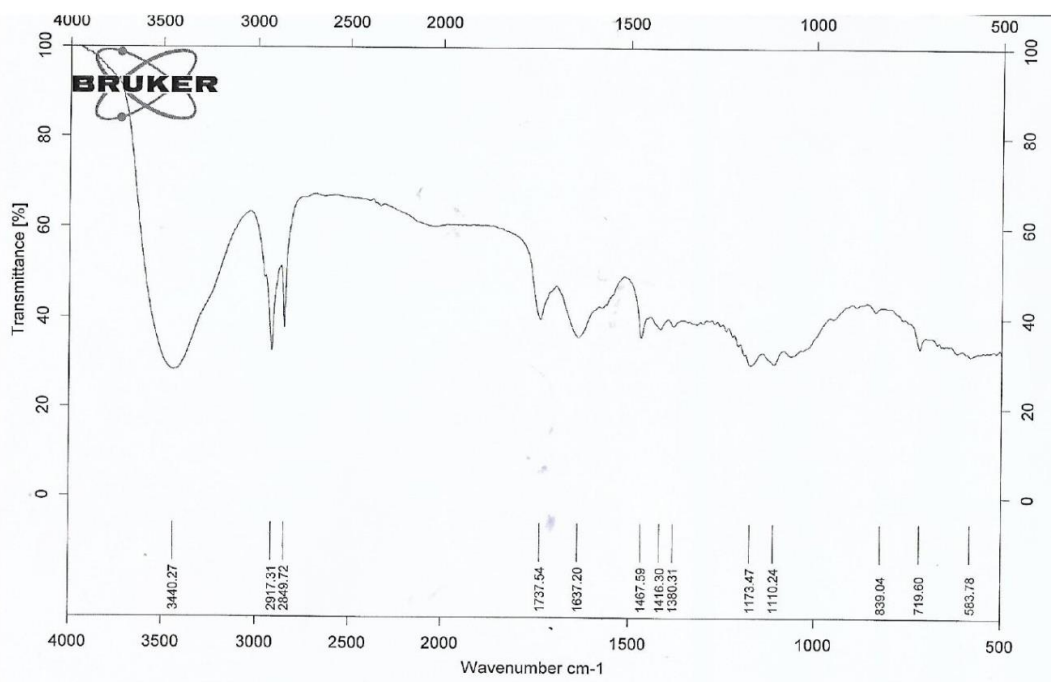


Fig. 3b: FT-IR spectra of physical mixture of clopidogrel bisulphate formulation F9 blend with HPMC K100M and Compritol 888 ATO.

Micromeritic properties

The micromeritic properties of pure drug of clopidogrel bisulfate showed good flow properties as per observed values of CI (11.11) and angle of repose (26.10). The flow

properties of the formulation powder blends were also showed fair flow properties as per observed values of CI and angle of repose. The micromeritic properties of pure drug and optimized batch of the formulation were shown in Table 3.

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

Parameters	Pure drug	F9
Angle of repose	26.10	30.54
Carr's index (%)	11.11	17.78
Hausner's ratio	1.12	1.21

Evaluation of physical parameters of floating mini tablets

All the prepared formulations were tested for various physical parameters such as thickness, weight variation, hardness and friability. Results of the physical tests were shown in Table 4. The hardness of all the formulations was

found to be in the range of 4-5 kg/cm². The friability of all the formulations was found to be <1%. The drug content of the formulations was in between 98% and 102%. Hence, all the clopidogrel floating mini 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 clopidogrel floating mini tablet formulations

