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Research Article

FORMULATION AND OPTIMIZATION OF CLOPIDOGREL BISULFATE IMMEDIATE RELEASE TABLET

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ABSTRACT

This investigation is undertaken with an aim to develop pharmaceutically equivalent, stable, cost effective and quality improved formulation of clopidogrel bisulfate immediate release tablets The current study involves preparation and evaluation of clopidogrel bisulfate tablets, comparison of dissolution rate of optimized formula with innovator's product and estimation of similarity and difference factors.The similarity and dissimilarity factor obtained for clopidogrel bisulfate was found to be within the standards.The formulation F-6 exhibited similar release profile to that of innovators product at each time point. Hence, F-6 was considered as the best formulation.

Key words: Clopidogrel bisulfate, Optimization, PEG6000.

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 desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient.During the development process it under gone the Preformulation studies , formulating the product, optimizing the formula and comparing the in vitro dissolution profile of final formula with the innovator.

MATERIALS AND METHODS

Materials

Clopidogrel bisulphate powder drug was given by the Orchid chemical labs, Mannitol, hydroxyl propyl cellulose, microcrystalline cellulose was given by the Signet chemicals, poly ethylene glycol 6000 was given by the Clariantchemicals, hydrogenated castor oil by Cosph care chemicals, colloidal silicon dioxide was given by Gem corporation,Opadry pink was gifted by Colorcon, India**.**

Methods

Preformulation studies

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 pH6.8The results were seen in the table-1&fig-1

Physico-mechanical characterization

Density measurement: Different types of density was determined to characterize the API and its flow property. The results were seen in the table-2

Bulk density=M/Vo

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

Tapped density=M/V_t

Where, M=mass of the powder
V_t=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

Compressibility index = 100(V_0-Vr)/V_0
Hausner ratio = V_0/Vr

Where, V_0 = bulk volume of the powder
Vr = final tapping volume of the powder

Angle of repose

Ø = $\tan^{-1}$(h/r)

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

Drug - Excipient compatibility studies

Drug will be in intimate contact with one or more excipients in all the dosage forms. Interaction could affect the stability of drug. Knowledge of drug-excipients interaction is useful in selecting an appropriate excipient.The results were seen in the table -3.

Standard graph of clopidogrel bisulfate
Preparation of Dilutions:

1ml of the standard solution was taken and made up to 10ml using the solvent which gives 100µg/ml of drug. From above solution, taken 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml and made the volume up to 10 ml using solvent to get 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml, 60 µg/ml of drug respectively. Calibration curve for the estimation of drug was constructed by employing buffer(pH 2.0 Hcl Buffer). The absorbance of the above solutions was measured in UV spectrophotometer at 249nm.The results were seen in the table -9 &fig-12.

Manufacturing process

Clopidogrel bisulfate, Mannitol, Microcrystalline cellulose, Low substituted hydroxyl propyl cellulose, colloidal silicon dioxide poly ethylene glycol 6000 and hydrogenated castor oil were shifted and passed through mesh # 20. The clopidogrel bisulfate, Mannitol and hydroxyl propyl cellulose were loaded in Rapid mixing granulator and mixed with the speed 100RPM for 5 mins then the material were transferred in a double cone blender and hydrogenated castor oil was added and lubricated for 5 mins. The material was transferred into roller compactor to form slugs. These slugs were passed over 1.0mm screen mesh which was fixed on oscillating granulator. The granules were passed over #60 mesh. Microcrystalline cellulose and colloidal silicon dioxide were added to granules and blend for 20 mins. To the blended material polyethylene glycol and hydrogenated castor oil were added and lubricated for 5 mins. The lubricated blend was transferred into mini tablet with compression machine with 18*8 oblong punch embossed with SN on upper punch and 08 on lower punch then this was compressed with speed of 15±2 RPM. The uncoated tablet was coated with opadry solution till the average tablet weight gains 2.5±0.5%w/w of core tablet weight.Different batches have

been planned by changing excipient ratio's were seen in the table-6.

