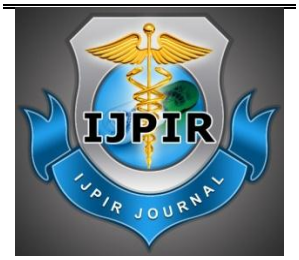
*Research Article*

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# Formulation and evaluation of clopidogrel bisulphate fast dissolving tablets by novel hole technology

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## ABSTRACT

The present objective of this research has formulate a Clopidogrel bisulfate fast dissolving tablets by novel hole technology. Clopidogrel bisulfate is an antiplatelet medication used to reduce the risk of heart disease and stroke in those at high risk. Basically Clopidogrel is a BCS Class-II type drug, the solubility of drug is low and it is enhanced by solid dispersion and physical mixture methods by using natural solubility enhancer which is processed and prepared by Vigna Radiata (Moong bean). The solubility of drug is enhanced by Solvent evaporation method with a Drug: Carrier ratio of 1:3, from this Solid dispersion equivalent weight to dose of drug is calculated and formulated fast dissolving tablets by using different super disintegrates. Different tests like pre and post compression parameters have been performed to evaluate prepared formulations. This quick disintegration of tablets is additionally influenced by the formation of latest absolute space. With In-Vitro dissolution studies the best formulation is optimized.

**Keywords:** Clopidogrel bisulfate; Vigna Radiata; Novel hole technology; Primo gel; Carbose; Kollidone; In-Vitro Dissolution studies.

## INTRODUCTION

The oral drug delivery has been celebrated for many years as it is the most generally accepted route for administration among the entire routes of administration which have been explored for general delivery of drugs [1]. The explanations that are achieved by the oral route could be partly attributed to its simple administration because of ancient belief that by oral administration the drug is still absorbed because the foodstuffs that are ingested daily [2].

The fast dissolving tablets ensure complete solubilization of the tablet through erosion, leading to the elimination of lag time for disintegration thereby increasing the absorption rate and also increasing the onset of action [3]. In recent years, attention had been increased to fast dissolving tablets, but conjointly orally disintegrating tablets that are intended to dissolve or disintegrate quickly

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in the mouth [4-6]. Fast dissolving tablets are solid unit dosage forms containing a active ingredient which disintegrates rapidly when placed upon the tongue. These are the most desirable formulation for the use of elder people which helps in easy swallowing. Since this tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place [7-12].

Hole technology is a novel approach to decrease the disintegration time and increase the patient compliance. By using this technology absolute surface area of the tablet increase due to hole formation. Immediate breaking of the tablet takes place due to the fluid enters into the hole formed in the tablet. Several technologies were developed to enhance the disintegration time but the tablets prepared by hole technology have increased surface area due to formation of hole and increased pore structure. The main principle involved in hole technology is sublimation [13].

Clopidogrel bisulphate is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP mediated activation of the glycoprotein GPIIb/IIIa complex [14].

The objectives of present research investigation were to formulate fast-dissolving tablets of clopidogrel bisulphate by improving its solubility and to be manufactured by commonly used production methods and equipment.

## MATERIALS AND METHODS

### Materials

Clopidogrel bisulphate, Vigna radiate, Primo gel, Kollidon, Carbose, Talc, Magnesium Stearate, Mannitol and Lactose.

### Solubility Enhancement by Vigna radiate

Vigna radiate is also known as moong bean or green gram or lentil. It belongs to the legume family and is cultivated in china, India, Southeast Asia. Many natural polymers are obtained from seeds and also have a prominent pharmaceutical application.

### Extraction of water-soluble contents from Vigna radiata

Seeds of vigna radiate were procured from the local market & weighed accurately 100g; crush them into small fragmented particles. The crushed fragmented particles were soaked in petroleum ether & ethanol for overnight to remove fatty materials & coloring materials. Then they are filtered & dried. Then the dried residue was soaked in water at 65°C in water bath for 5 h. The content was filtered, centrifuged at 2000rpm to get a supernatant liquid to which five times more acetone was added to obtain the precipitate. The precipitate was dried, pulverized into fine powder and purified by isopropyl alcohol.

