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Formulation and development of clopidogrel Bisulfate (75mg) immediate release tablets

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ABSTRACT
Preformulation can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass-produced. Detailed understanding of the properties of the drug substance is essential to minimize formulation problems in later stages of drug development, reduce drug development costs, and decrease the product's time to market (i.e., from drug substance to drug product)

Introduction

Characterisation of Drug

Following physico- chemical properties were studied uner this study:-

Physical Appearance : Physical appearances of API was examined for various properties like colour and state etc. The result is mentioned in Table 1

Table 1 : Physical properties of API

API	COLOUR	STATE
CLOPIDOGREL BISULFATE	White coloured	Granular powder

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 of the supernatant. Solubility of drug substance was performed in purified water, 0.1N HCl, Acetate buffer pH4.5 and Phosphate buffer pH6.8.

The results were seen in the table-1.

Melting Point : Melting point of API was determined by capillary fusion method ; one sided closed capillary was filled with drug and put into the melting point apparatus. Temperature was noted at which solid drug changed into liquid. The result of melting point is mentioned in Table 2.

Flow Properties : Different types of parameters were determined to characterize the API and its flow.

Bulk density(BD)=M/Vo

Where, M = mass of the powder
Vo= bulk volume of the powder

Tapped density(TD)=M/Vt

Where, M=mass of the powder
Vt=final tapping volume of the powder

Carr's Index(%)= [(TD-BD)*100]/TD

Hausner ratio = V0/Vr

Where, V0 = bulk volume of the powder
Vr = final tapping volume of the powder

Compressibility index = 100(V0-Vr)/V0

Angle of repose

Ø = tan-1(h/r)

Where, h=height of the pile
r=radius of the pile

The results of Flow Properties of API are shown in Table .

Drug - excipient compatibility studies

This study was performed to evaluate the compatibility of API with pharmaceutical excipients of common us esuch as filles, binder,glidants, lubricants etc.

Binary mixture of drug and excipients were prepared as given in Table (3) Various physical mixtures were kept at 40OC±2 OC /75%±2% RH .Samples were tested for physical and chemical changes at 0, 1, 2 months against control kept at refrigerated condition (2-8°C).Drug excipient stability studies showed no conformational changes in formulationals and found to stable at environmental condition as defined by ICH guidelines. The results are shown in Table 4.

Innovators Drug

The reference sample PLAVIX (75mg) was purchased from the market and its physical and chemical properties were evaluated . Basic description of the reference product is as follows:-

Brand Name : PLAVIX^{R}
Composition Clopidogrel Bisulfate
Equivalent to Clopidogrel –75mg
Excipients-------- q.s
Colour – Titanium dioxide I.P, Red Iron oxide.
Shelf life 3 yrs
Packaging description Alu-Alu Blister of 14 tablets
Physical Appearance
Light Pink Coloured , round,Biconvex tablets, one side "75" embossing, other side "1711" embossing
Weight 256 mg
Thickness 4.00 mm

Materials And Methods

List of materials used :

- Weighing Balance (with max. capacity 100kg, least count 0.02 kg)

Tele:
E-mail addresses: amneetk22@yahoo.in

- Mechanical sifter (with #20, @40, 60 S.S. screen)
- Octagonal Blender
- Rapid Mixer cum Granulator
- 27 stn. Double rotary / 20 stn. Single rotary compression machine / 5 stn. Double rotary compression.
- Electronic Weighing Balance(with least count of 1 mg)
- Mechanical Stirrer
- Hardness Tester
- Friability test apparatus Vernier caliper Colloidal mill
- Disintegrating Apparatus
- Halogen moisture Analyser
- **Selection of excipients :** The excipients were selected after the drug and excipient compatibility study and there was no major change observed physically.

Method selected for Tablet preparation :

After preformulation study and literature survey , Dry Granulation method for tablet manufacturing was selected for Clopidogrel bisulfate formulation. This method was used selected to form granules without using liquid solution because the product to be granulated may sensitive to heat. Forming granules without moisture requires compacting and densifying the powders . Dry Granulation can be conducted on a tablet press using slugging tooling or on a roller compacter known as chilsonater .

