

Design, development and evaluation of clopidogrel bisulfate floating tablets

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Abstract

Objective: The objective of the present work was to formulate and to characterize a floating drug delivery system for clopidogrel bisulphate to improve bioavailability and to minimize the side effects of the drug such as gastric bleeding and drug resistance development. **Materials and Methods:** Clopidogrel floating tablets were prepared by direct compression technique by the use of three polymers xanthan gum, hydroxypropyl methylcellulose (HPMC) K15M and HPMC K4M in different concentrations (20%, 25% and 30% w/w). Sodium bicarbonate (15% w/w) and microcrystalline cellulose (30% w/w) were used as gas generating agent and diluent respectively. Studies were carried out on 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 in 0.1 N hydrochloric acid (1.2 pH) and corresponding dissolution data were fitted to popular release kinetic equations in order to evaluate release mechanisms and kinetics. **Results and Discussion:** All the clopidogrel floating formulations followed first order kinetics, Higuchi drug release kinetics with diffusion as the dominant mechanism of drug release. As per Korsmeyer-Peppas equation, the release exponent “*n*” ranged 0.452-0.654 indicating that drug release from all the formulations was by non-Fickian diffusion mechanism. The drug release rate of clopidogrel was found to be affected by the type and concentration of the polymer used in the formulation ($P < 0.05$). As the concentration of the polymer was increased, the drug release was found to be retarded. **Conclusion:** Based on the results, clopidogrel floating tablets prepared by employing xanthan gum at concentration 25% w/w (formulation F2) was the best formulation with desired *in-vitro* floating time and drug dissolution.

Key words: Bioavailability, clopidogrel bisulfate, floating tablets, release kinetics, sustained release

INTRODUCTION

Controlled release drug delivery systems (CRDDS) are designed to enhance drug therapy and aimed to controlling the drug release rate and sustaining the duration of the action with or without targeted action. The CRDDS possessing ability of being retain in the stomach are called gastro-retentive drug delivery system (GRDDS) and they are designed to prolong the gastric residence time after oral administration and controlling the release of drug. Gastro retentive dosage forms have become a popular drug delivery

systems in the field of site specific orally administrated CRDDSs. The controlled gastric retention of formulation may be achieved by the various approaches such as mucoadhesion, sedimentation, expansion, floatation and modified shape systems. Among the various approaches, floating drug delivery system (FDDS) promises to be a potential approach for gastric retention of drug. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. 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.^[1,2]

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 an elimination half-life of about 7-8 h and acts by forming a disulfide bridge with the platelet ADP receptor.^[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.

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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.^[4] The aim of the present study was to formulate and to characterize clopidogrel bisulphate floating tablets using the polymers such as hydroxypropyl methylcellulose (HPMC) K4M, HPMC K15M and xanthan gum with increased bioavailability and sustained release properties up to 8 h.

MATERIALS AND METHODS

Clopidogrel bisulphate, HPMC K4M and HPMC K15M (gift samples from Dr. Reddy's laboratories, Hyderabad), xanthan gum, sodium bicarbonate, microcrystalline cellulose, magnesium stearate, talc (S. D. Fine Chemicals, Mumbai) and all other ingredients are of laboratory grade.

Solubility studies

Solubility of clopidogrel bisulfate was determined in distilled water, 4.5 pH acetate buffer, 6.8 pH phosphate buffer and 0.1 N (pH-1.2) hydrochloric acid (HCl). Solubility studies were performed by taking excess amount of clopidogrel bisulfate in different boiling tubes containing the buffers. The mixtures were shaken for 24 h at regular intervals. The solutions were filtered by using Whatmann's filter paper. The filtered solutions were analyzed spectrophotometrically.^[5]

Drug-excipient compatibility studies

Drug-excipient compatibility studies were performed for physical mixture of clopidogrel bisulfate with various polymers in the ratio 1:1. The physical mixture samples were subjected to fourier transform infrared studies by employing KBr pellet method. Spectra of drug and polymer were taken and analyzed for any major interaction.^[6]

Micromeritic properties

The pure drug and formulation powder blend prepared before compression is 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 (α) was calculated as: $\tan \alpha = (h/r)$.

