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PREFORMULATION, FORMULATION DEVELOPMENT AND DRUG RELEASE STUDIES OF CLOPIDOGREL BISULPHATE FLOATING MICROBALLOONS

S. Ramya Krishna *, A. Ramu, S. Vidyadhara and A. Prameela Rani

Department of Pharmaceutics, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur - 522510, Andhra Pradesh, India.

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Correspondence to Author:
Mr. S. Ramya Krishna

Department of Pharmaceutics, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur - 522510, Andhra Pradesh, India.

E-mail: ramya.krishna.seelam@gmail.com

ABSTRACT: Multi particulate systems are of greater importance than the single unit dosage forms in oral drug delivery. Floating micro balloons are among the best methods to increase gastric retention among all the multi particulate drug delivery systems. They offer more reproducible drug absorption, reduce the risk of local irritation and improve the bioavailability of the drug. In the current research work, clopidogrel, a BCS class - II drug, was formulated as controlled release micro balloons using ethyl cellulose as polymer and span 80 as the surfactant. The pre-formulation studies *viz.* solubility, partition coefficient, micromeritics were carried for the Clopidogrel bisulphate pure drug, and the drug excipient compatibility studies were carried using Fourier transform infrared spectrophotometer and Differential Scanning Calorimeter. Different formulations of floating micro balloons were prepared by solvent evaporation method by altering five process and formulation factors *viz.* concentration of surfactant, the volume of solvent, volume of internal phase, the concentration of polymer, speed of rotation. All the Clopidogrel micro balloons were subjected to *in-vitro* drug release and kinetic studies, and the results were analyzed suitably. The highest drug release rate was found to be 0.274 h -1 in the F15 formulation. The Peppas n values of all the formulations were above 0.5, indicating that the drug release mechanism of all formulated clopidogrel micro balloons was non-fickian diffusion.

INTRODUCTION: Clopidogrel bisulphate is a thienopyridine anti-platelet drug known chemically as methyl (+)-(S)-α -(2chlorophenyl)- 6, 7 dihydrothieno [3,2-c] pyridine-5 (4H)-acetate sulphate (1:1). It has a chemical formula ($C_{16}H_{18}C_lNO_6S_2$) and a molecular weight of 419.9 g/mol. Clopidogrel bisulphate, an anti-platelet agent [1].

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Structurally and pharmacologically similar to ticlopidine, is used to inhibit blood clots in a variety of conditions such as peripheral vascular disease, coronary artery disease and cerebrovascular disease. The drug specifically and irreversibly inhibits the P2Y12 subtype of adenosine diphosphate receptor found on the membranes of platelet cells, which is important in aggregation of platelets and cross-linking by the protein fibrin.

According to the Biopharmaceutical Classification System of drugs, Clopidogrel bisulphate comes under the class II drugs, which possess low solubility and high permeability where the bioequivalence problems may arise. For the drugs

with poor water solubility, drug release is the rate-limiting step, and hence such drugs are to be formulated so that their bioavailability is enhanced. Pre formulation studies [2, 3] is the prior step in the rational development of a drug into a suitable dosage form. It can be defined as determining the physical, chemical, and mechanical properties of a new drug substance alone and when combined with excipients. This could provide important information for formulation design or support the need for molecular modification. Every drug has intrinsic chemical and physical properties, which have been considered before developing a pharmaceutical formulation. This property provides the framework for drugs in combination with pharmaceutical ingredients in the fabrication of dosage form. The objective of the pre-formulation study is to develop the elegant, stable, effective, and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients, and establish physicochemical parameters of new drug substances.

Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms, and stability plays an important role in the pre-formulation study. The overall objective of pre-formulation studies is to generate information useful in developing stable and sustained release dosage forms with improved bioavailability. Clopidogrel bisulfate being a moderate acidic pKa drug; its absorption is pH-dependent and has a better absorption in the stomach and poor absorption in the intestine. When formulated into a normal controlled release dosage form, it crosses both the stomach and intestine due to gastric emptying; thereby, the plasma concentration cannot be maintained as the absorption decreases in the intestine.

Hence formulating clopidogrel into micro balloons helps in increasing the gastric retention time 4th ere by maintaining constant plasma concentration. In the current research work, clopidogrel bisulfate was formulated as floating micro balloons by emulsion solvent evaporation technique to improve its gastric residence time, thereby enhancing its bioavailability. In the current research work, one of the major quality characteristics of controlled release multi particulate systems *i.e.,* drug release profile and the release kinetics, were studied.

MATERIALS AND METHODS: Clopidogrel bisulfatepure drug was received as a gift sample from Mankind Pharma, Hyderabad. Ethylcellulose, span 80, methanol, diethyl ether, and liquid paraffin were purchased from SD Fine Chemicals Ltd, Mumbai.