Evaluation of tablets

Weight variation test

This is an in process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablets (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight

Hardness test

Hardness (diametric crushing strength) is a force required to break the tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufacturers and with the different types of tablets. The permissible limit for hardness is 4-12 kg/cm^2.

Thickness and diameter

The thickness and diameter of 10 tablets were recorded during the process of compression using verniercalipers

Friability test

Friability of the tablets was determined using Roche Friabilator (Electrolab, India). 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 revolutionThe friability (F %) is given by the formula

$$F\ \% = (1 - W_0 / W) \times 100$$

Where, W_0 is 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 Invitro and In vivo, several methods were proposed, developed and followed at their convenience. One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±0.5^{o}C and operated the apparatus for 15 minutes. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.The results were seen in the table -7.

Dissolution

Medium : pH 2.0 HCl
Apparatus : apparatus 2 (paddle)
Speed : 50 rpm
Temperature: 37±0.5°C
Run time : 60 mins

Procedure

6 tablets were placed in each of 6 dissolution flasks containing 900 ml of pH 2.0 HCl, previously maintained at 37±0.5°C. The apparatus was run for 60 minutes. A suitable volume of sample was withdrawn at regular intervals of time and filtered through 0.45 µm membrane filter. The absorbance of the sample preparations were measured at 249 nm, using pH 2.0 HCl as blank.The results were seen in the table -11& fig-14.

Assay

Chromatographic conditions

It was carried out by using ULTRON, ES-OVEN, 150 x 4.9mm, 5µ Column, by taking mixture of buffer and acetonitrile as a mobile phase and fixing the flow rate 1.0ml/min at a wave length of 220nm.

Standard preparation

Weighed accurately about 50.39 mg of clopidogrel bisulfate working standard into 50 ml volumetric flask, added 20ml of methanol, sonicated to dissolve and diluted to volume with mobile phase. Mixed well for 5 minutes.Transfered 5ml of this solution into

50ml volumetric flask and diluted to volume with mobile phase

Sample preparation

Grinded about 10 tablets of Clopidogrel bisulfate to fine powder in a dry mortar and weighed accurately the quantity of powder equivalent to 391.5mg of Clopidorel bisulfate into a 100ml volumetric flask. Added 60ml of methanol, sonicated to dissolve and dilute to volume with mobile phase. Mixed well and transfer 5ml of this solution into 50ml volumetric flask and diluted to volume with mobile phase

Procedure

Separately injected the standard preparation and the sample preparation into the liquid chromatography and recorded the area due to major peaks

Calculated the amount of clopidogrel bisulfate-300mg present in tablets, in % using the following equation.The results were seen in the table -8 & fig-5- 11.

$$\frac{A}{B} \times \frac{S_w}{100} \times \frac{5}{50} \times \frac{100}{Tw} \times \frac{5}{50} \times \frac{At}{L} \times P \times 100$$

A = principal peak area due to sample preparation

B= principal peak area due to standard preparation.

S_w= weight of clopidogrel bisulfate standard taken in mg.

T_w= weight of sample taken in mg.

P= Potency of the standard.

L= Label claim

A_t= Average weight

Similarity and difference factors

A model independent approach was used to estimate the dissimilarity factor (f_1) and similarity factor (f_2) to compare the dissolution profile of optimized formulation (F-6) with innovator product.The difference factor (f_1) calculates the percent difference between the reference and test curve at each time point and is a measurement of the relative error between two curves. The FDA suggested that two dissolution profiles were declared similar if f2 value between 50-100 and f1 was 0-15.The results were seen in the table -13.

Drug-excipient compatibility studies on optimized formulation by FTIR:

FTIR studies were done to verify if there was any interaction between the pure drug and excipients employed. The various FTIR graphs of pure drug, physical mixture and placebo are mixed and the blend was formulated into IR pellet and scanned.The results were seen in the table -5&fig-2,3,&4.

Stability studies

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 .The results were seen in the table -14.

Storage Conditions

In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long term testing should cover a minimum of 12 months study or at least three batches at the time of submission and should be continued for a period of sufficient time till it covers the proposed shelf life.

