

QUALITY CONTROL TESTING OF CONVENTIONAL CLOPIDOGREL BISULFATE TABLETS MARKETED IN IRAQ

MAZIN THAMIR ABDUL-HASAN¹, ABULFADHEL JABER NEAMAH AL-SHAIBANI¹, ALI N. WANNAS¹, KARRAR MOHAMMED HASAN AL-GBURI²

¹Department of Pharmaceutics, Faculty of Pharmacy, University of Kufa, Al-Najaf, Iraq, ²Department of Clinical Pharmacy, Faculty of Pharmacy, University of Kufa, Al-Najaf, Iraq
Email: mazinth.ahusseini@uokufa.edu.iq

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ABSTRACT

Objective: This study was employed to evaluate the quality of marketed oral tablets containing clopidogrel bisulfate. Tablets produced by various companies and commercialized in the Iraq market were used in the study.

Methods: Batches of clopidogrel bisulfate conventional tablets (containing 75 mg of drug) were exposed to the quality control tests. These tests involved friability, weight variation, hardness, drug content, disintegration time, and *in vitro* release study; these tests were conducted depending on USP pharmacopeia.

Results: The data indicate that all batches of clopidogrel bisulfate complied with the limitations of USP pharmacopeia for variation of weight, results of the hardness of tablets were 7.2-9.6 Kg/cm². Friability value (% loss) was less than one, which was within the required limits. The time of disintegration was less than 25 min in both artificial gastric fluid (AGF) and artificial intestinal fluid (AIF). Drug content was observed between 97.1 % and 99.8 %, indicating compliance with the limits of pharmacopeia (85-115 %). An *in vitro* release study of batches was greater than 80 % within 25 min.

Conclusion: All batches of clopidogrel bisulfate were manufactured within the criteria of tablet manufacturing. The quality control tests of tablets showed acceptable pharmaceutical properties (effectiveness and safety) that lie within the limits of USP pharmacopeia.

Keywords: Oral tablets, Clopidogrel bisulfate, Biopharmaceutics classification system (BCS) solubility

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INTRODUCTION

Quality control studies of drug products are regarded as a substantial process of the pharmaceutical industry, which includes all processes that are performed to ensure the desired level of quality of drug products [1]. The processes of quality control were performed before releasing a drug into the market, so it must be subjected to strict control to ensure that the quality and performance concerning safety, efficacy, potency, stability, and elegance of medications of the final drug product were accepted by consumers [2]. Currently, all solid oral conventional drug products require an *in vitro* dissolution study as part of their quality control appreciation; this includes testing the drug-release profile of various batches of a marketed product to confirm manufacturing and product consistency [3]. Products are available on the market in different companies which differ from each other in accuracy and quality level, so the quality level of the product is tested as a regular procedure in each step of manufacturing of the product and the results of tests are compared with standard characteristics under the Pharmacopoeia [4]. Clopidogrel bisulfate is a prodrug of a platelet inhibitor indicated for the treatment of myocardial infarction, stroke, and established peripheral arterial disease; it's a thienopyridine with molecular weight (419.9 g/mol), it has weak basic properties (pKa 5.3). The low water solubility (0.0118 mg/ml) and high membrane permeability (logP 4.03) indicate that the drug belongs to class II according to the biopharmaceutical classification system BCS [5]. Clopidogrel bisulfate is present as a film-coated tablet manufactured by various companies in the world. So this study aimed to make an evaluation of quality control for oral film-coated tablets of clopidogrel bisulfate that were fabricated by various pharmaceutical companies that possess standards of pharmacopeia and are available on the Iraq pharmaceutical market. Aklima, et al. performed a quality control study on different brands of carbamazepine conventional tablets marketed in Bangladesh, in this study, the tablets were subjected to various parameters such as weight variation, friability, hardness, disintegration time, and *in vitro* release study; the study indicates that all brands of

carbamazepine tablets meet the limits of USP (United State of Pharmacopeia). All brands meet the specifications in the test of weight variation, the tablets of carbamazepine disintegrated within 15 min and meet USP specification, the release different carbamazepine tablets were satisfactory within 45 min and ranged from 83.44% to 94.5%, so the study concluded that all brands of carbamazepine available in Bangladesh meet USP limitation for quality control testing [6].