Bd and Td of 10 g of powder blend were determined by using 50 ml graduated cylinder. The volume occupied by the granules was read and the (Bd) calculated in g/ml. The cylinder containing the granules was tapped until constant volume was obtained using Bd 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.^[7]

Preparation of clopidogrel bisulfate floating tablets

Clopidogrel bisulfate floating matrix tablets each containing 98 mg were prepared by direct compression method by effervescent approach. HPMC K4M, HPMC K15M and xanthan were used as polymers at varying concentrations (20%, 25%, 30% w/w) as shown in the Table 1. Sodium bicarbonate at concentration 15% w/w was optimized as gas generating floating agent with 30% w/w microcrystalline cellulose as diluent, 1% w/w talc as glidant and 1% w/w magnesium stearate as lubricant were used. The required quantities of drug, polymer and other ingredients were accurately weighed and mixed geometrically with each of the polymer and passed through sieve No. 44. These powder blends were then compressed into tablets using multi station punching machine using 9 mm punch. The total weight of the tablet was not constant because that would require the use of the additional amount of diluent for weight adjustment, which in turn may have caused variation in drug release profile.

Characterization of tablets

Tablet weight uniformity

A total of 20 tablets were weighed individually, average weight was calculated and the individual tablet weights were compared with the average weight. The tablets meet the USP test if not more

Table 1: Composition of floating tablets of clopidogrel bisulfate

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Clopidogrel bisulfate	98	98	98	98	98	98	98	98	98	98	98	98
Xanthan gum	60	88	126	—	—	—	—	—	—	21	42	63
HPMC K15M	—	—	—	60	88	126	—	—	—	—	—	—
HPMC K4M	—	—	—	—	—	—	60	88	126	105	84	63
Sodium bicarbonate	46	53	62	46	53	62	46	53	62	62	62	62
Microcrystalline cellulose	90	105	126	90	105	126	90	105	126	126	126	126
Magnesium stearate	3	3	4	3	3	4	3	3	4	4	4	4
Talc	3	3	4	3	3	4	3	3	4	4	4	4
Total weight	300	350	420	300	350	420	300	350	420	420	420	420

HPMC: Hydroxypropyl methylcellulose

than two tablets are outside the percentage limit and if no tablets differs by more than two times the percentage limit.

Crushing strength

The crushing strengths of the tablets were determined individually with the Monsanto hardness tester. Three tablets were used and the mean crushing strength was calculated and expressed in kg/cm²

Friability test

The friability of tablets was determined using Roche friabilator. Six 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 10 tablets were weighed and powdered. The quantity of powder equivalent to 100 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 ultra violet (UV) visible spectrophotometer at 270.5 nm.^[8]

In-vitro buoyancy studies

The *in-vitro* buoyancy was determined by floating lag-time method as per the method described by Rosa *et al.* 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.^[9]

Swelling index studies

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in 100 ml beaker of 0.1 N HCl and after 1, 2, 3, 4 and 5 h each, beaker containing tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance. Swelling index was calculated by using the following formula.^[10]

$$\text{Swelling index} = \frac{[\text{Wet weight of tablet} - \text{Dry weight of tablet}]}{\text{Dry weight of tablet}} \times 100$$

In-vitro drug release studies

Clopidogrel bisulfate drug release studies from different formulated tablets were performed by using USP Type II apparatus in 900 ml of 0.1 N HCl as the dissolution medium, with a rpm of 50 and the bath was maintained at a temperature of $37 \pm 0.5^\circ\text{C}$. Samples were withdrawn at regular intervals of time and these were replaced with an equivalent volume of the fresh dissolution media. The withdrawn samples were

analyzed after suitable dilutions at a wavelength of 270.5 nm using UV spectrophotometer. The cumulative percentage drug release was calculated using slope obtained from the standard curve.^[4]

Kinetic modeling of drug release

The dissolution data was fitted to popular release models such as zero-order, first-order, Higuchi and Peppas-Korsmeyer equation models. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppas-Korsmeyer equation.