Innovator sample details

Parameter	observations
Product Name	Clopidogrel bisulfate Tablets 300mg
Brand name	PLAVIX 300mg
Manufacturer	Sanfoi Aventis
Dosage Form	Tablet
Shape	oval
Coated	film coated
Color	pink
Diameter	17.73*9.66mm
Thickness	6.36mm
Hardness	22.9kp
Average weight	1014.3mg
Disintegration time	18mins
Pack	alu-alu blister pack

RESULTS AND DISCUSSION

Solubility

Table: 1 pH solubility study of clopidogrel bisulfate

Media	Mg/ml	criteria
Purified water	517.9	Freely 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

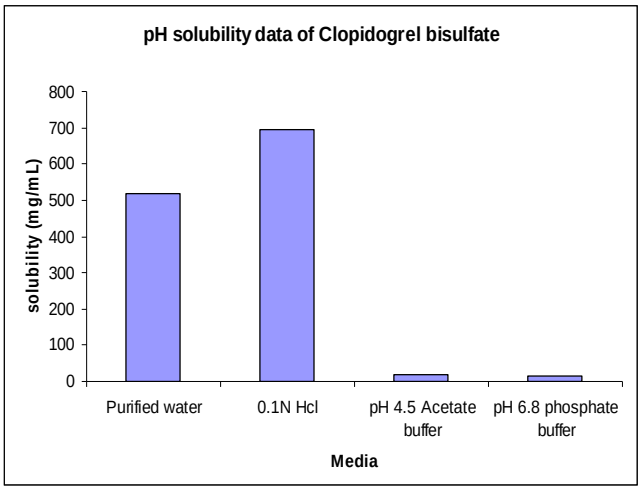


Fig. 1: pH solubility data of clopidogrel bisulfate

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.

Flow properties

Table: 2 Clopidogrel bisulfate flow properties

S.No	Flow property	Values
1.	Bulk density	0.4 g/ml
2.	Tapped density	0.55 g/ml
3.	Compressibility index	27%
4.	Hausner's ratio	1.375

DISCUSSION

Preformulation studies of pure drug wereconducted 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 27% indicating fair to flowable. The Hausner's ratio was 1.375 indicating free 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 40^{O}C±2 ^{O}C /75%±2% RH .Samples were tested for physical and chemical changes at 0, 1, 2 months against control kept at refrigerated condition (2-8℃)

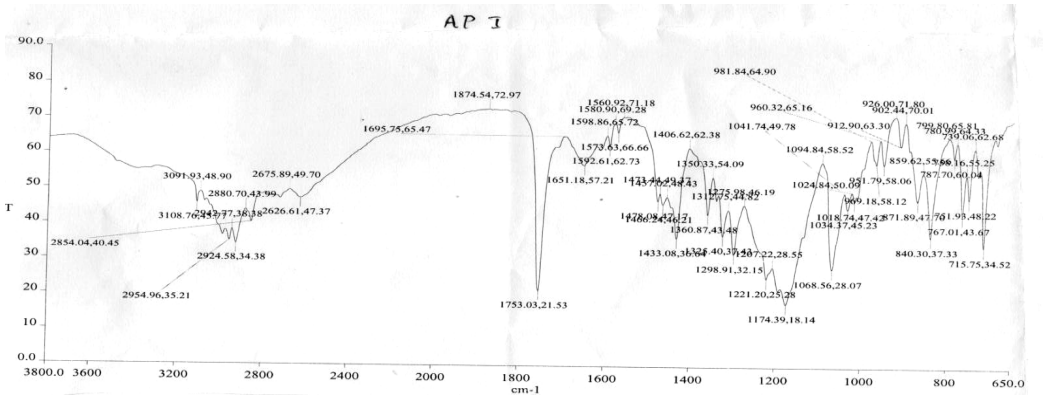
Table: 3 Drug excipients Compatibility studies