Formulation of clopidogrel bisulfate tablets

The technique of optimization is well reported in the literature for the development of formulation . The purpose of carrying out optimization is to select the best possible formulation from pharmaceutical as well as consumer point of view. The major objective of the product optimization stage is to ensure that the product selected for further development is fully optimized and complies with the design specification and critical quality parameters.

From the literature and Patent search , the most favourable excipients are short listed. All the excipients chosen are well known for their suitability and fitness of purpose. Each excipient is controlled by Pharmacopoeial specification and are the same or similar to those used in the reference innovators product.

Manufacturing Process

A. **Checking of dispensed material** : Check the weights of all the materials dispensed from stores on weighing balance as per attached ORML. Make sure that the balance is caliberated as per schedule.

B.**Sifting and Mixing :** MCC and Mannitol USP were sifted through mechanical sifter fitted with #40 S.S. screen to remove the extra matter if any. Collect all sifted material in double polyethylene lined drum and label accordingly. Mix all the sifted material.

C.**Drug paste preparation for granulation** : Dissolve Polyethylene Glycol 6000USP and Polysorbate 80 in purified water in a S.S. container. Then add Clopidogrel Bisulfate USP slowly with stirring and continue stirring until homogenous paste is obtained.

D. **Granulation** : Load the sifted material of step B in rapid mixer cum granulator (RMG). Start the mixer at low speed and chopper off and mix for 10 min then add drug paste to step C into the RMG at sllow speed, run impeller at fast speed for five minutes with chopper off and with chopper on for 2 minutes. Closing the material charging lid. Stop the RMG and scrap the walls of the mixer from inside then run the impeller at slow speed till homogenous dough was obtained, add extra purified water if required and recorded. Unload the granules in FBD bowl and record.

E.**Drying** : Run the FBD for 10 min on air , keeping steam valves closed. Open the steam valve and run the FBD for 15 min , maintain the temperature of inlet air between 55 to 60^0 C. Rake the the granules and dry till loss on drying of the granules on IR moisture balance at 105^0 C for 5 minutes is between 1.5 to 2.5% w/w.Record the temperature and time observed during drying.

F.**Milling and Sifting** : Sift the dried granules throygh mechanical sifter fitted with #20 screen and collect the granules in polyethylene-lined drums.

After addition of Lubricant , sift Low substituted Hydroxy Propyl Cellulose USP and Microcrystalline Cellulose USP on mechanical sifter with #40 SS screen and collect in polyethylene bag and load the sifted material with dried granules in octagonal blender and mix for 10 minutes. Then sift Hydrogenated castor oil USP and Magnesium Stearate USP on mechanical sifter fitted with #60 SS sieve and collect in polyethylene bag and load in octagonal blender and mix for 5 min.

G. **Compression** : Set the compression machine and surrounding area with parameter as follows :

- Standard machine : 27 stn.S.R./ 29stn. D.R./ 35 stn. D.R.

Punch specification : 9.8 mm circular shape SC puch sets with corresponding dies. U.P.-Plain, L.P. – Plain.

Temperature : 25+-2^0C Relative Humidity : 50+-5%

Film Coating : The uncoated tablets so obtained were coated with a coating solution .The coating solution was prepared by taking Purified Water USP in S.S. container and add with constant stirring Polyethylene Glycol 6000 USP . Then added Ferric Oxide (red) USP AND Titanium dioxide USP with container stirring to obtin a uniform dispersion. Added required amount of HPMC USP 2910 with constant stirring for about 30 mi

Different batches have been planned by changing excipient ratio's were seen in the Table (1).

Table 2. Formulation trials of clopidogrel bisulfate immediate release tablets

S.N	Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Clopidogrel bisulfate USP	98.474	98.474	98.474	98.474	98.474	98.474	98.474	98.474	98.474
2.	Microcrystalline cellulose Ph 102	139.026	139.026	139.026	133.026	145.026	141.026	137.026	____	____
3.	Lactose	30.00	___	___	__	__	__	__	__	__
3.	Mannitol	___	30.00	___	___	___	___	___	___	___
4.	Pearlitol	__	___	30.00	30.00	30.00	30.00	30.00	30.00	30.00
5.	HPCL	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
6.	PEG 6000	2.00	2.00	2.00	2.00	2.00	1.00	3.00	3.00	3.00
7.	Hydrogenated Castor oil	3.00	3.00	3.00	3.00	3.00	2.00	4.00	4.00	4.00
8.	Microcrystalline Cellulose pH112	___	___	___	___	___	___	___	137.026	131.026
9.	Magnesium Stearate									6.00

Evaluation

Pre Compression parameters or Blend Characteristics :

Density measurement:

The volume of a known quantity of the granules from each batch was obtained before and after tapping. The volume before tapping was used to determine the bulk density while the volume after tapping was employed to determine the tap density mathematically.