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the 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.

The release of the drug, which followed first order kinetics, can be expressed by the 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.

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 was further analyzed by Peppas and Korsmeyer equation: $M_t/M_\infty = K t^n$; 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.^[11]

RESULTS AND DISCUSSION

The present work was aimed to prepare a FDDS for clopidogrel bisulfate with increased bioavailability and controlled release property. Among the various approaches involved in the gastro retentive systems, effervescent floating approach was selected as they are easy to fabricate and produce buoyancy in the gastrointestinal tract and thereby enhancing the absorption of the drug. For this purpose, floating tablets were prepared by direct compression technique by the use of three polymers such

as xanthan gum, HPMC K4M and HPMC K15M in different concentrations (20%, 25% and 30% w/w).

Solubility studies

Solubility of clopidogrel bisulfate was determined in distilled water, 4.5 pH acetate buffer, 6.8 pH phosphate buffer and 0.1 N (pH-1.2) HCl. The results were shown in the Table 2. The solubility of clopidogrel bisulfate was found to be pH dependent and it was more soluble in 0.1 N (pH-1.2) HCl.

Drug-excipient compatibility studies

Drug polymer interaction was checked by comparing the infrared spectroscopy (IR) spectra of the physical mixture of drug with

the polymer used with the IR spectrum of pure drug as shown in Figure 1, clopidogrel bisulfate gives the peaks in IR spectrum nearby at 3106/cm¹ due to C-H stretching vibrations, 1749/cm¹ due to C=O stretching vibrations and the bands associated with C-O stretching appeared at nearby 1156/cm¹. Characteristic unique absorption bands for clopidogrel bisulfate amorphous form I were also seen at 836 and 2983/cm¹. Figure 1a-c revealed the presence of peaks nearby at 3106/cm¹, 1749/cm¹, 1156/cm¹, 836/cm¹ and 2983/cm¹. Frequencies of functional groups and unique absorption bands of pure drug remained intact in physical mixture containing different polymers. Hence, there was no major interaction between the drug and excipients used in the study.

Table 2: Solubility of clopidogrel bisulfate in different buffers

Buffer medium	Solubility (mg/ml)
Purified distilled water	518.5
0.1N (pH 1.2) HCl	694.5
pH 4.5 acetate buffer	18.0
pH 6.8 phosphate buffer	12.8

HCl: Hydrochloric acid

Micromeritic properties

The micromeritic properties of pure drug of clopidogrel bisulfate showed excellent flow properties as it is observed from the values of CI (10.40) and angle of repose (11.76). The flow properties of the formulation powder blend was also showed fair flow properties as it is observed from the values of CI (21-25) and angle of repose (41-45). Hence clopidogrel bisulfate as such can be compressed to formulate the tablets by direct compression method. The micromeritic properties