Formulation code	Thickness(mm)- (n=3)	Weight Variation (n=20)	Hardness (kg/cm ²) (n=10)	Friability (%) (n=6)	Assay (%) (n=3)
F1	2.62±0.02	50.29±1.10	4.16±0.06	0.12	101.21±0.88
F2	2.61±0.01	48.11±1.11	4.25±0.02	0.15	100.01±0.90
F3	2.61±0.02	49.84±1.15	4.18±0.07	0.17	99.95±1.17
F4	2.62±0.02	50.87±1.12	4.23±0.01	0.15	102.98±1.05
F5	2.64±0.03	50.22±1.10	4.20±0.08	0.16	99.23±1.23
F6	2.65±0.02	51.12±1.06	4.15±0.03	0.18	100.20±0.96
F7	2.62±0.02	48.99±1.15	4.17±0.02	0.19	101.12±1.20
F8	2.62±0.01	50.28±1.12	4.11±0.05	0.16	98.89±1.02
F9	2.63±0.02	48.99±1.15	4.16±0.09	0.18	99.98±1.22

Floating properties of clopidogrel floating mini matrix tablets

All the 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 CO₂ 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. Mini 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 CO₂ 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 (F9) was shown in Figure 4.

Table 5: In-vitro buoyancy data of clopidogrel floating minitabets

Formulation code	Floating Lag Time* (Seconds) (n=10)	Floating time (Hours)*
F1	NF	NF
F2	NF	NF
F3	NF	NF
F4	17±2.48	10
F5	18±1.75	>12
F6	18±2.36	>12
F7	23±1.84	10
F8	24±1.84	>12
F9	24±2.38	>12

*NF- Not Floated

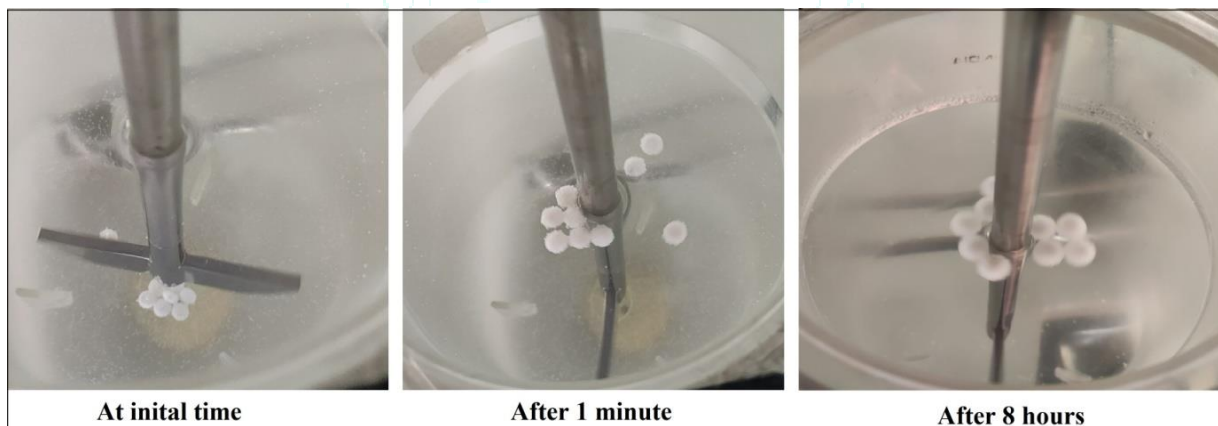


Fig. 4: Pictorial presentation of in-vitro buoyancy study of optimized formulation (F9)

In-vitro drug release studies

The release of clopidogrel bisulphate from all the mini tablet formulation was found to be slow and sustained. The *in-vitro* drug release profiles of the formulations prepared with hydrophobic polymer, Compritol are shown in Figure 5a. The drug release extended from 4-8 h and the 1 h initial drug release was varied between 21% and 49%. F1 formulation released more than 90% of drug within 4 h whereas formulation F2 and F3 showed 98% and 96% drug released in 7 and 8 h respectively. However, these formulations did not show any floating characteristics as the tablet formulations did not swell.