S.No	Composition details Drug-excipient ratio	Observations				
		Storage condition/duration				
		Initial	40℃/75%RH			2-8℃
			1M	2M	3M	3M
1	Clopidogrel bisulfate-300mg	A whitepowder	NCC	NCC	NCC	NCC
2	Drug+Mannitol(1:10)	A white powder	NCC	NCC	NCC	NCC
3	Drug + HPC(1:5)	A white powder	NCC	NCC	NCC	NCC
5	Drug + PEG(1:2)	A white powder	NCC	NCC	NCC	NCC
6	Drug+ Hydrogenated castor oil (1:1)	A white powder	NCC	NCC	NCC	NCC
7	Drug+ colloidal silicon dioxide(1:0.5)	A white powder	NCC	NCC	NCC	NCC
8	Drug+ Opadry pink (1:1)	-	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 study by FTIR



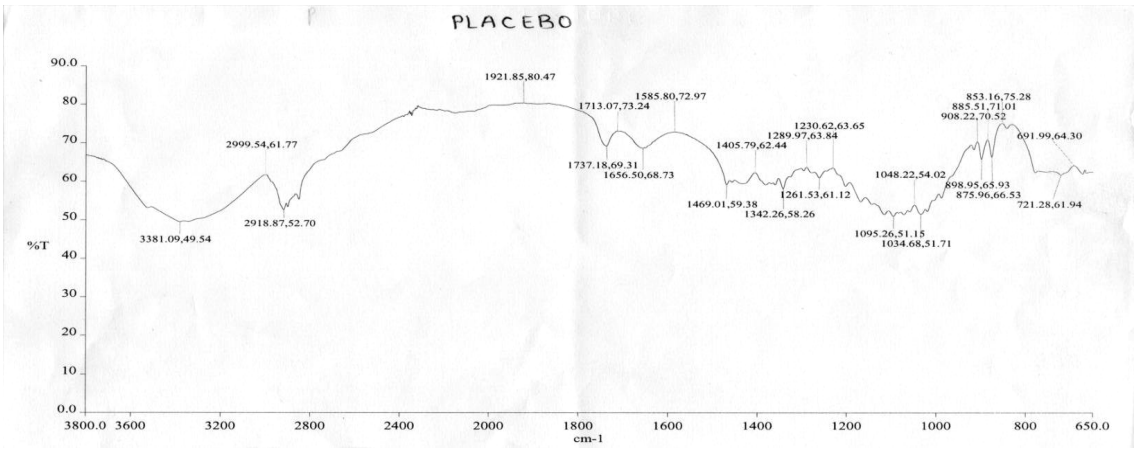


Fig 4: IR Graph of Placebo

Table: 5 IR interpretations

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

DISCUSSION

Drug excipient compatibility study showed no interactions as the principle peaks of drug were retained. Thus all the excipients were compatible with the drug.

Formulation trials of clopidogrel bisulfate immediate release tablets

Table 6: Formulation Trials

S. No	Composition	F1 Qty/(mg)	F2 Qty/(mg)	F3 Qty/(mg)	F4 Qty/(mg)	F5 Qty/(mg)	F6 Qty/(mg)
1	Clopidogrel bisulfate	391.5	391.5	391.5	391.5	391.5	391.5
2	Mannitol	406.5	396.5	396.5	376.5	364.5	361.3
3	Hydroxy propyl cellulose	40	60	70	80	80	80
4	Microcrystalline cellulose	120	110	105	105	105.2	105.2
5	Colloidal silicon dioxide	20	20	20	20	20	20
6	PEG 6000	12	12	12	12	24	24
7	Hydrogenated castor oil	10	10	10	15	15	18

Evaluation of the prepared formulations

Table 7: Physical properties of the prepared formulations

Batch No.	Average weight(mg)	Thickness(mm)	Hardness(kps)	Friability (%)	Disintegration time (mins)
F1	1018±4.1	6.31±0.02	21.7±0.7	0.56	25 mins
F2	1022±4.1	6.29±0.02	21.4±0.7	0.51	24mins
F3	1021±4.1	6.16±0.02	22.5±0.7	0.42	20 mins
F4	1017±4.1	6.26±0.02	23.1±0.7	0.48	20mins
F5	1019±4.1	6.27±0.02	22.2±0.7	0.37	17mins
F6	1020±4.1	6.34±0.02	24.0±0.7	0.33	16 mins

Discussion

The hardness was found to be in the range of 23±0.7 kps, thickness of tablets was found to be in the range of 6.30±0.5mm. The friability was found to be less than 1% for all formulations F-1 to F-6, weight variation results were within ±5 % and disintegration time was found to be in the range of 16 to 25 minutes respectively. The results of all formulations were within specification.