Preformulation Studies:

Construction of Calibration Curve: 50 mg of Clopidogrel bisulphate was dissolved in 5mL of methanol and made up to 50 mL with 0.1 M HCl buffer in a 50 mL of the volumetric flask (stock solution). 10 mL of the stock solution was taken, and to that 100 mL of 0.1 M, HCl was added to attain the working standard of 100 µg/mL. From that, series of dilutions were made to get 10, 20, 30, 40, 50 µg/mL concentrations.

The absorbance was measured using a double beam UV-visible spectrophotometer (Thermo Scientific) at wavelength maxima of 240 nm. From the obtained absorbance values, a standard calibration curve was constructed.

Physical and Physicochemical Properties of Clopidogrel Bisulphate

Solubility Determination: The solubility [5, 7] of Clopidogrel bisulphate was determined by using the shake flask method. In this method, the drug was added to 10 mL of 0.1 M HCl and shaken at a predetermined time. An excess amount of Clopidogrel was added to a saturation level. The saturation was confirmed by observing the presence of undissolved material. The flask was kept on an orbital shaker for 24 h. After a specified time, the slurry was filtered, and the filtrate was collected for analysis. The sample was analyzed after suitable dilution using a UV-Visible spectrophotometer at the maximum wavelength of 240 nm.

Partition Coefficient Determination: Log P of Clopidogrel bisulphate was determined by using the shake flask method 8.1 gm of the drug was dissolved in a mixture of 10 mL chloroform and 10 mL water, both phases were then mixed together in a separating funnel and shaken for about 1 h and then allowed to stand long enough for the phases to separate, and the concentration of solute was measured in each solvent by using UV-Visible spectrophotometer at the maximum wavelength of 240 nm.

Melting Point Determination: Capillary method 9 was used to determine the melting point of Clopidogrel bisulphate. The open end of the capillary tube was initially sealed by heating. Then the capillary tube was filled with Clopidogrel drug sample. The powder is then pushed to the bottom of the tube by repeatedly pounding the bottom of the capillary against a hard surface. A sample height between 2.0 mm to 3.0 mm was maintained for optimum results and reproducibility. Then the capillary tube was kept in the melting point apparatus, and the temperature at which the drug was melted was noted.

Micrometric Properties: Micro balloons were characterized for their micrometric [10, 11] properties such as particle size, angle of repose, compressibility index, and Hausner's ratio.

Bulk Density: 5 gms of accurately weighed drug (clopidogrel) was placed into 10 mL measuring cylinder. The volume occupied by the drug was noted without disturbing the cylinder, and the bulk density was calculated using the below equation (values expressed in gm/cm3)

Bulk density = Weight of sample/ Volume of sample

Tapped Density: 5 gms of the drug (clopidogrel) was placed in 10 mL measuring cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface for 100 times, from a height of one inch. The final volume was recorded, and the tapped density was calculated by the following equation (values expressed in gm/cm3)

Tapped density = Weight of sample/ Tapped Volume of sample

Carr's Index (%): The Carr's index is frequently used as an indication of the flowability of a powder. A Carr's index greater than 25% is considered to be an indication of poor flowability and below 15% of good flowability. Flow property of blend depends upon Compressibility index. The Carr's Index is an indication of the compressibility of a powder. It is calculated by the formula.

Carr's Index (%) = (Tapped density-Bulk density)/ Tapped density × 100

Angle of Repose (θ): The angle of repose is indicative of the flowability of the substance. A funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample powder was allowed to flow from the funnel, so the height of the pile just touches the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters. The angle of repose is calculated by using this formula:

Where, θ is angle of repose, h is height of the pile r is the radius of the pile. $\tan \theta = h/r = \theta = \tan^{-1} h/r$

Hausner's Ratio: Hausner's ratio is an indication of the compressibility of a powder. It is calculated by the formula:

Hausener's ratio = Tapped density/ Bulkdensity × 100

Hausner's ratio is frequently used as an indication of the flowability of the powder. Hausner's ratio value greater than 1.25 is considered to be an indication of poor flowability. The observations for the flow property determinations are recorded.

Drug-Excipient Compatibility Studies:

FT-IR Spectroscopy: The physicochemical compatibility between Clopidogrel and ethylcellulose used in the research was carried out by subjecting to IR spectral studies [12] using Fourier transform infrared spectrophotometer, Bruker. The samples were prepared by mixing 100 mg of drug with 100 mg of ethylcellulose used to prepare floating microspheres. These samples were scanned under diffuse reflectance mold and plotted the graph by the KBR pellet method, and spectra were recorded in the wavelength region between 4000 cm^{-1} to 400 cm^{-1}. The spectra obtained for the pure drug were compared with that of the physical mixtures of the drug with polymer.

DSC Study: Differential Scanning Calorimeter [13, 15] (DSC) allows the fast Evaluation of possible incompatibilities because it shows changes in the appearance, Shift of melting endotherms and exotherms and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drugs and other excipients were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10 °C /min over a temperature range of 50 °C to 300 °C.

