International Journal of Life Sciences Research (IJLSR)
Vol. 1, Issue 1, pp: (11-18), Month: October-December 2013, Available at: www.researchpublish.com

Formulation and Evaluavation of Clopidogrel Bisulfate Immediate Release Tablets

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Abstract: **The current aim is to study and development of Clopidogrel bisulfate immediate release tablets. Clopidogrel is an inhibitor of platelet activation and decreases subsequent platelet aggregation. Polyplasdone-XL 10 is used as super disintegrants. LHPC is used as binder agent. Microcrystalline is used as diluent and tablet disintegrant. Mannitol is used as diluents and sweetening agent. Castor oil as a lubricant. Seven different formulations are prepared by wet granulation method. From the dissolution study of Clopidogrel bisulfate immediate release tablets it is proved that crosspovidone acts as dissolution enhancing agent and helps increasing dissolution rate of tablet. The prepared immediate release matrix tablets were evaluated for various parameters like hardness test, friability, weight uniformity, drug content uniformity, in-vitro drug release and short term stability studies.**

Keywords: **Immediate release tablets, Clopidogrel Bisulfate**

I. INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the drug concentration in the drug delivery system, it should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Oral route is the most preferred route for administration of drugs. Tablet is the most popular among all dosage forms existing today because of its convenience of self administration and easy manufacturing. But in many cases immediate onset of action is required than conventional therapy such as analgesia, cardio-vascular disorders, sedation/hypnosis and many other conditions. To overcome these drawbacks, immediate release pharmaceutical dosage form as alternative oral dosage forms. [1]

Immediate release drug delivery system: It is a conventional type of drug delivery. It is designed to disintegrate and release their medicaments with no special rate controlling features. These are the dosage forms in which ≥ 85% of labeled amount dissolves with in 30 min. (Patel HP et al., 2011).

Mechanism of drug release from immediate release formulation: On exposure to aqueous fluids, hydrophilic matrices take up water and the polymer starts hydrating to form a gel layer. Drug release is controlled by diffusion barriers/ by surface erosions. An initial burst of soluble drug may occur due to surface leaching when a matrix containing a swell able glassy polymer comes in to contact with an aqueous solution, an unexpected change from a smooth to rubbery state associate with swelling process with time, water infiltration deep in to a case increasing the thickness by the gel layer. The outer layer becomes fully hydrated and starts dissolving or eroding. [2]

Disintegrants: These are substances or mixture of substances added to the drug formulation that facilitates the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in absence of Disintegrants. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1-10% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants are crosscaramellose, crosspovidone, sodium starch glycolate are examples of cross-linked cellulose, polymer and starch respectively. [3]

Mechanism of disintegrant action: **t**he tablets are broken into small particles and produce a homogenous suspension by:

1. By capillary action: Disintegration by capillary action is always the first step when we put the tablet into suitable solution, the solution penetrates into tablet and replaces the air adsorbed on the particulars, which weakens the intermolecular bond and breaks the tablet into fine particles. These disintegrants maintain low interfacial tension towards aqueous fluid is necessary which helps in disintegrations by creating a hydrophilic network around the drug particles.

2. By swelling action: Although not all effective disintegrants swell in contact with solution, swelling is supposed to be a mechanism in which certain disintegrating agents (such as starch) impart their disintegrating effect. By swelling in contact with medium, the gumminess of the ingredients in a tablet overcomes causing the tablet to fall apart.

3. Repulsion theory: Water penetrates through hydrophilic pores into tablet and a continuous starch network which conveys water from one to the next, impart hydrostatic pressure. The water penetrates in between the starch grains because of its affinity for starch surface, causing breakdown of hydrogen bonds and other forces holding the tablet.

4. Deformation theory: The deformation recovery theory implies that the shapes of the disintegrant particles are distorted during compression and return to their precompression shape upon wetting, causing the tablet to break down. [4]

II. MATERIALS AND METHOD

Clopidogrelbisulphate was a gift sample from MSN laboratories ltd, MCC pH 101, Mannitol are from Signet chemical corporation pvt ltd, LHPC-21 from Shin-etsu chemicals, Polyplasdone XL from ISP technologies, PEG-6000 from Clariant chemicals, castor oil from Cognis laboratories, Opadry pink from Colorcon Asia Pvt. Ltd

