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*Research Article*

# FORMULATION AND EVALUATION OF BILAYER TABLET CONTAINING FLOATING CLOPIDOGREL BISULPHATE LAYER AND IMMEDIATE RELEASE ASPIRIN LAYER

**Mangesh T Kapade[1]* and Manish S Junagade[2]**

[1]Department of Quality Assurance Technique, M.G.V's Pharmacy College, Panchvati, Nashik - 422012, Maharashtra, India.

[2]Department of Pharmaceutical Chemistry, M.G.V's Pharmacy College, Panchavati, Nashik - 422005, Maharashtra, India.

**ABSTRACT**

The use of a fixed dose combination (Clopidogrel bisulphate and Aspirin) tablet instead of the compounds is expected to be more convenient to patients (and thus improve compliance) by limiting the number of tablets they need to take. Clopidogrel bisulphate and Aspirin are considered the most important oral platelets aggregation inhibitors. So, it is widely used for treatment on prophylaxis of cardiovascular and peripheral vascular disease related to platelets aggregation. In this study Clopidogrel bisulphate and Aspirin were formulated together as floating and immediate release bilayer tablet. Eight types of different formulas of 75mg clopidogrel bisulphate were prepared by direct compression method; the physical and floating properties for this matrix were studied in addition to study the effect of polymer concentration (HPMC K-100) and its combination with carbopol, effect of different diluents and effect of increasing sodium bicarbonate on the release from compressed matrix. Five different types of formulas of 75mg aspirin were prepared by direct compression method as immediate release layer; natural superdisintegrants used to achieve rapid disintegration and its combination with microcrystalline cellulose (Avicel-102) and banana powder as superdisintegrants achieve rapid disintegration was selected for preparation of bilayer tablet.

**Keywords:** Clopidogrel bisulphate, Aspirin, Floating tablet, Bilayer tablet.

## INTRODUCTION

There are many ways to deliver drugs into the body like oral (through swallowing), sub mucosal (through buccal and sublingual mucosa), parenteral (through injection), transdermal (through skin), pulmonary (through inhalation) etc[1,2] tablets. The oral route remains the most considered one for administration of drugs and tablets of various types still the ruling dosage form since years. Multilayered tablets are a form of modified release tablets[3] and they are designed for many reasons:

- To control the delivery rate of either single or two different API's.[4,5]
- To separate incompatible API from each other to control the release of API from one layer by utilizing the functional property of the other layer.
- To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.[6,7]

- To administer fixed dose combinations of different APIs,[8] prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device,[9] buccal/mucoadhesive delivery systems,[10] and floating tablets for gastro retentive drug delivery.[11]

It is the best and most important aspects of layered tablets is gastro retentive system which is shown to improve bioavailability, reduces drug that are less soluble in a high $p^H$ environment. Clopidogrel bisulphate and Aspirin are known platelets aggregation inhibitors, the combination of these both drug was shown to be synergistic because they have different mechanism of action.

Clopidogrel bisulphate acts by inhibiting the ADP receptor on platelet cell membranes. It is a prodrug which requires CYP2C19 for its activation. The drug specifically and irreversibly inhibits the P2Y12 subtype of ADP receptor, which is important in activation of platelets and eventual cross-linking by the protein fibrin. The solubility of this drug is strongly $p^H$ dependent and it is very soluble and stable at $p^H$ value <3. In addition to that clopidogrel bisulphate has low oral bioavailability (50%), undergoes extensive first pass metabolism (85%) and frequent high doses are required to maintain the therapeutic level as a result, dose related toxic effects developed.

Aspirin in low dose use irreversibly blocks the formation of thromboxane $A_2$ in platelets, producing an inhibitory effect on platelet aggregation during the lifetime of the affected platelet (8-9days). This antithrombotic property makes aspirin useful for reducing the incidence of heart attacks. It appears that rapid release formulation of aspirin should be preferred in anti-platelet therapy either alone or in combination with other anti-platelet drugs. The goal of this study is to utilize Bilayer tablet approach to administer aspirin as immediate release layer and clopidogrel as sustained release floating layer in an attempt to improve bioavailability and to get maximum therapeutic benefits by patients that need the combination of aspirin and clopidogrel in cases of in acute coronary syndromes, including acute myocardial infarction and unstable angina, and in coronary stenting.

## MATERIAL AND METHODS

### Materials

Clopidogrel bisulphate was a gift sample from BlueCross Pharmaceutical, ltd, Nasik. Aspirin, HPMC K-100, Avicel-102, sodium bicarbonate, Carbopol 934K, citric acid, magnesium stearate, banana powder, talc, Manitol was obtained from Modern Science Pvt. Ltd, Nashik.

### Methods

### Drug and Excipients Compatibility Studies

### UV spectroscopy

The both drugs were scanned in UV Spectrophotometer to detect the λmax and to drawn the calibration curve of the drug in 0.1 N HCl as a solvent. The drugs were used in concentration ranges of 5-25 ppm. The spectra and calibration curve of both the drugs are as shown in Figure 1, 2, 3, 4 respectively.

### FTIR spectral studies

The infrared spectra of Clopidogrel bisulphate and Aspirin were recorded by SHIMADZU 84005 FTIR spectrometer, equipped with an Inferometer detector. Samples were prepared by KBr disc method (2 mg sample in 100 mg KBr) and examined in the transmission mode. Each spectrum was measured over a frequency range of 4000–400 cm−1. The spectra shown in Figure 5, 6, 7, 8 respectively.

### DSC studies

DSC analysis was performed using Shimadzu-Thermal Analyzer DSC 60 on 2-5mg samples. Sample was heated in an open nitrogen pan at a rate of 10°C/min conducted over a temperature range of 50 to 200°C for Clopidogrel bisulphate and Aspirin under nitrogen flow of 2 bar pressure. The spectra shown in Figure 9, 10, 11 respectively.

### Preparation of Clopidogrel bisulphate Floating matrix tablet by using direct compression

The controlled release floating matrix tablets of Clopidogrel bisulphate (F1-F8) were prepared by direct compression technique as per the composition in Table 1. Clopidogrel bisulphate, HPMC K-100, 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 sieve no, #60.Sifting was performed and the lubricated material was passed through the ploy bag and mixed for two minutes. Composition of different trial formulations for controlled release floating matrix tablets were given in Table no.1. The final weight of the controlled release floating matrix tablets was fixed to 350mg. composition was adjusted to obtain tablets with hardness in the range of 4-6kg/$cm^2$.

### Formula design

For this a $2^3$ factorial design was applied using three Excipients (HPMC K100, sodium

bicarbonate, Carbopol) at two concentration levels. Formulations coded as F1 to F8 respectively. The composition of formula is as shown in Table 1.

**Evaluation parameters (Clopidogrel bisulphate)**

**Evaluation of pre compression parameters of the powder blends[6]**

Pre-compression parameters of the prepared blend of all the formulations were studied by determining the Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose. The results are shown in Table 2.

**Evaluation of post compression parameters of the powder tablets[7]**

The compressed floating Clopidogrel bisulphate tablets were subjected to various physical tests which include hardness, friability, weight variation, thickness and drugs content uniformity. The results are shown in Table 3.