Preparation of Floating Micro Balloons [16, 17]: The polymer is dissolved in a mixture of methanol

and diethyl ether, to which drug was added and dissolved by placing on vertex mixture for 2 minutes to get the organic phase. Liquid paraffin was taken in another beaker, and 0.0% or 0.25% or 0.5% v/v of span 80 was added to it to get the oily phase. The oil phase was placed under the mechanical stirrer and operated at 400/550/700 rpm. The organic phase was added drop by drop to the oil phase under stirring. Stirring was continued for 4-5 h until the organic solvents were evaporated completely to yield hollow microspheres. The obtained hollow microspheres were washed with petroleum ether to remove paraffin and then dried. The compositions of various formulations were shown in **Table 1.**

TABLE 1: FORMULATION CODES OF CLOPIDOGREL BISULPHATE MICROBALLOONS

Standard order	Run order	Formulation code	Factor A	Factor B	Factor C	Factor D	Factor E
1	24	F1	50.00	20.00	7.50	0.25	550.00
2	25	F2	75.00	20.00	7.50	0.25	550.00
3	21	F3	50.00	60.00	7.50	0.25	550.00
4	40	F4	75.00	60.00	7.50	0.25	550.00
5	31	F5	62.50	40.00	5.00	0.00	550.00
6	36	F6	62.50	40.00	10.00	0.00	550.00
7	7	F7	62.50	40.00	5.00	0.50	550.00
8	16	F8	62.50	40.00	10.00	0.50	550.00
9	15	F9	62.50	20.00	7.50	0.25	400.00
10	20	F10	62.50	60.00	7.50	0.25	400.00
11	5	F11	62.50	20.00	7.50	0.25	700.00
12	3	F12	62.50	60.00	7.50	0.25	700.00
13	18	F13	50.00	40.00	5.00	0.25	550.00
14	6	F14	75.00	40.00	5.00	0.25	550.00
15	26	F15	50.00	40.00	10.00	0.25	550.00
16	19	F16	75.00	40.00	10.00	0.25	550.00
17	28	F17	62.50	40.00	7.50	0.00	400.00
18	23	F18	62.50	40.00	7.50	0.50	400.00
19	34	F19	62.50	40.00	7.50	0.00	700.00
20	2	F20	62.50	40.00	7.50	0.50	700.00
21	17	F21	62.50	20.00	5.00	0.25	550.00
22	14	F22	62.50	60.00	5.00	0.25	550.00
23	38	F23	62.50	20.00	10.00	0.25	550.00
24	11	F24	62.50	60.00	10.00	0.25	550.00
25	33	F25	50.00	40.00	7.50	0.00	550.00
26	41	F26	75.00	40.00	7.50	0.00	550.00
27	32	F27	50.00	40.00	7.50	0.50	550.00
28	10	F28	75.00	40.00	7.50	0.50	550.00
29	13	F29	62.50	40.00	5.00	0.25	400.00
30	1	F30	62.50	40.00	10.00	0.25	400.00
31	4	F31	62.50	40.00	5.00	0.25	700.00
32	22	F32	62.50	40.00	10.00	0.25	700.00
33	9	F33	50.00	40.00	7.50	0.25	400.00
34	37	F34	75.00	40.00	7.50	0.25	400.00
35	30	F35	50.00	40.00	7.50	0.25	700.00
36	12	F36	75.00	40.00	7.50	0.25	700.00
37	8	F37	62.50	20.00	7.50	0.00	550.00
38	35	F38	62.50	60.00	7.50	0.00	550.00
39	27	F39	62.50	20.00	7.50	0.50	550.00
40	39	F40	62.50	60.00	7.50	0.50	550.00
41	29	F41	62.50	40.00	7.50	0.25	550.00

Characterization of Micro Balloons [18, 22]:

Drug Release Studies: The *in-vitro* dissolution studies were performed for all the floating micro balloons utilizing USP II Dissolution test apparatus using 900 mL of 0.1M HCl as the dissolution medium. The apparatus was set at 100 rpm, and the sample was withdrawn every 30 min for the first 2 h and thereafter for every 1hr up to 12 h. The samples were analyzed after suitable dilutions if

necessary by using a UV-Visible spectro-photometer at the maximum wavelength of 240 nm.

Drug Release Kinetic Studies: Data obtained from *in-vitro* release studies are fitted to various kinetic equations to find out the mechanism of drug release. The kinetic models used are:

Qt = K0 t (zero-order equation), ln Qt = ln Q0 - K1 t (first-order equation), Qt = Kh t1/2 (Higuchi equation)

Where Qt is the amount of drug release in time t, Q0 is the initial amount of drug in the microsphere, and K0, K1, and Kh are rate constants of zero order, first order, and Higuchi equations, respectively. Further to confirm the mechanism of drug release, the first 60% of drug release was fitted in the Korsemeyer-Peppas model.

$$Mt / M\infty = k\ tn$$

where Mt is the amount of drug release at time t and M∞is the amount release at time t=∞, thus Mt /M∞is the fraction of drug released at time t, k is the kinetic constant, and n is the diffusion exponent which can be used to characterize both mechanisms for both solvent penetration and drug release.