MATERIALS AND METHODS

Materials

Clopidogrel bisulfate film-coated batches with the strength of 75 mg provided by private pharmacies in Baghdad, Iraq, and illustrated in table 1. Clopidogrel bisulfate powder was obtained from Zhejiang Menovo Pharmaceutical Co, LTD. Hydrochloric acid from Grin land chemical comp, United Kingdom. Na₂HPO₄, NaH₂PO₄, and distilled water were supplied by the laboratory of the pharmaceutical industry, University of Kufa, Faculty of Pharmacy.

Table 1: Different batches of marketed clopidogrel bisulfate coated tablets

| Batch name | Manufactured company | Country |
|-----------------|----------------------|----------------|
| Plagerine | Micro | India |
| Clopidogrel | Accord | United Kingdom |
| Clopidox | Armox | Switzerland |
| Clopacin | Acino | Switzerland |
| Apo-Clopidogrel | Apotex | Canada |

Methods

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 [7].

Drug calibration curves

Stock solutions of clopidogrel bisulfate (100 µg/ml) were prepared at pH (1.2) and pH (6.8). Different concentrations of clopidogrel bisulfate were prepared from stock solution, then the absorbance for these different concentrations of clopidogrel bisulfate was measured spectrophotometrically at 200-400 nm.

Maximum solubility determination

Saturated solution

An excess amount of clopidogrel bisulfate was added to a 10 ml tube containing dissolution media prepared at pH 6.8 and pH 1.2. These tubes were kept at 25±0.5 °C within 72 h and centrifuged at 3000 rpm for 10 min. After centrifugation, the supernatant was filtered using a filter membrane (0.45 µm) and diluted with the same medium, and then taken for analysis using a spectrophotometer [8].

Assessment of quality control

Weight variation

Weight variation of the batch was tested by selecting 20 tablets randomly, then these tablets weighed individually using a balance (GmbH, Germany). The average weight of 20 tablets was calculated and the percent of weight variation was determined [9].

Friability test

The friability test was performed using a friabilator to assess the tendency of the tablet to chip, crumble or break upon handling or compression as well as the strength of the tablet. A sample of a preweighed tablet is put in the friabilator (Erweka Friabilator tester). The friabilator was operated at 100 rpm [10]. The weight of the tablet was determined before and after a specified number of revolutions so the weight loss can be determined. Tablets are considered acceptable if the percentage of weight loss lies within the range of 0-1% of tablet weight. The percent friability can be determined using the following equation:

$$\text{Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100 \dots \text{Equation 1}$$

Hardness test

Hardness, the crushing strength of a tablet, can be defined as the force needed to diametrically break a tablet. The crushing strength of a tablet can be measured using an Erweka hardness tester. From each brand, a ten tablets sample was taken and the pressure needed to break the tablet was recorded as kg/cm².

Disintegration test

The disintegration time of the tablet was assessed by using a USP disintegration apparatus (Erweka, Germany); the apparatus is composed of 6 tubes open at both ends where the bottom of the tube is composed of a 10-mesh screen. The medium was artificial gastric fluid (AGF) and artificial intestinal fluid (AIF) and the temperature was kept at 37 °C. The disintegration time was determined when the complete disintegration of the tablet occurs [11].

Drug content assay

The content of clopidogrel bisulfate in an individual batch was determined where 10 tablets were weighed. Grinding of tablets into fine powder was carried out using mortar. A certain amount of crushed powder, which is equivalent to 75 mg of clopidogrel bisulfate, was added to a 100 ml volumetric flask containing the solution of pH 1.2, then the flask was shaken for one hour. After that, filtration was done. One ml from the filtered solution was diluted to 100 ml with HCl (pH 1.2), the absorbance was scanned using a spectrophotometer. The batch will be accepted if the content of the drug present in each tablet lies within 85% to 115 % of the drug content indicated on the label [12].