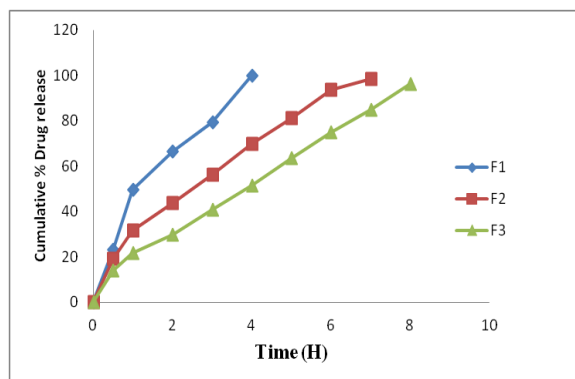


Fig. 5a: Cumulative percentage drug release of formulations with Compritol 888 ATO

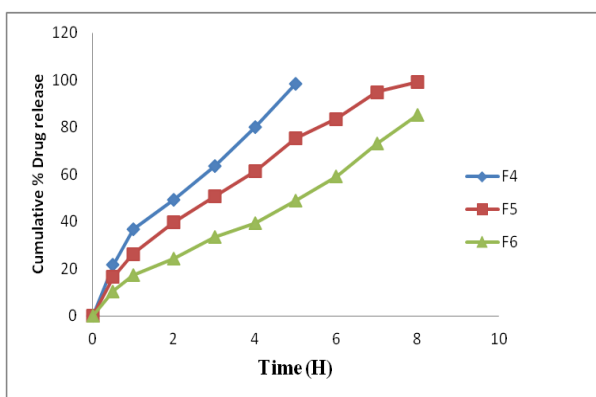


Fig. 5b: Cumulative percentage drug release of formulations with HPMC K100M

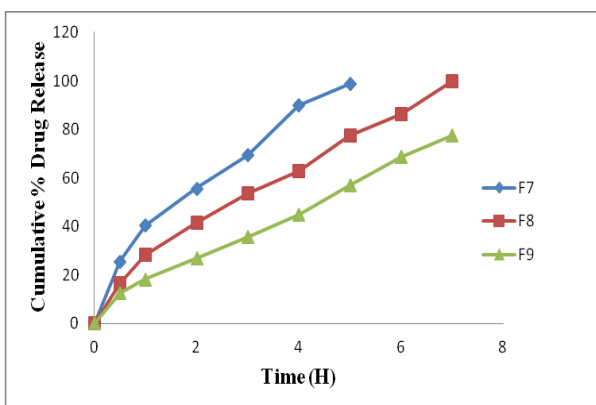


Fig. 5c: Cumulative percentage drug release of formulations with combination of Compritol 888 ATO and HPMC K100M

The in-vitro drug release profiles of the formulations prepared with hydrophilic polymer, HPMC are shown in Figure 5b. The 1 h initial drug release was varied between 17-36%. F4 and F5 formulations released more than 90% of drug within 5 h and 7 h respectively whereas the drug

release from F6 formulation was slow and failed to release the complete drug at 8 h. It shows that the increase of HPMC content affects significantly the matrix tablet release behaviour. The formulations prepared with hydrophilic polymer HPMC showed greater drug release retardation than the hydrophobic polymer Compritol formulations at their defined respective concentrations as more than 96% drug was released in 8 h from matrix tablets containing 30% compritol but matrix tablets containing 30% HPMC only released 85 % drug at the same time.

The in-vitro drug release profiles of the formulations prepared with combination of Compritol and HPMC are shown in Figure 5c. The 1 h initial drug release was varied between 18-40%. F7 and F8 formulations released almost 90% of drug within 4 h and 6 h respectively. F9 formulation released more than 90% of drug within 8 h and showed better and desired drug release profile, hence it was considered as an optimized formulation. Incorporation of compritol with HPMC increases drug release from the formulation. This may be attributed to increased penetration of the solvent molecules in presence of the hydrophobic polymer, leading to enhance drug diffusion from the matrix. Formulations F1, F4 and F7 showed rapid/bust drug release almost 35-50% in 1 h which may be due to insufficient polymer concentration.