**Hardness test**

For each formulation, the hardness of three tablets was checked using the Monsanto hardness tester (LAB- HOSP) average values are shown in Table.

**Thickness**

The thickness of tablet is important for uniformity of tablet size. The thickness of the tablets was determined using a Vernier Calliper. Three tablets from each batch were used and average values are shown in Table.

**Friability**

Friability is the measure of tablet strength. In this test, number of tablets subjected to combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25rpm, dropping the tablets at a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche Friability tester (Kumar Mfg. Ltd.) This was then operated for 100 revolutions. The tablets then dedusted and reweighed. Permitted friability limit is 1.0%. Tablets were then weighed and friability values were determined and are reported in Table.

**Friability = (W2 – W1 / W1) X 100**

Where W1 is the initial weight and W2 is the final weight of the tablets.

**Weight variation**

Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The percent deviation was calculated using the following formula.

**Determination of swelling index**

The swelling behavior of dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1 N HCl at 37±0.5ºc.after 0.5,1,2,3,4,5,6,7 and 8 hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighted on the analytical balance (Metler).The experiments was performed in triplicate for each time point swelling index was calculated by using the following formula. The results are shown in Table 4.

**Swelling index = Wet weight of tablet – Dry weight of tablet / Dry weight of table**

***In-vitro* Determination of floating time**

The In-vitro buoyancy was characterized by floating lag time and total floating time. As per the method described by ***Bhanuprasad 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. The results are shown in Table 5.

***In - vitro* Drug Release Study**

An *in-vitro* drug release studies of the prepared eight formulations of floating release tablets were conducted for a period of 12hrs. Using, an eight station USP type 2 apparatus (paddle type) (Electrolab). The agitation speed was 50 rpm. Prepared floating tablets were added to 900 ml of 0.1 N HCl at 37 ± 0.5° C and stirred at 50 rpm.5 ml aliquots were withdrawn at time intervals of 30,60,.....720 min. And filtered through Whatmans No. 41, filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analyzed. Cumulative percentage of labeled amount of drug released was calculated.

**Preparation of Aspirin immediate release tablet by using direct compression (Aspirin)**

Weigh accurately aspirin all excipients. Mixed both drugs and Superdisintegrants were blended first in mortar and pestle and pass through sieve no. 60. After that next step is add Mannitol act as filler. Mix it then add Magnesium stearate and Talc as lubricant and diluents. Again mix it properly, weighed and compressed the blend.

**Formula design**

For this a $2^2$ factorial design was applied using two Superdisintegrants (Banana powder, MCC) at two concentration levels. Formulations coded as F1 to F4 respectively. The composition of formula is as shown in Table 6.

**Evaluation parameters (Aspirin)**

**Evaluation of pre compression parameters of the powder blends**

Pre-compression parameters of the prepared blend of all the formulations were studied by determining the Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose. The results are shown in Table 7.

**Evaluation of post compression parameters of the powder tablets**

The compressed immediate release tablets were subjected to various physical tests which include hardness, friability, weight variation, thickness and drugs content uniformity. The results are shown in Table 8.

**Drug Content Uniformity Study**

Five tablets were weighed individually and powdered. The powder equivalent to 25 mg of Aspirin was weighed and dissolved in 20 ml of 0.1 N HCl. The volume was made to 100ml with 0.1 N HCl. From this stock solution, 25 µg/ml dilutions were prepared. The drug contents of the resulting solution were calculated from UV absorbance at 228.2 nm.

**Wetting Time**

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a Petri dish containing 0.2% w/v solution of amaranth (10ml). One tablet was carefully placed on the surface of the tissue paper. The time required for develop blue color due to amaranth water soluble dye on the upper surface of the tablets was noted as the wetting time. Figure 15.

**Water Absorption Ratio**

A small piece of tissue paper folded twice was placed in a small Petridish containing 6ml of water. A tablet was put on the paper. The wetted tablet was then weighed. Water absorption ratio, R was determined by using following formula

$$R = Wa – Wb/ Wb \times 100$$

Here, R = Water absorption ratio,
Wb = Weight of tablet before water absorption
Wa = Weight of tablet after water absorption

**Disintegration time study**

The *in-vitro* disintegration studies were carried out using Tablet Disintegration Test Apparatus. One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in one-liter beaker containing water maintained at $37\pm2^0$C. The basket was then moved up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded. The test was performed for tablets of all type of formulation (F1-F4).

***In - vitro* Drug Release Study**

An *in-vitro* drug release studies of the prepared nine formulations of Immediate release tablets were conducted for a period of 30 minutes using an eight station USP type 2 apparatus (paddle type)(Electrolab).The agitation speed was 50 rpm. Prepared Immediate release tablets were added to 900 ml of 0.1 NHCL at 37 ± 0.5° C and stirred at 50 rpm.5 ml aliquots were withdrawn at time intervals of 5, 10, 15, 20, 25, 30 min. and filtered through Whatmans No. 41 filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analyzed. Cumulative percentage of labeled amount of drug released was calculated.

**Formulation and evaluation of bilayer tablet**

In bilayer tablet Optimized formula of aspirin (F2) from immediate release formulation and Clopidogrel bisulphate (F5) from floating released formulation were selected for bi-layer tablet. The required weight from each layer which is equivalent to active ingredients of both aspirin and Clopidogrel bisulphate were individually weighed, the Clopidogrel bisulphate layer manually filled into the 11.5mm die and compressed slightly so that flat rough surface required for adhesion of the Clopidogrel bisulphate layer was created .

Then aspirin layer was poured into the 11.5mm die above the Clopidogrel bisulphate layer, both layers finally were subjected to the final compression. The tablet was compressed by using compression machine and hardness was adjusted the up to 5-6kg.Bilayer tablet of aspirin and Clopidogrel bisulphate was ejected from the die.

**Evaluation parameters[12]**

**Evaluation of bilayer tablets**

Bilayer tablets were evaluated for hardness, thickness, uniformity of weight, friability, contents of active matter, floating lag time, buoyancy, and disintegration time as procedure mention in Table 9.

***In - vitro* Drug Release Study**

*In vitro* drug release study of the sample was carried out using USP –type II dissolution apparatus (Paddle type).the dissolution medium, 900ml of 0.1 N HCl for 12 hrs. was placed into the dissolution flask maintaining the temperature of 37±0.5°c and rpm of 50.one tablet of Clopidogrel bisulphate and aspirin was placed into a jar of dissolution apparatus. The apparatus was allowed to run for 30 min. samples measuring 5ml were withdrawn after5, 10, 15, 20, 25,30min and after each hrs. up to 12hrs manually and samples were filtered. The fresh dissolution medium was replaced every time with the some quantity if the sample withdrawn. Collected samples were analyzed at 228.2 and 270 nm with proper dilution using solvent against blank.

