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Comparative *In Vitro* Quality Evaluation of Some Clopidogrel Tablets, Commercially Available in Bangladesh Drug Market

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Abstract

Clopidogrel is a potent anti-platelets and antithrombotic drug. It is film coated and 75 mg tablet. The objective of our study was to evaluate the quality parameters of some marketed clopidrogel tablet and to compare the parameters among them. To assess the quality, nine different marketed clopidogrel 75 mg tablet were selected and in-vitro dissolution test, potency, disintegration time were carried out. Other general quality parameters of these tablets like weight variation, hardness, friability were also determined according to established protocols. All the brands comply the requirements of "United State Pharmacopoeia" as they showed acceptable weight variation range. Friability of all brands was less than 1%. No significant differences were founding disintegration time as they disintegrated within 15 minutes. In case of dissolution profile all brands showed better dissolution time as they released more than 75% of drug in 45 minute. The hardness of one brand was within the range 40-60N. The limitation of the potency must be within 95-105%. All three brands meet this specification. This study suggested that most commercially available clopidogrel tablet in Bangladesh maintain the quality and comply with the USP specifications which are essential for better therapeutic activity of these anti-platelet drug.

Keywords: Clopidogrel; Physicochemical parameters; Potency; Dissolution profile; Cardiovascular

Introduction

Quality control is a process that is carried out to ensure a desired level of quality in a product or service. It might include whatever actions a business deems necessary to provide for the control and verification of certain characteristics of a product or service [1]. Most often, it involves thoroughly examining and testing the quality of

products or the results of services. ISO 8402-1986 standard defines that quality is the totality of features and characteristics of a product or service that bears its ability to satisfy stated or implicated needs [2]. Clopidogrel is a routine component of the clinical management of patients after acute coronary syndrome. It has been reported that this drug would reduce rates of major cardiovascular adverse events. It is approved for the reduction of atherosclerotic events in patients with stroke, myocardial infection, cardiovascular disease and acute coronary syndrome. Its action may be related to an adenosine diphosphate (ADP) receptor on platelet cell membranes. It specifically and irreversibly inhibits the platelet P2Y12 subtype of the ADP receptor, which is important in the aggregation of platelets and cross-linking by the protein fibrin 2. As a result, activation of the glycoprotein IIb/IIIa complex, which is involved in platelet activation and stabilization of the platelet aggregate, is also inhibited [3]. The purpose of this study is to evaluate whether the sample brands of clopidogrel tablet maintain the USP specifications and at which level they maintain the quality. This study is also conducted to obtain a brief idea about physico-chemical parameters of those brands and to make a comparison in quality among the sample brands.

Materials and Method

Recruitment of sample product

The marketed samples of nine brands (about 20 tablets of each brand) of Clopidogrel tablet were purchased at M.R.P from different Retail pharmacy at Dhaka in Bangladesh. These tablets of nine brands were coded as M1, M2, M3, M4, M5, M6, M7, M8 and M9. The samples were properly checked for their physical appearance, name of manufacturer, batch number, and manufacturing date, expiry date, manufacturing license number, D.A.R. number & maximum retail price at the time of purchase. There are approximately Twenty eight different brands of clopidogrel are available in Pharma market of Bangladesh (according to BD.DRUGS.COM). Here nine different available brands are chosen from well known pharmaceutical company of Bangladesh [4].

Weight Variation Test

For each brand, 20 tablets were randomly and weighted individually using an analytical balance (TE214S, sartorius Germany). The average weights were determined using the following formula.

$$X = (X1+X2+X3+\ldots\ldots+Xn)/10$$

Then the percentage weight deviations were determined by using the following formulas [5].

% of Deviation (+) = (maximum weight- average weight)/average weight ×100.

% of Deviation (-) = (minimum weight- average weight)/average weight ×100.

Hardness Test

10 tablets were taken randomly and hardness was measured using automatic Hardness Tester (VEEGO, INDIA). The hardness of tablets, which is the force required to break a tablet in a diametric compression force. If the tablet is too hard, it may not disintegrate in the required period of time or meet the dissolution specification, if it is too soft, it will not withstand the handling during subsequent processing such as coating or packaging and shipping operations [6].

Friability Test

Friability test should be performed to evaluate the ability of Clopidogrel tablet to withstand abrasion during packaging, handling & transporting. 20 Clopidogrel tablets were taken randomly & weighted together. Clopidogrel tablets were then placed into the Roche friabilator & subjected to 100 rpm for 1 minute at Clopidogrel tablets were re-weighted. This loss of weight indicates the friability of Clopidogrel tablet. Finally the percent of weight of loss was calculated by following way [5]

$$\text{Loss of \% of Weight loss} = \frac{(\text{Initialweight} - \text{Finalweight}) * 100}{\text{Initialweight}}$$

Disintegration Test

Disintegration test is performed to find out that within how much time the Clopidogrel tablet disintegrates. Disintegration test is very important for all coated & uncoated tablet because the dissolution rate of drug depends on the disintegration time, which ultimately affect the rate of absorption of drug. About 900ml buffer solution was taken in both 1000 ml beaker & then these beakers were placed into the device. One Clopidogrel tablet was placed in each tube of basket rack & a plastic disk was placed over each tablet & then the basket rack was accurately positioned into the beaker. The temperature was maintained as 37˚C i.e. body temperature. The time at which all the Clopidogrel tablets passed through the sieve was the disintegration time & the average disintegration time were calculated [5].

