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Controlled Release Floating Matrix Tablets for Clopidogrel Bisulfate Based on Gas Generating System: Development, Optimization and *In-Vitro* Evaluation

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ABSTRACT

The objective of the present work was to formulate and characterize a Gastro retentive drug delivery system (GRDDS) for Clopidogrel Bisulphate to improve bioavailability and to minimize the side effects such as gastric bleeding and drug resistance development. Clopidogrel floating tablets were prepared by direct compression technique by using HPMC K-100M(Hydroxy Propyl Methyl Cellulose), PEO(polyethylene oxide POLYOX WSR 303) and Carbopol 971P as release retarding agents in different concentrations. Sodium bicarbonate and microcrystalline cellulose (MCC) were used as gas generating agent and diluents respectively. Studies were carried out on floating behavior and influence of polymer type on drug release rate. All the formulations were subjected to various quality control and *in-vitro* dissolution studies. All the 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 0.381-0.561 indicating that drug release from all the formulations was by non-Fickian diffusion mechanism. The 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. Based on the results, Clopidogrel floating matrix tablets prepared by employing HPMCK100M at concentration 35% w/w (F9) was the best formulation with desired *in-vitro* floating time and dissolution. The FT-IR and DSC studies revealed that there was no interaction between drug and excipients.

Keywords: Clopidogrel bisulfate, Gas generating system, floating matrix tablets, *in-vitro* buoyancy.

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INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems[1]. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances[2,3]. However, this approach has with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastro intestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 hrs through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose[4]. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem[5].These considerations have led to the development of a unique oral controlled release dosage form with gastro retentive properties. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract [6].Controlled release Gastro retentive drug delivery systems (GRDDS) are the systems which are retained in the stomach for a prolonged period of time and thereby improved the bioavailability[7].Floating Drug Delivery Systems (FDDS) first described by Davis (1968), are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro retention time and reduces fluctuations in plasma drug concentration [8]. 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 hrs and acts by forming a disulfide bridge with the platelet ADP receptor[9]. It is practically insoluble in water at neutral pH but freely soluble at pH 1.0[10]. Following oral administration, it is well-absorbed with bioavailability of about only 50% due to poor solubility in intestinal pH. A controlled release floating formulations of Clopidogrel is required to the improve solubility of drug and to prevent the development of drug resistance and thereby improving the patient compliance. Hence, in the present investigation Clopidogrel floating tablets were formulated by direct compression technique by using sodium bicarbonate as gas generating agent and HPMC K100 M, PEO and Carbopol as release retarding agents. Tablets were evaluated for physicochemical properties, buoyancy lag time, total floating time and *In-vitro* drug release.

MATERIALS AND METHOD

Materials

Clopidogrel bisulfate was a gift sample from Natco pharm Ltd, Hyderabad. Talc, Magnesium stearate, Sodium bi carbonate, Micro crystalline cellulose was procured from S.D. Fine Chem. Ltd, Mumbai. HPMC K100M, Poly ethylene oxide, (POLYOX WSR 303), Carbopol 971P was obtained from Colorcon Asia Pvt Ltd, Mumbai. All other reagents used were of analytical grade.

Methods

Drug-excipient Compatibility studies:

FTIR Spectral studies:

Samples of Clopidogrel Bisulphate and Clopidogrel formulations were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm^{-1}at a resolution of 1.0 cm^{-1}. The powder sample was simply placed onto the ATR crystal and the sample spectrum was collected.

DSC Studies

Thermo grams of Clopidogrel Bisulphate and Formulations were recorded using Differential Scanning Calorimeter analysis (DSC, Perkin –Elmer –Pyris 6 DSC, and Salem, MA). In DSC analysis of weighed (5mg), hermetically sealed in flat-bottomed aluminum pans, and heated over a temperature range of 50-250^{0}c in an atmosphere of nitrogen (920ml/min) at a constant increasing rate of 10^{0}c/min.

Preparation of Clopidogrel bisulfate floating matrix tablets by direct compression method

The controlled release floating matrix tablets of Clopidogrel bisulphate (F1-F9) were prepared by direct compression technique as per the composition in Table 1. Clopiodogrel bisulphate, Carbopol 971P, PEO WSR 303 and MCC were passed through sieve no. #40. All the above were mixed in

geometric proportion in a polybag for 15 minutes. Talc and magnesium Stearate were passed through sieveno#60. Sifting was performed and the lubricated material was passed through the poly bag and mixed for two minutes. Composition of different trial formulations for controlled release floating matrix tablets were given in Table 1. The final weight of the controlled release floating matrix tablets was fixed to 300mg[11].Compression was adjusted to obtain tablets with hardness in the range of 4-6 kg/cm^2.