### Preparation of Solid dispersion (SD) and Physical mixture (PM)

PM by cogrinding drug and carrier in different ratios were prepared and denoted as PM 1:1, PM 1:2, and PM 1:3. Meanwhile, SD of clopidogrel bisulfate was also prepared by solvent evaporation method using vigna radiate as the natural carrier in the ratio of SD1:1, SD1:2, and SD1:3.

### Method of preparation of clopidogrel bisulphate tablets

All the ingredients are weighed accurately and taken. Plain 100 mg camphor granules are taken and then compressed into tablets. In the next step, Drug, excipient and super disintegrate were mixed. Magnesium stearate and Talc were passed through sieve # 60 & mixed with initial mixture. This mixture is then placed in the die cavity at the center of the die cavity, previously compressed camphor tablets were kept and compressed into tablets. After compression, these tablets were dried at 60°C by keeping the tablets in a hot air oven until complete removal of camphor to make tablets with hole at the center leading to formation of extra absolute surface area.

**Table .No1: Formulation Table**

| Name of the Excipient | $F_0$ | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ | $F_9$ | $F_{10}$ | $F_{11}$ | $F_{12}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SD3 Equivalent to dose | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 | 270 |
| Kollidon | --- | 10 | --- | --- | 20 | --- | --- | 30 | --- | --- | 15 | 15 | --- |
| Primogel | --- | --- | 10 | --- | --- | 20 | --- | --- | 30 | --- | 15 | --- | 15 |
| Carbose | --- | --- | --- | 10 | --- | --- | 20 | --- | --- | 30 | --- | 15 | 15 |
| Lactose | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Mg.S | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Talc | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Mannitol | Q.S.P | | | | | | | | | | | | |
| Camphor | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Total weight after sublimation | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |

*** All weights are in mg

## EVALUATION

### Pre compression parameters

Characteristics like tapped density, bulk density, carr's index, Hausner's ratio were studied for powder blend of formulations which are ready to compress into tablets.

### Angle of repose

Angle of repose is defined as the maximum angle viable between the surface of a pile of the powder and horizontal aircraft [14].

$\tan \Theta = h/r$

Where,

Ɵ is the angle of repose his height of pile,

r is radius of the base of pile

### Bulk Density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another [15].

Loose bulk density= Weight of the powder (M)/volume of the packing (Vo)

### Tapped bulk density

The measuring cylinder containing mass of blend was tapped for a fixed time. The minimum volume occupied on the cylinder and weight of the powder blend as measured [16].

Tapped Bulk Density = weight of the powder/ Tapped volume of packing

### Carr's compressibility index

The compressibility index is measure of the prophecy of the powder to be compressed. As such they are the measures of relative importance of inter-particulate interactions. It is indirectly related to the relative flow rate [17].

Carr's compressibility index = [(TBD-LBD) ×100] / TBD

### Hausner's ratio

Hausner's ratio indirectly the flow property of the powder and measured by the ratio of tapped density to bulk density [18].

Hausner's ratio = Tapped density / bulk density

### Post compression parameters

All the prepared tablets were subjected to various physical Characteristics like Tablet Hardness, Friability, Thickness, Diameter, Hole depth, Disintegration time, Wetting time, Weight variation, Drug content.

### Weight variation test

Weight variation test has to be done by weighing 20 tablets individually, by using electronic balance. Calculating the average weight and comparing the individual tablet weight to the average weight [19].

### Tablet thickness

The thickness has to be measured by placing tablet between two arms of the Vernier calipers. 5

tablets were taken and their thickness has to be measured. It is expressed in millimeter (mm) [20].

### Tablet hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study will be Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring. It is expressed in $kg/cm^2$ [21].

### Tablet friability

The friability of the tablets has to be measured in a Roche friabilator. About 10 previously weighed tablets were placed in the friability apparatus chamber, which was given 100 revolutions in 4minutes and the tablets reweighed [22].

Friability= Initial weight – Final Weight/ Initial weight ×100

### In-vitro disintegration time

In the disintegration time study, the tablets are taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus has to be positioned into a 1lt beaker containing 900 ml of distilled water and time of disintegration was recorded at 37 ± 2°C [23].