RESULTS AND DISCUSSION:

Pre-formulation Studies:

Construction of Calibration Curve: Estimation of Clopidogrel was carried out by double beam UV spectrophotometer (Thermo Scientific) in 0.1 M HCl. The absorbances were measured at λ max of 240 nm shown in **Table 2.** The linear coefficient was found to be closer to 1 (*i.e.* 0.9978) at a concentration range between 10-50 µg/mL. The regression equation generated was y = 0.0161 × as shown in **Fig. 1.**

TABLE 2: CALIBRATION CURVE DATA FOR CLOPIDOGREL BISULPHATE

S. no.	Concentrartion (µg/mL)	Absorbance (avg ± SD)
1	10	0.169±0.05
2	20	0.314±0.04
3	30	0.494±0.06
4	40	0.619±0.02
5	50	0.816±0.03

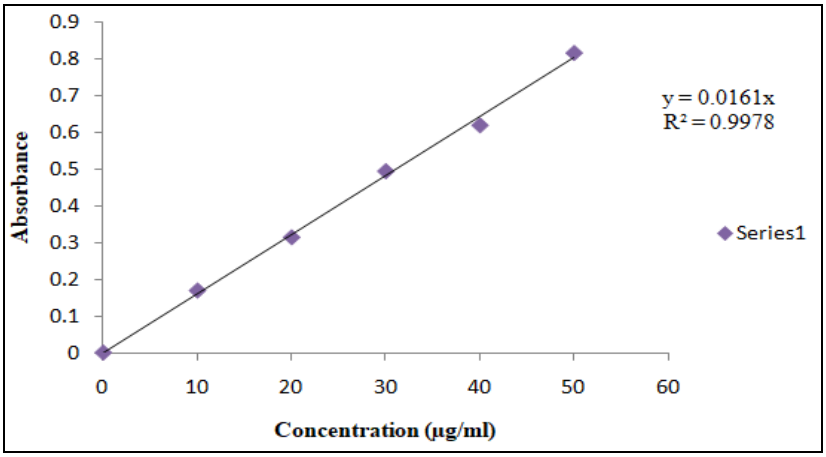

FIG. 1: CALIBRATION CURVE FOR CLOPIDOGREL BISULPHATE

Physical and Physicochemical Properties of Clopidogrel: In the pre-formulation studies, the physical and physicochemical properties of Clopidogrel bisulphate were determined for solubility, melting point, partition coefficient, and micromeritics. The results were shown in **Table 3,** which were all correlated with literature values.

Drug-Excipient Compatibility Studies:

FT-IR Spectroscopy: Compatibility studies of drug and polymer were conducted by employing I.R spectral studies. IR spectra of pure Clopidogrel and the physical mixtures of drug and polymers were shown in **Fig. 2** and **3,** respectively.

The characteristic peaks of the Clopidogrel bisulfate were observed with the spectra of Clopidogrel bisulphate and the physical mixtures were shown in **Table 4.** As the identical principle peaks were observed in all the cases, it was confirmed that no interaction existed between the drug and polymers.

TABLE 3: PHYSICAL AND PHYSICOCHEMICAL PROPERTIES OF CLOPIDOGREL BISULPHATE

S. no.	Property		Experimental Values
1	Solubility (mg/L)	Water	201.8
		0.1N HCl	2792.8
		0.1N NaOH	213.08
		Phosphate buffer pH 3.4	295.85
		Phosphate buffer pH 5.8	1295.8
2	Partition coefficient (log P)		2.32
3	Dissociation exponent (pK_a)		4.8
4	Melting point (^0C)		151
5	Flow properties	Bulk density (g/mL)	0.606
		Tapped density (g/mL)	0.833
		Hausner's ratio	1.375
		Carr's index (%)	27.25
		Angle of Repose (^{0})	17.54

TABLE 4: FT-IR DRUG EXCIPIENT COMPATIBILITY STUDIES

S. no	Peak feature	Wavelength (cm^{-1})	
		Clopidogrel bisulfate	Clopidogrel bisulfate + ethyl cellulose
1	Chlorophenyl CH stretch	2954.20, 3077.37	3077.37
2	C=O	1752.42	1752.27
3	Chlorphenyl spatial bend	749.28,723.11,697.10	723.64
4	Pyridine-methylene rock	1068.09	1068.26
5	Pyridine methylene wag	1439.65	1440.59