Table 1: Composition of Clopidogrel bisulphate floating matrix tablet formulations

Ingredients(mg/Tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clopidogrel Bisulfate	98	98	98	98	98	98	98	98	98
PEO (POLYOX WSR 303)	45	75	105	-	-	-	-	-	-
Carbopol 971P	-	-	-	45	75	105	-	-	-
HPMC K 100 M	-	-	-	-	-	-	45	75	105
MCC	102	72	42	102	72	42	102	72	42
Sodium bicarbonate	45	45	45	45	45	45	45	45	45
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total weight	300	300	300	300	300	300	300	300	300

Evaluation parameters

Evaluation of pre compression parameters of the powder blends [12]

Pre compression parameters of the prepared powder blend of all the formulations were studied by determining the Bulk density, Tapped density, Compressibility Index, Hausner's ratio and Angle of repose

Evaluation of Post compression parameters of floating Clopidogrel tablets[13]

The compressed floating Clopidogrel tablets were subjected to various physical tests which include hardness, friability, weight variation, thickness and drug content uniformity**.**

Hardness test

The hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-66, India). The results reported were average of 6 tablets for each formulation.

Friability test

For each formulation 10 tablets were weighed, placed in Friabilator (M/S Campbell Electronics, India) and were subjected to 100 rotations in 4min. The tablets were reweighed and friability was calculated by the following formula:

$$\text{Friability} = (W_2 - W_1 / W1) \text{ X } 100$$

Where W_1 is the initial weight and W_2 is the final weight of the tablets.

Weight variation

The individual and total weight of 20 tablets from each batch was determined. Percentage deviation of the individual weights from the average weights was calculated.

Tablet thickness

The thickness of five tablets was measured using vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined. The diameter was also determined using vernier calipers.

Drug Content Uniformity

Ten tablets were weighed and powdered. The accurately weighed powder sample equivalent to 100mg of Clopidogrel bisulfate was dissolved in 100 ml of 0.1N hydrochloric acid. Then the solution was filtered, diluted suitably and absorbance was measured at 270.4nm using an Elico SL 150 UV-visible spectrophotometer (Elico Ltd; Hyderabad).

***In-vitro* buoyancy[14, 15]:**

The *In-vitro* buoyancy was characterized by floating lag time and total floating time. As per the method described by Rosa et al, the tablets were placed in a 100 ml beaker containing 0.1N HCl, which was maintained at 37°C. The time required for the tablet to rise to the surface of the medium was determined as the buoyancy lag time or floating lag time. The duration of which the dosage form constantly remained on the surface of medium was determined as the total buoyancy time or total floating time.

***In-vitro* dissolution studies[16, 17]**

In-vitro dissolution studies were carried out in 900 mL of 0.1N HCl as dissolution medium using USP XXI type II (Paddle method) Dissolution Rate Test Apparatus (LABINDIA, DS 8000) at 50 rpm for 12hrs. The temperature was maintained constant at 37±0.5^{0}C. Samples were withdrawn at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12hrs and each sample withdrawn was replaced with an equal amount of fresh medium, to maintain sink conditions throughout the experiment. Concentration of drug in each sample was determined at 270.4 nm after suitable dilution of the samples. The amount of drug present in the samples was calculated using standard curve. The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The prepared floating matrix tablets were evaluated for thickness, weight variation, hardness, friability, drug content, *in-vitro* buoyancy studies and *in-vitro* drug dissolution studies. All the studies were performed in triplicate, and results are expressed as mean ± SD.

Drug Excipient Compatibility Studies

a) FTIR Spectral Analysis

FTIR spectra of pure Clopidogrel bisulphate and the optimized formulations are shown in Figures 1 to 3. The FTIR spectrum of Clopidogrel bisulphate showed Stretching vibrations at1171.24 cm^{-1} for C-N bond in Pyridine ring, 714.50 cm-1 for C-Cl bond in phenyl ring, 1475.65 cm^{-1} for C=C in aromatic alkane and 1751.44 cm^{-1} for ester. All these characteristic bands were all retained in formulations indicating that there is no interaction between drug and polymers.