ASSAY

Table 8: Assay values of formulations

(%Labeled amount)

Innovator	F1	F2	F3	F4	F5	F6
99.6	97.2	98	99.2	101	99.5	97

% of clopidogrel bisulfate

$$\frac{A}{B} \times \frac{S_w}{100} \times \frac{5}{50} \times \frac{100}{Tw} \times \frac{5}{50} \times \frac{At}{L} \times P \times 100$$

A = principal peak area due to sample preparation
B = principal peak area due to standard preparation.
S_w = weight of clopidogrel bisulfate standard taken in mg.
T_w = weight of sample taken in mg.
P = Potency of the standard.
L = Label claim
A_t = Average weight

ASSAY CHROMATOGRAMS

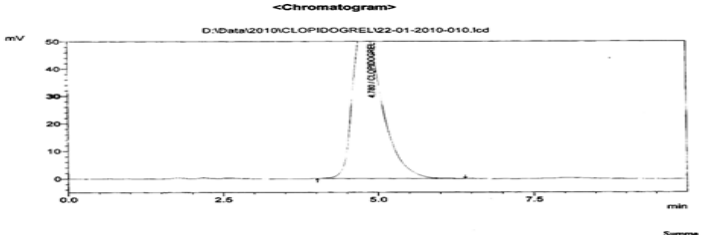


Fig. 5 :Standard Chromatograms of Clopidogrel bisulfate

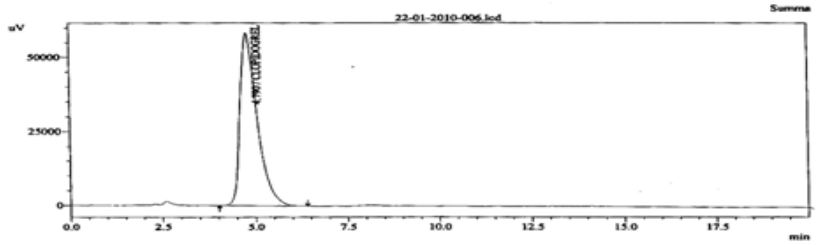


Fig. 6: Chromatograms of Clopidogrel bisulfate f1

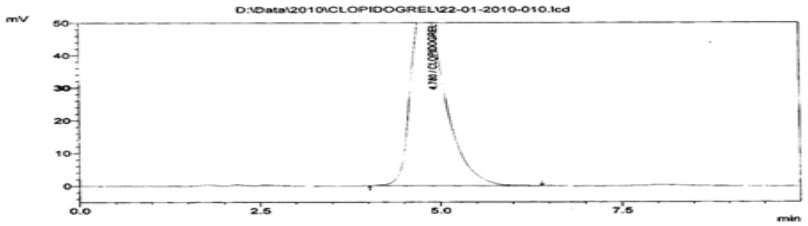


Fig. 7:Chromatograms of Clopidogrel bisulfate f2

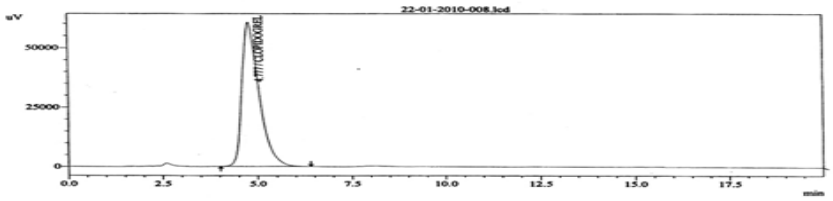


Fig. 8 Chromatograms of clopidogrel bisulfate f3