### Drug content analysis

Total 10 tablets are weighed and powdered. The powder equivalent to Drug has to be taken and dissolved in Buffer. After that an aliquot of the filtrate has to be diluted and analyzed spectro-photometrically [24].

### In-vitro dissolution study

The in-vitro dissolution study has to be carried out in the USP dissolution test apparatus type 2 (paddle). 900 ml of the dissolution medium has to be taken in vessel and the temperature was maintained at 37 ± 0.5°C. The speed of the paddle is set at 50 rpm. 5 ml of the dissolution medium has to be withdrawn and the same amount of fresh medium is replenished to the dissolution medium. The sample withdrawn has to be filtered and diluted with the buffer prior to analysis in the UV Spectrophotometer at 271.3 nm [25].

### Disintegration time study

In the disintegration time study, the tablets are taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus has to be positioned into 1 liter beaker containing 900 ml of distilled water and time of disintegration was recorded at 37 ± 2°C [26].

## RESULTS

### Estimation of Clopidpgrel by UV absorption method

**Table.no2: Illustrates the concentration and absorbance**

| CONCENTRATION (µg) | ABSORBANCE |
|---|---|
| 0 | 0 |
| 10 | 0.045 |
| 20 | 0.102 |
| 30 | 0.145 |
| 40 | 0.196 |
| 50 | 0.239 |
| 60 | 0.285 |