Methodology: The process in consideration is the wet granulation technique as the flow property is found to be poor. Dispense all the excipients and the API in required quantities and label them. Sift MCC, Mannitol, and polyplasdone XL through 40#,Clopidogrel bisulphate through 20#, PEG 6000,cutina HRPH through 60#. Dry mixing-load sifted MCC, Mannitol into a polybag and mix for 40 mins. Binder solution made by dissolving HPLCF and added to the mixture and kneaded for 180secs.The mixture is then placed in RMG. Impeller speed is maintained at 200RPM, chopper speed 1000rpm. Wet screening is done by passing the mass through 18#. The obtained granules are dried at 70^0C for 1hour 30min. Dry screening is done by passing the granules through 20#. Load dried granules and add PEG6000, Clopidogrel bisulphate and polyplasdone into blender and mix for 20min. Cutina HRPH is added to the above mixture and mix for 10min. Finally compressed by using 8 station rotary punching machine. [5]

Preparation of coating solution: A stainless steel (SS) 316 container is taken 6.3gms of purified water is taken. Stirrer is fixed and started to form a vortex. Opadry pink powder is added into the vortex slowly to avoid any lump formation. Addition is completed within 5-10min under stirring and stirring is continued for 45min.

TABLE I: FORMULATION TABLE

Wt-(mg/tab)	F1	F2	F3	F4	F5	F6	F7
Drug	98	98	98	98	98	98	98
MCC	80	75	70	85	80	75	70
LHPC-21	5	10	15	-	-	-	-
Crosspovidone	-	-	-	-	5	10	15

Mannitol-DC	45	45	45	45	45	45	45
PEG6000	10	10	10	10	10	10	10
Opadry pink	0.27	0.27	0.27	0.27	0.27	0.27	0.27
Castor oil	10.5	10.5	10.5	10.5	10.5	10.5	10.5
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s

III. RESULTS

Preformulation studies:

Standard graph for Clopidogrel bisulfate: The absorbance value and calibration graph of the drug. The UV Spectrophotometric procedure was used to analysis the drug release from prepared formulations.

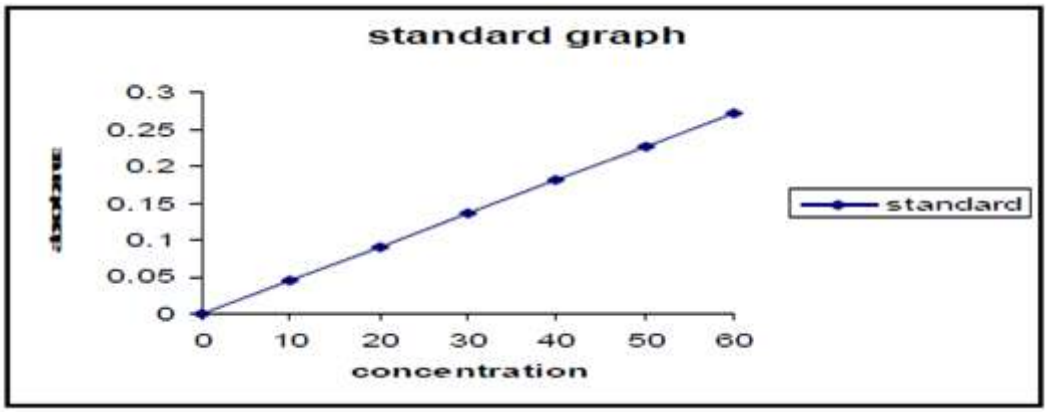

Fig.1

TABLE II: Absorbance values of drug at 220nm

S.No.	Concentration(µg/ml)	Absorbance
1	0	0
2	10	0.045
3	20	0.090
4	30	0.136
5	40	0.181
6	50	0.226
7	60	0.271

Solubility: Solubility can be determined by placing the drug in a vial along with the solvent. The tightly closed vial is then agitated at constant temperature and the amount of drug in solution is determined periodically by assay of filtrate sample. Drug solubility was performed in purified H_20, 0.1N HCl, Acetate buffer pH4.5 and Phosphate buffer pH6.8. [6]

TABLE III:SOLUBILITY STUDY

Media	mg/ml	Criteria
Purified water	17.9	Sparingly soluble
0.1N HCl	693.3	Freely soluble
pH 4.5 Acetatebuffer	17.8	Sparingly soluble
pH 6.8 phosphate buffer	13.3	Sparingly soluble

