INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

*Research Article*

# FORMULATION AND EVALUATION OF CLOPIDOGREL BISULPHATE FLOATING TABLETS

**Chirravuri S Phani Kumar[1*], A. Hemanth Kumar[1],**

**V. Jyothi Krishna Reddy[1] and DMK. Chakradhar[2]**

[1]Department of Pharmaceutical Technology, Lydia college of Pharmacy, Ethakota, Ravulapalem, Andhra Pradesh- 533 23, India.
[2]Department of Pharmaceutical Technology, Adarsa College of Pharmacy, G. Kothapalli, Gokavaram, Andhra Pradesh- 533 285, India.

**ABSTRACT**

Clopidogrel bisulphate floating tablets were designed to overcome the gastric bleeding, drug resistance and oral bioavailability problem of the drug by keeping the drug in absorption window for prolonged duration of period i.e. more than 12 hrs in stomach. The floating tablets were prepared using wet granulation method and type of floating is effervescent technique by using sodium bicarbonate as gassing agent. Herein, HPMC K100M(F1 & F2) , HPMC K4M(F3 & F4), Guar gum(F5 & F6) & Xanthum gum(F7 & F8) were used as release rate retardants. All the pre & post compression parameters, *in-vitro*floating lag time, Total floating time& dissolution tested for the prepared tablets. Based on*in-vitro*floating lag time, Total floating time and especially based on dissolution data final formulation was selected. F1 is the final formulation, retarding the release for12 hrs, floating lag time is 19 seconds and Total floating time is up to 12 hours, following the first-order release kinetics and non- fickian diffusion mechanism of drug release (n = 0.63).

**Keywords:** Clopidogrel Bisulphate, HPMC, Guar gum & Xanthum gum.

## INTRODUCTION

The present study was aimed to develop a novel drug delivery system of Clopidogrel bisulphite matrix floating tablets for controlled release. The mechanism involved was explained in four steps 1) Delivery of tablets to stomach through oral cavity 2) Floating of matrix tablet on stomach fluid due to effervescence 3) Diffusion of drug from the matrix 4) Prolonged release of Clopidogrel bisulphate from the matrix. The main aim and objective of present work was to develop an optimized floating tablets with prolonged drug delivery by comparing four polymers at two differentpolymeric concentrations.

Clopidogrel[1]is an anti-platelet drug used in various conditions like peripheral vascular disease, coronary artery disease, and cerebrovascular diseases. The drug is having poor oral bioavailability, this can be enhanced by prolonging gastric residence time for longer duration of period. Because Clopidogrel bisulphate has good solubility in lower pH condition[2].

## MATERIALS

Clopidogrel bisulphite, remaining all excipients and chemicals gifted by SK Health Care Formulations limited, Bolaram, Hyderabad.

## METHODS[3,4]

### I. Analytical Method Development

### 1. Preparation of 0.1 N Hydrochloric Acid (pH 1.2)

8.5 ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000 ml.

**2. Determination of $\lambda_{max}$ of Clopidogrel in 0.1N HCl**

50mg of Clopidogrel was weighed and dissolved in 50ml 0.1N HCl and then made up to a volume of 50ml with 0.1N HCl to give 1000µg/ml concentrated stock solution(Working standard). From the working standard solution, 1ml was diluted to 100ml with 0.1N HCl it will give 10 µg/ml concentrated solution. This solutions was scanned at the range of 200-400nm wavelength light corresponding scan spectrum curve was noted .the corresponding wavelength having highest absorbance is noted as $\lambda_{max}$, it was found 238 nm for the drug.

**3. Construction of calibration curve of Clopidogrel in 0.1N HCl**

50mg of Clopidogrel was weighed and dissolved in 50ml 0.1N HCl and then made up to a volume of 50ml with0.1N HCl, it gives1000 µg/m concentrated stock solution(Working standard). From the working standard solution 1ml was diluted to 100ml with 0.1NHcl it will give 10 µg/ml concentrated solution(Dilution 1). From dilution 1 , 1.5,2,2.5,3ml of solutions were taken and diluted up to mark in 10ml volumetric flask to obtain 10,15,20,25,30 µg/ml concentrated solutions and analyzed at $\lambda_{max}$ 238 nm using 0.1 N HCl solution as blank in UV- Spectrophoto meter.