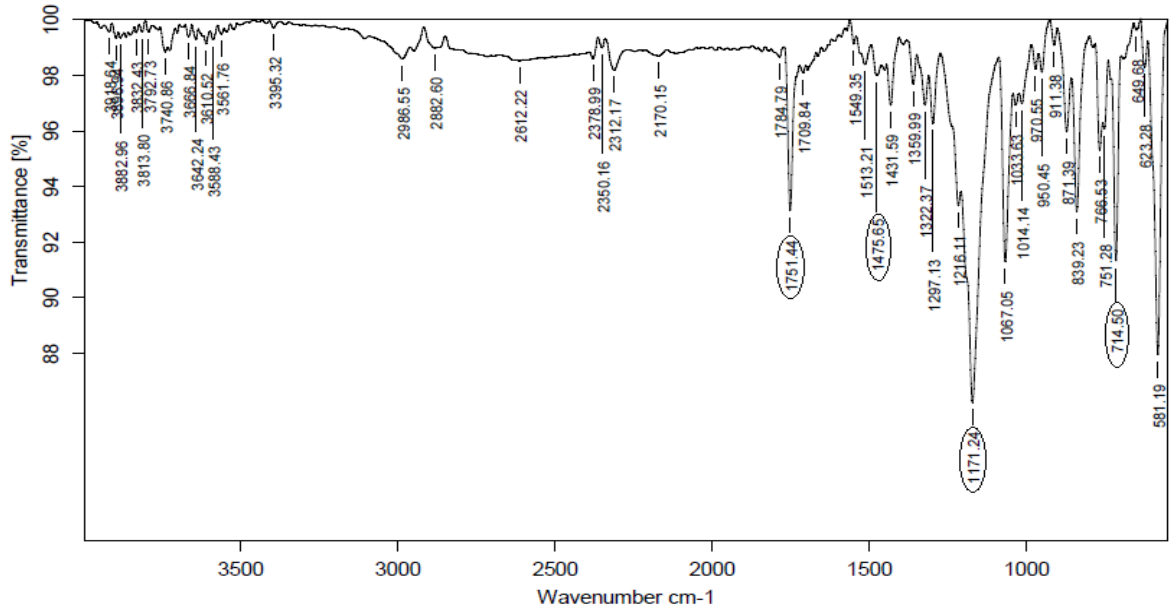


Figure 1: FTIR Spectrum of pure Clopidogrel bisulphate

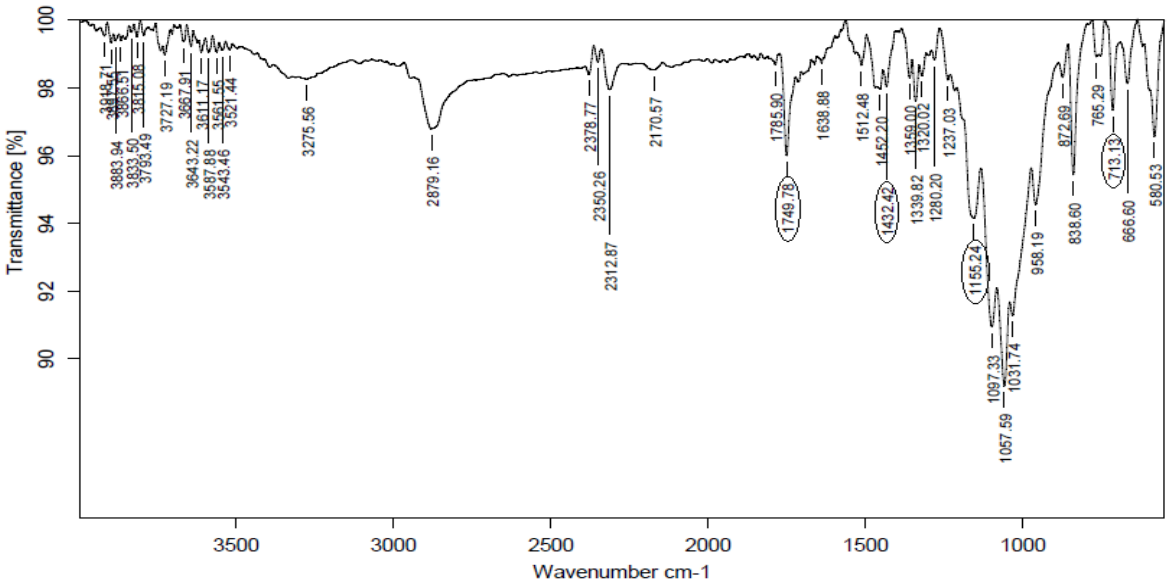


Figure 2: FTIR Spectrum of Formulation F9

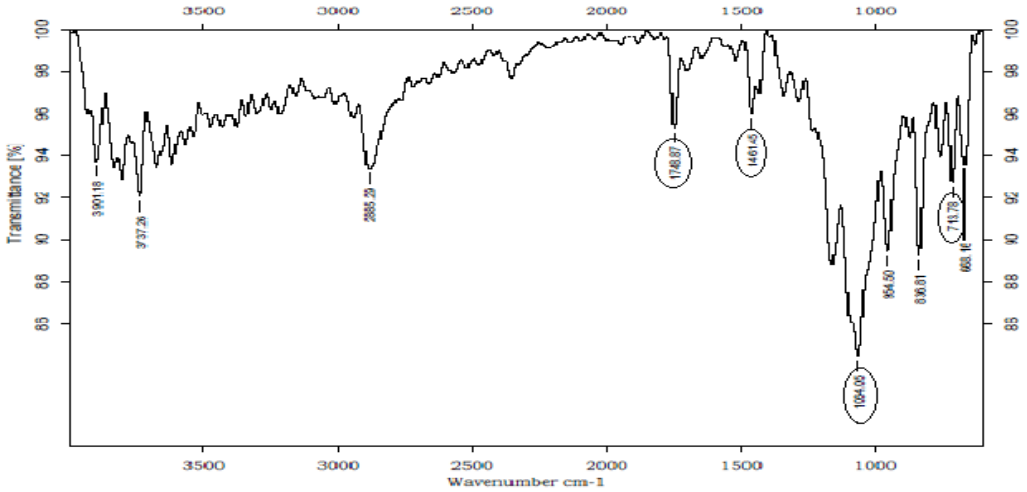


Figure 3: FTIR Spectrum of Formulation F3

b) DSC analysis

DSC thermograms of Clopidogrel bisulphate and optimized formulations were shown in Figures 4 and 5. Clopidogrel showed sharp endothermic peak at 184.11^{0}C corresponding to its melting point. Clopidogrel formulations showed weak peaks compared to pure Clopidogrel. Overall DSC curves indicate that there is no interaction observed between drug and excipients.