Furthermore, Hausner's quotient and Carr's compressibility index used to determine the flow and compressibility properties of granules were obtained from the equations The results were seen in the Table (2)

Bulk density(BD)=M/Vo

Where, M = mass of the powder

Vo= bulk volume of the powder

Tapped density(TD)=M/Vt

Where, M=mass of the powder

Vt=final tapping volume of the powder

Flow properties

These differences are reflected in the compressibility index and the hausner'ratio.

It can be calculated by using the following equation

Carr's Index(%)= [(TD-BD)*100]/TD

Hausner ratio = V0/Vr

Where, V0 = bulk volume of the powder

Vr = final tapping volume of the powder

Table 3: Effect of Carr's Index and Hausner's Ratio on flow property

Carr's Index	Flow character	Hausner's ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

Compressibility index = 100(V0-Vr)/V0

Angle of repose

Ø = tan-1(h/r)

Where, h=height of the pile

r=radius of the pile

Table 4 : Effect of angle of repose on flow property

Flow property	Angle of repose (degree)
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable----may hang up	41-45
Poor	46-55
Very poor	56-65
Very very poor	>65

Post Compression Parameters of Prepared Tablets

- Description
- Thickness
- Hardness
- Friability
- Weight Variation
- Disintegration
- Dissolution Time
- Assay

Description : The general appearance of tablet , its visual identity and overall 'elegance' is essential for consumer acceptance. The colour, shape,odour,surface texture and legibility of identifying marking are all noted for the tablet prepared.

Thickness : Thickness depends mainly on die filling , physical properties of materials to be compressed and the compression force. The thickness was measured by using vernier caliper.

Hardness : It is defined as force required to break the tablet in a diametric compression test. Hardness is determined by using Monsanto or Pfizer hardness tester . This parameter is important to know that the tablet has sufficient strength to withstand mechanical shocks of handling in manufacturing , packaging and shipping.

Friability : It is intended to determine the loss of mass under defined conditions. The friability of tablets is determined by Roche Friabilator in the laboratory . In a wider sense chipping and fragmentation can also be included in friability.

The Roche Friabilator consist of acicular plastic chamber, divided into two compartments. The chamber was rotated at a speed of 25 rpm and tablets to a 15cm distance. Reweighed tablets were placed in the apparatus which was given 100 revolutions after which tablets were weighed again.

The ratio of difference between the two weights represents friability. The weight loss should not be more than 1%>

$$\text{Friability} = \frac{W_0 - W}{W_0} \times 100$$

W_0 – Weight of 20 tablets before friability test.

W- weight of 20 tablets after friability test.

Weight Variation test : It is desirable that every individual tablet in tha batch is uniform in weight and variation if any is in permissible limits. Non uniformity in weights may lead to variation in dosing.

20 tablets were weighed collectively and individually ,from the total weight ,average weight was calculated. Each tablet tablet weight was compared with average weights to ascertain whether it is within permissible limits or not.

Table 5 : Weight Variation Specification

Average weight of tablet (mg)	Maximum %age difference allowed (B.P)
<80	10
80-250	7.5
>250	5

Disintegration test : Disintegration time is considered to be one of the important criteria in selection of the best formulation. Thus Disintegration test was done by placing one tablet in each glass tube of DT Apparatus and the assembly was suspended into a 1000 ml beaker containing dissolution medium maintained at 37+/- 0.5^0 C. If one or two tablets fail to disintegrate completely , repeat the test on additional 12 tablets. The test passes if not less than 16 tablets out of total 18 get disintegrated within specified time.

The results can be seen in Table..

Dissolution test:

PARAMETERS

Medium : Ph 2.0 HCl

Apparatus: Dissolution apparatus 2 (Paddle)

Temperature : 37+/- 0.5^0C

Speed : 50 rpm

Running Time : 60 mins

Procedure : Tablets were added into 6 dissolution flasks containing 900 ml of HCl (Ph 2.0) maintained at 37+/- 5^0C and was run for 60 mins. A suitable amount of ample was withdrawn at regular intervals through 0.45 µm membrane filter. The absorbance of sample preparation was measured at 220 nm, using HCl (Ph 2.0) as blank. The results were seen in the Table and fig.