**II. Formulation of gastro retentive floating tablets by Wet granulation method**

The matrix tablets were prepared by following the General Methodology as follows, all ingredients (Clopidogrel + Avicel PH 102 + polymer) were weighed accurately into a mortar and triturated to get a dough mass using water as a solvent, the dough mass was passed through #22 sieve and dried for 20 minutes in a tray dryer for 20 minutes, the dried granules were passed through # 24 sieve. The granules were lubricated with # 40 Sieve passed Magnesium stearate & talc. The final blend was then compressed into tablets using 16 station tablet compression machine(Cadmach) with an average hardness of 4.0Kg, by using 8mm die.

**Table 1: Formulation table for Clopidogrel Bisulphate floating tablets**

| Ingredients | Qty/Tablet (mg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| Clopidogrel Bisulphate | 98 | 98 | 98 | 98 | 98 | 98 | 98 | 98 |
| HPMC K100M | 49 | 73.5 | -- | -- | -- | -- | -- | -- |
| HPMC K4M | -- | -- | 49 | 73.5 | -- | -- | -- | -- |
| Guar gum | -- | -- | -- | -- | 49 | 73.5 | -- | -- |
| Xanthum gum | -- | -- | -- | -- | -- | -- | 49 | 73.5 |
| $NaHCO_3$ | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Talc | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Mg.Stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Avicel PH-102 (MCC) | 101 | 76.5 | 101 | 76.5 | 101 | 76.5 | 101 | 76.5 |
| **Total** | **280** | **280** | **280** | **280** | **280** | **280** | **280** | **280** |

**III. EVALUATION OF TABLETS**

The formulated tablets were evaluated for the following Pre, post compression quality control studies & In vitro Buoyancy studies and dissolution studies

**A) Pre Compression studies**

**1. Angle of Repose**

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Angle of Repose of granules was determined by the funnel method. Accurately weighed tablet powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\theta = \tan^{-1}(h/r)$$

Where: $\theta$ = angle of repose, h = height in cms,

r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

**2. Density**

**a) Bulk density (BD)**

It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

**Bulk density = weight of powder / Bulk volume.**

$D_b = \frac{M}{V_0}$ Where, M = mass of the powder

$V_0$ = bulk volume of the powder

**b) Tapped density (TD)**

It is the ratio of total mass of powder to the tapped volume of powder

Weigh accurately 25 g of granules, which was previously passed through 22# sieved and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula.

Tapped density = Weigh of powder / Tapped volume

$$Dt = (M) / (V_f)$$

Where, M = mass of the powder $V_f$ = tapped volume of the powder.

**3.Carr's Index**

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below:

**Compressibility index**

$$= \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

**4. Hausner's Ratio**

Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

**B) Post compression studies**

**1. General appearance**

The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

**2. Average weight/Weight Variation**

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

$$\%\text{weight variation} = \frac{\text{Average weight} - \text{Weight of tablet}}{\text{Average weight}} \times 100$$

**3. Thickness**

Thickness of the tablets (n=3) was determined using a Vernier callipers.

**4. Hardness test**

Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a

spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

**5. Friability test**

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting.

Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

$$\%Friability = [(W_1-W_2)/W_1] X 100$$

Where, $W_1$= weight of tablets before test,

$W_2$ = weight of tablets after test

**6.Assay Procedure**

Weighed and finely powdered not less than 20 tablets. Transferred an accurately weighed portion of the powder equivalent to about 10mg of model drug into a 10 ml volumetric flask. Added approximately 6ml of 0.1N HCl and shake and sonicated for 10 min to complete the extraction and volume filled with methanol. 1ml aliquot was Pipetted into a 10ml volumetric flask, diluted with methanol to volume, mixed and filtered. From this 1ml aliquot was withdrawn and made up to mark with buffer.

Calculate the quantity in mg of model drug in the portion taken by the formula

**Assay = {(Test absorbance/Standard absorbance) X (standard concentration/sample concentration) X (purity of drug/100)} X100**

**7. *In-vitro* Buoyancy studies**[5]

The *in-vitro* buoyancy was determined as per the method described by Rosa et al.