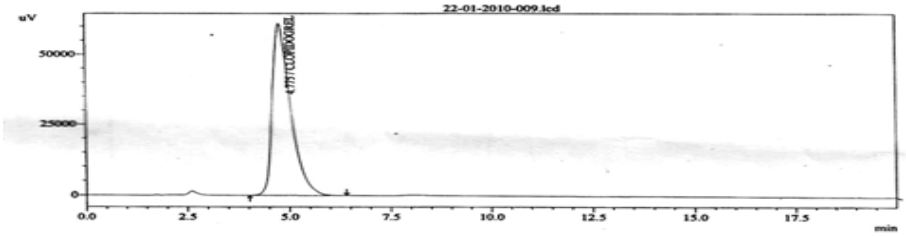


Fig. 9:Chromatograms of clopidogrel bisulfate f4

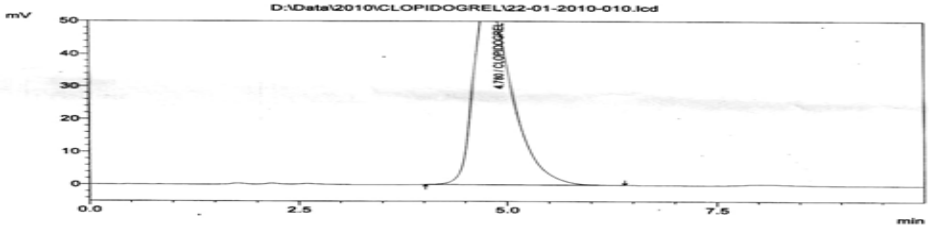


Fig. 10: Chromatograms of clopidogrel bisulfa

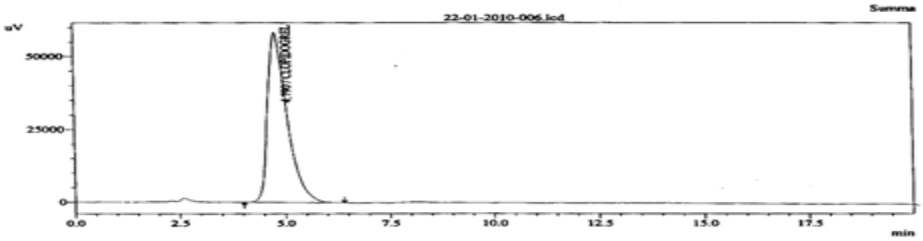


Fig. 11: Chromatograms of clopidogrel bisulfate f6

DISCUSSION

The assay for the clopidogrel bisulfate immediate release tablets was done using HPLC method. The HPLC standard chromatogram obtained was shown in the Fig-5, as a sample representation. From the peaks, percentage of drug is calculated using the below mentioned formula. The % of drug (clopidogrel bisulfate) present in the various formulations was shown in the Table-8. It was observed that the amount of drug present in the formulations F-1 to F-6 (prepared direct compression method) was found to be well within the USP specification limits (90-110%). Based on these results, dissolution studies were conducted for formulations F-1 to F-6.