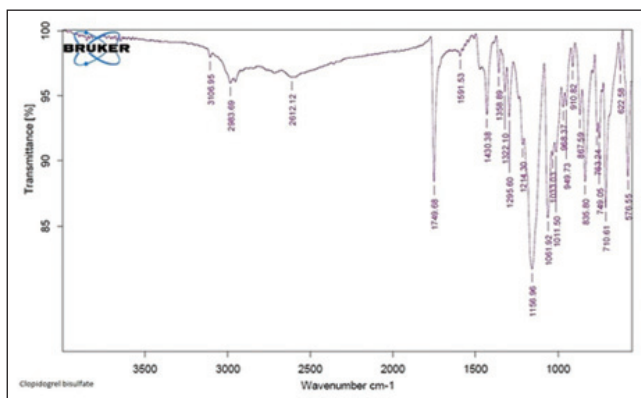


Figure 1: Fourier transform infrared spectra of pure clopidogrel bisulfate

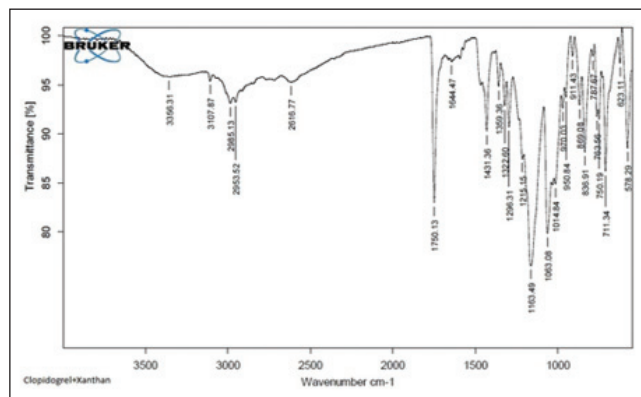


Figure 1a: Fourier transform infrared spectra of physical mixture of clopidogrel bisulfate with xanthan gum

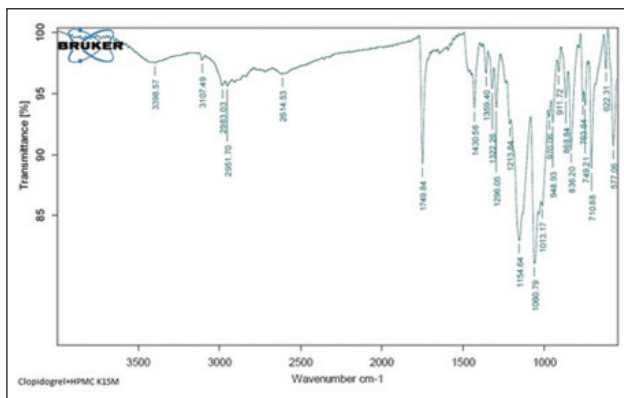


Figure 1b: Fourier transform Infrared spectra of physical mixture of clopidogrel bisulfate with hydroxypropyl methylcellulose K15M

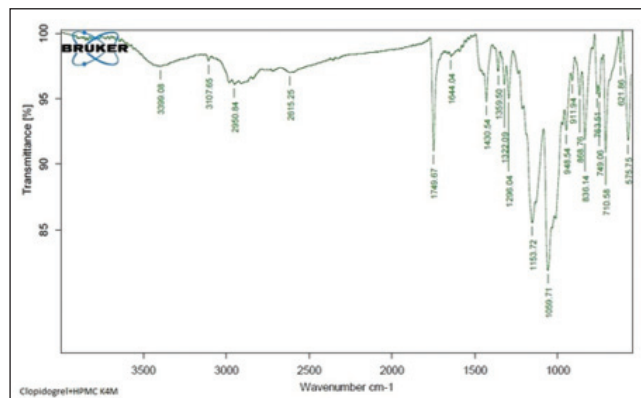


Figure 1c: Fourier transform Infrared spectra of physical mixture of clopidogrel bisulfate with hydroxypropyl methylcellulose K4M

of drug and optimized bathes of the formulations were shown in Table 3.

Characteristics of tablets

All the formulations were subjected to various quality control tests as per pharmacopoeial specifications. Post compression parameters like weight variation, thickness, hardness and friability of all the formulations were shown in the Table 4. the hardness of all the batches was found to be in the range of 4-6 Kg/cm². The friability of all the formulations was found to be <1% and the drug content of the formulations were in between 96% and 105%. Hence, all the clopidogrel floating tablets formulated by employing different concentrations of polymers and selected combinations were of good quality and fulfilled the official specifications with regard to drug content, hardness and friability.

Floating characteristics of tablets

The formulations were subjected to *in-vitro* buoyancy studies and results were shown in the Table 5. the optimized 15% w/w concentration of sodium bicarbonate was used as a gas generating agent. The effervescent mixture in the tablets produced carbon dioxide when it comes in contact with dissolution fluid. Due to the production of carbon dioxide

from the tablet, decreases the density of tablet below one making those tablets buoyant. All the formulations floated in the buffer solution for more than 12 h except formulation F4, F7, and F8 which were floated for 10, 8 and 10 h respectively, whereas F1 floated for 12 h. F2, F3, F6 and F12 formulations showed better and desired floating characteristics than F5, F9 and F11 formulations. The FLT was observed to be <2 min for all the formulations. Pictorial presentation of *in-vitro* buoyancy study results of optimized formulation (F2) was shown in Figure 2.