Kinetic modeling 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. Higuchi plots were found to be linear with " r^2 " > 0.9633 in all the clodidogrel floating mini tablets. In the analysis of release data as per Korsmeyer-Peppas equation, the release exponent " n " was in the range 0.561-0.758 indicating non-fickian diffusion as the release mechanism from all the clodidogrel floating minitables. The drug release rate of clodidogrel 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 minitabket formulations for different kinetic models

Formulation code	R2				Peppas (n)	Zero order rate constant (K)
	Zero	First	Higuchi	Korsmeyer-Peppas		
F1	0.9354	0.8294	0.9841	0.9480	0.758	22.98
F2	0.9678	0.8721	0.9869	0.9914	0.587	13.40
F3	0.9932	0.8111	0.9633	0.9888	0.634	11.39
F4	0.9710	0.7887	0.9758	0.9864	0.576	17.89
F5	0.9758	0.8283	0.9828	0.9994	0.623	11.95
F6	0.9882	0.8934	0.9645	0.9917	0.667	9.75
F7	0.9558	0.8621	0.9903	0.9954	0.561	18.37
F8	0.9794	0.6268	0.9785	0.9957	0.632	13.19
F9	0.9935	0.8702	0.9674	0.9874	0.637	10.65

CONCLUSION

In this research work, an attempt has been made to develop multi-unit floating mini-tablets of clodidogrel bisulphate by effervescent approach using the polymers HPMC K100M and Compritol 888 ATO to sustain the drug release properties up to 8 h with more predictable drug release kinetics avoiding all or nothing emptying effect in order to improve bioavailability and to minimize the side effects of the drug

such as gastric bleeding and to prevent the development of drug resistance. According to the above results, optimised floating mini-tablet formulation (F9) prepared by employing combination of 20% w/w HPMC K100M and 20% 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 mini matrix tablets. Thus all the major objectives of this investigation were fulfilled.

REFERENCES

1. Swarbrick J. Encyclopedia of Pharmaceutical Technology. 3rd ed. Vol 2. New York: Informa Healthcare; 2007. pp. 1082-103.
2. Kawashima Y, Takeuchi H, Yamamoto H. Handbook of Pharmaceutical Controlled Release Technology. New York: Marcell Dekker Inc; 2000. pp. 505-25.
3. Meka L, Kesavan B, Kalamata VN, Eaga CM, Bandari S, Vobalaboina V, Yamsani MR, Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive floating drug delivery systems for furosemide, J. Pharm. Sci. 2009; 98: 2122-2132
4. Ishak RAH, Awad GAS, Mortada ND, Nour SAK. Preparation, in vitro and in vivo evaluation of stomach-specific metronidazole-loaded alginate beads as local anti-Helicobacter pylori therapy. J. Control Release. 2007; 119: 207-214.
5. Priyanka, Kumar K, Teotia D, A comprehensive review on pharmaceutical mini tablets, Journal of Drug Delivery and Therapeutics. 2018; 8(6):382-390
6. Patel PR, Kothari JS, Roy SB. Modified release clopidogrel formulation. U.S. Patent US20100145053 A1, Jun 10, 2010.
7. Rao KR, Lakshmi KR. Design, development and evaluation of clopidogrel bisulfate floating tablets. Int J Pharm Investig. 2014; 4(1), 19-26.
8. Koradia V, Chawla G, Bansal AK. Qualitative and quantitative analysis of clopidogrel bisulphate polymorphs. Acta Pharm 2004; 54, 193-204.
9. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Varghese Publication House 1987; p. 171-96.
10. Saadet Dermiş, Ekrem Aydoğan. Rapid and accurate determination of clopidogrel in tablets by using spectrophotometric and chromatographic techniques. Commun.Fac.Sci.Univ.Ank. Series B V 2009; 55 (1), 1-16.
11. Sally A, El-Zahaby, Abeer A. Kassem , Amal H. El-Kamel. Design and evaluation of gastroretentive levofloxacin floating minitablets-in-capsule system for eradication of Helicobacter pylori. Saudi Pharmaceutical Journal 2014; 22, 570-579.
12. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm 2010; 67, 217-23.

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