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**Research article**

# Formulation and Evaluation of Fast Dissolving Tablets using Solid dispersion of Clopidogrel bisulphate

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**Abstract**

The present investigation was aimed to formulate and evaluate of fast dissolving tablets of clopidogrel bisulphate solid dispersion. The solid dispersion was prepared by fusion method using PEG 6000 as carrier in various ratios. The physio-chemical characterization of solid dispersion was carried out by various parameters like drug content, dissolution study and Differential Scanning Calorimetry. The optimized solid dispersion of clopidogrel bisulphate was used in the preparation of fast dissolving tablets by direct compression method with varying concentrations of superdisintegrants like crospovidone, crosscarmellose sodium and sodium starch glycolate. The formulations were further evaluated for pre & post compression parameters and *in vitro* dissolution studies. The study reveals that the formulation F3 (10% of cross povidone) is found to be the optimized formulation with 99% drug release in 60 minutes in comparison with other super disintegrants. The kinetics study shows that the fast dissolving tablet formulation followed Higuchi model explaining the diffusion controlled release mechanism.

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**Key Words**
Clopidogrel bisulphate
Solid dispersion
Fast dissolving tablet

## INTRODUCTION

In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists[1]. Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Several techniques have been developed over the years to enhance the dissolution of the drug, such as inclusion complexation, salt formation, solid dispersion and solvent deposition.

In other hand, with conventional tablets, physical problems such swallowing (dysphagia) can occur at any age but are particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatric, pediatric and psychiatric patients. Difficulties and resistance to tablet-taking are common in all patient groups. Currently, fast disintegrating tablet (FDT) technologies that make tablets disintegrate in the mouth without chewing and additional water intake has drawn a great deal of attention. The FDT is also known as *fast melting, fast dispersing, rapid dissolve, rapid melt,* and/or *quick disintegrating tablet.* All FDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term *orodispersible* tablet for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good FDTs varies from several seconds to about a minute[2].

Clopidogrel a thienopyridine, an irreversible antagonist of the ADP receptor $P2Y_{12}$ is indicated for prevention of vascular ischemic events in patients with symptomatic atherosclerosis and acute coronary syndrome without ST-segment elevation (NSTEMI). One of the major problems with this drug is its very low solubility (0.0099mg/ml) in biological fluids, which results into poor bioavailability after oral administration. Hence we attempted to prepare solid dispersion using PEG 6000 in order to enhance the dissolution[3] and then formulate into suitable dosage forms like fast dissolving tablets as well, using various superdisintegrants.

## MATERIALS AND METHODS

### Materials

Clopidogrel bisulphate procured from Candila Pharmaceuticals Ltd., Ahmadabad, Polyethylene Glycol, Cross povidone, Sodium starch glycolate, Lactose monohydrate, Croscarmellose sodium were from S.D. Fine Chem. Ltd., Mumbai.

### Methods

#### *Preparation of solid dispersion of Clopidogrel bisulphate* [4, 5]

The drug and the carrier (PEG-6000) were taken in different ratios by weight as shown in table 1. The carrier was melted and the drug was

finely dispersed into it. The molten mixture was then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized, sieved and preserved in airtight container for evaluation and preparation of fast dissolving tablets.

***Preparation of fast dissolving tablets using solid dispersion Clopidogrel bisulphate***

Fast dissolving tablets of the solid dispersion clopidogrel bisulphate were prepared by direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations as presented in table 2.

**Compatibility studies by FTIR and DSC analysis**

The compatibility between drug and excipients was detected by IR spectra (Corporation, Japan). The pellets were prepared on KBr-press. The spectra were recorded over the wave number range of 4000 to 500 cm-1.
Thermogram was obtained by using a DSC at a heating rate of 10°C/min over a temperature range of 50-300°C. The sample was thermetically sealed in an aluminium crucible

**Pre-compression evaluation**

*Micromeritic properties* [6]

The powder blends were evaluated for various precompression parameters such as bulk density, tapped density, angle of repose, carrs index and Hausner's ratio. The results are presented in table 3.

**Post compression evaluation** [7]

All the tablets were evaluated for different parameters as hardness, friability, uniformity of weight and disintegration time. The evaluations were performed in triplicate. The results are shown in the table 4.