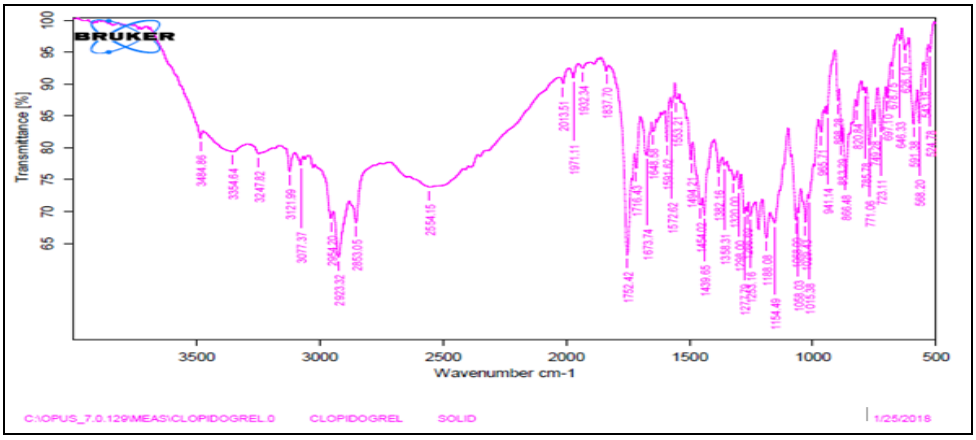

FIG. 2: FT- IR SPECTRA OF CLOPIDOGREL BISULFATE

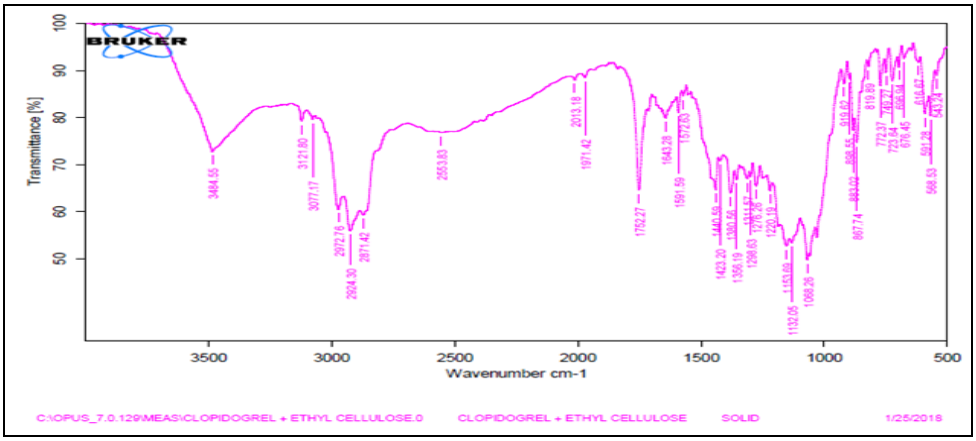

FIG. 3: FT - IR SPECTRA OF CLOPIDOGREL BISULFATE AND ETHYL CELLULOSE PHYSICAL MIXTURE

DSC Study: Drug excipient interactions play a vital role with respect to the release of drug from the formulation, amongst others. DSC has been used here to study the physical and chemical interaction between the drug and excipients used. In the present study, it has been observed that there

is no chemical interaction between Clopidogrel bisulphate and the polymer used as there wasn't any difference in the melting point of clopidogrel which was found to be 171.20 °C for clopidogrel alone and 170.60 °C for clopidogrel with ethyl cellulose as shown in **Fig. 4a** and **Fig. 4b.** respectively.

