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Research Article

Formulation and Evaluation of Orodispersible Tablets of Clopidogrel Bisulfate Using Natural Superdisintegrants

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ABSTRACT

The main objective of this study was to formulate and evaluate the orodispersible tablets of Clopidogrel bisulfate with natural, synthetic Superdisintegrants. Clopidogrel bisulfate an antiplatelet drug used is an inhibitor of platelet activation and decreases subsequent platelet aggregation. Clopidogrel bisulfate has its oral bioavailability (50) and biological half life (5-10 hrs). In the present study an attempt was made to formulate oral disintegrating tablets of Clopidogrel bisulfate with a view to achieve a better disintegration and dissolution rate and further improving the bioavailability of the drug. Orodispersible tablets were prepared using various concentrations (10%, 15%) of super disintegrants like *Moringa oleifera, Plantago Ovata*, and co-processed excipients like 1:1 ratios of *Moringa oleifera* along with by direct compression method. The preformulation studies by FTIR confirmed no interactions between drug and polymers. The prepared formulations were evaluated for the precompression parameters and the values were within prescribed limits and indicated good free flowing properties. The tablets prepared by direct compression method were evaluated for physical parameters, wetting time, disintegration time, content uniformity and *In-vitro* dissolution. Amongst all the prepared formulations, F4 and F7 which comprised of *Moringa oleifera* and *Plantago Ovata* 1:1 ratio at 10% concentration prepared by direct compression method was found to the best formulation as it exhibited satisfactory physical parameters.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance[1].Fast dissolving tablets (FDTs) are solid single-unit dosage forms that are designed to provide quick onset of action when placed in mouth, tablet is disperse/dissolve very fast in the saliva without the need of water [2].Many techniques are available to formulated Fast dissolving tablets are by like tablet molding,[3] spray drying,[4] lyophilization,[5] sublimation,[6] and addition of disintegrants[7]. During the last decade Fast disintegrating tablets (FDTs) received ever-increasing demand and the field has become a rapidly growing area in the pharmaceutical industry [8]. United States food and drug administration (FDA) defined ODT's as "A solid dosage form containing medicinal substance or active ingredients which disintegrate rapidly usually within a matter of second when placed upon the tounge."[9]

The oral drug delivery most generally used route of administration among all the routes form many year and used for the general delivery of drugs in form of varied pharmaceutical product of different indefinite quantity forms [10]. They have many advantages amoung other drug delivery systems like convenient, easy to administer, low economic cost, tamper-proof, easy in packing and transport and more stable than other oral dosage forms [11].

Clopidogrel is a class of thienopyridine, inhibit P2Y12 adenosine 5′-diphosphate (ADP) platelet receptors and used to inhibit blood clots in coronary artery disease, cerebrovascular disease and peripheral vascular disease [12].It is pro-drug of carboxyl clopidogrel activated by enzyme

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cytochrome P450 and CYP2C19 in the liver [13]. As per biopharmaceutics classification system (BCS), Clopidogrel is categorized as a class II agent (low solubility and highly permeability) so, it is good candidate for formulating Fast Dissolving [14]. Clopidogrel is rapidly absorbed after oral administration [15]. Clopidogrel inhibits platelet aggregation by binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex [16]. It is a potent oral antiplatelet agent often used in the treatment of coronary artery disease, peripheral vascular disease and cerebrovascular disease [17].

MATERIALS AND METHODS

Materials

Clopidogrel bisulfate was purchase from Yarro Chemicals Mumbai. *Moringa oleifera* gum and *Plantago Ovata* seeds was obtained from local market. Mannitol, Magnesium stearate, Talc was obtained from S.D. FINE chemicals, Mumbai.