**a. Floating Lag Time (FLT)**

A tablet was placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as the Floating Lag Time (FLT).

**b. Total Floating Time (TFT)**

A tablet was placed in a 100 ml beaker containing 0.1N HCl. The duration of time up to which the tablet constantly floats on the dissolution medium was noted as the Total Floating Time (TFT).

**c. Matrix integrity**

During the period of TFT the swelled matrix tablets were observed for integrityfor 12 hrs.

**8. In vitro Dissolution Study**

900 ml of 0.1N HCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37$^0$C±0.5$^0$C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 12 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at $\lambda_{max}$ =238 nm using a UV-spectrophotometer (Lab India).

**9. In vitro Release Kinetics Studies**

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from FDDS was studied by using Higuchi equation and the Peppa-Korsemeyer's equation.

**1. Zero Order Release Kinetics**

It defines a linear relationship between the fractions of drug released versus time.

$$Q=k_0t.$$

Where, Q is the fraction of drug released at time t and $k_o$is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

**2. First Order Release Kinetics**

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\text{Log } C = \text{Log } C_o - kt/2.303$$

Where C is the amount of drug dissolved at time t,
$C_0$ is the amount of drug dissolved at t=0 and
k is the first order rate constant.
A graph of log cumulative of log % drug remaining vs. time yields a straight line.Will be linear if the release obeys the first order release kinetics.

**3.Higuchi equation**

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$Q = K_2 t^{1/2}$$

Where $K_2$ is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

**4.Peppa-Korsemeyer's equation (Power Law)**

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa-Korsemeyer's equation (Power Law).

$$M_t / M_\infty = K.t^n$$

Where, Mt is the amount of drug released at time t
$M_\infty$is the amount released at time α,
$M_t/M_\infty$is the fraction of drug released at time t,
K is the kinetic constant and n is the diffusion exponent.
To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted .A plot between log drug release up to 60% against log of time will be linear if the release obeys Peppa-Korsemeyer' s equation and the slope of this plot represents "n" value. The kinetic data of the formulations were included .
Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using MS EXCEL

**Table 2: Drug release kinetics mechanism**

| Diffusion exponent(n) | Mechanism |
|---|---|
| 0.45 | Fickian diffusion |
| 0.45 < n <0.89 | Anomalous( Non- Fickian) diffusion |
| 0.89 | Case II transport |
| n > 0.89 | Super Case II transport |

**RESULTS & DISCUSSION**

**Table 3: Standard Calibration graph values of Clopidogrel Bisulphate 0.1N HCl at $\lambda_{max}$ = 238 nm**

| Conc.(µg / ml) | Absorbance at $\lambda_{max}$ = 238 nm |
|---|---|
| 0 | 0 |
| 10 | 0.165 |
| 15 | 0.254 |
| 20 | 0.317 |
| 25 | 0.399 |
| 30 | 0.481 |