ASSAY : The drug content analysis of prepared formulations of clopidogrel bisulfate immediate release formulations was done

using hplc method under chromatographic conditions mentioned below. From the peaks , percentage of drug present in the formulations was calculated using below mentioned formula. The % drug present in various formulations was shown in table

Chromatographic conditions :

Column : L57 (150 × 4.6) , 5 m
Flow rate : 1.0 ml/min
Wavelenght : 220nm
Injector volume : 10 µl
Mobile Phase : Acetonitrile 250
Phosphate buffer : dissolve 1.36 g of monobasic potassium phosphate in 1000 ml double distilled water Ph 7.0 .
Diluent Methanol

Calculations:

Clopidogrel bisulfate USP
Standard preparation

Wt. of STANDARD (w1) 37.2mg----------100ml methanol
2ml----------50ml methanol
Test 1 tablet----------1000ml methanol
5ml----------25ml methanol

Calculation

Area of sample W1 2 1000 25 P . o.7664
----------X --------X------X--------X--------X------X--- X100
Area of standard 50 50 w2 5 100
W2 = wt. of drug in tablet (75 mg)
P= purity of standard (i.e. 98.26%)

Results And Discussions

Solubility

Table 6 : Solubility of API

API	SOLUBILITY		
	WATER	0.1N HCL	Phosphate Buffer (Ph 4.5)
CLOPIDOGREL BISULFATE	Freely soluble	Freely soluble	Sparingly soluble

Discussion

The drug clopidogrel bisulfate is freely soluble in purified water (at pH 1) and 0.1N Hcl where as it is sparingly soluble in pH 4.5 Acetate buffer and pH 6.8 phosphate buffer.

Melting Point

Table 7: Melting point of API

API	Melting Point
CLOPIDOGREL BISULFATE	181^{0C}C

Flow Properties

Table: 8 Clopidogrel bisulfate flow properties

S.No	Flow property	Values
1.	Bulk density	0.472 g/ml
2.	Tapped density	0.77 g/ml
3.	Compressibility index	22.723%
4.	Hausner's ratio	1.16%
5.	Angle of repose	42^0

Discussion : Preformulation studies of pure drug were conducted for Angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The results indicate that Angle of repose of pure drug was greater than 40 indicating poor flow properties. The carr's index was found to be 22% indicating fair flow. The Hausner's ratio was 1.16% indicating fair flowability. These results indicated the drug possessed poor flow properties and compressible characteristics.

Drug- Excipient Compatibility Studies

Binary mixture of drug and excipients were prepared as given in table-3 Stability studies were conducted at 40OC±2 OC /75%±2% RH.Samples were tested for physical and chemical changes at 0, 1, 2 months against control kept at refrigerated condition (2-8˚C)

Table: 9 Result of Drug excipients Compatibility Studies

S.No.	Composition details Drug excipient ratio	Initial		OBSERVATIONS Storage Conditions / duration 40^0 C/75%%RH $2\text{-}8^0$ C 1M 2M 3M 3M		
1.	Clopidogrel bisulfate-300mg	White powder	NCC	NCC	NCC	NCC
2.	Drug+Mannitol(1:10)	White Powder	NCC	NCC	NCC	NCC
3.	Drug + HPC(1:5)	White Powder	NCC	NCC	NCC	NCC
4.	Drug + PEG(1:2)	White Powder	NCC	NCC	NCC	NCC
5.	Drug+ Hydrogenated castor oil (1:1)	White Powder	NCC	NCC	NCC	NCC
6.	Drug+ colloidal silicon dioxide(1:0.5)	White Powder	NCC	NCC	NCC	NCC

Discussion : Drug excipient compatibility studies showed that there was no interaction or physical change between the drug and excipients. So the selected excipients were found to be compatible with the drug.