**RESULT 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 and Excipients Compatibility Studies**

**UV Spectroscopy**

The λmax of Clopidogrel bisulphate and Aspirin obtained at 269.8 nm,228.2nm respectively and the calibration curve was constructed using concentration range 5-25 ppm, equation was found to be y = 0.002 X + 0.015,y = 0.019 X + 0.057 respectively and the regression coefficient $R^2$ = 0.989, $R^2$ = 0.989 respectively. Spectra and calibration curve showed Figure 1, 2, 3, 4.

**FTIR spectral studies : (Clopidogrel bisulphate)**

FTIR spectra of pure Clopidogrel bisulphate and the optimized formulations are shown in Figures5, 6. 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.

**FTIR spectral studies:( Aspirin)**

FTIR spectra of pure Aspirin and the optimized formulations are shown in Figures7, 8. The FTIR spectrum of Aspirin showed Stretching vibrations at1604 $cm^{-1}$ for C=C bond in aromatic ring, 1725 $cm^{-1}$ for C-=O bond in ester, 1720 $cm^{-1}$ for C=O in carboxylic acid and 1091 $cm^{-1}$ for ester. All these characteristic bands were all retained in formulations indicating that there is no interaction between drug and polymers

**DSC analysis (Clopidogrel bisulphate)**

DSC Thermograms of Clopidogrel bisulphate and optimized formulations were shown in Figures 9. Clopidogrel bisulphate showed sharp endothermic peak at 158.26°C corresponding to its melting point. Clopidogrel bisulphate formulations showed weak peaks compared to pure Clopidogrel bisulphate. Overall DSC curves indicate that there is no interaction observed between drug and excipients.

**DSC analysis (Aspirin)**

DSC Thermograms of Aspirin and optimized formulations were shown in Figures 10. Aspirin showed sharp endothermic peak at 135.55°C corresponding to its melting point. Aspirin formulations showed weak peaks compared to pure Aspirin. Overall DSC curves indicate that there is no interaction observed between drug and excipients.

**DSC study of bilayer formulation**

The DSC curve of Clopidogrel bisulphate and Aspirin bilayer tablet shows sharp endothermic peak at 155.03°C and 136.69°Crespectively. The drug do not undergoes decomposition following its melting. This indicating that there is no probable chemical interaction between drug and excipients mixture.Thermograms is as shown in Figure11.

**Pre compressional parameters (Clopidogrel bisulphate)**

The powder blends was prepared by mixing of various ingredients mentioned in Table 2 and used for characterization of various flow properties of powder.Table reports the values for Compressibility Index (CI) and Hausner's ratio (HR) for all prepared batches. According to the literature, powders with CI values between 9% -13% are suitable for producing the tablets and those with a Hausner's ratio values below 1.25 and angle of repose values in between 20-40˚ indicate good flow properties of powders. The results are shown in Table 2.

**Post compressional parameters**

The present work undertaken to formulate and evaluated floating tablet of Clopidogrel bisulphate by direct compression method. Polymers at different concentration levels were included to assist floating tablet. The results are shown in Table 3.

**In-Vitro buoyancy studies**

Buoyancy studies were performed using $p^H$1.2 (0.1 N HCL) buffer at $37^0$C. All the formulations were found to exhibit short lag times due to presence of sodium bicarbonate. Formulations prepared with highest amount of all polymers showed shorter lag times compared to Carbopol and HPMC K100 M. Formulation F5 containing HPMC K100 M, showed floating lag time of 2.96min. And total floating time of more than 12hrs. The results were given in Table 5 and shown in Figure 12.

**In-*vitro* dissolution studies**

*In –vitro* dissolution studies were carried out in 900ml of 0.1N HCl as dissolution medium using USP XXI type II (paddle method) dissolution rate test apparatus (Electrolab) at 50rpm for 12hrs. The temperature was maintained constant at 37±0.5$^0$C. The dissolution experiments were conducted in triplicate. The formulation F1-F8 with different concentration of polymers HPMC K-100, Sodium bicarbonate, Carbopol in high level 140, 50, 15 and low level 70, 30, 5 were taken respectively.as compared to other batches F1, F5, F8 batches give prolong drug release in time 6, 12, 8 hrs. Batches give % DR 99.23±0.75, 95.89±0.22, 79.49±0.84 respectively. The batch having highest concentration of all polymers was given good result.so, the batch F5 was selected as optimized batch for floating layer. The comparative graphical representation shown in Figure13.

**Drug Release Kinetics[13]**

The value of n indicates the drug release mechanism. For a slab the value n = 0.5 indicates Fickian diffusion and values of n between 0.5 and 1.0 or n =1.0 indicates non-Fickian mechanism. In case of cylinder n = 0.45 instead of 0.5 and 0.89 instead 1.0.these model is used to analyze the release from polymeric dosage forms, when the release mechanism is not well known or when there is possibility of more than one type of release phenomenon being involved. To confirm the diffusion mechanism, the data was fitted into korsmeyer peppas equation which resulted in "n" value between 0.214 and 0.648 thus indicating the mechanism of drug release followed anomalous transport (non –Fickian) with slow erosion of polymeric matrix followed by diffusion of drug resulting in linear drug release over a prolonged period of time. The results are shown in Table 10.

**Pre compressional parameters (Aspirin)**

The powder blends was prepared by mixing of various ingredients mentioned in Table 7 and used for characterization of various flow properties of powder.Table reports the values for Compressibility Index (CI) and Hausner's ratio (HR) for all prepared batches. According to the literature, powders with CI values between 9% -13% are suitable for producing the tablets and those with a Hausner's ratio values below 1.25 and angle of repose values in between 20-40˚ indicate good flow properties of powders.

**Post compressional parameters**

The present work undertaken to formulate and evaluated immediate release tabletof Aspirin by direct compression method. Superdisintegrants at different concentration levels were included to assist fast disintegration. The results are shown in Table 8.

**Disintegration time**

Immediate release tabletof Aspirin should disintegrate within minute. Three Tablets of each formulation were taken and placed in 6 tubes of disintegration apparatus. The time taken for complete disintegration was noted.The disintegration time for formulation F1-F4 was found to be in the range of 15 to 19sec, this reflects that the optimum concentration of superdisintegrants, rapid will be disintegration, the tablet containing maximum concentration banana powder of Formulation F2 containing 16mg showed less disintegration time among the F1-F4 formulation.

**In-*vitro* dissolution studies**

*In –vitro* dissolution studies were carried out in 900ml of 0.1N HCl as dissolution medium using USP XXI type II (paddle method) dissolution rate test apparatus (Electrolab) at 50rpm for 12hrs. The temperature was maintained constant at 37±0.5$^0$C. The dissolution experiments were conducted in triplicate. The formulation if four batches F1, F2, F3, and F4 containing drug and banana powder as superdisintegrants more is the concentration of banana powder rapid disintegration and drug release occur. The F1, F2, F3, and F4 batches give results % DR 65.03±0.2, 91.70±0.33, 65.55±0.42, 72.51±0.24 respectively. The comparative graphical representation was shown in Figure14. By observing results the F2 batch was selected as optimized batch for immediate release layer.