Drug release study

To assess the quality of conventional clopidogrel bisulfate tablets, dissolution experiments were carried out on marketed tablets manufactured by different companies. *In vitro* drug release study was carried out using USP Apparatus 1 (basket) operated at 37.0±0.5 °C and 50 rpm. Marketed tablets of different companies were placed in 600 ml (0.1N HCl). An aliquot of 5 ml of release medium was taken at predetermined time intervals (5, 10, 15, 20, 25, 30 min) and replaced with an equal volume of fresh medium to maintain a constant volume. These aliquots of release medium were filtered through a 0.45µm cellulose acetate membrane filter unit before analysis. Analysis of samples was scanned at 269 nm using a Cary 50 UV-Visible spectrophotometer [13].

RESULTS AND DISCUSSION

Melting point

The measured melting point of clopidogrel bisulfate was 183 °C to 184 °C, which is similar to the official melting point of the drug and revealed drug purity utilized in the study [14].

Drug calibration curves

The calibration curve of clopidogrel bisulfate was carried out using UV-Vis spectroscopy by plotting the concentration of the drug using a stock solution of clopidogrel bisulfate against the absorbance. A standard solution of clopidogrel bisulfate was prepared at pH1.2 and pH 6.8. A calibration plot of concentration as a function of absorbance was obtained using linear regression analysis (fig. 1 and fig. 2).

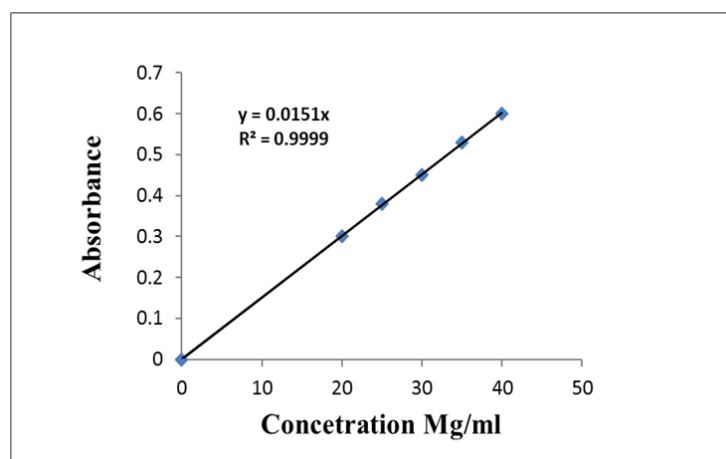


Fig. 1: Calibration curve of clopidogrel bisulfate in (pH1.2)

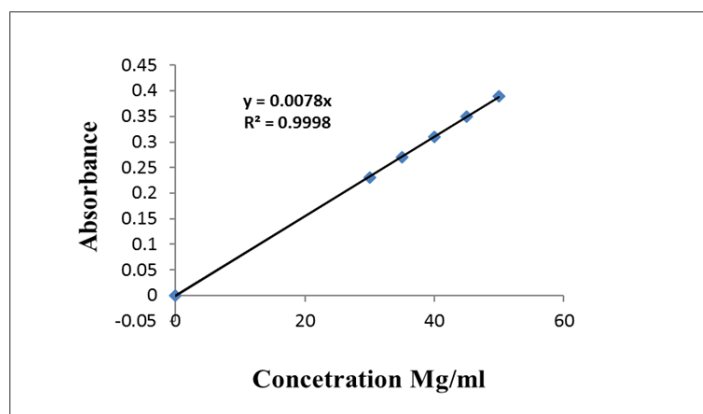


Fig. 2: Calibration curve of clopidogrel bisulfate in (pH 6.8)

Saturated solubility of the drug

Saturated solubility of clopidogrel bisulfate in different media indicates that the highest solubility of the drug presents in HCl buffer (pH 1.2), which is (265.9 mg/ml), while drug solubility in phosphate buffer (pH 6.8) was (32.7 mg/ml), these results revealed the weak basic properties of drug, highest solubility was found in the acidic medium [15].