Drug Excipient Compatibility By Ftir Study

Caliberation Curve

Table 10. Result of Pre-compression or Blend parameters of blend

Formulation	Bulk Density (g/ml)	Tapped D (g/ml)	Hausners Ratio	Angle of Repose (degrees)
F1	0.35	0.567	1.58	40.1
F2	0.39	0.57	1.56	38.0
F3	0.41	0.59	1.33	37.3
F4	0.47	0.60	1.32	37.1
F5	0.49	0.63	1.30	36.2
F6	0.51	0.64	1.29	36.4
F7	0.54	0.64	1.27	35.2
F8	0.59	0.65	1.26	36.1
F9	0.61	0.67	1.25	35.2

Evaluation of Prepared Formulations

Formulation trials of Clopidogrel Bisulfate immediate release tablets were shown in Table 6 .These formulations were subjected to various physical tests.

Results of the physical tests are shown in table 11.

Table 11 : Physical properties of prepared formulations

	Average Weight (mg)	Thickness (mm)	Hardness (kps)	Friability (%)	Disintegration Time (mins)
F1	274	3.97±0.02	4.2±0.7	0.25	4-5 min
F2	275	3.96±0.02	4.5±0.7	0.28	4 min
F3	276	3.98±0.02	4.5±0.7	0.30	5 min
F4	274	3.96±0.02	5.1±0.7	0.23	6 min
F5	275	3.97±0.02	4.8±0.7	0.20	6 min
F6	274	3.97±0.02	4±0.7	0.24	6-7 min
F7	273	3.98±0.02	4.5±0.7	0.29	8 min
F8	275	3.96±0.02	3±0.7	0.21	3-4 min
F9	275	3.96±0.02	3±0.7	0.20	3-4 min

Optimum conditions are as follows÷

a) Wt. of 20 tablets – 5.50 ± 2% gm
b) Theoratical wt. per tablet – 275 mg
c) Uniformity of wt .– Average net ± 7.5%
d) Diameter – 9.8 ± 0.2 mm
e) Thickness – 3.9 ± 0.1 mm
f) Hardness – 2-5 kg/cm^2
g) Friability – NMT 1.0% w/m
h) D.T – NMT 15 minutes

Observations

After the evaluation of the blend parameters and post compression parameters of the formulations prepared, it was observed that ÷

F1 – The powder flow of the granules was found to be very poor and the tablets so formed showed colour change which might be due to the presence of lactose, as a diluent and the hardness was also not within the given specifications. Therefore, the formulation F1 was not taken forward.

Action Plan – It was decided to replace mannitol as a diluents in next formulation, with similar remaining formula.

F2 – Again, the flow of granules was very poor with angle of repose 38 degrees. Sticking was also observed within the tablets. Therefore, the formulation F2 was nor taken forward.

Action Plan – In the next trail, it was decided to take directly compressible Mannitol (Pearlitol SD-200) within the same quantity and keeping the remaining formula similar.

F3 – The flow of powder was observed to be fair. But in this formulation the sticking as again observed, although after sometime. Therefore, the formulation F3 was nor taken forward.

Action Plan – In the next trail, the quantity of MCC pH 102 (directly compressible diluents in granular form) was decreased and that of Pearlitol was increased, but within the specified limits.

F4 – The flow of granules was fair but this formulation was again showed sticking and hardness problem. The hardness was beyond the specified range so this formulation F4 was nor taken forward.

Action Plan - In the next trial, the quantity of MCC pH 102 was increased and that of Pearlitol was decreased within specified limits.

F5 – This formulation again showed the sticking and hardness problem. So, this formulation F4 was nor taken forward.

Action Plan – In the next trial, the quantity of lubricants used in the formulation that is PEG-6000 and Hydrogenated Castor oil were increased within the specified range.

F6 – Sticking problem again persist so couldn,t take this formulation ahead.

Action Plan - In the next trial, the quantity of lubricants used in the formulation that is PEG-6000 and Hydrogenated Castor oil were decreased within the specified range.

F7 – Hardness was beyond the specified range and sticking was again observed but after long time. So, this formulation F7 was nor taken forward.

Action Plan – Since, MCC pH 102 is more granular and has more moisture content, so it was decided to replace it with MCC pH 112 that is less granular, has more fines and has low moisture content.

F8 – Good match was observed after a long time with possible flow of granules, no sticking, hardness was also within the limits DT was also less than 15 minutes.

Action Plan – In order to avoid any sticking and granular flow problem in future, Magnesium Stearate was added in a small quantity.