**Formulation and evaluation of bilayer tablet**

Bilayer tablets were evaluated for hardness, thickness, uniformity of weight, friability, contents of active matter, floating lag time, buoyancy and disintegration time as procedure mention in method. The results are shown in Table 9.

**In-*vitro* dissolution studies**

All tests of bilayer tablet are within limit and drug release profile was slightly deviated from their individual release.

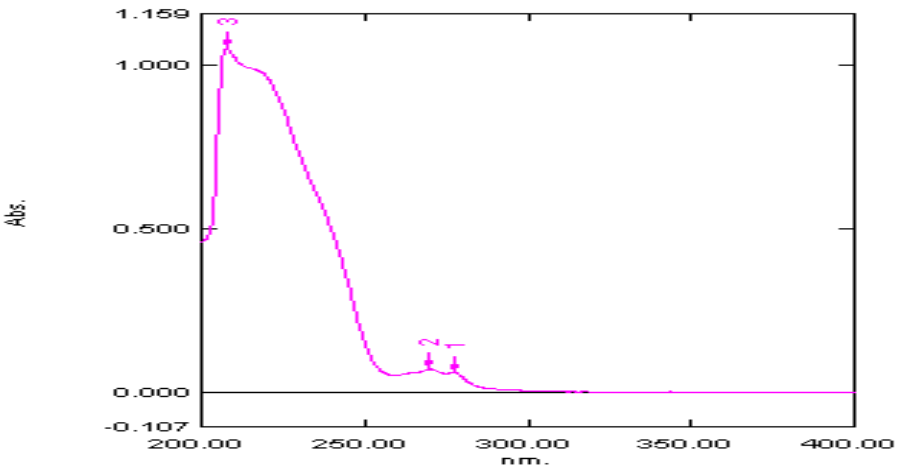


**Fig. 1: UV Spectrum of Clopidogrel bisulphate in 0.1 N HCl**

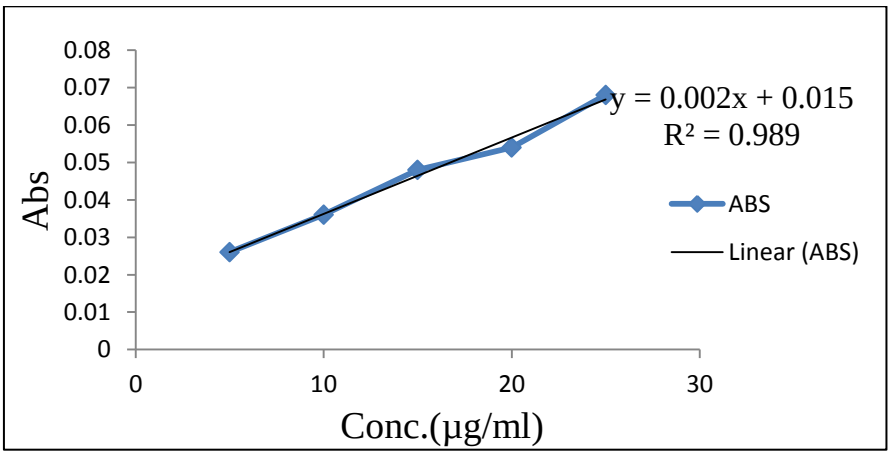


**Fig. 2: Calibration Curve of Clopidogrel bisulphate in 0.1 N HCl**

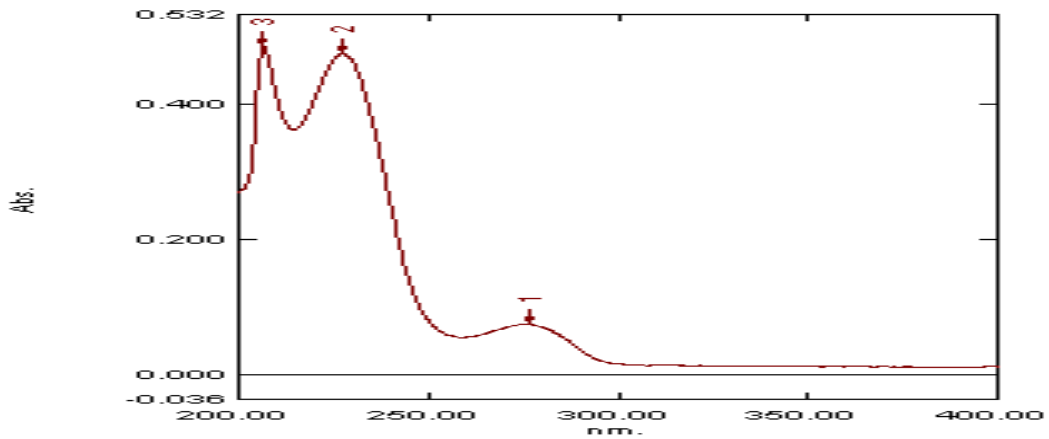


**Fig. 3: UV Spectrum of Aspirin in 0.1 N HCl**

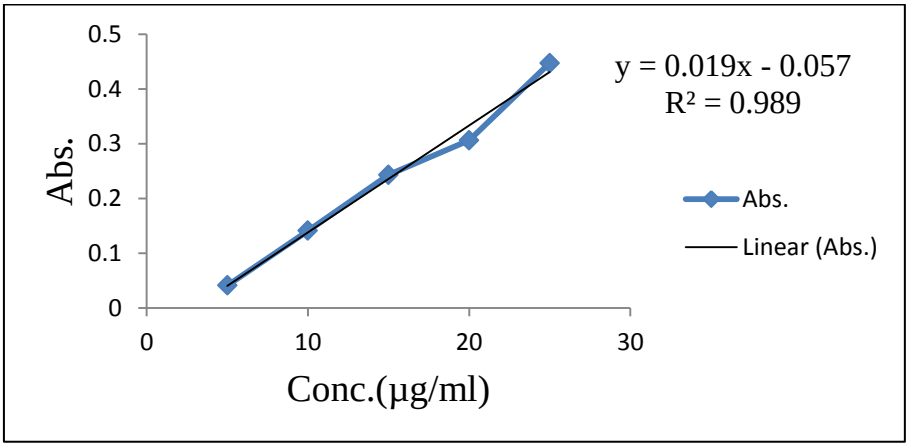


**Fig. 4: Calibration Curve of Aspirin in 0.1N HCl**

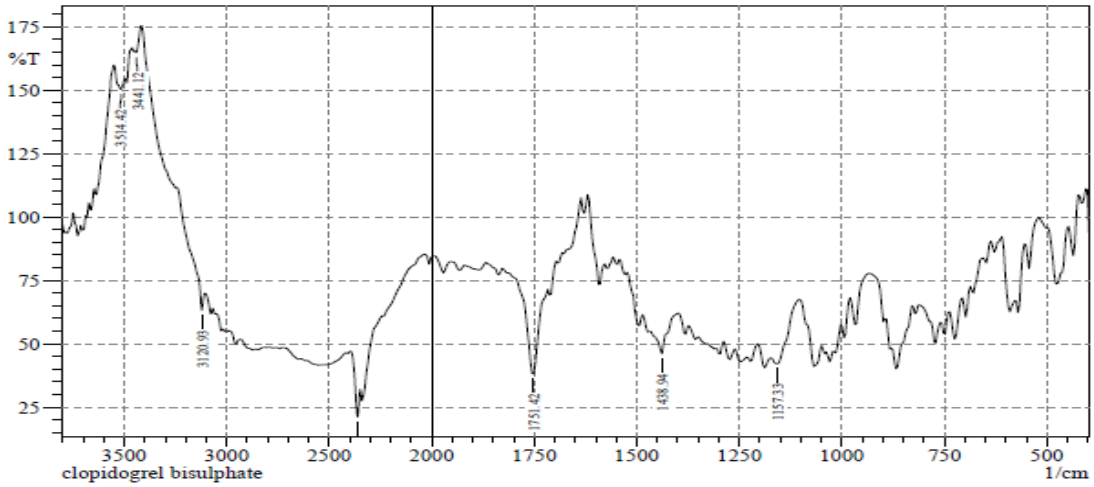


**Fig. 5: FT-IR Spectrum of Clopidogrel bisulphate**

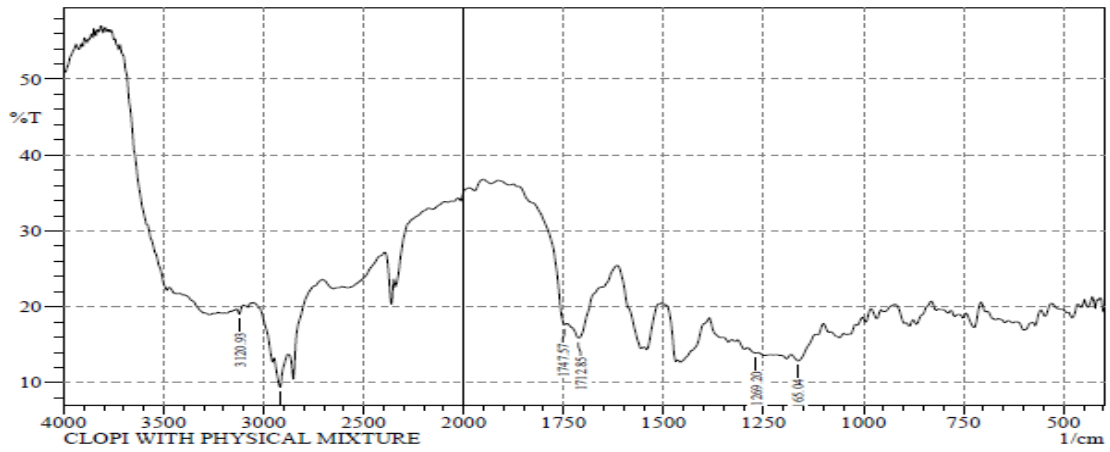


**Fig. 6: FT-IR study of Clopidogrel bisulphate and excipients mixture**

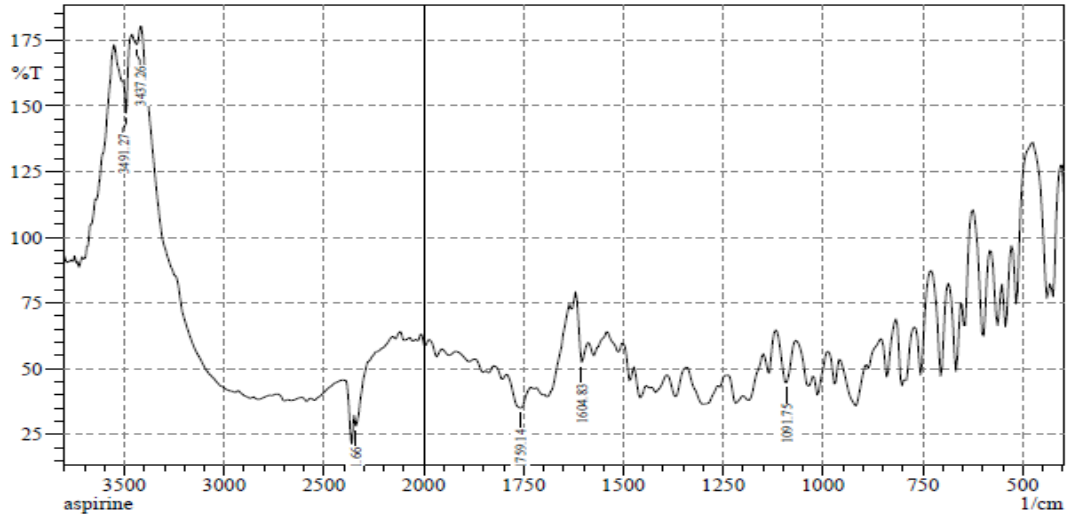


**Fig. 7: FT-IR Spectrum of Aspirin**

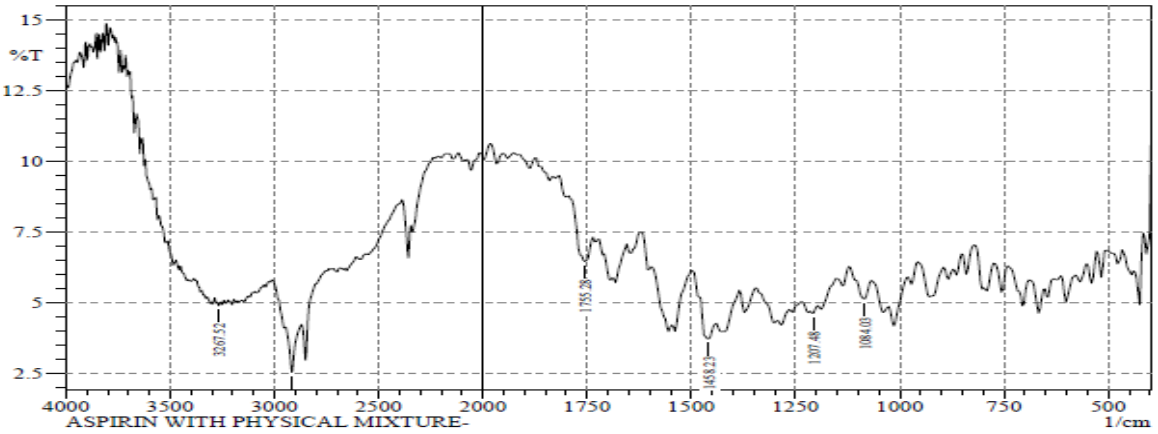