Percentage swelling index of all formulations were given in Table 6 and graphically shown in Figure 3. the formulations F1 and F4 starts disintegrating after 3h and 2 h respectively after complete swelling. This may be due to insufficient amount of xanthan gum and HPMC K15M to maintain the matrix integrity in their respective formulations. The formulations F7 and F8 starts disintegrating after 1 h and 2 h respectively after complete swelling. This may be due to insufficient amount and low molecular weight of HPMC K4M to maintain the matrix integrity. The swelling behavior of all the formulations is due to the formation of hydrogel by hydrophilic polymer and as the polymer concentration was increased, the percentage swelling index of tablets was found to be increased.

Table 3: Micromeritic properties of drug and optimized batches of clopidogrel blend with various polymers

Parameters	Pure drug	F2	F6	F12
Angle of repose	11.76	38.79	40.23	39.26
Bulk density (g/cc)	0.862	0.55	0.55	0.53
Tapped density (g/cc)	0.963	0.72	0.73	0.71
Carr's index (%)	10.395	23.6	24.7	25.35
Hausner's ratio	1.11	1.31	1.32	1.33

In-vitro drug release studies

All the formulations were subjected to *in-vitro* dissolution studies in 0.1 N HCl (1.2-pH) and corresponding results were shown in Figure 4a and b. The drug release extended from 5-12, 4-8 and 3-6 h as the xanthan gum, HPMC K15M and HPMC K4M concentrations varies from 20% to 30% w/w respectively. As HPMC K4M alone didn't shown desired 8 h sustained release, HPMC K4M and xanthan gum were mixed as 25% + 5%, 20% + 10% and 15% + 15% at 30% w/w concentration and drug release extended from 6 to 8 h. the initial drug release for the 1st h was varied between 18% and 70% depending upon polymer

Table 4: Physical characteristics of clopidogrel floating tablets formulated with various polymers

Formulation code	Thickness (mm)	Average weight (mg)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
F1	0.343±0.005	310.66±7.63	4.66±0.57	0.852	98.85
F2	0.403±0.005	315.66±7.63	5.33±0.28	0.721	102.31
F3	0.453±0.005	425.00±5.00	5.50±0.50	0.786	97.63
F4	0.350±0.01	308.33±6.23	4.66±0.28	0.590	97.64
F5	0.400±0.01	350.00±5.00	5.16±0.28	0.524	98.72
F6	0.450±0.01	423.33±5.77	5.33±0.57	0.459	104.97
F7	0.346±0.004	301.66±7.63	4.50±0.50	0.710	99.38
F8	0.406±0.005	345.00±5.00	4.83±0.28	0.592	96.42
F9	0.460±0.01	421.66±10.41	5.16±0.28	0.552	99.63
F10	0.456±0.011	418.33±7.63	5.00±0.50	0.592	98.74
F11	0.460±0.01	423.33±7.63	5.16±0.28	0.473	95.55
F12	0.450±0.01	418.33±7.63	5.33±0.28	0.749	103.88

*Each data represents mean±SD (n=3)

Table 5: *In-vitro* buoyancy data of clopidogrel floating tablets formulated with various polymers

Formulation code	Floating lag time in s	Total floating time in h
F1	30	12
F2	55	16
F3	78	21
F4	28	10
F5	31	14
F6	44	16
F7	21	8
F8	38	10
F9	35	13
F10	31	12
F11	45	14
F12	50	16