Tab 1. Drug to carrier ratio of Solid dispersion

| Formulation code | Clopidogrel bisulphate : PEG 6000 ratio |
|---|---|
| SD1 | 1:1 |
| SD2 | 1: 2 |
| SD3 | 1: 3 |

Tab 2. Depicts the composition of fast dissolving tablets

| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| SD of clopidogrel(mg) | 391.5 | 391.5 | 391.5 | 391.5 | 391.5 | 391.5 | 391.5 | 391.5 | 391.5 |
| CP(%) | 5 | 7.5 | 10 | - | - | - | - | - | - |
| CCS(%) | - | - | - | 5 | 7.5 | 10 | - | - | - |
| SSG(%) | - | - | - | - | - | - | 5 | 7.5 | 10 |
| Lactose(mg) | 36 | 24.7 | 13.5 | 36 | 24.7 | 13.5 | 36 | 24.7 | 13.5 |

SD=solid dispersion; CP=crospovidone; CCS=crosscarmellose sodium; SSG= sodium starch glycolate

**In vitro dissolution study of solid dispersion and compressed tablet [8]**

The quantity of solid dispersion (SD) equivalent to 20mg of clopidogrel was filled in colourless hard gelatin capsule by hand filling method. The dissolution study was carried out using dissolution testing USP apparatus 1 (basket type) in 900 ml of 0.1N HCl at 37±0.5°C and 50 rpm. In case of compressed fast dissolving tablet, USP dissolution testing apparatus 2(paddle type) was used. 5ml of aliquot was withdrawn for each case at predetermined time interval and equivalent amount of fresh medium was replaced in order to maintain sink condition and analyzed spectrophotometrically at 240nm.

**Drug release Kinetics [9]**

The mechanism of release was determined by fitting the release data into various kinetic models such as Zero order, First-order, Higuchi, and Korsemeyer-Peppas.

**Accelerated stability studies [10]**

The stability study for the selected formulation was carried out as stated by ICH guidelines at 40±2°C/75 ±5% RH for three months by storing the samples in stability chamber and in vitro dissolution studied.

## RESULTS AND DISCUSSION

The results of the dissolution study for SDs prepared with three variable concentrations of PEG 6000 over the period of 1 h are shown in figure 1. It is evident that onset of dissolution of SDs is rapid compared to pure clopidogrel bisulphate and SD3 shows enhanced dissolution rates considerably within 10 min compared to other two formulations due to higher concentration ratio of carrier to drug possibly modification of the surface properties and hence reduction of the value of the contact angle which improves the wettability of the powder should lead to an increase of dissolution profile[11]. The value of $\%DE_{10min}$ ranked in order of SD3> SD2> SD1. The selection of the optimized formulation is based on the greater solubility of the drug.

Compatibility of drug and excipients used in the formulation was confirmed with FTIR spectra. Clopidogrel bisulphate characterized peak at 2689cm$^{-1}$ and 1335cm$^{-1}$ due to N-H $3^0$ amine stretching and saturated alkane respectively[12] were observed in the formulation FTIR spectra (Fig2).

DSC scan of the solid dispersion is presented in Fig 3. The thermogram exhibited an endothermic peak at 119.8°C which reduces from its melting point[13] range 158-160 °C. It indicates that the drug was dispersed into the carrier, which may be the possible reason for increased solubility of the drug.

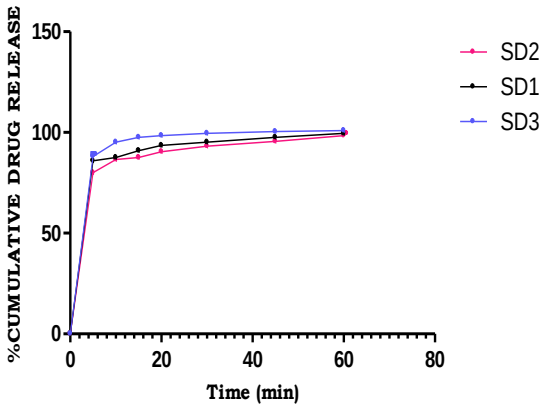


Fig 1. Comparision of %drug release of different formulations of solid dispersion

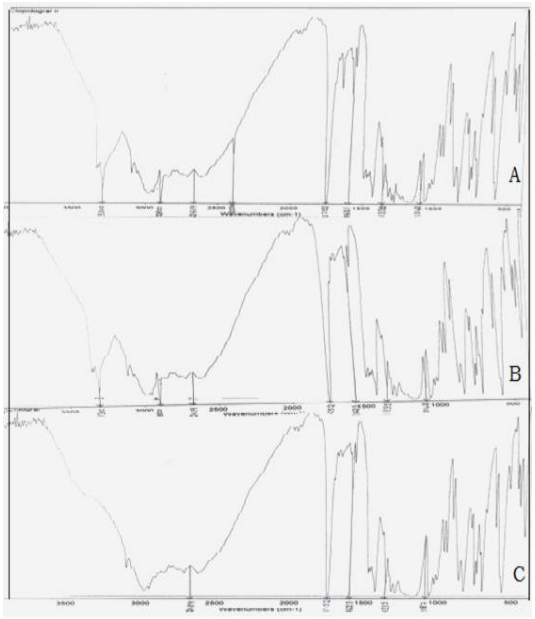


Fig. 2 (a) FTIR spectra of Clopidogrel bisulphate pure; (b) solid dispersion of Clopidogrel bisulphate; c) formulation F3

