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# "A Quality Control Study of Different Brands of Clopidogrel Tablets"

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ABSTRACT

Clopidogrel is an orally administered medicine that lowers the risk of heart disease. The production process is defined by drug quality, and every pharmaceutical business aims for it, although it is often difficult to attain. The purpose of this study was to look at the quality control parameters of several commercially available Clopidogrel tablets. Four distinct marketed brands of Clopidogrel 75 mg tablets available in the Mangalore market were collected from different pharmacies in Mangalore city to examine the quality. Weight variation, hardness, thickness, and friability, among other quality indicators, were determined according to established protocols. Then there was the in-vitro dissolution test, potency, and disintegration time. All of the brands met the requirements of the Pharmacopoeia since they had a weight fluctuation range that was acceptable. All brands were less than 1% friable, and there were no significant differences in disintegration times, since they all dissolved within 15 minutes. In terms of dissolution profile, all brands had an acceptable dissolving time, releasing more than 60% of the drug in less than 45 minutes. All brands' hardness fell inside the range. All of the brands also meet the potency requirements. This investigation found that the majority of commercially available Clopidogrel pills in Mangalore are of good quality and meet pharmacopoeia requirements.

**Keywords:** Clopidogrel, Physicochemical, Dissolution profile, Potency

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# INTRODUCTION

The Quality, release rate, purity of two APIs should be comparable if the are similar in action and structure. They must be in the same dosage form and intended for the same route of administration. Manufacturing methods and the excipients used in the production processes could contribute to the quality and release skilfulness of the medicament. So to make sure of the required standard, the manufacturer should evaluate the product right from the stage of raw material to the finished product, and the storage stages.[1] Accordingly, to ensure that the generic and branded drugs products are pharmaceutically equivalent cannot be overemphasized. So, the selection of one product from several generic drug products of the same active ingredients is concerned important for healthcare professionals.[2]

**Quality control tests**

Quality is not an accident. It is the result of intelligent effort. To ensure the quality of pharmaceuticals, regulatory bodies are continuously developing their requirements towards pharmaceutical companies. In pharmaceutical industry the maximum quality of pharmaceuticals, depends on the tests performed during manufacturing and after manufacturing of the pharmaceuticals as per specifications of the respective pharmacopoeia and the regulatory requirements of the particular countries to assure the maximum quality of pharmaceuticals for human health. Quality control refers to a procedure or a set of steps taken during and after the manufacturing of a product to ensure that it meets the requirements and that the product is reproducible.[3] The FPQC tests for pharmaceutical tablets are:

1. Size, shape, Diameter and thickness
2. Friability
3. Weight variation (uniformity of weight)
4. Disintegration
5. Dissolution Test
6. UV Spectrophotometric method

**Drug profile**

The drug under study in this work is Clopidogrel Bisulphate (figure 1) which is an Anti platelet agent acts by inhibiting the ADP (adenosine Diphosphat) receptor on platelet cell membranes. It is used in management of thrombotic diseases including stroke, acute myocardial infarction (AMI), acute coronary syndrome (ACS), angina, percutaneous coronary intervention (PCI), cardiac surgery, primary and secondary cardiovascular disease prevention, peripheral vascular disease and thrombotic disorders such as Atrial fibrillation. [(4,5)]

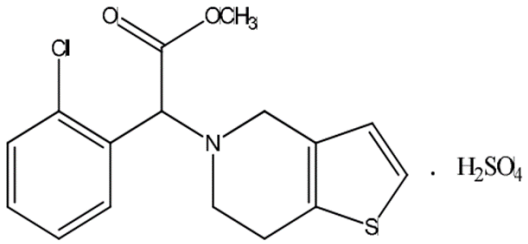


**Figure 1: Chemical structure of Clopidogrel Bisulphate**

- Category is Anti-Platelet agent
- Chemical formula is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$
- IUPAC Name Methyl 2- (2- Chlorophenyl) -2- (6,7- dihydro thieno Pyridine- 5 (4H)-yl) Acetate sulphate
- Molecular Weight is 419.90 gm/mol
- Characteristic is White Crystalline Powder
- Solubility Soluble in Methanol, Acetonitrile, DMSO and Ethyl acetate

**Aim and Objectives**

The aim of the study is to perform comparative analytical studies of different marketed brands of Clopidogrel bisulfate tablet available in India.