**Standard calibration curve for Clopidogrel**

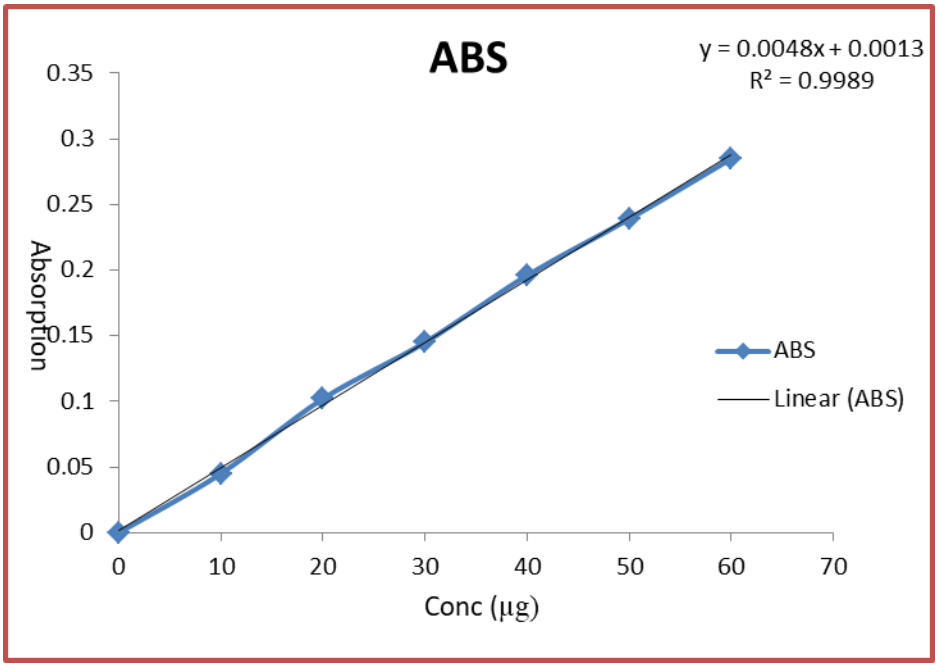



**Table.no3: Showing the results of pre compression parameters**

| Formulation code | Bulk density | Tapped density | Carr's index | Hausner's ratio | Angle of repose |
|---|---|---|---|---|---|
| F1 | 0.43 | 0.51 | 13.52 | 1.22 | 29.25 |
| F2 | 0.51 | 0.66 | 21.79 | 1.19 | 28.93 |
| F3 | 0.51 | 0.61 | 17.28 | 1.25 | 31.26 |
| F4 | 0.47 | 0.54 | 12.80 | 1.21 | 33.73 |
| F5 | 0.48 | 0.61 | 16.75 | 1.32 | 29.13 |
| F6 | 0.51 | 0.52 | 13.22 | 1.25 | 31.48 |
| F7 | 0.51 | 0.61 | 21.79 | 1.19 | 29.25 |
| F8 | 0.51 | 0.61 | 12.80 | 1.32 | 28.93 |
| F9 | 0.51 | 0.51 | 13.52 | 1.22 | 29.13 |
| F10 | 0.51 | 0.66 | 21.79 | 1.19 | 28.93 |
| F11 | 0.51 | 0.61 | 17.28 | 1.25 | 31.26 |
| F12 | 0.47 | 0.54 | 12.80 | 1.21 | 33.73 |

**Table.no4: Showing the results of post compression parameters**

| Formulation code | Thickness | Diameter | Hardness | Friability | Weight variation | Drug content |
|---|---|---|---|---|---|---|
| F1 | 2.47 | 3.40 | 5.57 | 0.17 | 501.00 | 98.45 |
| F2 | 2.50 | 3.33 | 6.60 | 0.33 | 497.30 | 95.57 |
| F3 | 2.37 | 3.37 | 6.43 | 0.15 | 501.30 | 92.95 |
| F4 | 2.53 | 3.57 | 5.53 | 0.26 | 499.30 | 100.34 |
| F5 | 2.43 | 3.47 | 6.37 | 0.32 | 499.00 | 97.77 |

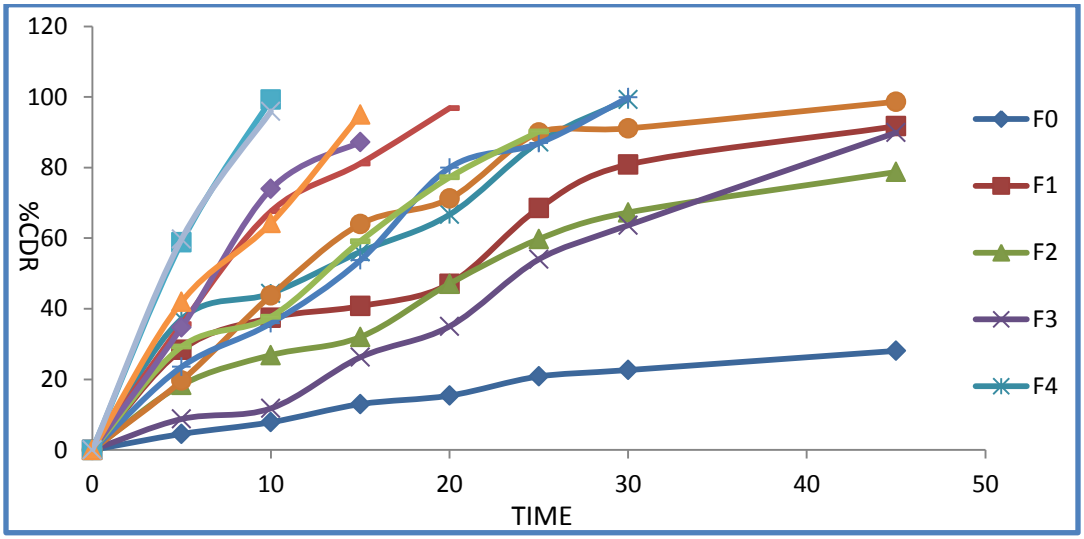
| | | | | | | |
|---|---|---|---|---|---|---|
| F6 | 2.43 | 3.67 | 6.07 | 0.34 | 499.60 | 99.65 |
| F7 | 2.50 | 3.37 | 6.43 | 0.15 | 497.30 | 95.57 |
| F8 | 2.47 | 3.57 | 5.53 | 0.26 | 501.30 | 92.95 |
| F9 | 2.43 | 3.47 | 6.37 | 0.32 | 499.30 | 100.34 |
| F10 | 2.50 | 3.33 | 6.60 | 0.33 | 497.30 | 99.67 |
| F11 | 2.37 | 3.37 | 6.43 | 0.15 | 501.30 | 92.95 |
| F12 | 2.53 | 3.57 | 5.53 | 0.26 | 499.30 | 100.34 |