METHODS

Characterization of drug

UV Spectroscopy

Calibration curve of Clopidogrel bisulfate was plotted in water, and buffer of pH 1.2, 7.4 and 6.8 with different concentration (1, 2, 3, 4, 5 µg/mL). The absorbance of the solution was taken at wavelength 220 nm against the blank solution using UV spectrophotometer.[18]

(Drug excipient interaction study) Fourier Transform Infrared (FT-IR) Spectroscopy

Infrared spectroscopy was used to predict possible interaction between drug and excipients using a FTIR spectrometer (Jasco 4600) at 4000-650cm $^{-1}$. [18]

Differential Scanning Calorimeter (DSC)

The drug and excipients were passed through the #60 sieve and mixed. Accurately transferred 5 mg of drug alone, a mixture of drug and excipients into the pierced DSC aluminum pan and scanned at the temperature range of 25-210°C heating rate of 10°C/min. The thermograms obtained were compared for any interaction between the drug and excipients with that of thermogram of drug alone. [19]

Isolation procedure natural disintegrants

1. Isolation and purification of *Moringa oleifera* gum

The gum was collected from trees (injured site).It was dried, ground and passed through sieve no #80. Dried gum (10 g) was stirred in distilled water (250 mL) for 6-8 h at room temperature. The supernatant was obtained by centrifugation. The residue was washed with water and the washing was added to separate supernatant. The procedure was repeated four more times Finally the supernatant was made up to 500 mL and treated with twice the volume of acetone by continuous stirring .The precipitated material was washed with distilled water and dried at 50-60 °C under vacuum.[20]

2. Isolation of *Plantago Ovata* mucilage

Seeds of *Plantago ovata* were soaked in distilled water for 48 h and then boiled for few minutes so that mucilage was completely released into water. The material collected was squeezed through muslin cloth for filtering and separating out the marc. Subsequently, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The separated mucilage was dried (in an oven at temperature less than 60º C), powdered, sieved (#80) and stored in a desiccators until further use. [21]

Preparation of Orodispersible tablets by direct compression method

All ingredients were passed through #60 sieve. Then required quantity of all ingredients were weighed for a batch size of 100 tablets and mixed uniformly in a mortar except talc and magnesium stearate. Finally magnesium stearate and talc were added as lubricant and mixed for 5 min. This uniformly mixed blend was compressed in to tablets containing 75 mg drug using 9 mm flat face surface punches on a Rimek-1 rotary tablet machine by direct compression method. Total weight of tablet was kept 250mg. [22]

Evaluations of powder blend (precompression parameters)

The powder mix was evaluated for various flow properties such as angle of repose, bulk density and tapped density, Hausner's ratio, and Carr's index.

Angle of repose (h)

The angle of repose of powder blends was determined by the funnel cone method. Accurately weighed powder blends were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blends (2 cm). The powder blends were allowed to flow through the funnel freely onto its surface. The diameter of the powder cone was measured and angle of repose was calculated.[23]

Table 1: Composition for different formulations of orodispersible tablets

composition mg/tablet	F1	F2	F3	F4	F5	F6	F7	F8
Clopidogrel bisulfate	75	75	75	75	75	75	75	75
Moringa oleifera	5	10	15	20	-	-	-	-
Plantago Ovata	-	-	-	-	5	10	15	20
Aspartame	15	15	15	15	15	15	15	15
MCC	60	55	50	45	60	55	50	45
Mannitol	85	85	85	85	85	85	85	85
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	250	250	250	250	250	250	250	250

Bulk density and Tapped density [23]
The powder weighing 5g from each formula was introduced into a 25mL measuring cylinder. It was initially shaken lightly to break agglomerates that may have formed. The initial volume was noted, and the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2 to 3 second intervals. The tapping was continued until a constant volume was observed. Then LBD (Loose bulk density) and TBD (Tapped bulk density) were calculated using the following formulas:
LBD=Weight of powder/volume of the packing
TBD= Weight of powder/ tapped volume of the packing

Compressibility index and Hausner's ratio [24]
The following formula was used to determine the compressibility index of powder:

$$\text{Carr's compressibility index (Carr's index)} = \frac{(\text{TBD} - \text{LBD})}{\text{TBD}} \times 100$$

Hausner's ratio was calculated by the following formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of tablet (post compression evaluation)