Drug - excipient compatibility studies: Drug will be in intimate contact with one or more excipients in all the dosage forms. Interaction could affect the drug. Storage condition 40° C/75%RH at 2-8°C is maintained and checked periodically for the detection of changes if any.Knowledge of drug-excipients interaction is useful in selecting an appropriate excipient. The results of Drug - excipient compatibility studies are shown in the table IV. [7]

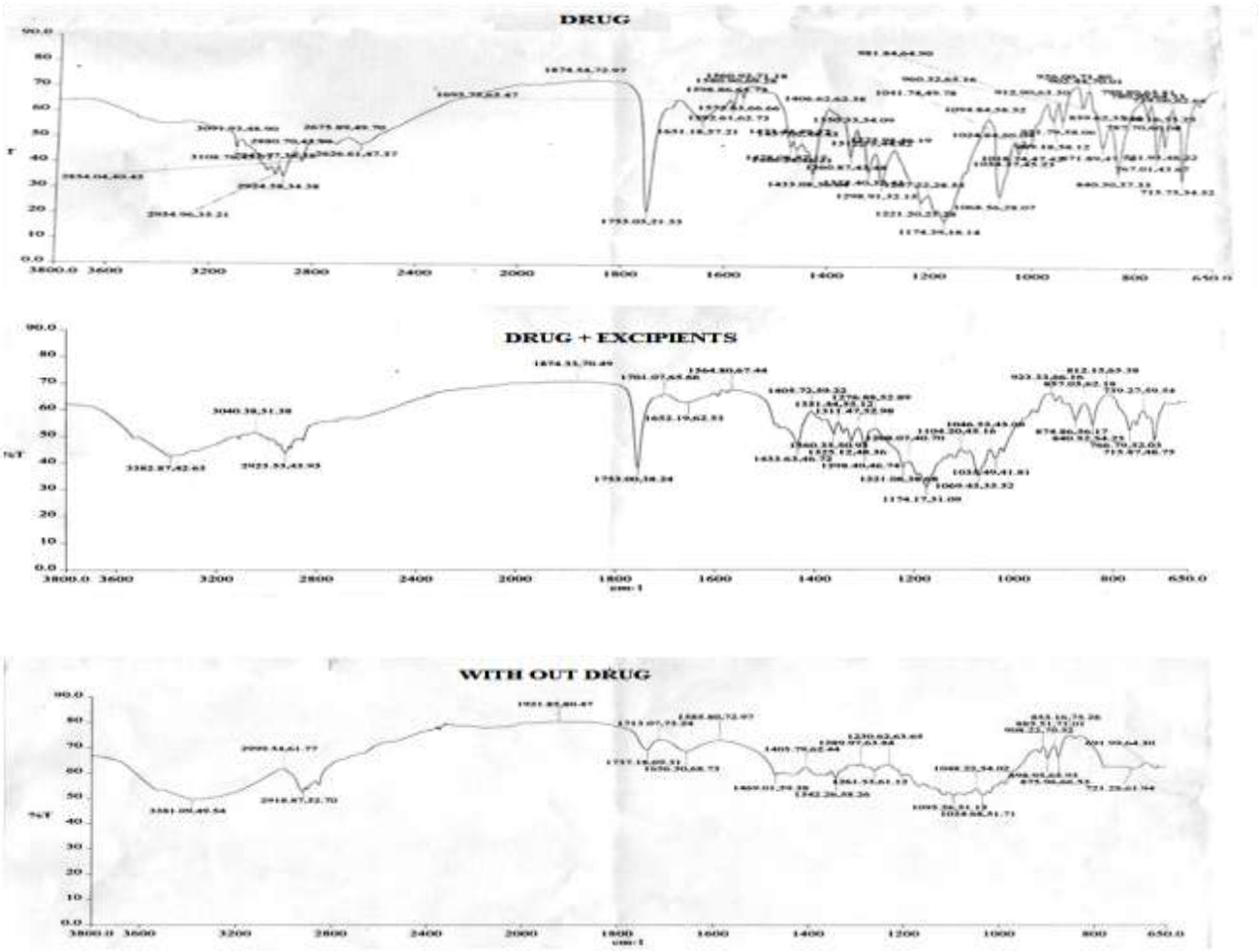

Fig.2

Table IV: IR interpretations

S. No	Region in cm-1	Type of vibration	group present
1	1753.03	C=O stretching	ketone
2	1651.18	C=C	ethers
3	1174.39	C-O	esters
4	2924.96	C-H	alkane

Density measurement: Different types of density were determined to characterize the API and its flow property.