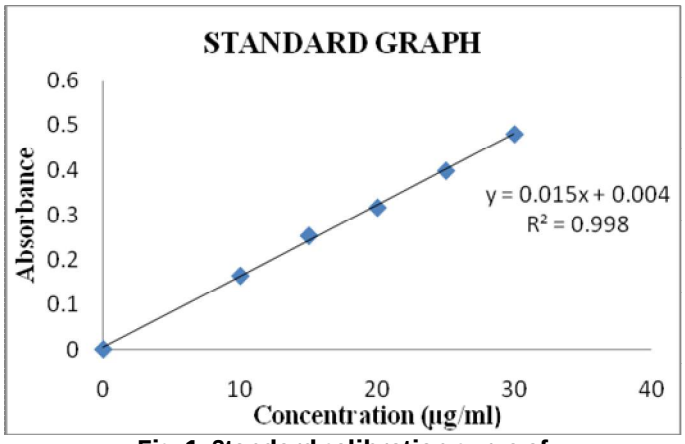


**Fig. 1: Standard calibration curve of ClopidogrelBisulphate in 0.1N HClat $\lambda_{max}$ = 238 nm**

**Table 4: Pre compression studies of Clopidogrel Bisulphate Floating tablets *n=3**

| Formulation Code | Bulk density (Kg/cm³) | Tapped density (Kg/cm³) | Carr's index | Hausner's ratio | Angle of repose (˚) |
|---|---|---|---|---|---|
| **F1** | 0.40 | 0.48 | 16 | 1.2 | 12.73 |
| **F2** | 0.39 | 0.48 | 18 | 1.23 | 11.96 |
| **F3** | 0.50 | 0.58 | 13 | 1.16 | 11.58 |
| **F4** | 0.44 | 0.50 | 12 | 1.1 | 9.92 |
| **F5** | 0.37 | 0.41 | 9.75 | 1.1 | 12.35 |
| **F6** | 0.37 | 0.41 | 9.75 | 1.1 | 11.14 |
| **F7** | 0.37 | 0.41 | 9.75 | 1.1 | 11.14 |
| **F8** | 0.41 | 0.45 | 8.8 | 1.0 | 11.85 |

**Table 5: Post compression studies of Clopidogrel Bisulphate floating tablets**

| Formulation Code | % weight variation | Thickness (mm) | % friability | %Drug Content | Hardness (Kg/cm²) |
|---|---|---|---|---|---|
| F1 | pass | 5.03 | 0.132 | 99.6 | 3.63 |
| F2 | pass | 5.03 | 0.143 | 98.9 | 3.2 |
| F3 | pass | 4.93 | 0.110 | 100.2 | 4.7 |
| F4 | pass | 5.1 | 0.133 | 100.5 | 4.53 |
| F5 | pass | 5.06 | 0.142 | 101.3 | 4.56 |
| F6 | pass | 5.06 | 0.151 | 102.3 | 5.03 |
| F7 | pass | 5.03 | 0.62 | 100.1 | 5 |
| F8 | pass | 5.1 | 0.154 | 100.7 | 4.63 |

**Table 6: In vitro Buoyancy Studies of Clopidogrel Bisulphate floating tablets**

| Formulation Code | Floating lag time | Total floating time | Matrix Integrity upto 12 hrs. |
|---|---|---|---|
| F1 | 19 sec | Up to 12hrs | Non eroding |
| F2 | 31 sec | Up to 12hrs | Non eroding |
| F3 | 31 sec | Up to 12hrs | Non eroding |
| F4 | 19 sec | Up to 12hrs | Non eroding |
| F5 | 19 sec | Up to 4 hs | Eroding |
| F6 | 44 sec | Up to 6hs | Eroding |
| F7 | 13 sec | Up to 4hrs | Eroding |
| F8 | 13 sec | Up to 5hrs | Eroding |

**Table 7: Invitro Dissolution results of Formulation trails with HPMC K100M, HPMC K4M, xanthum gum & guar gum for Clopidogrel Bisulphate**

| Time(hr) | Cumulative % drug released | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| 0 | **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | **22** | 18 | 35 | 29.16 | 49 | 37 | 36 | 34 |
| 2 | **35** | 29 | 46 | 43 | 65 | 68 | 45 | 43 |
| 4 | **55** | 41 | 65 | 62 | 96 | 85 | 68 | 59 |
| 6 | **64** | 58 | 80 | 78 | 100 | 100 | 81 | 72 |
| 8 | **78** | 65 | 96 | 91 | | | 98 | 86 |
| 10 | **90** | 78 | 100 | 99 | | | 100 | 95 |
| 12 | **99** | 84 | | 100 | | | | 100 |