Standard graph for clopidogrel bisulfate

Table: 9 Absorbance values of drug at 249nm

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

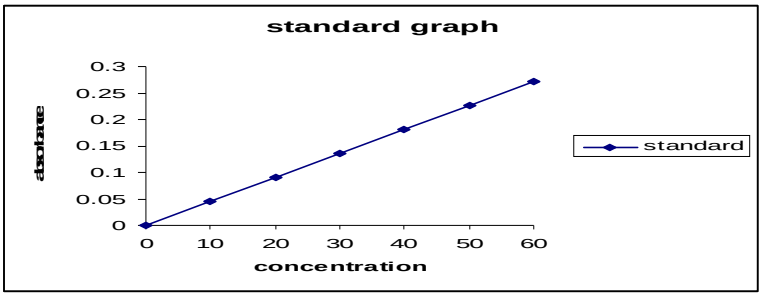


Fig. 12: Calibration curve of clopidogrel bisulfate

Innovators product dissolution profile

Table 10: Innovators product (Plavix) cumulative % drug release

S. No.	Time(mins)	Cumulative %drug Release
1	5	16
2	10	36
3	15	52
4	30	88
5	45	92
6	60	99

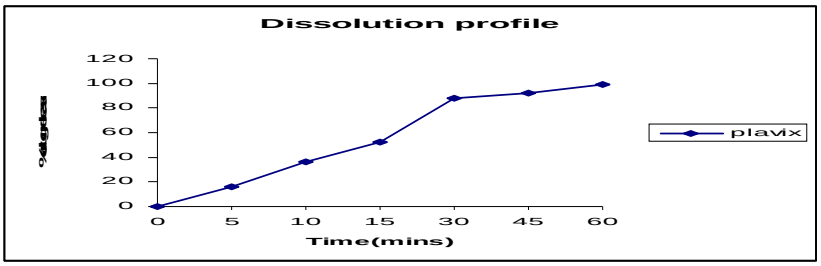


Fig -13: Innovators product dissolution profile

Discussion: Plavix tablets released 16% of drug in 5 mins, 36% of drug in 10mins, 52%of drug in 15 mins, 88%of drug in 30 mins, 92% of drug in 45 mins, 99% of drug in 60 mins.

In-vitro dissolution profiles of clopidogrel bisulfate tablets

Table 11: Cumulative % drug release of drug formulation

S.No.	Time (mins)	Cumulative %drug release of drug formulations					
		F1	F2	F3	F4	F5	F6
1	5	10	12	14	16	17	17
2	10	28	31	33	35	36	38
3	15	45	48	50	51	54	55
4	30	82	83	85	88	88	90
5	45	89	90	92	93	94	94
6	60	95	96	98	97	97	97

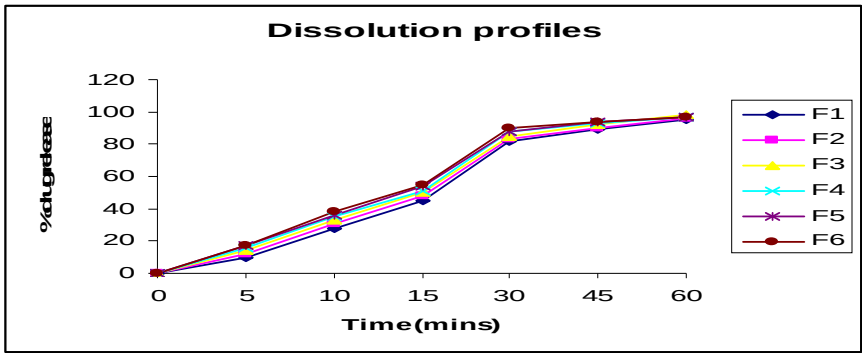


Fig -14: Dissolution profiles of formulation trials

DISCUSSION

The results of *In-vitro* release of drug from formulations F-1 to F-6 were shown in Table-11,& fig-14. But the formulation F-6 exhibited similar release profile to that of innovators product at each time point. Hence, F-6 was considered as the best formulation.

Comparison of release profile of F6 with Innovators product

Table 12: In-vitro release profile of F6 with innovators product

S.No.	Time (min)	Cumulative % ofdrug release	
		Innovators product	F-6
1	5	16	17
2	10	36	38
3	15	52	55
4	30	88	90
5	45	92	94
6	60	99	97