**Fig. 8: FT-IR study of Aspirin and excipients mixture**

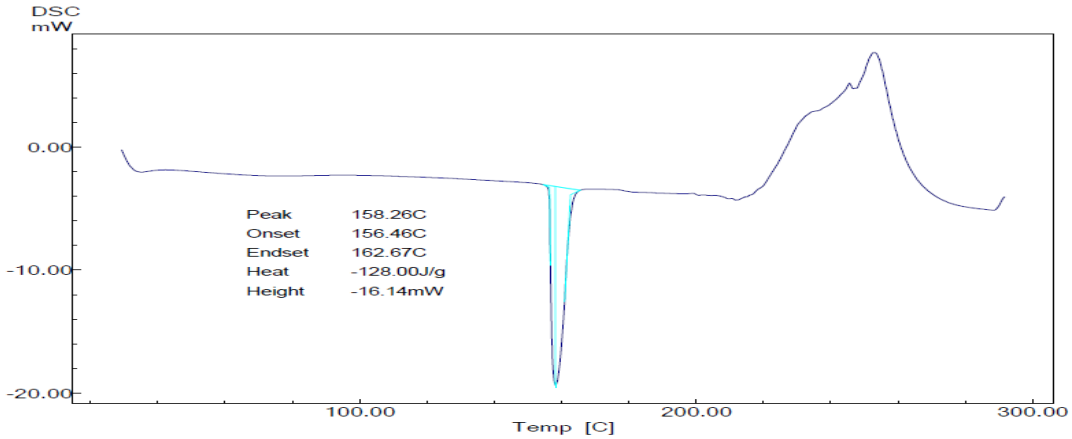


**Fig. 9: DSC study of Clopidogrel bisulphate**

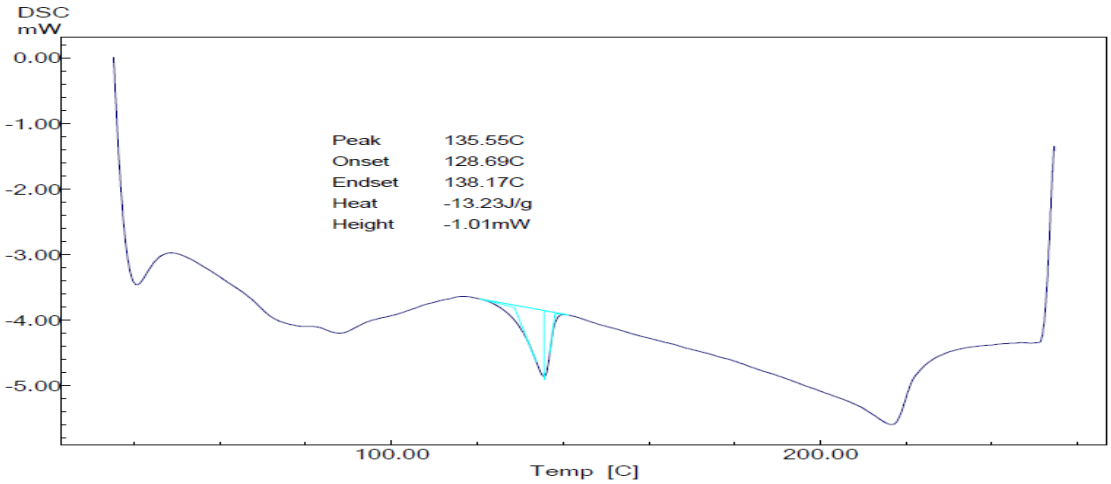


**Fig. 10: DSC Study of Aspirin**

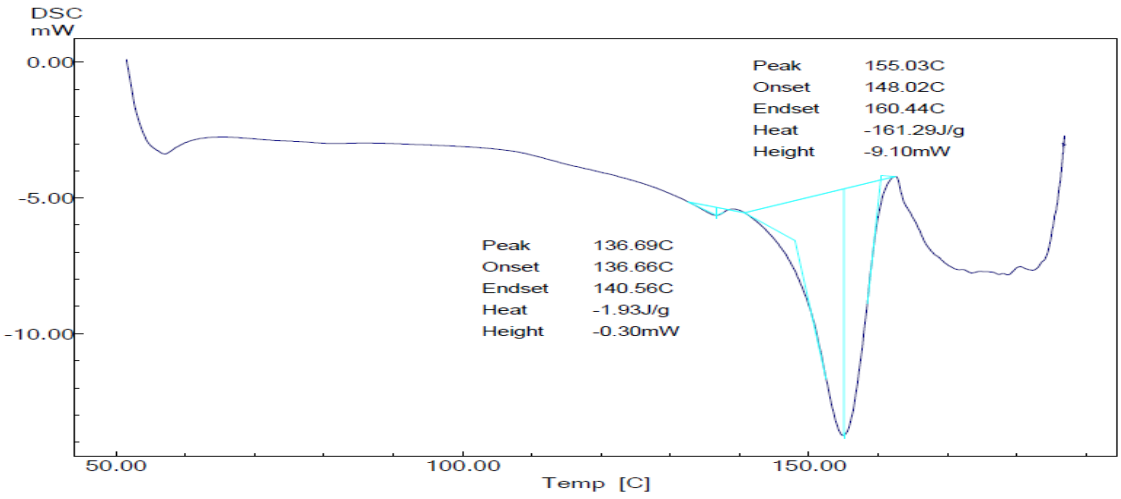


**Fig. 11: DSC of bilayer formulation**


**Fig. 12: In-Vitro buoyancy studies**

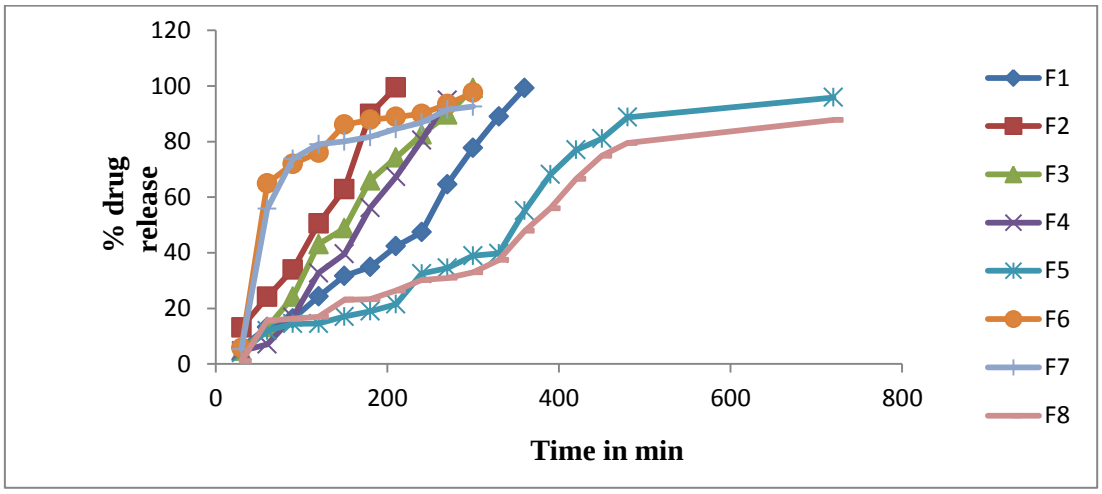


**Fig. 13: Dissolution profiles of floating tablets of Clopidogrel bisulphate**

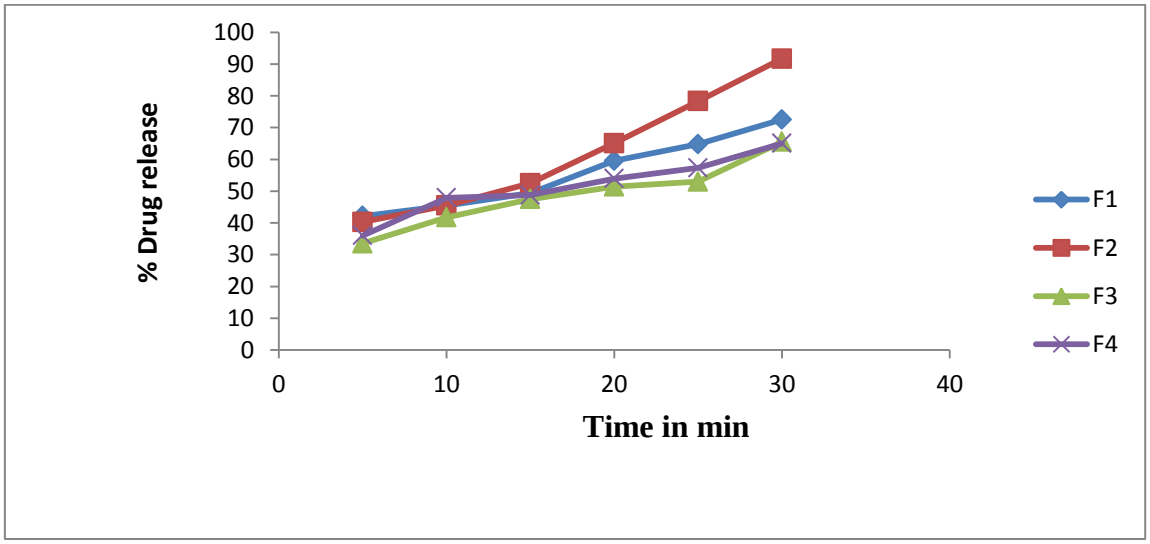


**Fig. 14: Dissolution profile of immediate release tablet of aspirin**

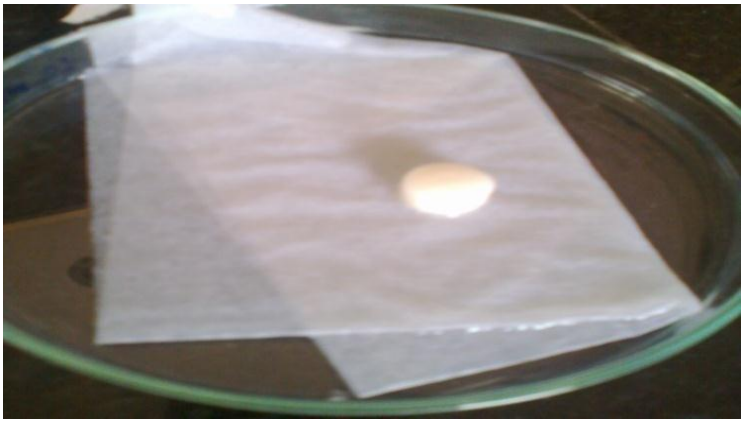

**Fig. 15: Wetting time determinations of immediate release aspirin tablet**

**Table 1: Formulation Batches of floating tablets**

| Sr. no. | Ingredients (mg) | Formulation | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| 1 | Clopidogrel bisulphate | 75 | 75 | 75 | 75 | **75** | 75 | 75 | 75 |
| 2 | **HPMC K 100** | **140** | **70** | **70** | **140** | **140** | **70** | **70** | **140** |
| 3 | **Sod Bicarbonate** | **30** | **30** | **50** | **50** | **50** | **30** | **50** | **30** |
| 4 | **Carbopol 934K** | **5** | **15** | **15** | **5** | **15** | **5** | **5** | **15** |