Thickness and Hardness
Thickness of tablet was determined by using vernier caliper and Hardness of crushing strength of the tablets was measured using a Monsanto hardness tester three tablets from each formulation batch were tested randomly and the average reading noted.[25]

Weight Variation
Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.[26]

Friability [26]
Twenty tablets were weighed and placed in a Roche friabilator. Twenty reweighed tablets were rotated at 25 rpm for 4 min. The tablets were then deducted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets were measured as per the following formula,

$$\text{Percentage friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

Wetting time
A piece of circular tissue paper (8cm) folded twice was placed in a Petri dish (Internal Diameter = 9cm) containing 10 mL of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.[27]

***In-vitro* disintegration time**
Tablet was placed in a beaker containing 20mL of phosphate buffer solution, pH 7.4 at 37±0.5 °C. Time for complete disintegration of the tablet was measured in triplicate.[28]

Drug content
Five tablets from each formulation were weighed individually and crushed to fine powder. The Powder equivalent to 75mg of Clopidogrel bisulfate was introduced into 100mL volumetric flask and extracted using pH 6.8 phosphate

buffer. This solution obtained was filtered, and filter was suitably diluted with pH 6.8 phosphate buffer and the solution was analyzed by measuring the absorbance at 220nm by UV–visible spectrophotometer using pH 6.8 buffer as the blank.[29]

In-vitro dissolution study

In vitro release of Clopidogrel bisulfate from tablets was monitored by using 900 mL of simulated intestinal fluid, SIF (USP phosphate buffer solution, pH 7.4) at 37±0.5 °C and 50 rpm using programmable dissolution tester 5 mL Aliquots were withdrawn at one minute time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions, were analyzed by spectrophotometrically at 220 nm.[30]

Stability studies of the tablet formulations

The optimized orodispersible release tablets were subjected to stability studies (as per ICH guide lines) at 40°C ± 2°C or 75% ± 5% RH. The products were evaluated for their physical characteristics, drug content, and In-vitro drug release profiles over a period of three months by storing the samples in stability chamber.[31]

RESULT AND DISCUSSION

Drug Characterization

UV Spectroscopy

From calibration curve of Clopidogrel bisulfate, UV absorption maximum of drug was found at 220 nm. As per calibration curve, the correlation coefficient was found to be 0.9978 (pH 2), and 0.997 (pH 6.8). Calibration curve obeyed Beer's law in the range of 1-5 µg/mL.

FT-IR spectroscopy

The drug-excipients compatibility was assessed by comparing IR spectra of the drug and drug-excipient mixture. From the interpretation of spectra it was found that there was no worth change in the wave numbers of the drug and drug-excipients combination. Hence, the drug and excipients were found to be compatible with each other. [Figure 1 and 2]

Differential Scanning Calorimeter (DSC)

Selected formulations of Clopidogrel bisulfate orodispersible tablet were characterized for DSC. The pure Clopidogrel bisulfate showed a sharp endothermic peak at 184.28^{0}c. Similar endothermic peaks were observed at similar temperature in the prepared tablets with their excipients 170.90 °C show in Fig. 3 and Fig. 4.