The following are the specific objectives of present study:

- To carry out UV Spectrophotometric analysis of Clopidogrel bisulfate
- To perform various quality control tests of tablets as per Indian Pharmacopoeia such as weight variation, content uniformity, hardness, friability, disintegration and dissolution tests.

## MATERIALS AND METHODS

**Materials required**

- Different brands of Clopidogrel bisulfate tablets (Clodrel 75mg- A, Clopikind75mg – B , Cloflow 75mg- C, Platloc 75mg-D)
- Reagent for buffer preparation
- Vernier caliper
- Monsanto hardness tester
- Roche friabilator
- Disintegration apparatus
- Dissolution apparatus
- UV visible spectrophotometer

**Quality control tests:**

**Measurement of melting point**

The melting point of clopidogrel bisulfate was determined using a capillary tube where a few amount of powdered clopidogrel bisulfate is inserted into a capillary tube and placing the tube in an instrument and the melting temperature was fixed when complete melting of the powdered drug occurs

**General Appearance Test**

Observe the tablets and note the shape, color, odor and taste. Determine the thickness and crown diameter of the tablets using a micrometer screw gauge or a vernier calipers.

**Hardness Test**

Apparatus used is the Monsanto Hardness tester. Tablet is placed on the lower plunger along with noting the zero reading. Apply the force until the tablet breaks by bringing the upper plunger on the tablet. The force of fracture is recorded and the zero reading is deducted from it[7.]

**Friability Test:**

Roche friabilator has a plastic chamber which can rotate at 25 rpm. About 20 tablets are weighed together and then placed in the chamber. The friabilator is operated for 100 revolutions and the tablets are subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drop them 6 inch on each revolution. The tablets are then dusted and reweighed. The loss in weight should not exceed 1.0% of their original weight [8.]

**Uniformity of Weight Test (Weight Variation test)**

Weigh 20 tablets individually. Also weigh all together and then calculate the average weight. Compare the weight of each tablet with the average weight and then calculate the percentage by which the former deviates from the latter. The tablets comply with the test if no more than two tablets have a percentage deviation outside the permissible limit and if no tablet differs by more than twice this limit as per table 1[9.]

**Table 1: Weight uniformity**

| Average wt of tablets(mg) | Max. Permissible limit for deviation (%) |
|---|---|
| 80 or less | ±10 |
| 80 to 250 | ±7.5 |
| 250 or more | ±5 |

**Disintegration Test**

The U.S.P Disintegration test apparatus is used. One tablet is placed in each of the six tubes, followed by the plastic discs. The basket rack assembly is positioned in one liter beaker of water maintained at 37±2$^0$C. A distance of 2.5 cm buffer is kept from the liquid surface to the bottom

while operation. The time taken for the tablets to disintegrate and for the particles to completely pass through the screen without any residue remaining is observed. If any residue remains, it should be a soft mass with no palpable firm core. The disintegration time should be within prescribed limit for the tablets (uncoated) to comply with the test[10].

**Determination of absorbance maximum**

Prepare 100 µg/mL conc of clopidogrel bisulfate in solution(distilled water pH-1with OPA) and absorption spectra was taken in UV region (200-400 nm) figure 2 . The procedure is repeated with 0-60µg/mL to check the effect of dilution.

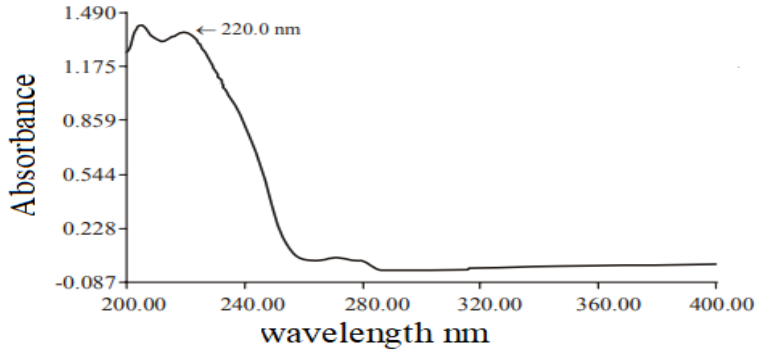


**Figure 2: Determination of lambda max of clopidogrel**

**Preparation of Phosphate Buffer pH 6.8**

13.87 gm of potassium dihyrogen phosphate, 35.08 gm of disodium hydrogen phosphate is dissolved and made upto 1litre and stored in cold place.