Bulk density: It is determined by pouring drug powder into a graduated cylinder and measuring the volume and weight in cm^3. Bulk density=M/Vo; Where, M = mass of the powder,Vo= bulk volume of the powder

Tapped density: It is defined as the ratio of weight of powder bed volume was reached. It is defined as the ratio of weight of sample in rams to the volume (Tapped volume) in cm^3. Tapped density=M/Vt ; Where, M=mass of the powder, Vt=final tapping volume of the powder.

Flow properties of Clopidogrel: These differences are reflected in the compressibility index and the hausner'ratio. Calculated by using the following equation **Compressibility index = 100(Vt-Vb)/Vb ; Hausner ratio = Vb/Vt**

Where, Vb = bulk volume of the powder; Vt = final tapping volume of the powder

Angle of repose: Angle of repose was determined by using funnel. Powder was poured from a funnel until a maximum height (h) was obtained. The radius of the heap was measured. The angle of repose (Ø)can be calculated as

Ø = tan-1(h/r) ; Where, h=height of the pile; r =radius of the pile [8]

TABLE V: Blend Properties

Formulation	Blend Property				
	B.D(gm/ml)	T.D(gm/ml)	C.I (%)	H.R	Property
F1	0.483	0.681	29.03	1.409	poor
F2	0.593	0.787	24.657	1.327	passable
F3	0.371	0.483	23.188	1.299	passable
F4	0.588	0.754	22.05	1.028	passable
F5	0.526	0.787	28.12	1.39	poor
F6	0.453	0.583	22.299	1.288	passable
F7	0.579	0.769	24.638	1.327	passable

Evaluation of tablets:

Weight variation test: Individual weights of 20 tablets were taken and the average weight was calculated by using the following formula. This is an in process quality control test to be checked frequently (every half an hour).

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

Hardness: Hardness of the tablets was observed by the use of hardness tester. Hardness (diametric crushing strength) is a force required to break the tablet across the diameter.

Thickness: Thickness of the tablets was calculated by the use of vernier calipers. Desired thickness was 2-3mm.

Friability: Friability of the tablets was calculated by the use of friabilator. This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Friability should be less than 1. The friability (F %) is given by the formula : $F\ \% = (1-W_o/W)\times 100$

W_o : weight of the tablets before the test and W is the weight of the tablets after test.

Disintegration test: Disintegration time is considered to be one of the important criteria in selection the best formulation. To achieve correlation between disintegration time several methods were developed and followed at their convenience. One tablet placed in one tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±0.5 ^{0}C and operated the apparatus for 15 minutes. [9]

Table VI: Physical properties of the formulations

Batch No.	Average Weight(mg)	Thickness (mm)	Hardness(Kg/Cm^2)	Friability (%)	Disintegration time (mins)
F1	249±2%	3.94	6	0.8%	15
F2	250±2%	3.98	5.3	1%	16

F3	249±2%	3.92	4	2%	17
F4	245±2%	4.01	5.6	0.9%	13
F5	246±2%	4.01	5.4	1.5%	14
F6	247±2%	3.96	4	1.8%	13
F7	249±2%	3.95	4.2	2%	13

Dissolution study: The dissolution test is carried out in a dissolution apparatus (paddles type), one tablet is placed in each vessel containing 900 ml of 2.0 pH HCL at 37^0C and rotate paddles with 75 rpm for 30 minutes. Collect the sample at every 5 minutes of interval time and filter the sample through whattman filter paper, discard the first 10 ml of filtrate. The filtrate is diluted upto 10 ml with 2.0 pH HCL liquid. Each sample was analyzed at 220 nm using double beam UV and Visible Spectrophotometer against blank reagent. [10]

TABEL V:Dissolution study

Time (mins)	F-1	F-2	F-3	F-4	F-5	F-6	F-7
5	50.44	58.28	62.7	59.22	60.68	64.73	70.8
10	58.15	64.47	66.24	64.82	65.74	72.82	78.51
15	63.21	69.15	72.6	69.48	69.28	78.48	84.70
30	66.37	75.35	76.11	73.17	74.34	82.30	89.76
45	70.16	79.90	82.17	79.6	80.2	85.71	92.6
60	75.22	84.70	85.96	84.39	85.7	88.5	94.18