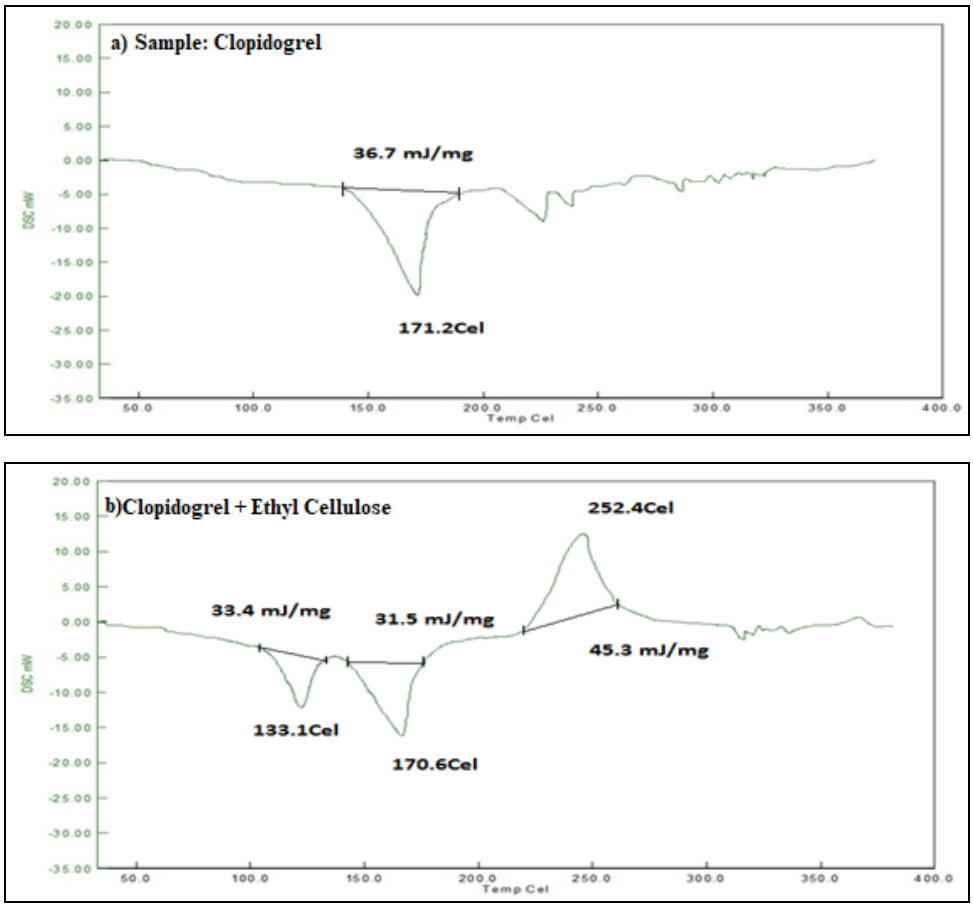

FIG. 4: DSC STUDIES

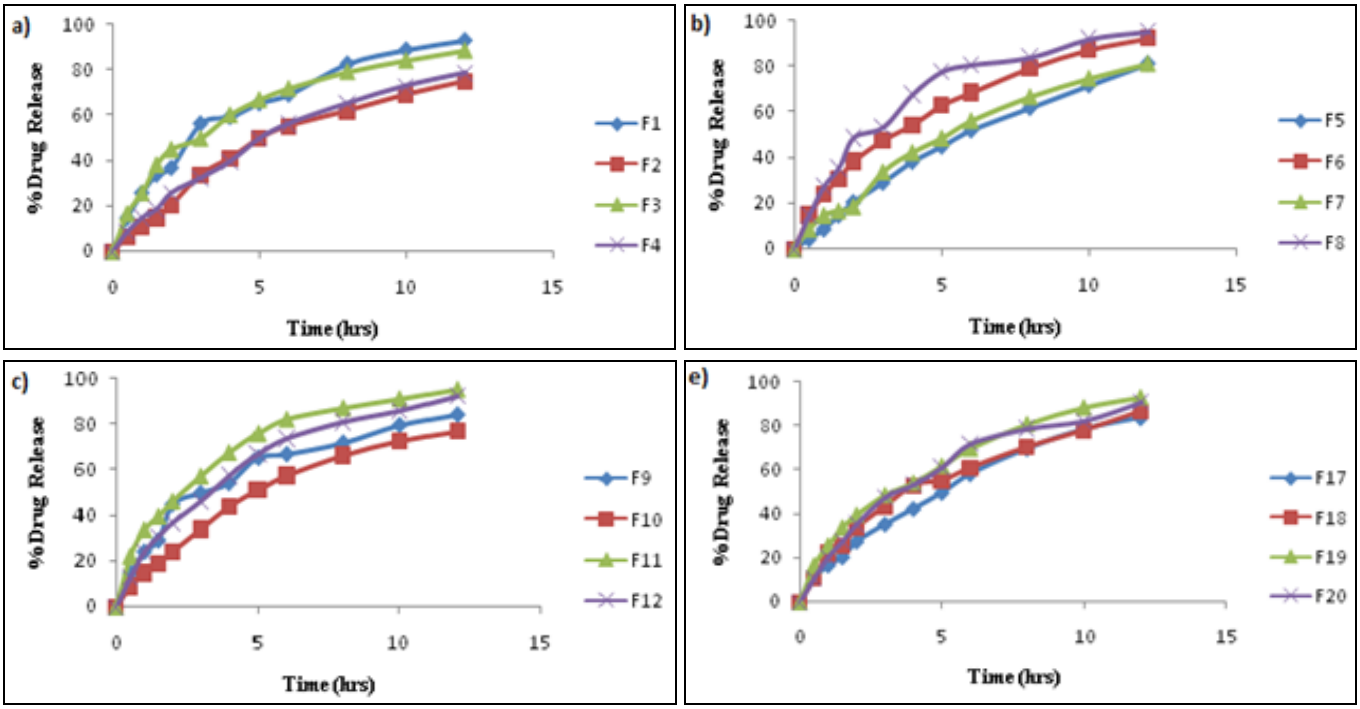

FIG. 5: DRUG RELEASE PROFILES OF (A) F1 TO F4; (B) F5 TO F8; (C) F9 TO F12 AND (D) F13 TO F16

Characterization of Micro Balloons:

Drug Release Studies: The *in-vitro* drug release studies were carried out for all the prepared micro balloon formulations, and the drug release was found to be controlled to a maximum of around 20 hours to release 95% in the case of F34 with a release rate constant of 0.11 h 1 and F15 showed rapid highest drug release at a rate of 0.274 h 1which required around 8 hours to release 95% of the drug. **Fig. 5.** represents the drug release profile of F1 to F16, **Fig. 6.** represents the drug release profile of F17 to F32, and **Fig. 7.** represents the drug release profile of F33 to F41.