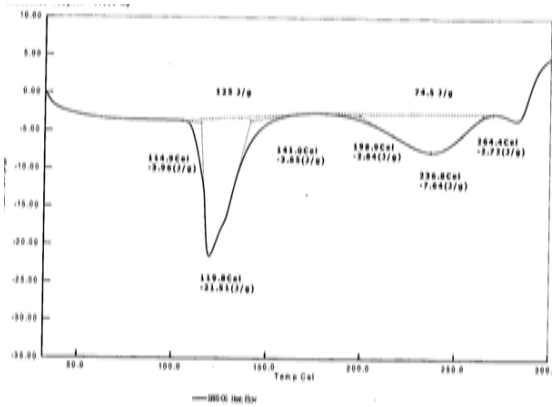

Fig 3 Shows the DSC spectra of the solid dispersion of clopidogrel bisulphate

For each designed formulation, blend of drug and excipients was prepared and evaluated for Micromeritic properties depicted in table 3.

Table 3.shows the precompression parameters of powder blends of FDTs

| Formulation code | Angle of repose (θ) | Bulk density (g/cc) | Tapped density (g/cc) | Carr's index (%) | Hausner Ratio |
|---|---|---|---|---|---|
| **F1** | 27.61±0.68 | 0.371±0.005 | 0.421±0.01 | 11.87 | 1.13 |
| **F2** | 28.94±0.91 | 0.353±0.002 | 0.409±0.006 | 13.69 | 1.15 |
| **F3** | 27.76±0.51 | 0.342±0.005 | 0.398±0.007 | 14.07 | 1.16 |
| **F4** | 28.36±0.44 | 0.378±0.005 | 0.420±0.004 | 10 | 1.11 |
| **F5** | 30.25±0.65 | 0.386±0.003 | 0.459±0.000 | 15.90 | 1.18 |
| **F6** | 30.67±0.49 | 0.386±0.006 | 0.448±0.004 | 13.83 | 1.16 |
| **F7** | 26.92±0.31 | 0.353±0.002 | 0.409±0.006 | 13.69 | 1.15 |
| **F8** | 27.01±0.45 | 0.358±0.005 | 0.416±0.007 | 13.94 | 1.16 |
| **F9** | 29.53±0.66 | 0.368±0.009 | 0.433±0.004 | 15.01 | 1.17 |

Table 4. Shows the postcompression parameters of FD tablets

| Formulation code | Average weight(mg) | Disintegration time (Sec) | Friability (%) | Hardness (Kg/cm²) |
|---|---|---|---|---|
| F1 | 449.6±0.78 | 10 | 0.153± 0.5 | 4.5±0.31 |
| F2 | 449.5±0.75 | 8.5 | 0.16±0.56 | 4.3±0.41 |
| F3 | 449.8±0.80 | 8 | 0.37±0.64 | 4.2±0.24 |
| F4 | 450.2±0.52 | 25 | 0.47±0.42 | 5.2±0.32 |
| F5 | 449.2±0.92 | 23 | 0.23±0.42 | 5.0±0.21 |
| F6 | 450.1±0.23 | 20 | 0.51±0.72 | 4.8±0.52 |
| F7 | 449.4±0.76 | 17 | 0.27±0.45 | 4.5±0.13 |
| F8 | 450.2±0.52 | 13 | 0.24±0.54 | 4.8±0.59 |
| F9 | 449.7±0.72 | 10 | 0.106±0.62 | 4.9±0.47 |

Tab 5 shows the regression co-efficient of all the formulations

| Formulation | Zero Order | First Order | Higuchi | Peppas | |
|---|---|---|---|---|---|
| | r² | r² | r² | r² | n value |
| F1 | 0.983 | 0.908 | 0.945 | 0.974 | 1.64 |
| F2 | 0.984 | 0.972 | 0.995 | 0.982 | 1.02 |
| `F3 | 0.979 | 0.984 | 0.994 | 0.981 | 1.04 |
| F4 | 0.975 | 0.856 | 0.995 | 0.939 | 1.25 |
| F5 | 0.988 | 0.925 | 0.989 | 0.952 | 1.52 |
| F6 | 0.986 | 0.904 | 0.991 | 0.971 | 1.27 |
| F7 | 0.982 | 0.943 | 0.994 | 0.981 | 1.02 |
| F8 | 0.980 | 0.979 | 0.993 | 0.978 | 1.04 |
| F9 | 0.979 | 0.952 | 0.995 | 0.984 | 1.02 |

Bulk density was found to be between 0.342±0.005-0.386±0.006gm/cc and tapped density between 0.398±0.007 and 0.459±0.000gm/cc for all formulations. Angle of repose and Carrs indices were found to be in the

range of 26.92±0.31-30.67±0.490and 10-15.90% repectively. Hausner ratio was found below 1.18. All the formulation shows the good blend properties for direct compression and hence tablets were prepared by using direct compression.