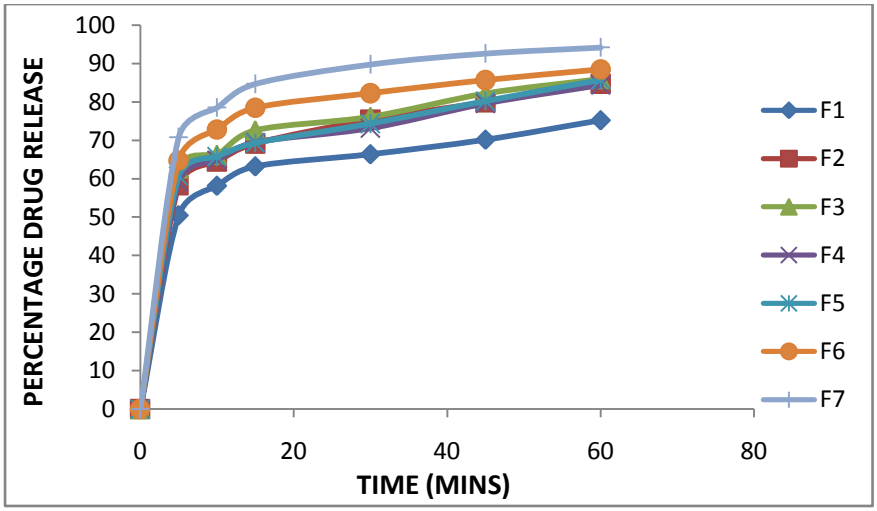

Fig.3

Short term stability studies: For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. It include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behaviour and properties of the drug substance and formal stability studies on the drug substance. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH guidelines. [11]

TABLE VI: Stability studies of the optimized batch

S.No	Test	Specifications	Initial	1st month	3rd month
1	Description	Pink oblong tablet	Complies	Complies	Complies
2	Identification	The retention time of major peak in the chromatogram of the assay preparation correspond to that in the chromatogram of the standard preparation.	Complies	Complies	Complies
3	Dissolution (pH2.0 Hcl)	97% release within 60 Min	97%	97%	97%
4	Related substances	NMT 1.5%	Complies	Complies	Complies
5	Assay (by HPLC)	NLT 97% AND NMT 101.5%	98.8%	98%	98%

IV. DISCUSSION

The aim of the present study was to prepare and evaluate 75 mg of Clopidogrel bisulfate immediate release tablets. Seven batches of formulations were prepared by wet granulation technique. Drug Polymer Interaction, Chemical interaction between drug and the polymeric material was studied by using FTIR. IR value of Clopidogrel bisulfate pure drug was observed as No difference between the IR patterns of the physical mixture of resodronate sodium and polymer. The flow properties of the granules are vital for the performance of the tablet. Hence the flow properties were analysed before compression of the tablets. The Hasuners ratio is ≤1.409 and compressability index ≤29.03 values indicated a passable. Hardness is from 15.5-18.2 kp and friability values are 0.18-0.57% indicated that tablets had a good mechanical strength table. The disintegration time for tablets to disintegrate is between 13-17 mins among all formulations F3,F4,F7 showed best disintegration time. The drug release Clopidogrel bisulfate immediate release tablets among all the formulations formulation F7 shows best dissoluition. F7 formulation contains highest percentage of super disintegrant crosspovidone which enhances the dissolution rate of tablet and is considered as best formulation. The best formulation F7 had passed short term stability studies.

V. CONCLUSION

The present study was undertaken to develop Clopidogrel bisulfate immediate release tablets of 75mg. Based on the results, suitable excipients were selected for formulation development. Various formulae of Clopidogrel bisulfate were prepared by using wet granulation method. The powder blend was subject to various physical characteristics tests such as bulk density, tapped density, Hausner's ratio, compressibility index and core tablets were evaluated for weight variation, hardness, thickness, disintegration time and the results were within specification. As Clopidogrel possess stability problem core tablets were coated with coating suspension and were evaluated for disintegration time, assay and *In-vitro* release studies. The optimized batch tablets were packed in HDPE containers and performed stability studies at 40°C/75%RH. Stability samples were evaluated initially and after two months. All the results were found to be satisfactory. Hence the designed and developed formula of Clopidogrel was stable.

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