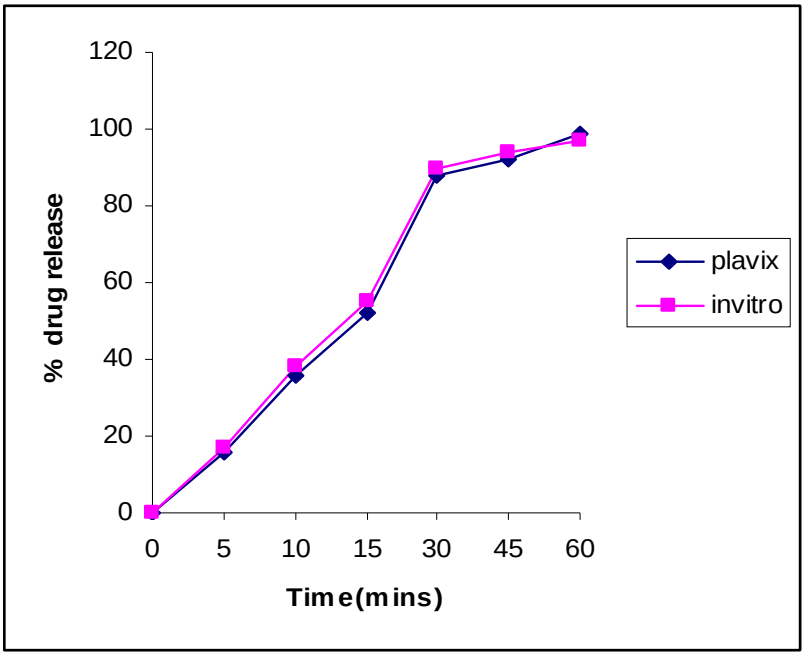


Fig -15: Comparisons of *In-vitro* profiles of F6 and Innovator

DISCUSSION

The data for *in-vitro* dissolution studies of clopidogrel bisulfate immediate release tablets were shown in Table-12 and in Fig -15. The results of the optimized formulation F-6 were compared with that of innovator product which was shown in Table 10 and in Fig-13 , and similarity factor was estimated.

Similarity and Difference Factors: For each dissolution run, a mean of six determinations was recorded for marketed product. The in vitro dissolution of clopidogrel bisulfate immediate release tablets were prepared and matched with innovator product by calculating the similarity and difference factors.

A model independent approach was used to estimate the dissimilarity factor (f1) and similarity factor (f2) to compare the dissolution profile of optimized formulation (F6) with innovator's preparation. The following equations were used for calculating f1 and f2.

$$f1 = \{[\Sigma\, t=1n\, |Rt-Tt|] / [\Sigma\, t=1nRt]\} \times 100$$

The similarity factor (f2) is given by the fallowing equation:

f2= 50×log {[1+ (1/n) Σ t=1n (Rt-Tt) 2] -0.5×100}
Where n = no of time points, Rt = dissolution value of the reference batch at time t,

Tt=dissolution value of the test batch at same time point.

Table 13: Calculation of similarity (f2) and dissimilarity (f1) factors

N	Innovator (Rt)	F-6 (Tt)	D=(Rt-Tt)	(Rt-Tt)²	f1	f2
5	19	13.7	6	12		
15	57	57	0	0		
30	88	87	1	1	5.017	74.07
45	96.0	91.0	5	25		

DISCUSSION

The data for calculation of f1 and f2 were shown in Table 13. The similarity and dissimilarity factor obtained for clopidogrel bisulfate was found to be within the standards. The standards for similarity factor and dissimilarity factor are 50-100 and 0-15.

Stability studies

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light enables recommended storage conditions, re-test periods and half-life's to be established. Clopidogrel bisulfate immediate release tablets were evaluated for accelerated stability studies at 40 ± 2°C / 75 ± 2 % RH conditions. Stability results are presented in Tabl-14.

Stability studies of the optimized batch

Table 14: Accelerated stability studies

S.No	Test	Specifications	Initial	After 1 month	After 2 months
1.	Description	Pink oblong tablet	Complies	Complies	Complies
2.	Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay.	Complies	Complies	complies
3.	Dissolution (pH2.0 Hcl)	97% release with in 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%	99.9%	98%

DISCUSSION

From Table-14, it was observed that the immediate release tablets retained their properties. The % of drug retained (clopidogrel bisulfate) was within the specified limits.

SUMMARY AND CONCLUSION

The present study was undertaken to develop Clopidogrel bisulfate immediate tablets of 300mg, comparable to the innovators product. (Plavix-sanfoiaventis). Based on the results , suitable excipients were selected for formulation development.Various formulas of clopidogrel bisulfate were prepared by using direct compression method. The powder blend were subject to various physical characteristics tests such as bulk density, tapped density, Hausners 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. *In-vitro* dissolution profile of developed formula was compared with innovator's product (Plavix) and release from formula was found to be similar to innovator product and compared with the reference product of Plavix. The *In-vitro* dissolution profile of formula 6 was similar to that of reference product.

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.Clopidogrel bisulfate immediate release tablets developed in the present work was found to be pharmaceutically equivalent to innovators product.

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