Quality control tests

Weight variation

The limits for this test according to USP indicate that the accepted deviation percent of the tablet (130 mg to 324 mg) is (± 7.5) as shown in products (Plagerine, Clopidogrel, Clopidox and Apo-clopidogrel) and

for tablet more than 324 mg was (± 5) as noted in the product (Clopacin) [16], the data of weight variation test revealed that marketed products of clopidogrel bisulfate manufactured by different companies meet USP specification. Table 2 and fig. 3 illustrate the lowest percent as well as the highest percent of weight variation.

Friability test

The friability (% loss) test was performed to determine the tablet's ability to resist scraping that occurs during processes of packaging, handling, and shipping. According to USP, the batch was accepted when friability was less than or equal to 1% [17], table 3 explains the friability values of marketed tablets (0.17-0.82); this reveals that marketed tablets of clopidogrel bisulfate used in this study meet USP specifications.

Table 2: Weight variation of marketed products of clopidogrel bisulfate

| Name of batch BN | Weight of individual tablet (mg) | | The average weight of 20 tablets | Percent deviation (%) | |
|---------------------|----------------------------------|----------------|----------------------------------|-----------------------|-----------------|
| | Lowest weight | Highest weight | Average weight (mg) | Lowest percent | Highest percent |
| Plagerine | 311 \pm 0.12 | 322 \pm 0.21 | 316 \pm 0.21 | 1.60 \pm 0.13 | 1.86 \pm 0.31 |
| Clopidogrel | 275 \pm 0.16 | 288 \pm 0.11 | 280 \pm 0.18 | 1.81 \pm 0.11 | 2.77 \pm 0.24 |
| Clopidox | 274 \pm 0.24 | 277 \pm 0.16 | 275 \pm 0.11 | 0.36 \pm 0.20 | 0.72 \pm 0.13 |
| Clopacin | 380 \pm 0.12 | 389 \pm 0.13 | 384 \pm 0.24 | 1.05 \pm 0.16 | 1.28 \pm 0.21 |
| Apo-clopidogrel | 179 \pm 0.11 | 185 \pm 0.12 | 181 \pm 0.16 | 1.11 \pm 0.12 | 2.16 \pm 0.19 |

Data are represented as (mean \pm SD, n = 3).

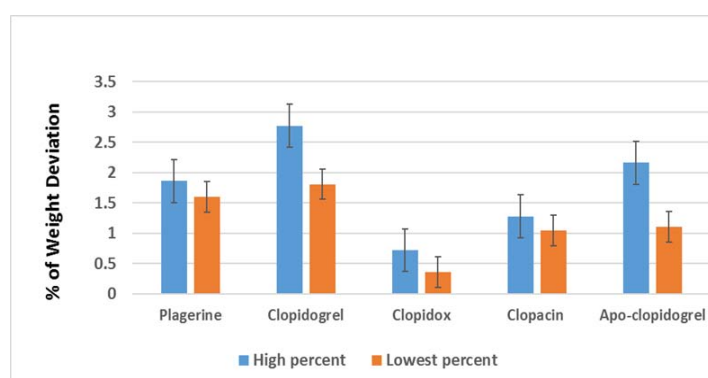


Fig. 3: Lowest and the highest percentage of weight deviation (mean \pm SD, n= 3)

Table 3: Friability values of marketed products of clopidogrel bisulfate

| Batch name | Number of tablets | Weight before the test (gm) | Weight after the test (gm) | Friability (%loss) |
|-----------------|-------------------|-----------------------------|----------------------------|--------------------|
| Plagerine | 20 | 6.35 | 6.33 | 0.31 |
| Clopidogrel | 20 | 5.62 | 5.61 | 0.17 |
| Clopidox | 20 | 5.53 | 5.50 | 0.54 |
| Clopacin | 20 | 7.73 | 7.73 | 0.25 |
| Apo-clopidogrel | 20 | 3.64 | 3.61 | 0.82 |

Test of hardness

The hardness of tablets was evaluated to determine the impact of mechanical strength on a tablet during processes of packaging, handling, and transportation. There was a relationship between hardness, disintegration time, and drug dissolution (release). According to USP, the crushing strength of (40-100 Newton) that represents (4-10 Kg cm²) was accepted for film-coated tablets [18], hence the data of hardness test in this study revealed that all marketed products showed an acceptable limit (table 4).