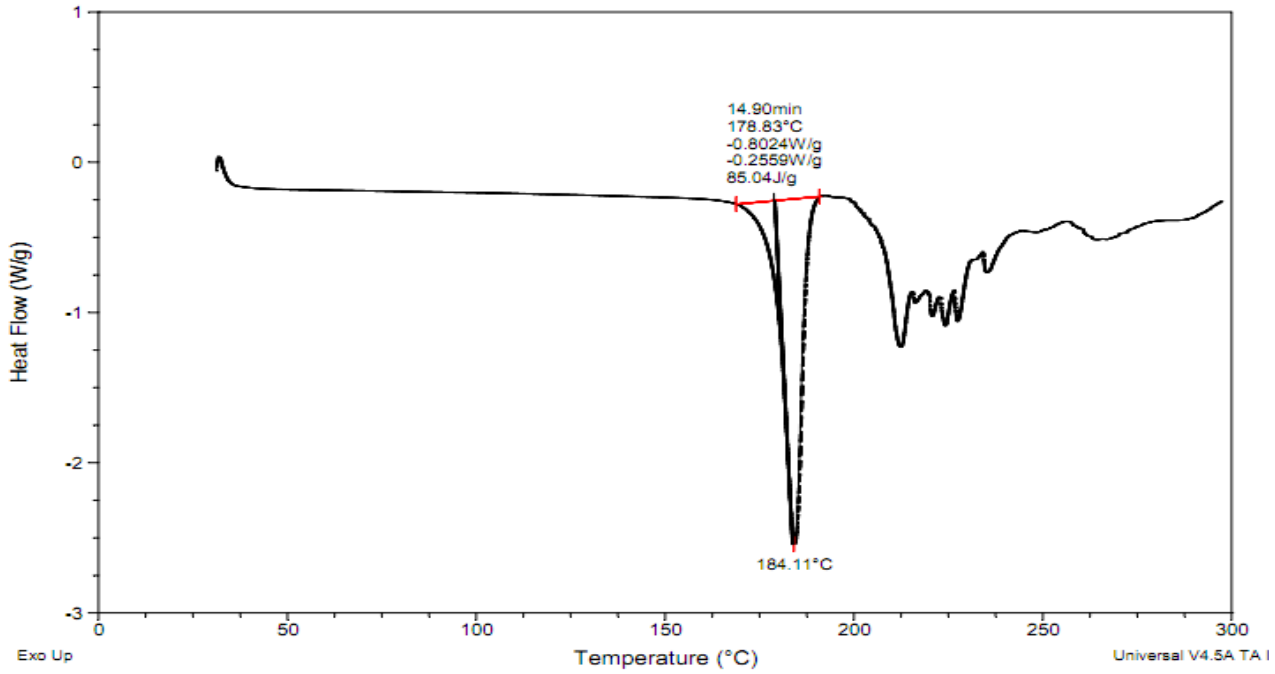


Figure 4: DSC thermo gram of pure Clopidogrel bisulphate

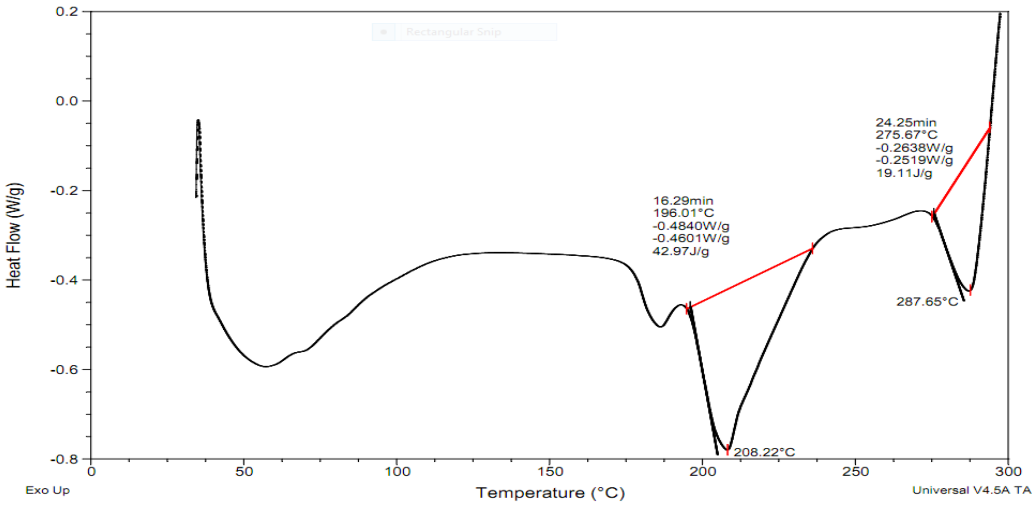


Figure 5: DSC thermo gram of formulation F9

Pre Compressional parameters

The powders prepared for compression of floating tablets were evaluated for their flow properties, the results were shown in Table 2. Bulk density and tapped density for all the formulations were within the range of 0.513 ± 0.05 to 0.592 ±0.03 and 0.597 ± 0.03 to 0.684 ± 0.06 indicating that the powder was not bulky. The Carr's index for all the formulations was found to be below 15% indicating that the powders have good compressibility properties. The Hausner's ratio for all the formulations was found to be <1.25, indicating good flow properties. Angle of repose was in the range of 25.42 ± 0.51 to 28.37 ± 1.24 which indicates good flow of the powder for all formulations.

Table 2: Pre Compression Parameters of Clopidogrel bisulphate floating matrix tablets

Formulations	Bulk Density (g/mL)	Tapped density (g/mL)	Compressibility Index (%)	Hausner's Ratio	Angle of repose (θ)
F1	0.574 ± 0.02	0.680 ± 0.05	16.75 ± 1.02	1.15 ± 0.36	27.12 ± 0.67
F2	0.527 ± 0.01	0.664 ± 0.02	15.93 ± 1.54	1.17 ± 0.48	28.23 ± 0.72
F3	0.540 ± 0.02	0.597 ± 0.03	12.81 ± 0.95	1.14 ± 0.50	25.42 ± 0.51
F4	0.564 ± 0.04	0.620 ± 0.01	14.26 ± 1.47	1.21 ± 0.37	25.56 ± 0.90
F5	0.579 ± 0.02	0.635 ± 0.07	12.51 ± 1.32	1.16 ± 0.24	26.95 ± 0.53
F6	0.513 ± 0.05	0.652 ± 0.05	13.65 ± 1.73	1.14 ± 0.11	28.37 ± 1.24
F7	0.531 ± 0.03	0.599 ± 0.02	15.12 ± 1.56	1.17 ± 0.58	27.79 ± 1.51
F8	0.584 ± 0.01	0.684 ± 0.06	16.01 ± 1.79	1.20 ± 0.31	26.51 ± 0.72
F9	0.592 ± 0.03	0.623 ± 0.03	15.27 ± 1.64	1.14 ± 0.45	28.17 ± 0.99

Post Compressional parameters

The tablets of 300mg were subjected for evaluation of the post Compressional parameters such as hardness, friability, weight variation, thickness and drug content uniformity. The results complied with the pharmacopoeial limits. The values were depicted in Table 3. The drug content of the