| 5 | Citric Acid | 25 | 25 | 25 | 25 | **25** | 25 | 25 | 25 |
| 6 | Magnesium Stearate | 2 | 2 | 2 | 2 | **2** | 2 | 2 | 2 |
| 7 | Microcrystalline Cellulose (Avicel 102) | q.s | q.s | q.s | q.s | **q.s** | q.s | q.s | q.s |
| | Total (mg) | 350 | 350 | 350 | 350 | 350 | 350 | 350 | 350 |

**Table 2: Evaluation of powder blend containing Drug and Excipients**

| Formulation batches | Physical properties | | | | |
|---|---|---|---|---|---|
| | Loose bulk density | Tapped bulk density | Hausner's Ratio | Compressibility Index (%) | Angle of repose |
| **F1** | **0.49±0.015** | **0.52±0.026** | **1.18** | **9.13±0.0353** | **36.84±0.017** |
| **F2** | **0.48 ±0.010** | **0.52±0.010** | **1.10** | **11.31±0.0264** | **33.80±0.015** |
| **F3** | **0.50±0.0173** | **0.53±0.0173** | **1.14** | **10.76±0.0173** | **33.34±0.070** |
| **F4** | **0.49±0.0158** | **0.55±0.010** | **1.17** | **12.62±0.010** | **29.32±0.328** |
| **F5** | **0.48±0.0158** | **0.53±0.0158** | **1.09** | **8.49±0.020** | **34.60±0.877** |
| **F6** | **0.48±0.0173** | **0.53±0.0173** | **1.13** | **9.88±0.010** | **35.73±0.523** |
| **F7** | **0.48±0.0158** | **0.54±0.010** | **1.12** | **10.76±0.0264** | **33.80±0.070** |