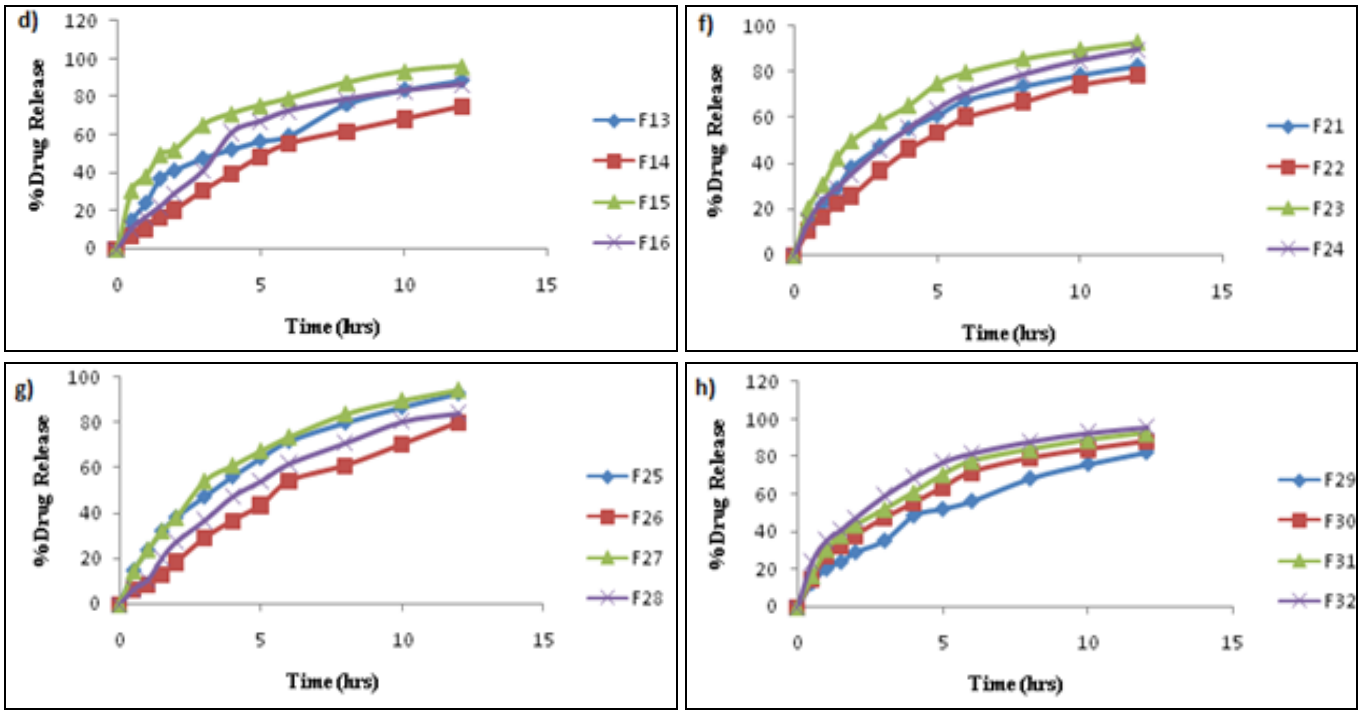

FIG. 6: DRUG RELEASE PROFILES OF (E) F17 TO F20; (F) F21 TO F24; (G) F25 TO F28 AND (H) F29 TO F32

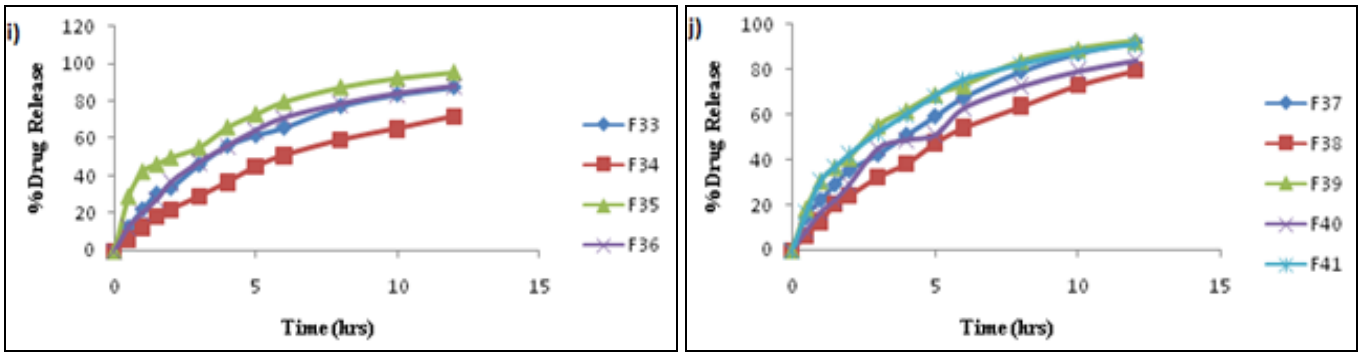

FIG. 7: DRUG RELEASE PROFILES OF (I) F33 TO F36 AND (J) F37 TO F41

It was inferred from the results that upon increase in the polymer concentration, the drug release rate was found to be decreased. This might be attributed to the increased path length at high polymer concentrations (due to bigger size) for the diffusion of an entrapped drug, which leads to a decrease in the drug release rate. Upon an increase in the concentration of methanol in the internal phase, the drug release rate was found to be decreased. The slow evaporation rate under a high concentration on methanol might result in controlled formation of microspheres with tight surface and thus lead to a decrease in drug release rate. Upon increase in the volume of the internal phase, there was an increase in the drug release rate. The high internal phase volumes resulted in microspheres with smaller size due to less viscosity of the dispersed phase. Small size particles have more surface area so that contact with dissolution medium is more, which leads to an increase in drug release rate. The drug release rate was found to be decreased with the increase in the speed of rotation.

The high speed of rotation resulted in microspheres with smaller sizes. Small size particles have more surface area, so the contact with dissolution medium was more, which lead to an increase in drug release rate.

Drug Release Kinetic Studies: The drug release kinetics of all Clopidogrel micro balloon formulations were represented in **Table 5.** It was inferred that almost all the formulations were found to have followed the first-order kinetics of drug release. The exponent (n value) from Peppas plots of the majority of the formulations was found to be above 0.5, thus indicating the drug release mechanism was non-Fickian diffusion.

TABLE 5: DRUG RELEASE KINETICS OF CLOPIDOGREL MICROBALLOONS

S. no.	Formulation	Regression values			Peppas 'n' value	Drug release rate constant ($k\ hr^{-1}$)