**Table.no5: Disintegration time & wetting time**

| Formulation code | Parameters | |
|---|---|---|
| | Disintegration (Seconds) | Wetting Time (Seconds) |
| F1 | 38 | 52 |
| F2 | 29 | 36 |
| F3 | 27 | 39 |
| F4 | 118 | 107 |
| F5 | 34 | 44 |
| F6 | 25 | 46 |
| F7 | 21 | 28 |
| F8 | 114 | 150 |
| F9 | 46 | 25 |
| F10 | 17 | 23 |
| F11 | 31 | 48 |
| F12 | 26 | 31 |

**Table.no6: In-Vitro Dissolution Studies**

| TIME | F0 | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 4.53 | 28.36 | 18.40 | 8.75 | 37.11 | 19.61 | 23.53 | 35.60 | 29.26 | 34.69 | 58.83 | 41.93 | 59.73 |
| 10 | 7.84 | 37.41 | 26.85 | 11.77 | 44.35 | 43.74 | 35.90 | 67.57 | 37.71 | 73.91 | 99.25 | 64.26 | 95.93 |
| 15 | 12.97 | 40.73 | 31.98 | 26.25 | 56.11 | 63.95 | 53.70 | 81.15 | 59.13 | 87.18 | | 95.03 | |
| 20 | 15.39 | 47.06 | 47.06 | 34.99 | 66.67 | 71.19 | 79.94 | 96.84 | 77.23 | | | | |
| 25 | 20.82 | 68.48 | 59.73 | 54.00 | 87.18 | 89.90 | 86.88 | | 90.20 | | | | |
| 30 | 22.63 | 80.85 | 67.27 | 63.65 | 99.25 | 91.10 | 99.85 | | | | | | |
| 45 | 28.06 | 91.71 | 78.74 | 89.90 | | 98.65 | | | | | | | |
| 60 | 40.42 | 98.34 | 89.90 | | | | | | | | | | |




**Graph.no2: Showing the graphs of dissolution of all the formulations**

## SUMMARY & CONCLUSION

The present work depicts an investigation on "Formulation and evaluation of clopidogrel bisulfate fast dissolving tablets by novel hole technology".

Clopidogrel bisulfate is an antiplatelet medicine used to decrease the danger of coronary illness and stroke in those at high hazard, which is explicit for quick dissolving tablets and speaks to major therapeutic advance. This medication was chosen for the investigation since it has all the earmarks of being increasingly dynamic in antiplatelet prescription in the decrease of heart stroke.

In the current research the regular solubility enhancer Vigna Radiata (Moong bean) was utilized to improve its solvency by strong scattering. Various proportions medication and bearer were set up by two distinct strategies like physical blend (PM) and Solid dispersion (SD) Solvent evaporation method. Among the all proportions of PM and SD plans SD3 having Drug: Carriers proportions of 1:3 has most extreme solubility than PM.

The 100mg plain camphor is compacted into tablets, set these camphor tablets in to conclusive formulations with various super detergents like Primo gel (sodium starch glycolate), Carbose (cross carmellose sodium) and Kollidon (crosspovidone). These readied details were put in a sight-seeing oven at $60^0$C until camphor gets sublimated and opening is framed inside the tablets.

- This hole formation itself is responsible for the formulation to get disintegrate and released very fast.
- The pre and post pressure parameters were superb for the plans arranged with various super disintegrates.
- The disintegration data information demonstrated that the formulation F10 has the most minimal crumbling time whereas the others have noteworthy qualities.
- In-vitro release investigations of the considerable number of formulations were done utilizing USP-II paddle type mechanical assembly. The discharge was most elevated for the formulation F10.
- The best formulation was compared with the formulation F0 arranged without super disintegrates. Subsequently, in light of the above outcomes out of 12 plans F10 was picked as the best formulation.

From the examination it was presumed that Vigna Radiata is successfully utilized as solubility enhancer and formulation F10 might be the best formulation having great In-vitro disintegration and In-vitro drug release profile. In light of the outcomes from the examination further utility of the dose structure may rely upon the Pharmacokinetic information. Forthcoming research work of novel hole technology may contribute in the challenging area.

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