| **F8** | **0.50±0.010** | **0.52±0.0158** | **1.13** | **12.62±0.020** | **33.34±0.877** |

**Table 3: Evaluation of floating Clopidogrel bisulphate Tablets**

| Formulation batches | Parameters | | | | |
|---|---|---|---|---|---|
| | Thickness (mm) ±SD(n=3) | Hardness ($Kg/cm^2$) (± SD) (n=5) | %Drug content (± SD) (n=3) | Weight variation in (Mg) | Friability (%) (± SD) (n=30) |
| **F1** | **4.30 ± 0.158** | **5.6 ± 0.658** | **92.63 ± 1.93** | **341.6±5.08** | **0.68 ± 0.06** |
| **F2** | **4.44 ±0.177** | **5.5 ± 0.435** | **108.48 ± 6.77** | **342.7±5.3** | **0.95 ± 0.245** |
| **F3** | **4.48 ±0.115** | **5.6 ± 0.663** | **121.17 ± 2.45** | **342.8±6.2** | **0.81 ± 0.230** |
| **F4** | **4.57 ±0.092** | **5.6 ± 0.625** | **112.45 ± 3.56** | **340.1±6.4** | **0.74 ± 0.148** |
| **F5** | **4.34 ±0.144** | **5.5 ± 0.684** | **99.62 ± 1.63.** | **343.7±4.8** | **0.83 ± 0.234** |
| **F6** | **4.40 ±0.066** | **5.7± 0.677** | **95.50±2.43** | **342.5±4.2** | **0.69 ± 0.065** |
| **F7** | **4.48±0.092** | **5.6 ± 0.435** | **96.25± 1.63.** | **341±5.2** | **0.83± 0.148** |
| **F8** | **4.44±0.115** | **5.5 ± 0.658** | **109.48±3.56** | **342.5±4.2** | **0.85± 0.234** |