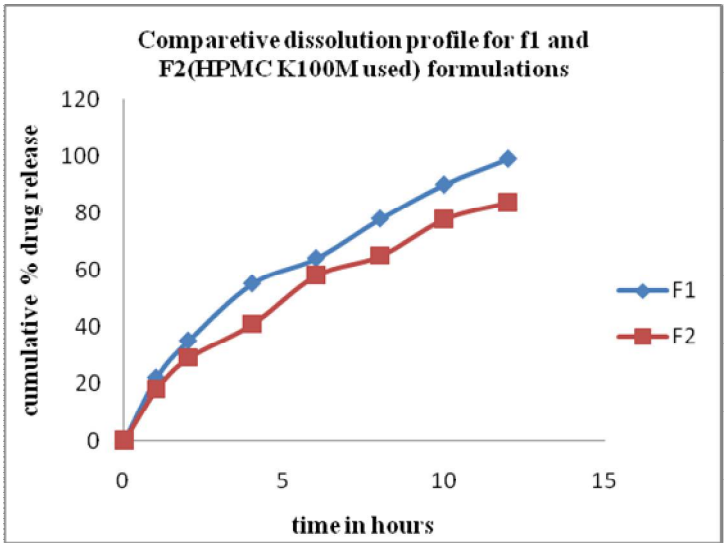


**Fig. 2: Comparative disso profile for HPMCK100M used series**

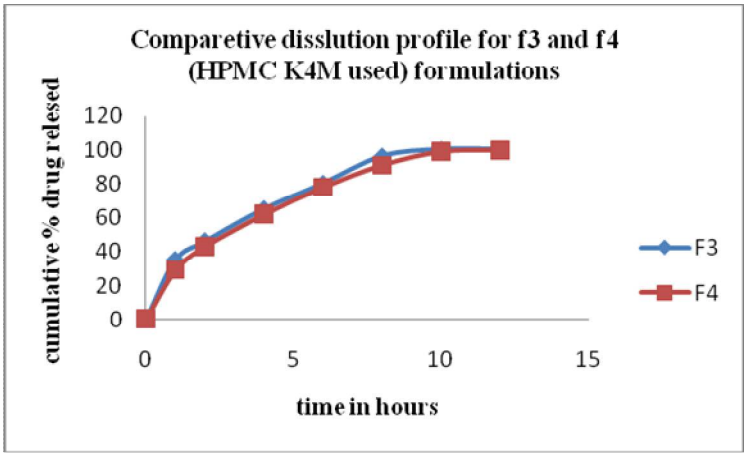


**Fig. 3: Comparative disso profile for HPMCK4M used series**

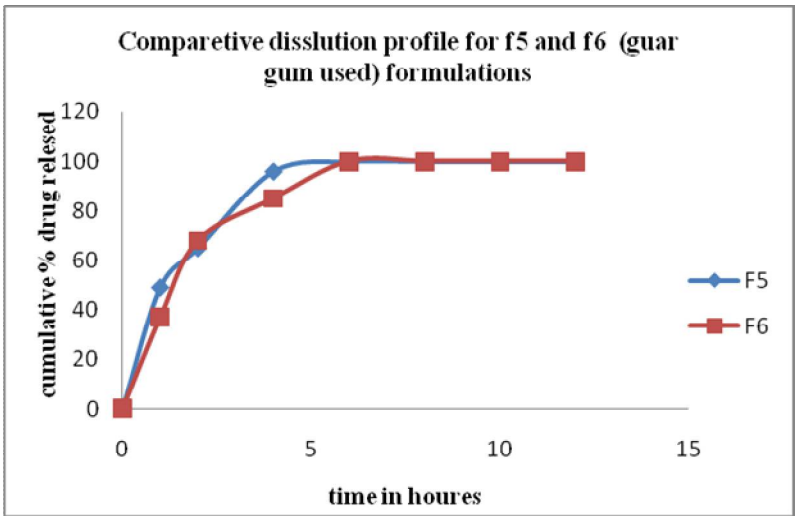


**Fig. 4: Comparative disso profile for GUAR GUM used formulations**

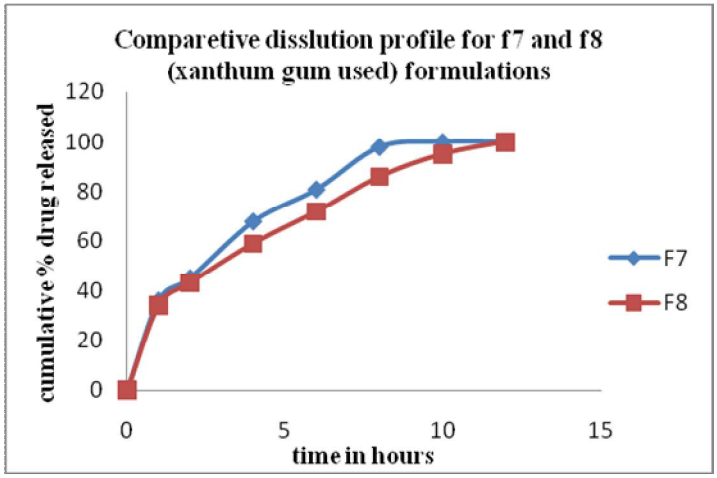


**Fig. 5: Comparative disso profile for XANTHUM GUM used formulations**

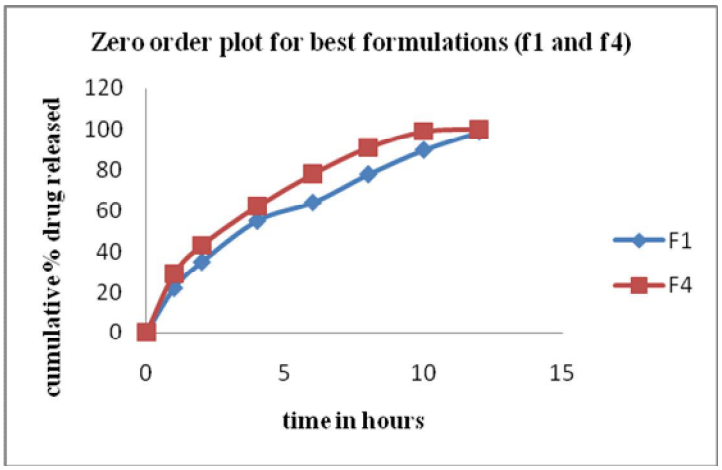