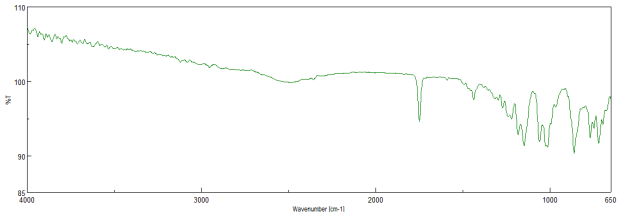

Figure 1: FTIR for pure Clopidogrel bisulfate

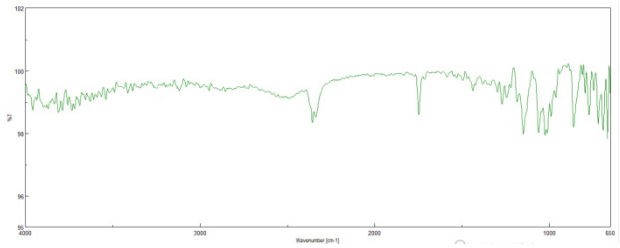

Figure 2: FTIR for drug-excipient mixture

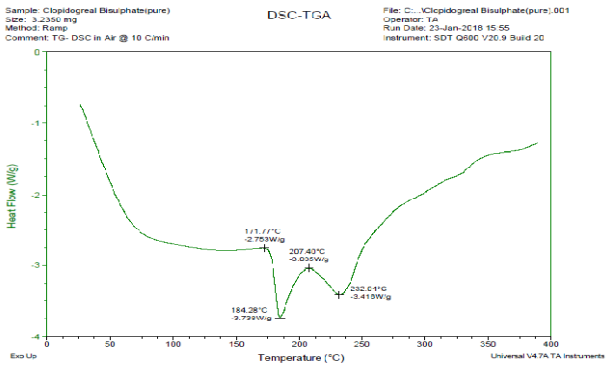

Figure 3: DSC for pure Clopidogrel bisulfate

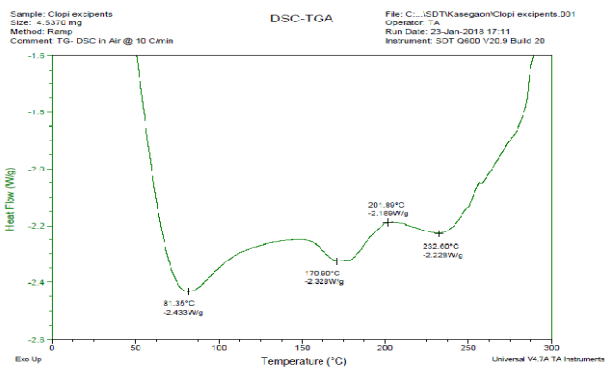

Figure 4: DSC for drug-excipient mixture

Precompression parameters of powder blend

The results of precompression parameters evaluations indicated good free flowing properties of the powder blend show in Table 2.

Table 2: Pre-compression parameters of powder blend

Batch Code	Angle of repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio
F1	30.10±0.92	0.50±0.005	0.646±0.004	22.67±1.30	1.28±0.04
F2	29.22±0.98	0.507±0.005	0.636±0.005	20.37±1.62	1.24±0.03
F3	28.72±1.22	0.493±0.001	0.654±0.003	24.7±1.64	1.32±0.003
F4	28.03±1.20	0.491±0.01	0.650±0.005	24.54±0.76	1.32±0.01
F5	27.67±0.99	0.522±0.005	0.649±0.005	19.55±0.005	1.23±0.01
F6	26.34±1.75	0.514±0.002	0.635±0.002	18.89±0.002	1.22±0.02
F7	30.74±1.23	0.547±0.001	0.627±0.005	13.12±0.003	1.14±0.04
F8	29.11±0.93	0.539±0.005	0.629±0.003	14.39±0.54	1.16±0.01

Table 3: Post-compression parameters of orodispersible tablets of Clopidogrel bisulfate

Batch Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variations
F1	2.45±0.10	4.45±0.201	0.68±0.03	250.2±0.30
F2	2.32±0.11	4.41±0.174	0.63±0.03	250.6±0.62
F3	2.42±0.04	4.34±0.12	0.72±0.04	248.7±0.64
F4	2.40±0.20	4.25±0.242	0.79±0.02	250.2±0.76
F5	2.22±0.15	4.36±0.15	0.69±0.05	250.1±0.55
F6	2.14±0.19	4.47±0.03	0.70±0.024	249.7±0.74
F7	2.20±0.23	4.46±0.12	0.66±0.051	250.4±1.14
F8	2.24±0.17	4.30±0.15	0.59±0.04	250.5±1.02

Table 4: Post-compression parameters of orodispersible tablets of Clopidogreal bisulfate