Table 6: Swelling index studies data of clopidogrel bisulfate floating tablets

Formulation code	Percentage swelling index of formulations				
	1 h	2 h	3 h	4 h	5 h
F1	38.10	77.14	86.03	61.27	53.02
F2	27.22	60.00	75.00	84.72	105.55
F3	29.76	54.76	75.71	94.05	113.10
F4	45.16	69.35	51.61	14.52	—
F5	23.28	53.42	64.38	73.97	90.41
F6	25.88	44.71	65.88	84.71	103.53
F7	58.33	28.33	16.66	—	—
F8	33.33	66.66	77.77	51.38	30.55
F9	28.57	52.38	66.66	77.38	85.71
F10	30.23	51.16	67.44	76.74	86.05
F11	31.33	55.42	69.88	80.72	95.18
F12	28.57	57.14	72.62	83.33	101.19

type and proportion. Formulations F1, F4 and F7 showed rapid drug release may be due to insufficient amount of xanthan gum, HPMC K15M and low molecular weight of HPMC K4M to maintain the matrix integrity in their respective tablets. Formulations F2 and F6 showed better and desired drug release profiles than F5, F8 and F9 formulations. the drug release from F3 formulation was slow and failed to release the complete drug at 8 h. Formulation F12 containing a combination of xanthan gum (15% w/w) and HPMC K4M (15% w/w) showed desired drug release than F10 and F11. Based on drug release studies, the xanthan gum (25% w/w) formulation F2 was considered better over HPMC K15M (30% w/w) formulation F6 as it showed desired drug release at low concentration.

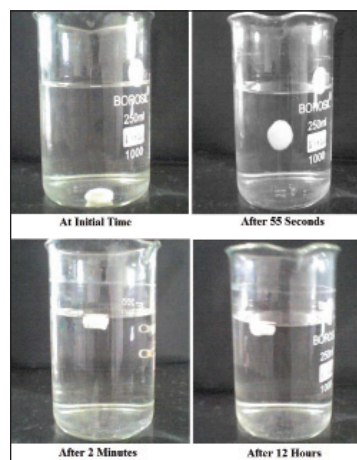


Figure 2: Pictorial presentation of *in-vitro* buoyancy study of optimized formulation (F2)

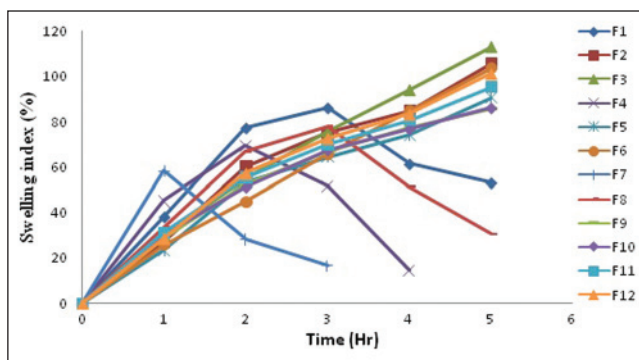


Figure 3: Swelling index profiles of different formulations of clopidogrel floating tablets

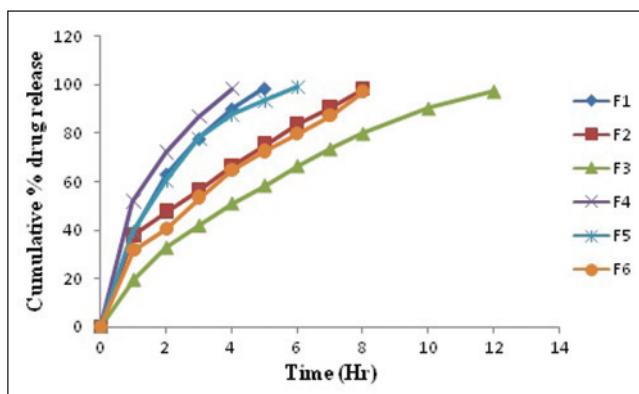
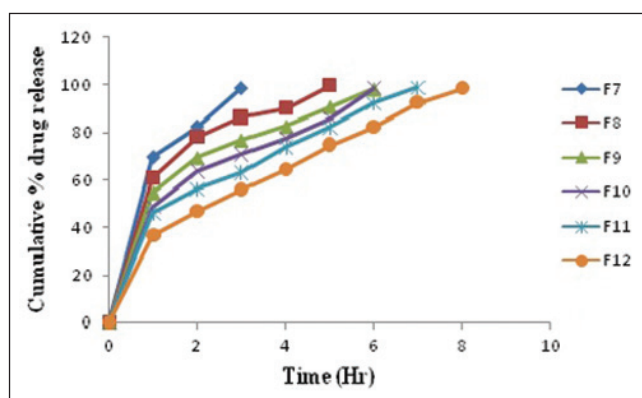