		Zero-order	First-order	Higuchi		
1	F1	0.67	0.991	0.986	0.613	0.219
2	F2	0.885	0.989	0.943	0.873	0.121
3	F3	0.539	0.961	0.977	0.557	0.195
4	F4	0.886	0.997	0.964	0.762	0.132
5	F5	0.956	0.99	0.923	0.986	0.129
6	F6	0.734	0.994	0.995	0.619	0.205
7	F7	0.915	0.998	0.945	0.797	0.138
8	F8	0.566	0.984	0.964	0.619	0.255
9	F9	0.567	0.933	0.972	0.585	0.168
10	F10	0.858	0.989	0.964	0.764	0.13
11	F11	0.456	0.984	0.966	0.503	0.26
12	F12	0.722	0.994	0.984	0.659	0.209
13	F13	0.662	0.973	0.988	0.564	0.178
14	F14	0.896	0.992	0.946	0.86	0.12
15	F15	0.182	0.97	0.919	0.397	0.274
16	F16	0.762	0.967	0.946	0.767	0.184
17	F17	0.888	0.997	0.968	0.715	0.15
18	F18	0.763	0.984	0.99	0.697	0.163
19	F19	0.706	0.991	0.997	0.578	0.215
20	F20	0.761	0.989	0.98	0.71	0.192
21	F21	0.636	0.948	0.981	0.628	0.163
22	F22	0.814	0.983	0.977	0.699	0.137
23	F23	0.417	0.963	0.958	0.513	0.238
24	F24	0.722	0.994	0.989	0.621	0.193
25	F25	0.717	0.994	0.993	0.617	0.211
26	F26	0.954	0.99	0.918	0.916	0.125
27	F27	0.69	0.997	0.985	0.637	0.233
28	F28	0.882	0.998	0.951	0.89	0.158
29	F29	0.814	0.991	0.987	0.634	0.145
30	F30	0.649	0.979	0.988	0.59	0.189
31	F31	0.56	0.984	0.98	0.56	0.226
32	F32	0.412	0.987	0.961	0.481	0.269
33	F33	0.725	0.991	0.988	0.648	0.183
34	F34	0.889	0.992	0.963	0.801	0.11
35	F35	0.282	0.977	0.941	0.398	0.261
36	F36	0.72	0.987	0.98	0.682	0.189
37	F37	0.798	0.992	0.99	0.63	0.202
38	F38	0.912	0.998	0.957	0.824	0.131
39	F39	0.567	0.988	0.985	0.54	0.225
40	F40	0.824	0.992	0.971	0.764	0.157
41	F41	0.566	0.981	0.983	0.556	0.215

CONCLUSION: Clopidogrel was studied extensively for its pre-formulation parameters in order to develop floating micro balloons. Emulsion solvent evaporation technique was employed to formulate floating micro balloons by considering five different formulation and process variables *viz*. polymer concentration, surfactant concentration, the volume of internal phase, the concentration of

methanol in the internal phase and speed of rotation, thus resulted in 41 formulations. All the formulations were studied for drug release and release kinetic studies effectively, and the results were suitably analyzed.

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