Batch No.	Wetting time	*In vitro* disintegration time	Drug content
F1	45.13±0.39	60.24±0.26	98.2±0.07
F2	42.39±0.33	58.23±0.54	100.84±0.05
F3	37.05±0.41	46.65±0.82	99.21±0.2
F4	26.30±0.23	33.38±0.94	98.65±0.78
F5	54.17±0.25	70.64±0.45	99.38±0.12
F6	49.62±0.49	62.34±0.53	99.78±0.47
F7	48.90±0.43	54.23±0.42	100.65±0.01
F8	39.01±0.17	46.96±0.75	99.48±0.54

Post-compression parameters of orodispersible tablet of Clopidogrel bisulfate

The thickness and Hardness of tablets was determined and was found to be in the range of 2.10 to 2.45mm and 4.20-4.50 kg/cm^2. Friability was observed to be between 0.50% and 0.80% which less than 1% was indicated as that the tablet had a good mechanical resistance it was summarized in Table 3. The wetting times are important criteria for understanding the capacity of a disintegrate to swell in the presence of a small amount of water. The wetting time for all formulations was found to be between 26.30±0.23seconds and 54.17±0.25seconds in Table 4. The *In vitro* disintegration times for all formulations are summarized in Table 4. The percentage drug content of all formulations was found to be between 98.2% w/w and 100.84%w/w. The results of post-compression parameters are summarized in Table 3 and Table 4.The *In vitro* drug release profile represented in [Figure 5].

In-vitro dissolution studies

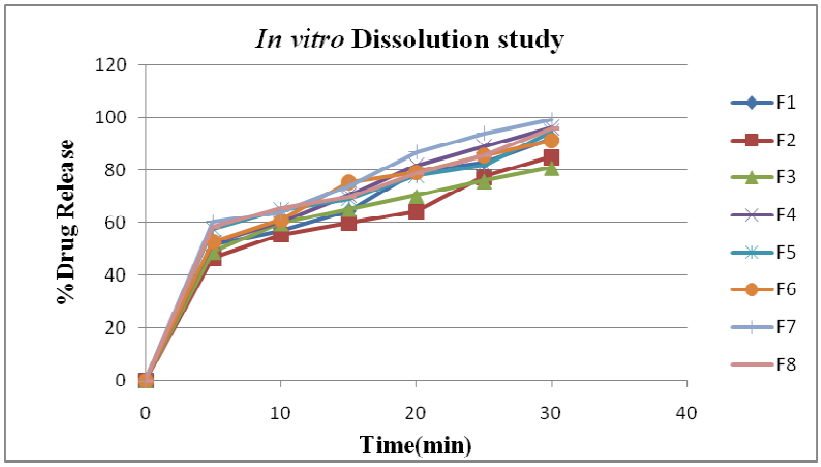

Figure 5: *In-vitro* Dissolution studies

Table 5: Stability study data for batch F4 and F7

Parameters	After 3 month stability study data	
	F4	F7
Hardness(kg/cm²)	4.23±0.24	4.56±0.15
% Friability	0.78±0.01	0.65±0.05
Drug content s(%)	98.45±0.78	100.11±0.2
Disintegration time	32.37±0.90	53.23±0.52

Stability study data

The stability study indicated that there was no significant change in the physical as well as chemical characteristics of the tablet, and the optimized formulations batch F4 and F7 containing formulations was stable at 40⁰c temperature and 75% RH humidity for 3 months it was summarized in Table 5.

CONCLUSION

Orodispersible tablet of Clopidogrel bisulfate were prepared with the *Moringa oleifera* gum and *Plantago Ovata* Mucilage. The batch F4 and F7 show better results least as disintegration time, wetting time and highest % drug release in 30 minutes. The co-processed superdisintegrants showed superior flow property and compression characteristics than physical mixture of superdisintegrants. Thus, the data obtained from this study revealed that use of co-processing superdisintegrants i.e. *Moringa oleifera* and *Plantago Ovata* significantly enhanced the disintegration and dissolution which may contribute to improve bioavailability of the drug.

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