F9 – No physical problems were observed. The formula was finalized and was taken forward for further studies to.

Drug content analysis of final formulation (f9)

The drug content analysis of Clopidogrel Bisulfate immediate release tablets so formed was done by HPLC method.

% of Clopidogrel Bisulfate =

$$\frac{\text{Area of sample}}{\text{Area of standard}} \times \frac{W1}{50} \times \frac{2}{50} \times \frac{1000}{w2} \times \frac{25}{5} \times \frac{P}{100} \times 0.7664 \times 100$$

W2 = wt. of drug in tablet (75 mg)

P= purity of standard (i.e. 98.26%)

Table 12. Assay result of innovator drug and various dosage forms of F9

(% Labelled Amount)						
Innovator	Formulation (F9)					
	1	2	3	4	5	6
98.26	92.56	97.38	95.77	98.08	94.87	97.78

Discussion: The drug content of prepared tablets of formulation F9 was within the limits specified in USP (90-110%) and was very close to that of innovator drug (PLAVIX).

Chromatograms

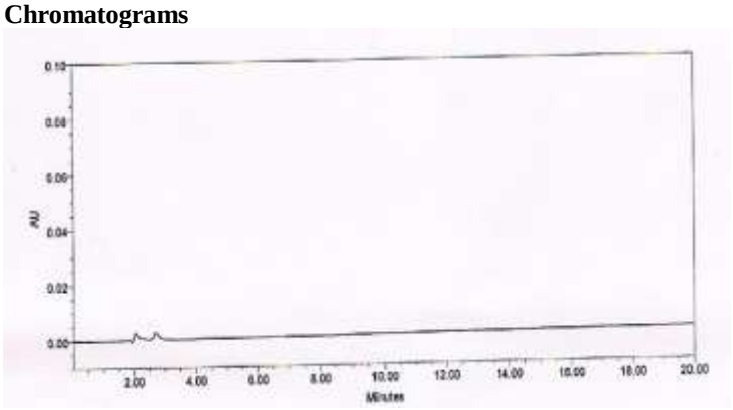

Fig 8 . Chromatogram of Blank sample

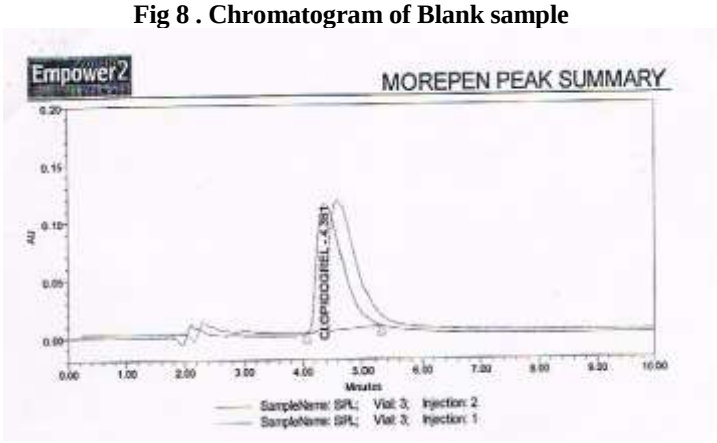

Fig. 9. Chromatogram of Sample Clopidogrel Bisulfate (f9)

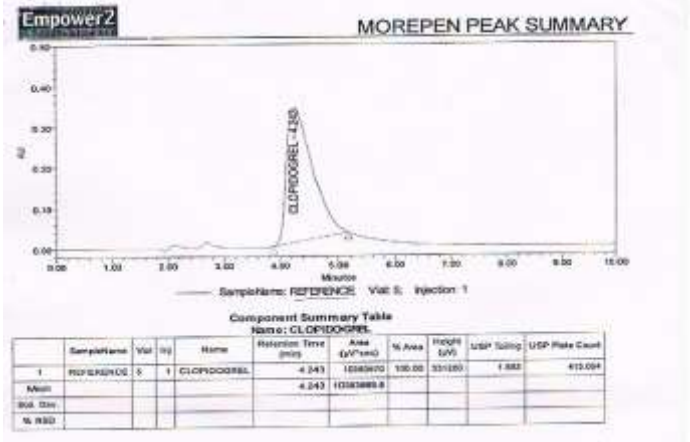

Fig 10 . Standard Chromatogram of Clopidogrel Bisulfate

Standard Curve for Clopidogrel Bisulfate

Table 13 : In-Vitro release profile of F9 with innovators product

S.No.	Time (mins)	Cumulative % release of Innovator pdt.	Cumulative % of drug release F9
1	5	42.31	40.12
2	10	79.51	78.62
3	15	81.70	80.12
4	20	84.16	82.11
5	25	87.31	88.61
6	30	90.60	90.21