**Preparation of Calibration Curve**

Accurately weighed 100 mg of Clopidogrel was dissolved in 100 ml of methanol so as to give the first stock solution of concentration 1000 µg/ml. The second stock solution was prepared by diluting 10 ml from first stock solution in 10 ml methanol in a 100 ml volumetric flask to give the concentration 100µg/ml. The standard solutions were diluted with phosphate buffer pH 6.8 to obtain various dilutions (0, 10, 20, 30, 40, 50 and 60 µg/ml) in standard volumetric flasks 10 ml. Measure the absorbance of the solutions in the wavelength range of 234 nm in UV visible spectrophotometer. Plot the values of absorbance against respective concentrations in MS Excel and determine the slope and intercept it as mentioned in figure 3 [11].

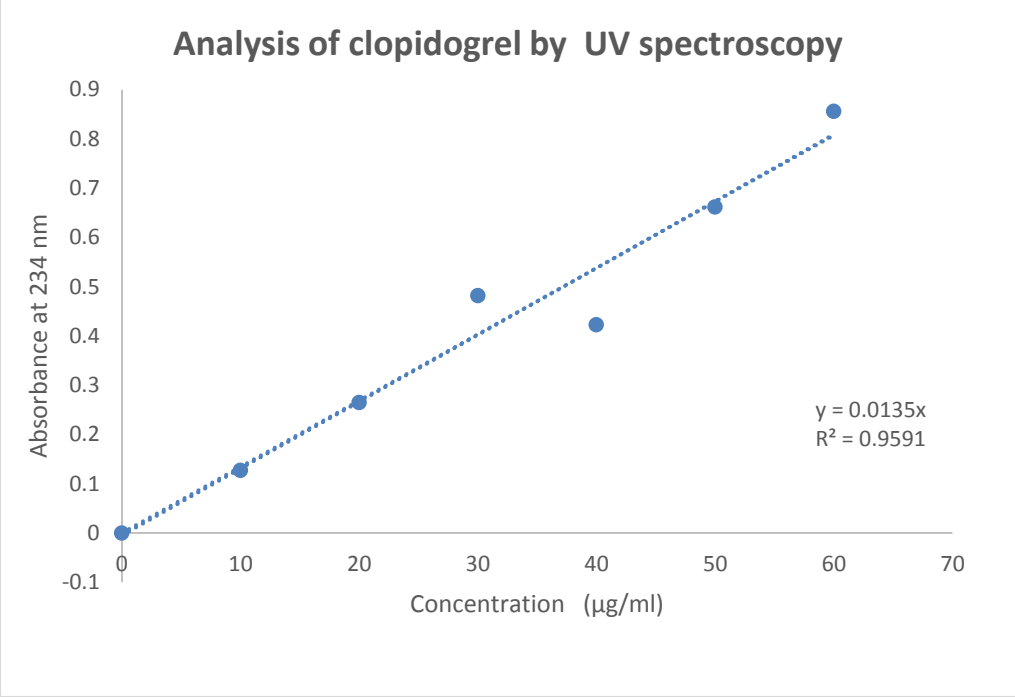


**Figure 3: Standard plot of clopidogrel**

**Dissolution Test**

TYPE-I or paddle type apparatus is used for the test. Introduce 900ml of phosphate buffer of pH 6.8 as dissolution medium into the vessel of the apparatus. Warm the dissolution medium to a temperature of 37±0.5°C. The paddle is introduced into the medium and fixed so that it's the lower surface is at a height of 2.5cm from the bottom of the vessel. Introduce one tablet into the medium and allow it to sink to the bottom of the vessel.