Figure 4a: Cumulative percentage drug release profiles of clopidogrel floating tablets formulated with different concentrations of xanthan gum and hydroxypropyl methylcellulose K15M

The dissolution data were fitted to popular release kinetic equations. Analysis of the drug release data as per zero order and first order kinetic models indicating that all the formulations followed first order kinetics and different *in-vitro* dissolution parameters such as dissolution rate constant (K), time required for 50% drug dissolution (T50) and 90% drug

Table 7: Kinetic parameters of clopidogrel bisulfate floating tablets formulated with various polymers

Formulation code	Correlation coefficient (r^2)				Release kinetics			Exponential coefficient (n)
	Zero order	First order	Huguchi	Peppas	K (h^{-1})	T _{50%} (h)	T _{90%} (h)	
F1	0.9024	0.9677	0.9995	0.9988	0.5822	1.2	4.0	0.466
F2	0.8951	0.9185	0.9976	0.9929	0.3404	2.0	6.8	0.473
F3	0.9338	0.9457	0.9991	0.9901	0.2223	5.4	10.4	0.654
F4	0.9109	0.9483	0.9998	0.9993	0.8629	0.8	2.7	0.463
F5	0.8848	0.9428	0.9961	0.9912	0.6355	1.1	3.6	0.521
F6	0.9305	0.9320	0.9955	0.9948	0.3244	2.1	7.1	0.553
F7	0.8854	0.9703	0.9893	0.9744	1.0222	0.7	2.3	0.452
F8	0.7557	0.9661	0.9920	0.9734	0.6516	1.1	3.5	0.469
F9	0.7594	0.9528	0.9947	0.9789	0.4995	1.4	4.6	0.482
F10	0.8197	0.8888	0.9906	0.9886	0.5364	1.3	4.3	0.468
F11	0.8463	0.9085	0.9935	0.9868	0.4624	1.5	4.9	0.499
F12	0.9067	0.9089	0.9970	0.9922	0.3810	1.8	6.0	0.488

**Figure 4b:** Cumulative percentage drug release profiles of clopidogrel floating tablets formulated with hydroxypropyl methylcellulose (HPMC) K4M and combination of HPMC K4M and xanthan gum

dissolution (T₉₀) were determined and presented in Table 7. Plots of percent release versus $\sqrt{\text{time}}$ (Higuchi plots) were found to be linear with " r^2 " > 0.9941 in all the cases indicating diffusion as the release mechanism from all the clopidogrel floating matrix tablets. In the analysis of release data as per Korsmeyer-Peppas equation, the release exponent " n " was in the range 0.452-0.654 indicating non-fickian diffusion as the release mechanism from all the clopidogrel floating matrix tablets.

The drug release rate of clopidogrel 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. The release rate constant (K) values observed from the formulations was treated statistically with one-way analysis of variance and the difference in release rate constant values was found to be statistically significant ($P < 0.05$).

CONCLUSION

FDDSs are promising dosage forms for clopidogrel, which could be a better alternative to the conventional oral dosage forms in order to improve bioavailability by increasing the gastric retention time of the drug and to minimize the side effects of the drug such as gastric bleeding and to prevent the development of drug resistance. Xanthan gum is suitable as compared to HPMC K15M and HPMC K4M polymers for the development of clopidogrel floating tablets based on the results obtained. Clopidogrel bisulfate floating tablets prepared by employing xanthan at concentration 25% w/w with 15% w/w sodium bicarbonate and 30% w/w microcrystalline cellulose (formulation F2) was the best formulation with desired *in-vitro* floating time and drug dissolution. Thus all the major objectives of this investigation were fulfilled.

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