formulations was found to be uniform as the amount of the active ingredients in each of the 10 units tested were within the range of 97.54 ± 0.05 to 99.72 ± 0.05% indicating uniform mixing of the drug, binders and other excipients. The mean values for the hardness, weight variation and thickness were found to be in the range of 5.16 ± 0.1 to 5.39 ± 0.2, 295.63 ± 1.7 to 305.29 ± 1.11 and 2.58 ± 0.04 to 2.66 ± 0.05 respectively. All the formulations exhibited friability less than 0.8% during the friability determination.

Table 3: Post Compression Parameters of Clopidogrel bisulphate floating matrix tablets

Formulations	Hardness (Kg/cm^2)	Friability (% wt loss)	Weight variation(mg)	Thickness (mm)	Drug content(%)
F1	5.39 ± 0.2	0.41 ± 0.17	304.22 ± 2.1	2.65 ± 0.04	98.57 ± 0.02
F2	5.22 ± 0.4	0.37 ± 0.29	303.49 ± 1.3	2.64 ± 0.06	98.43 ± 0.06
F3	5.16 ± 0.1	0.33 ± 0.43	300.56 ± 1.6	2.59 ± 0.03	99.14 ± 0.04
F4	5.25 ± 0.2	0.38 ± 0.56	297.41 ± 1.4	2.66 ± 0.05	97.54 ± 0.05
F5	5.18 ± 0.4	0.34 ± 0.49	295.63 ± 1.7	2.63 ± 0.03	98.26 ± 0.02
F6	5.28 ± 0.6	0.29 ± 0.74	300.27 ± 1.9	2.65 ± 0.02	99.20 ± 0.06
F7	5.35 ± 0.4	0.36 ± 0.50	302.11 ± 1.4	2.64 ± 0.02	99.36 ± 0.04
F8	5.27 ± 0.3	0.54 ± 0.12	305.29 ± 1.1	2.61 ± 0.03	99.72 ± 0.05
F9	5.20 ± 0.1	0.46 ± 0.25	300.38 ± 1.6	2.58 ± 0.04	97.89 ± 0.07

***In-vitro* buoyancy studies**

Buoyancy studies were performed using pH1.2 (0.1 N HCL) buffer at 37^0C. All the formulations were found to exhibit short lag times due to presence of sodium bicarbonate. Formulations prepared with PEO showed shorter lag times compared to Carbopol and HPMC K100 M Formulation F9 containing HPMC K100 M, showed floating lag time of 58 sec and total floating time of more than 12hrs. The results were given in Table 4 and shown in Figure 6.