Disintegration time

Time of disintegration is a vital parameter to be assessed in quality control studies of conventional oral tablets for example, those that are used in the treatment of chronic diseases where a rapid onset of

action is required and immediate release are required as in the case of hypertension and heart failure. Based on USP, disintegration time for a conventional tablet of coated type is 30 min [19]. In the study, all tablets demonstrated an acceptable disintegration time (not more than 15 min) in AGF as well as AIF (table 4).

Drug content

The amount of clopidogrel bisulfate meets the USP limitations. The percent of clopidogrel bisulfate present in all batches was over the range of (97.1-99.8%), revealing the compliance with the limitation of pharmacopeia where no tablet exceeds the range of (85-115%). These results give an indication that distribution was excellent and acceptable components were present in the tablets of different manufacturers [20] as demonstrated in table 4.

Table 4: Drug content, hardness, and disintegration time, where disintegration time and hardness

| Batch | Hardness (Kg/cm ²) | Disintegration time (min) in AGF | Disintegration time (min) in AIF | Drug content (%) |
|-----------------|--------------------------------|----------------------------------|----------------------------------|------------------|
| Plagerine | 9.6±0.43 | 27.24±0.24 | 27.01±0.19 | 97.10 |
| Clopidogrel | 9.1±0.52 | 8.12±0.14 | 7.59±0.17 | 98.30 |
| Clopidox | 7.2±0.21 | 4.1±0.11 | 4.19±0.14 | 99.80 |
| Clopacin | 7.9±0.13 | 12.4±0.18 | 13.57±0.21 | 99.50 |
| Apo-clopidogrel | 9.3±0.25 | 15.38±0.41 | 14.16±0.31 | 98.90 |

Data of hardness and disintegration time are represented as (mean±SD, n= 3).

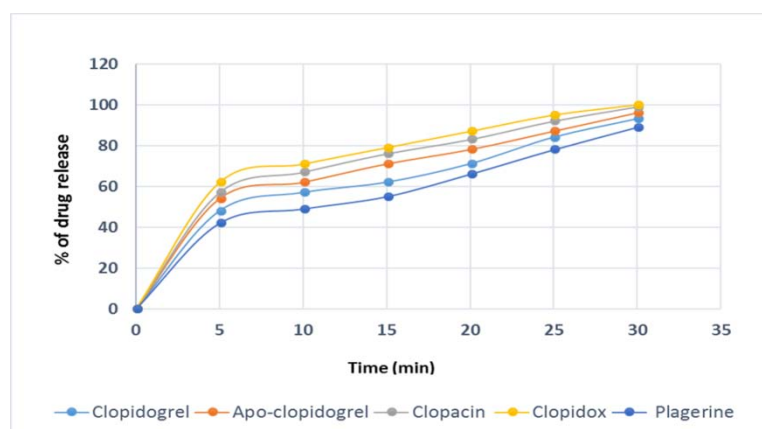


Fig. 4: Release profile of clopidogrel bisulfate marketed products

Study of *in vitro* release

Clopidogrel bisulfate bioavailability of oral film-coated tablets is based on the dissolution of the drug. So, it is essential to determine the dissolution rate and make a comparison to the dissolution profiles of clopidogrel bisulfate oral tablets marketed by different companies. Depending on USP, the dissolution profile of conventional oral tablets within one hour should be at least 80%. In this study, plots of *in vitro* release showed that all products of clopidogrel bisulfate manufactured by different companies meet USP limitations. That means the release was more than 70% within 25 min. Fig. 4 revealed that the clopidox batch released a higher amount of drug (99.98%), while the plagerine batch released less amount among different batches (89.21%).

CONCLUSION

In this study, the properties of all Marketed products of clopidogrel bisulfate available on the Iraqi market were in agreement with the specifications of the USP Pharmacopeia. The tested properties were weight variation, friability, hardness, disintegration time, and release of the drug. Disintegration time in all brands was less than 15 min and drug content was 97.1-99.8 %. The release was more than 70 % within 25 min. The analysis of marketed products of clopidogrel bisulfate demonstrated that tablets were manufactured in a satisfactory manner that is recommended for the objectives.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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