**Table 4: Study of swelling characteristics of Floating layer of Clopidogrel bisulphate**

| Batch Code | Time in hrs.(% swelling) | | | |
|---|---|---|---|---|
| | 2 | 4 | 6 | 8 |
| F1 | 73.26 | 105.47 | 67.14 | 58.46 |
| F2 | 64.17 | 92.33 | 60.47 | 54.75 |
| F3 | 116.43 | 174.34 | 186.42 | 104.24 |
| F4 | 87.22 | 120.72 | 78.56 | 73.19 |
| F5 | 107.26 | 167.82 | 163.75 | 94.13 |
| F6 | 83.12 | 123.75 | 72.17 | 65.73 |
| F7 | 60.47 | 94.34 | 68.65 | 78.89 |
| F8 | 95.65 | 85.75 | 95.65 | 103.43 |

**Table 5: In-Vitro buoyancy study of Clopidogrel bisulphate Floating layer**

| Batch Code | Floating Lag Time(Min) | Floating Time(Hours) |
|---|---|---|
| F1 | 2.2 | >12 |
| F2 | 1.7 | >10 |
| F3 | 2.42 | >11 |
| F4 | 1.3 | <10 |
| F5 | 2.96 | <12 |
| F6 | 2.3 | > 8 |
| F7 | 4.3 | >6 |
| F8 | 2.53 | >8 |

**Table 6: Formulation Batches of immediate release tablets**

| Sr. No. | Ingredients (mg) | Formulations | | | |
|---|---|---|---|---|---|
| | | $F_1$ | $F_2$ | $F_3$ | $F_4$ |
| 1. | Aspirin | 75 | **75** | 75 | 75 |
| 2. | **MCC(Avicel 102)** | **30** | **20** | **30** | **20** |
| 3. | **Banana powder** | **8** | **16** | **16** | **8** |
| 4. | Talc | 2 | **2** | 2 | 2 |
| 5. | Magnesium Stearate | 2 | **2** | 2 | 2 |
| 6. | Mannitol | q.s | **q.s** | q.s | q.s |
| | Total (mg) | 150 | **150** | 150 | 150 |

**Table 7: Evaluation of powder blend containing Drug and Excipients**

| Formulation batches | Physical properties | | | | |
|---|---|---|---|---|---|
| | Loose bulk density | Tapped bulk density | Hausner's Ratio | Compressibility Index (%) | Angle of repose |
| F1 | 0.46±0.015 | 0.54±0.026 | 1.20 | 16.13±0.0353 | 25.84±0.017 |
| F2 | 0.45 ±0.010 | 0.56±0.010 | 1.19 | 19.35±0.0264 | 25.24±0.015 |
| F3 | 0.46±0.0173 | 0.53±0.0173 | 1.18 | 17.76±0.0173 | 27.34±0.070 |
| F4 | 0.45±0.0158 | 0.55±0.010 | 1.17 | 18.62±0.010 | 29.32±0.328 |

**Table 8: Evaluation of immediate release tablet**

| Formulation batches | Parameters | | | | |
|---|---|---|---|---|---|
| | Thickness (mm) ±SD(n=3) | Hardness ($Kg/cm^2$) (± SD) (n=5) | %Drug content (± SD) (n=3) | Weight variation in (Mg) | Friability (%) (± SD) (n=30) |
| F1 | 3.01±0.0070 | 3.15±0.05 | 99.48±0.773 | 142.9± 1.59 | 0.525±0.092 |
| F2 | 3.02±0.0141 | 3.21±0.0141 | 99.03±1.67 | 146 ± 1.3 | 0.48±0.075 |
| F3 | 3.01±0.0141 | 3.17±0.026 | 99.48±0.773 | 148± 0.48 | 0.42±0.061 |
| F4 | 3.06±0.0158 | 3.20±0.05 | 99.03±0.77 | 143 ± 1.3 | 0.49±0.114 |

**Table 9: Evaluation of bilayer tablets**

| Thickness (mm) | Hardness (Kg/cm$^2$) | Friability (%) | Floating lag time | Floating Duration | Weight variation in (Mg) | Water absorption ratio | %Content uniformity |
|---|---|---|---|---|---|---|---|
| 4.78 | 5 | 5.57 | 90 sec | > 12hrs | 491±1.2 | 68.36 | Aspirin 98%,Clopidogrel 99.3% |

**Table 10: Drug Release Kinetic Data treatment**

| Batch | Zero | First | Highuchi | Hixson-Crowell | Weibull | Korsemeyer-peppas | |
|---|---|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | $R^2$ | $R^2$ | N |
| **F1** | 0.965 | 0.730 | 0.901 | 0.842 | 0.487 | 0.985 | 0.214 |
| **F2** | 0.960 | 0.784 | 0.964 | 0.883 | 0.568 | 0.980 | 0.531 |
| **F3** | 0.987 | 0.876 | 0.985 | 0.963 | 0.665 | 0.980 | 0.380 |
| **F4** | 0.943 | 0.835 | 0.941 | 0.915 | 0.611 | 0.983 | 0.528 |
| **F5** | 0.912 | 0.888 | 0.876 | 0.907 | 0.583 | 0.988 | 0.393 |
| **F6** | 0.623 | 0.651 | 0.740 | 0.941 | 0.910 | 0.954 | 0.360 |
| **F7** | 0.619 | 0.935 | 0.740 | 0.907 | 0.662 | 0.931 | 0.648 |
| **F8** | 0.917 | 0.822 | 0.839 | 0.860 | 0.581 | 0.925 | 0.309 |

## CONCLUSION

Bilayer tablet of Clopidogrel bisulphate and Aspirin was formulated with suitable polymers and excipients. The floating layer of Clopidogrel bisulphate was prepared by using HPMC K100 polymer which is swellable rate controlling polymer, sodium bicarbonate as gas generating agent and Carbopol as adhesive agent. For immediate release layer was formulated with microcrystalline cellulose (Avicel PH 101), banana powder, used as natural superdisintegrating agent.

In case of floating tablets HPMC K100 in different ratio with sodium bicarbonate and Carbopol used for preparation of optimized batch. Eight batches were formulated for floating sustained release layer tablet from all of them; where, F5 was optimized batch which contained HPMC K100 (140mg), sodium bicarbonate (50mg), and Carbopol (15mg) which gave 95.89% release within 12hrs, and in case of Immediate release layer tablets banana powder in different ratio with microcrystalline cellulose (Avicel PH 101) used for preparation of optimized batch. Four batches were formulated for immediate release layer tablet from all of them, F2 was an optimized batch which contained MCC (20mg), banana powder (16mg) which disintegrates within 15 sec. and also gave highest drug release i.e. 91.70% in 30min.

So, F5 batch for SR and F2 batch IR were directly compressed together and bilayer tablet was formulated .the tablet gave 96.91% DR within 12hrs.it helped to reduce frequency of administration Clopidogrel bisulphate and aspirin for patient compliance.

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