Operate the apparatus immediately at a speed of 50 R.P.M. run the apparatus for 60 min. withdraw 5ml of the dissolution medium from a zone midway between the surface of the dissolution medium and top of the rotating blade but not less than 10mm from the wall of the vessel at 0, 10, 20, 30, 40, 50,60 mins. Filter the sample through a Whatmann filter paper. Reject the first 1 to2 ml of the filtrate and continue filtering the remaining solution. Pipette out 1ml of the filtrate and dilute with phosphate buffer to 50ml and measure the absorbance of the resulting solution at about 234 nm. The concentration of this solution is calculated from the standard plot for Clopidogrel [12].

**Assay of marketed tablets**

Accurately weigh and powdered 20 tablets. Weighed powder equivalent to 100mg of clopidogrel bisulfate into 100 ml volumetric flask add 20 ml of distilled water pH 1, sonicated for 15 mins to dissolve clopidogrel bisulfate and made up to mark with the same. This solution was filtered with whatman filter no. 40. 10 ml of the above filtrate was diluted to 20µg/ml with distilled water pH-1, and absorbance was taken at 222 nm against blank[13]

## RESULTS AND DISCUSSION

The quality control tests and analysis by UV Spectroscopy of different brands of Clopidogrel was performed and results were obtained as shown below.

**Measurement of melting point**

By capillary method the melting point of the four sample were found to be 198°C, 203°C, 197°C, and 200°C. for brand A, B, C and D respectively.

**Assay (Table 6):**

As shown in table 6 brand A has shown a drug content of 75.44 mg (100.59%) , Brand B 74.46 mg (99.28%) , Brand C 75.97mg(101.30%) , Brand D 74.66mg (99.55%) against the label claim of 75 mg

**Appearance:**

As shown in table 2 the general appearance test of Clopidogrel tablets, shape of these brands were identified as round, color as white; all the tested brands were tasteless and odorless. Crown diameter of Brand A, B, C, D, were 5.1mm, 5.4 mm, 5.8 mm and 5.9mm respectively. The thicknesses of these brands were analyzed as 3.81mm, 4.02mm, 3.45mm and 3.93mm.

**Table 2: General appearance test of different brands of Clopidogrel**

| SL.NO | General appearance | Brand | | | |
|---|---|---|---|---|---|
| | | Brand A | Brand B | Brand C | Brand D |
| 1 | Shape | Oval | Oval | Oval | Oval |
| 2 | Color | White | White | White | White |
| 3 | Taste | No Taste | No taste | No taste | No taste |
| 4 | Odor | odorless | odorless | odorless | odorless |
| 5 | Crown diameter | 5.1mm | 5.4 mm | 5.8 mm | 5.9mm |
| 6 | Thickness | 3.81mm | 4.02mm | 3.45mm | 3.93mm |

**Hardness (Table 3):**

Shows the hardness variation of different brands of Clopidogrel, and the results were analyzed as Brand A, B, C and D had hardness as 4.1 kg/cm$^2$, 4.3 kg/cm$^2$, 5.2 kg/cm$^2$ and 4.8 kg/cm$^2$ respectively. Here, all the brands was within the range (4-10 kg/cm$^2$ ) and was found satisfactory, the batches were considered as of good quality.

**Table 3: Test for hardness friability uniformity of weight and disintegration test**

| Brand | Hardness test | Friability test | Uniformity of weight test | Disintegration test |
|---|---|---|---|---|
| A | 4.1 kg/cm$^2$ | 0.831 % | 0.0536 g | 6.5 ± 0.15 min |
| B | 4.3 kg/cm$^2$ | 0.81 % | 0.0486 g | 7.4 ± 0.23 min |
| C | 5.2 kg/cm$^2$ | 0.757 % | 0.0471 g | 7.1 ± 0.87 min |
| D | 4.8 kg/cm$^2$ | 0.729 % | 0.0518 g | 7.9 ± 0.29 min |

**Friability (Table3):**

Shows the results of friability tests conducted in different brands of Clopidogrel, the percentage friability of Brand A, B, C and D is 0.831 % is 0.81 %, 0.757 %, and 0.729 % respectively. Here, six brands have percent friability below 1% which indicates tablets will not face difficulty during storage or transportation.