Table 4: *In-vitro* buoyancy study data for Clopidogrel bisulphate

Formulations	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
F1	20	8
F2	46	10-12
F3	53	14
F4	26	12
F5	40	14
F6	67	16-18
F7	33	8
F8	49	13
F9	58	16-18

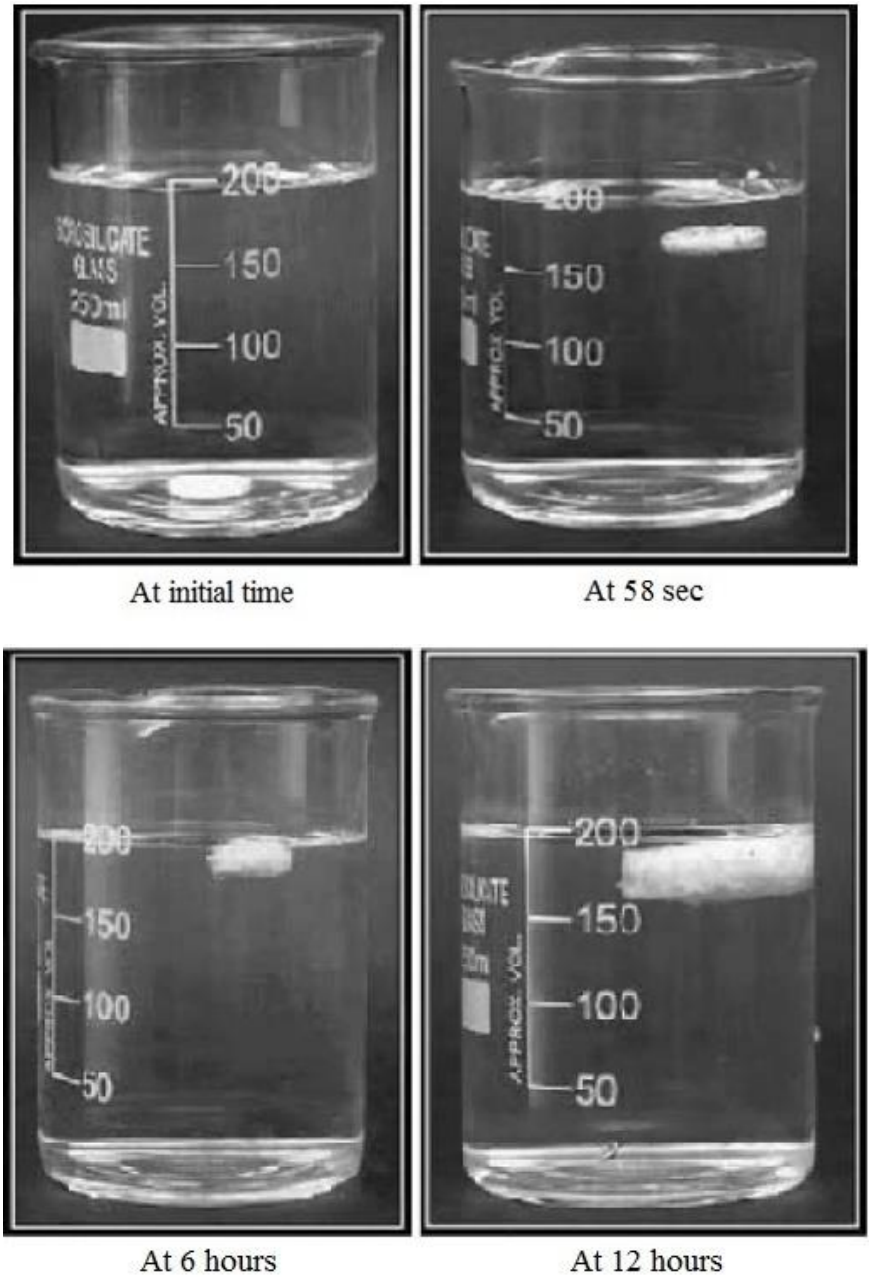
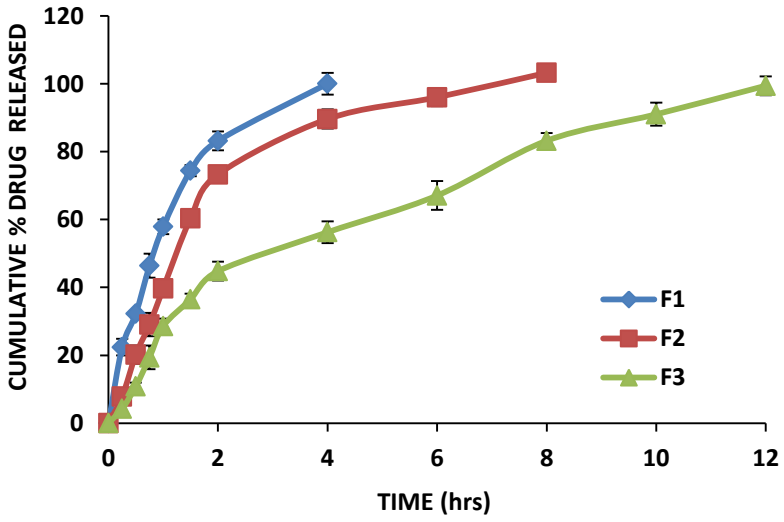