**Fig. 6: Zeroorder plot for better formulations F1 & F4**

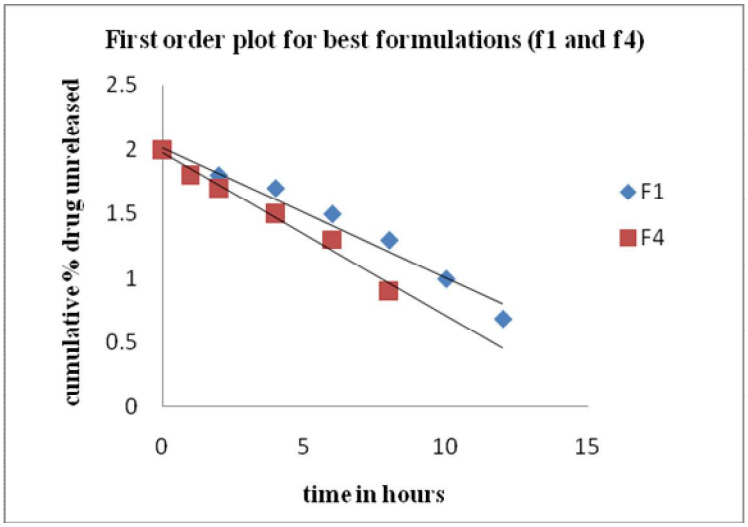


**Fig. 7: First order plot for better formulations F1 & F4**

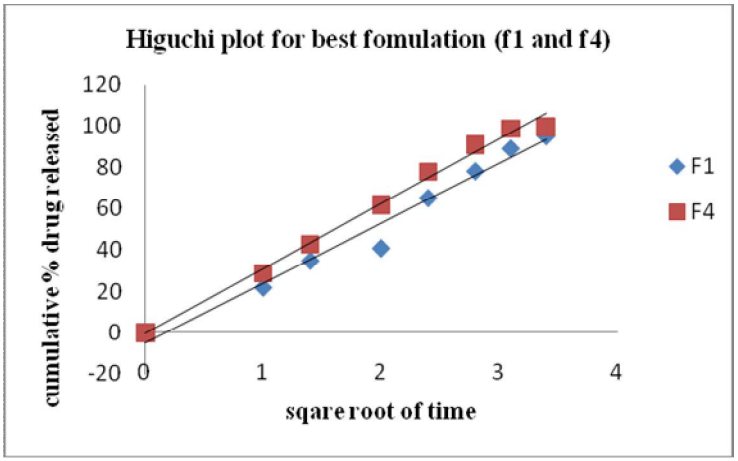


**Fig. 8: Higuchi plot for better formulations F1 & F4**

**Table 8: $r^2$ value and n result table**

| Formulation code | $r^2$ square value | | | | n value |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi plot | Korsemeyer-Peppas plot | |
| F1 | 0.98 | 0.98 | 0.99 | 0.925 | 0.633 |
| F4 | 0.946 | 0.99 | 1 | 0.964 | 0.5 |