The tablets prepared were round and its appearance good without any surface imperfections. No tablet defects were observed during compression. The Results of postcompression evaluations are shown in table 4. Weight of tablet for all formulations was found to be within the range of 449.2±0.92 to 450.2±0.52 mg. A tablet requires certain amount of hardness. The hardness of the all formulated tablet shows great deal to withstand the mechanical shocks during handling, packaging and at the time of application varied from 4.2±0.24 to 5.2±0.32 Kg/cm$^2$. The friability of all the formulation was found to be less than 1.0 % which resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging and shipment.

The rapid disintegration was seen in the formulation containing Crospovidone as disintegrants rather than the Croscarmellose sodium and Sodium starch glycolate. All cases, as the increment in concentration of superdisintegrants the disintegration time decreases upto certain concentration i.e.upto 10%, however in case of Crospovidone exhibits superiority in disintegrating tablets than other two disintegrants used. Crosspovidine disintegrants are reported to act by a wicking mechanism; drawing water into tablet through capillary action due to its porous particle morphology, resulting secondary swelling and rupture of interparticulate bonds[14] and in tablet disintegration.

Effect of various disintegrants and it concentrations *in-vitro* dissolution studies of fast dissolving tablets are present in figure 4.

Fast dissolving tablet prepared with crosspovidine as disintegrants depicts higher dissolution rate compared to other disintegrants, however dissolution of drug from the formulations F9 and F2 shown more or less similar rate % $DE_{30min}$ 89.04 and 88.7, which were prepared with higher concentration of crospovidone and sodium starch glycolate respectively. The effect of varying concentrations of crospovidone in dissolution of drug, the formulation F3 shows good deals in dissolution rate and rapid disintegartion as well, compared to other two formulations.

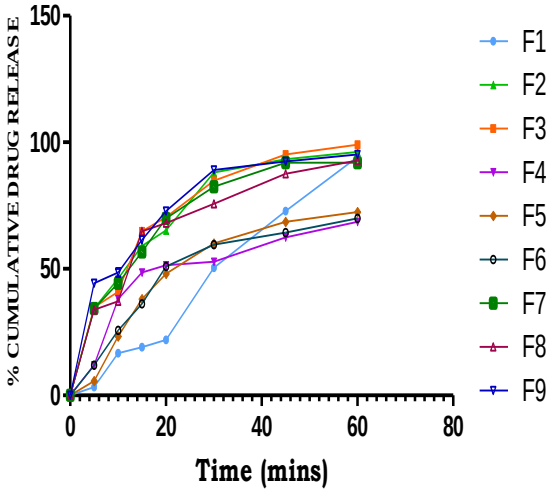


Fig 4 dissolution profiles of all fast dissolving tablets

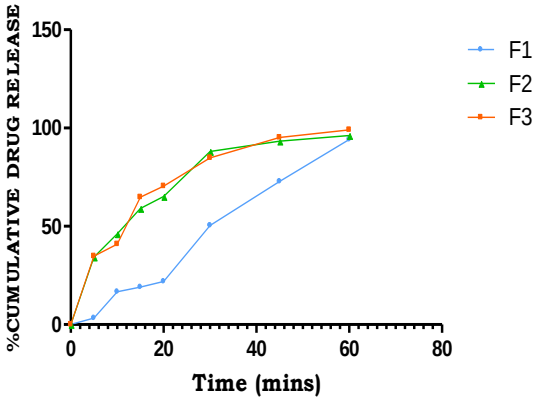


Fig 5.Effect of varying concentration of cross povidone (F1, F2, F3)

The regression coefficients of determination ($r^2$) values are presented in the table 6. The coefficient of determination indicated that the release data was best fitted to zero order and Higuchi model explains the diffusion release mechanism.

The formulations kept under short and long term stability studies showed no noticeable changes in drug release profile.

## CONCLUSION

In the present study an attempt was made to formulate and evaluate fast dissolving tablet using solid dispersion of clopidogrel bisulphate. The solid dispersion of clopidogrel bisulphate (SD3) prepared by fusion method showed better dissolution compared to pure drug. Further it was formulated to fast dissolving tablets with optimised SD using different concentration of superdisintegrants.

From the observations of pre & post compression evaluations of all the fast dissolving tablets formulation were acceptable with reasonable limits of standards required for fast dissolving tablets. The study reveals that the formulation prepared by 10% Crospovidone (F3) is the best formulation in comparison with other superdisintegrants. Undoubtedly the availability of various technologies and the manifold advantages of FDT will surely enhance bioavailability, rapid onset of action and lowers dose load, thereby reduces side effects and improves the therapy.

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