Figure 6: *In-vitro* buoyancy studies for Clopidogrel bisulfate

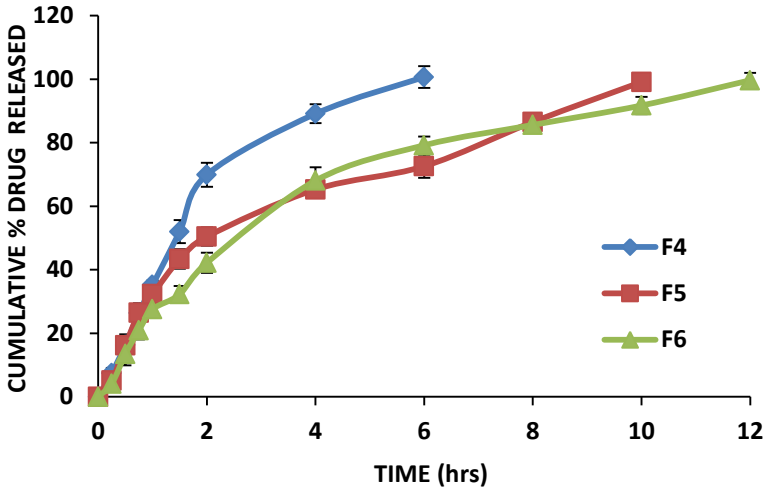
***In-vitro* dissolution studies**

In-vitro dissolution studies were carried out in 900 mL of 0.1N HCl as dissolution medium using USP XXI type II (Paddle method) Dissolution rate test apparatus (LABINDIA, DS 8000) at 50 rpm for 12hrs. The temperature was maintained constant at 37±0.5^{0}C. The dissolution experiments were conducted in triplicate. The formulations F1, F2 and F3 containing drug and PEO in 15%, 25% and 35% concentrations respectively showed 100.3 ± 0.19, 103.22 ± 2.37 and99.42 ± 2.79 releases at the end of 4h, 8h and 12h respectively. The comparative profiles were shown in Figure 7. F1 showed complete Clopidogrel release in 4hr which may be due to less polymer concentration

in the formulation. F2 and F3 showed prolonged drug release rates when compared to F1 that can be attributed to increase in polymer concentration. Increase in polymer concentration would have resulted in formation of more uniform gel barrier around the tablet therefore decreasing the drug release. The formulations F4, F5 and F6 containing drug and Carbopol as release retardant polymer in 15%, 25% and 35% respectively showed 100.67±3.44, 99.13 ± 2.80 and98.68 ± 2.35 Clopidogrel release at the end of 6h, 10h and12h respectively. The comparative profiles were shown in Fig7. F6 formulation with higher concentration of HPMC K100 M showed prolonged drug release rates compared to F4 and F5. Prolonged release rates observed with Carbopol formulations (F4, F5 and F6) when compared to formulations with PEO as release retardant polymer (F1, F2 and F3) can be attributed to higher viscosity of Carbopol forming a more viscous gel barrier around the tablets. The formulations F7, F8 and F9 containing HPMC K100M as polymer in 15%, 25% and 35% respectively showed 102.58 ± 1.20, 99.54 ± 2.01 and90.13 ± 2.64 Clopidogrel release at the end of 8, 12, 12hrs respectively. The comparative profiles were shown in Fig 7. HPMC K100M formulations showed more controlled release rates compared to other formulations and this may be due to higher viscosity of HPMC K100M which resulted in less hydration of formulations in dissolution medium. Overall, the dissolution profiles of the formulations (F1-F9) clearly indicated a controlled release pattern over a period of 6-12 hrs. The controlled release of Clopidogrel from the tablets can be attributed to presence of release retardant materials, HPMC, PEO and Carbopol. These polymers swelled upon contact with dissolution medium and formed gel layer on surface of tablets. The gel layer had retarded further uptake of fluid and subsequent drug release.