**I. Analytical Method**

**A) Calibration curve**

The standard calibration curve of Clopidogrel in 0.1N HCl showed good correlation with regression value of 0.998

**II. Evaluation of Tablets**

**A) Pre compression parameters**

The blends prepared for wet granulation of tablets were evaluated for their flow properties, the results for the blends of compression tablets were shown in Table:4. The bulk density and the tapped density for all formulations were found to be almost similar. The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 to 1.23 respectively, indicating good flow and compressibility of the blends.The angle of repose for all the formulations was found to be in the range of 9.92-12.73° which indicating passable flow (i.e. incorporation of glidants will enhance its flow).

**B) Post compression parameters**

The variation in weight was within the range of ±7.5% complying with pharmacopoeia specifications of USP.The thickness of tablets was found to be between 4.9-5.2 mm. The hardness for different formulations was found to be between 3.2 to 5.0 kg/cm$^2$, indicating satisfactory mechanical strength. The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content was found to be within limits 98 to 102 %.

**C) In-vitro floating studies**

The FLT was found to be within limits of < 5 min. The formulations having matrix integrity &TFT unto 12 hrs(i.e. With HPMC K100M as F1,F2& With HPMC K4M as F3,F4).

**D) In-vitro dissolution studies**

Among the different control release polymers HPMC k100m was showing highest dug release retarding capacity. F1 anf4 was showing the satisfactory results, in between these two f1 was having better sustainability. When we plot the release rate kinetics of best formulations, f1 was following first order&f4 following zero order release. For both the f1 and f4 formulations diffusion exponent n value id in between 0.45 to 0.89 so they age following non fickian anomalous diffusion model. The order of release rate retardation was as follows

HPMC K100M > HPMC K4M > Xanthum gum > Guar Gum

**CONCLUSION**

From the experimental data, it can be concluded that floating Tablets of Clopidogrel are formulated to increase gastric residence time and thereby improve its therapeutic efficacy. Higher the viscosity grade of the HPMC greater the retarding rate of model drug and the order of Controlled release is: HPMC K100M >HPMC K4M. HPMC K100M was respectively showed better Sustained drug release of Clopidogrel Bisulphate. Synthetic polymers were showing more rate retarding dug release and matrix integrity, the order of better controlled release polymers are HPMC K100M > HPMC K4M > xanthum gum > guar gum. When polymer concentration increases the release rate decreases this is because of reason when the concentration of polymer increases the diffusion path length increases. Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity and *in vitro* drug release. Formulation F1 gave better-controlled drug release and floating properties in comparison to the other formulations. The release pattern of the F1 formulations was best fitted to Korsemeyer-Peppas model, Higuchi and first-order model. The most probable mechanism for the drug release pattern from the formulation was non-Fickian diffusion or anomalous diffusion.

**ACKNOWLEDGEMENT**

The authors are thankful to Sri. Gollapalli Sridhar, secretary & Prof. Dr. T. Satyanarayana, Principal of Lydia College of pharmacy, Ravulapalem And Sri R Ganesh, MD of SK Health Care Formulations Pvt Ltd, Hyderabad for their enormous cooperation and guidance.

**REFERENCES**

1. www.drugbank.com. Clopidogrel.
2. Panda S. American Journal of Pharm Tech Research. 2014;4(2):503-516.
3. Srujana. Int J Drug Dev and Res. January - March 2014;6(1):135-148.
4. KPR Chowdary. JGTPS; 2013;4(1):1053-1058
5. Narang*et.* Int J Pharm Pharm Sci. 2010;3(1):208-211.