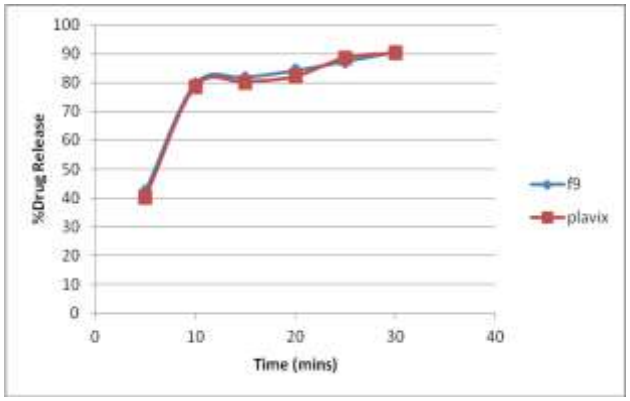

Figure : Comparison of In Vitro profiles of F9 and Innovator

The data of in-vitro release of clopidogrel bisulfate immediate release tablets were shown in Table and in Fig. . The results of optimized formulation F9 were compared with that of innovator product which was shown in Table and in Fig , and similarity factors were estimated.

Table 13: Results of STABILITY STUDIES

S.No.	Test	Specifications	Initial	After 1 month	After 2 months
1	Description	Light Pink, circular , biconvex film coated tablets.	Complies	Complies	Complies
2	Identification	The retention time of major peak in the chromatogram of assay preparation corresponds to the standard preparation as obtained in the assay.	Complies	Complies	Complies
3	Dissolution (Ph 2.0 HCl)	NLT 80% of labeled amount is dissolved in 30 min.	NLT 80% of labeled amount is dissolved in 30 min.	NLT 80% of labeled amount is dissolved in 30 min.	NLT 80% of labeled amount is dissolved in 30 min.
4	Assay (by HPLC)	90.0-110% (67.5-82.5 mg)	90.0-110% (67.5-82.5 mg)	90.0-110% (67.5-82.5 mg)	90.0-110% (67.5-82.5 mg)

Conclusion

The present study was carried out to develop an immediate release tablet dosage form of Clopidogrel Bisulfate and to analyse whether the prepared dosage form posess similar physicochemical properties as that of Innovator's drug (PLAVIX).

From the study conducted , the following conclusions are drawn :

- Direct Compression Dry Granulation method was found to be most suitable for the formulation of drug under study in comparison to wet granulation method because the drug is Hygroscopic (moisture sensitive) in nature and it may be sensitive to heat as well.
- During the preparation of various formulations it was concluded that MCC Ph 102, if used as a Diluent, the flow of granules was not acceptable. But when MCC pH102 was substituted by MCC pH112 in a formulation trial , the flow properties of the granules were improved. This may be because MCC pH102 is more granular and has more moisture content , whereas MCCpH 112 has more fines and has low moisture content, it improved the granular flow and prevents sticking.
- The tablet dosage forms of all formulation trials were subjected to evaluation of various physical characteristics such as Bulk Density, Tapped Density , Hausners Ratio, Compressibility Index and Core tablets were evaluated for Weight Variation , Hardness , Thickness ,Disintegration time. From the various formulations it was found that formulation F9 showed satisfactory results , so F9 was taken forward for further study.
- Analytical parameters such as Assay of formulation F9 was within the limits and is comparable to the reference product.
- The Dissolution profile indicates that the formulation F9 shows equivalent % drug release as compared to the innovator drug.
- The optimized batch of tablets was packed in HDPE containers and stability studies were performed at 40^0 C/75% RH. Stability samples were evaluated initially and after 2 months. All the results were found to be satisfactory.

Hence, the designed and developed formula of Clopidogrel was stable. Clopidogrel bisulphate immediate release tablet developed in the present work were found to be pharmaceutically equivalent to the innovators product.

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