(A)



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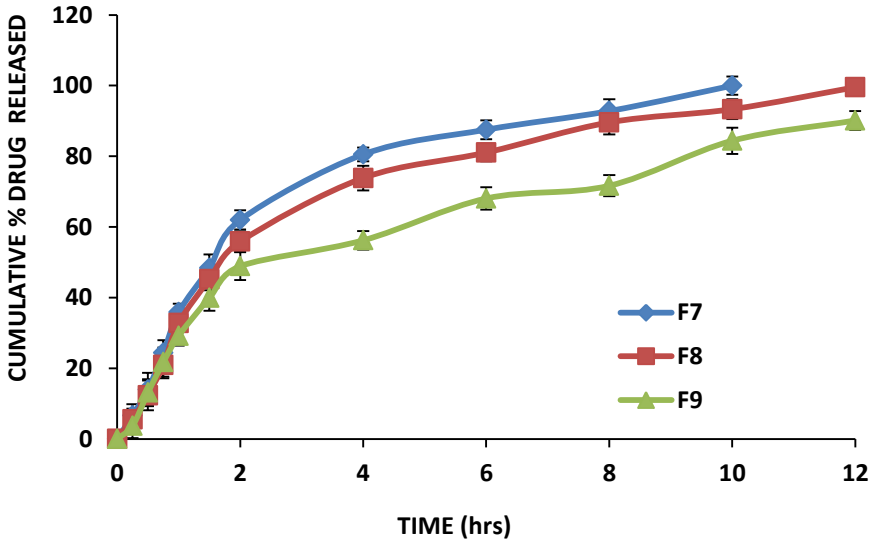

(C)

Figure 7: *In-Vitro* drug release profile of Clopidogrel bisulfate floating matrix tablets formulated with (A) PEO; (B) Carbopol 971P; (C) HPMC K100 M.

Drug Release Kinetics

To ascertain the mechanism of drug release, the *in-vitro* drug release data was fitted into various release kinetics models such as zero order, first order, Higuchi and Peppas models. For formulations F1-F9 when cumulative % drug release values were plotted against time, straight lines were obtained indicating that the drug release from the floating tablets followed first order kinetics. The regression coefficients (R^2) obtained for first order kinetics were found to be higher when compared to zero order kinetics indicating that drug release, from all the formulations followed first order kinetics. To evaluate the drug release mechanism from the tablets, plots of %

drug released vs. square root of time were plotted. In all the cases the plots were found to be linear indicating that the drug release mechanism from the floating tablets might be diffusion controlled as proposed by Higuchi for insoluble matrices. To confirm the diffusion mechanism, the data was fitted into korsmeyer-peppas equation which resulted in "n" value between 0.381 and 0.561 thus indicating the mechanism of drug release followed anomalous transport with slow erosion of polymeric matrix followed by diffusion of drug resulting in linear drug release over a prolonged period of time. The release kinetic data were given in the Table 5.

Table 5:*In-vitro* drug release kinetic data for Clopidogrel bisulphate floating matrix tablets

Formulations	Zero order		First order		Higuchi		Peppas	
	K ($mol.L^{-1}h^{-1}$)	R^2	K (h^{-1})	R^2	K ($mg/hr^{1/2}$)	R^2	'n' Value	R^2
F1	23.37	0.812	1.141	0.984	54.30	0.968	0.381	0.949
F2	12.39	0.795	0.567	0.995	41.03	0.934	0.412	0.889
F3	7.897	0.920	0.326	0.851	30.32	0.986	0.483	0.991
F4	16.96	0.875	0.739	0.971	46.92	0.957	0.561	0.925
F5	8.991	0.889	0.365	0.846	32.08	0.978	0.445	0.983
F6	8.157	0.897	0.363	0.855	31.63	0.980	0.534	0.977
F7	9.597	0.821	0.403	0.959	35.06	0.947	0.418	0.942
F8	7.940	0.833	0.357	0.907	31.51	0.953	0.416	0.957
F9	6.894	0.866	0.174	0.971	27.02	0.967	0.408	0.968

CONCLUSION

In the present investigation Clopidigrel Bisulphate floating formulations were prepared by direct compression technique using Sodium bicarbonate as gas generating agent and HPMC K4M, PEO and Carbopol as release retarding agents. All the formulations showed good flow properties and mechanical properties. The drug release from the formulations is affected by polymer viscosities and concentration. As concentration of polymer increased, the drug release was found to be retarded. The drug release from all formulations was sufficiently controlled and the drug release was found to be more controlled in the order of HPMC K 100M > CARBOPOL > PEO. The F9 formulation containing 35% w/w of HPMC K100M showed more controlled drug release rates compared to other formulations. Hence it can was concluded that controlled release of Clopidogrel bisulfate can be achieved by formulating effervescent-based floating drug delivery system was promising approach to improve the controlled release floating matrix tablet formulations of Clopidogrel Bisulphate.

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