**Weight Variation (Table 3):**

Shows the Weight variation of different brands of Clopidogrel, the mean average weight of Brands A, B, C and D were analyzed as 39 mg 46 mg, 45 mg and 45 mg respectively. Not more than 2 tablets should differ from the average weight by more than 7.5% and none should deviate by 15% of average weight. The weight variation was found to be within limits for all the brands of tablet.

**Disintegration (Table 3):**

Shows the results of disintegration tests of different brands of Clopidogrel, the disintegration time of Brands A, B, C and D were 6.5 ± 0.15 min, 7.4 ± 0.23 min, 7.1 ± 0.87 min and 7.9 ± 0.29 min respectively. BP specifies that uncoated tablets should disintegrate within 15 minute, which is 30 minute in case of USP. All the brands passes the criteria.

**Determination of absorbance maximum**

From the figure 2 the maximum wavelength observed was at 220 nm for Clopidogrel

Standard wavelength for drug was at 222nm

**Calibration Curve determination**

From the (figure 3/ table 4) the calibration was found to be linear and the value of regression was 0.9868 which falls within the limits of beer-lambert's law and hence the results were found to be satisfactory

**Table 4: Calibration curve of Clopidogrel by UV spectroscopy**

| Sl.no | Concentration (µg/ml) | Absorbance at 234 nm |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 10 | 0.127 |
| 3 | 20 | 0.265 |
| 4 | 30 | 0.482 |
| 5 | 40 | 0.423 |
| 6 | 50 | 0.662 |
| 6 | 60 | 0.856 |

**Dissolution**

Dissolution profile (table 5) of all the investigated brands was found within the limit. The evaluation showed that almost all the 4 brands dissolved 100% within 60 minutes indicating that the release pattern of drugs were same although the brands were manufactured by different

companies using different excipient in different ratio but on the basis of releasing factor they can be used interchangeably

**Table 5: Dissolution test of different brands of Clopidogrel**

| Sl.no | Time in min | Brand wise % release | | | |
|---|---|---|---|---|---|
| | | A | B | C | D |
| 1 | 0 | 0 | 0 | 0 | 0 |
| 2 | 10 | 32.3 ± 2.15 | 38.2 ± 2.45 | 35.8 ± 1.35 | 36.9 ± 1.15 |
| 3 | 20 | 45.7 ± 1.65 | 45.6 ± 1.84 | 44.8 ± 1.65 | 48.2 ± 1.15 |
| 4 | 30 | 62.8 ± 1.32 | 63.9 ± 2.29 | 60.4 ± 1.25 | 65.3 ± 1.15 |
| 5 | 40 | 79.4 ± 1.67 | 75.3 ± 2.26 | 73.7 ± 1.85 | 71.6± 1.15 |
| 6 | 50 | 84.2 ± 1.29 | 77.1 ± 1.57 | 80.3 ± 1.15 | 85.4 ± 1.15 |
| 7 | 60 | 98.2 ± 2.15 | 87.6 ± 1.15 | 94.2 ± 3.15 | 97.5 ± 2.45 |

**Table 6: Assay test of different brands of Clopidogrel**

| Tablet Sample (N=3) | Label claim | Actual content ± SD | Percentage actual content ± SD |
|---|---|---|---|
| A | 75 mg | 75.44 ± 0.265 | 100.59 ± 0.354 |
| B | 75 mg | 74.46 ± 0.301 | 99.28 ± 0.401 |
| C | 75 mg | 75.97 ± 0.153 | 101.30 ± 0.204 |
| D | 75 mg | 74.66 ± 0.252 | 99.55 ±0.337 |

## CONCLUSION

The established approach has been found to be sensitive, precise, and repeatable, and it may be utilized for routine quality control analysis of clopidogrel in bulk and various pharmaceutical formulations. In the current industrial practice, in-vitro testing play a key part in comparing multi-brand generic molecules and providing enough therapeutic activity of the dosage form. According to the statistics, all four brands of clopidogrel tablets studied appear to be of good overall quality, with a satisfactory dissolve rate and disintegration time. The current situation of several quality indicators of drug goods manufactured by local enterprises is depicted in this study. It is a common perception that drug items manufactured by mid- or small-sized businesses are inferior to those produced by market leaders. However, this inquiry will aid in changing people's minds.

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