Potency Test

The potency of Clopidogrel tablet should comply with the specification because very highly potent drug may give toxic effect & very less potent drug may give sub-therapeutic effect. Four tablets of each brand were taken and the average weight was determined. Those 4 tablets of each brand were crushed in mortar and pestle. Amount of powdered tablet containing 10mg of Clopidogrel drug was determined by calculation. Determined amount of powdered tablet was taken in 100 ml volumetric flask and buffer solution was added up to 100 ml. Solution was filtered and 20 ml filtrate was taken in a test tube and was diluted with 100 ml of buffer solution. Absorbance of the sample was determined at 220nm wavelength [7].

$$\%\text{Potency} = \frac{\text{Conc(mg./ml)} \times \text{dilutionfactor} \times \text{totalvolume} \times \text{Avg.wt} \times 100}{\text{sampletaken} \times \text{Strenght}}$$

Dissolution Test

About 900ml of buffer media was filled into 1000ml beaker of dissolution apparatus. One Clopidogrel tablet was placed into each beaker. 37˚C i.e. body temperature & 50rpm i.e. rotation per minute was adjusted & then motor was started. 10ml solution was withdrawn from beaker at 10, 15, 30, 45, 60 minutes interval which was replaced with 10ml media & then withdrawn solution was immediately filtered The withdrawn solution of Clopidogrel tablet was 5 times diluted & absorbance was measured at 220nm by using UV spectrophotometer. Finally the percent release of Clopidogrel tablet was determined by following equation [8].

% of release = drug cont. (mg) x100/ strength (mg)

Results and Discussion

Weight Variation Determination

Tablet weight is mainly affected by factors such as tooling of the compression machine, head pressure, machine speed and flow properties of the powder. Inconsistent powder or granulate density and particle size distribution are common sources of weight variation during compression. According to USP 29 specification for uniformity of weight which states that tablets weighing 324 mg or more, weights of not more than 2 tablets should not differ from the average weight by more than 5% The tablets of nine brands undergo this test to assure their uniformity of weight except brand M1, M2, M3 and M4 according to USP specifications [9] (Table 1).

Tablet	Potency (%)	Weight variation
M1	100±5.00	340.65±7.01
M2	97.3±5.23	334.4±11.55
M3	88.35±8.38	218.2±5.58
M4	105±7.07	256.9±8.54
M5	93±5.23	217±3.05
M6	97±5.29	269.1±4.51
M7	94.33±5.97	328.7±6.01
M8	99.17±5.02	254.45±4.98
M9	96.35±5.50	255±4.50

Table 1: potency and weight variation of different brands of clopidogrel tablet collected from local market in Bangladesh.

Hardness Test

Hardness was monitored using a Automatic Tablet hardness and the result is tabulated at Table 2 and figure 3. Hardness specification according to USP, 2008 is not more than 5-8.0 $kg.cm^{-1}$(1kg= 10 N). Only M4 and M8 cross the specification.

Friability Test

It is the tendency for a tablet to chip, crumble or break following compression. This tendency is normally confined to uncoated tablets and surfaces during handling or subsequent storage. The USP specification for friability test is 1% [10]. It was monitored that nine different brand of clopidogrel tablets were in accordance with USP guideline (Table 2).

Tablets	Hardness(N)	Friability (%)	Disintegration time (min)
M1	125±4.95	0.168	14.52±0.21
M2	51.66±3.03	0.169	2.46±0.13
M3	64.33±7.34	0.589	10.14±0.34
M4	84±5.09	0.443	1.76±0.37
M5	36±2.44	0.392	1.56±0.52
M6	50.67±2.05	0.318	1.06±0.03
M7	45±4.98	0.262	3.88±0.15
M8	102±3.74	0.452	2.68±0.14
M9	79±7.77	0.280	3.77±0.25

Table 2: Average drug release (%) of nine different brands of clopidogrel tablets.

Disintegration Test

Disintegration tests are performed as per the pharmacopoeia standards. Disintegration is a measure of the quality of the oral dosage form like tablets and capsule pharmacopoeia like the USP, BP, IP etc. each have their

own set of standards and specify disintegration tests of their own. The disintegration test is performed to find out the time it takes for a solid oral dosage form like a tablet or capsule to completely disintegrate. The time of disintegration is a measure of the quality. This is because, for example, if the disintegration time is too high; it means that the tablet is too highly compressed or the capsule shell gelatin is not of pharmacopoeia quality or it may imply several other reasons. And also if the disintegration time is not uniform in a set of samples being analyzed, it indicates batch inconsistency and lack of batch uniformity. According to USP, 2013 the specification of disintegration time requirements 5 to 30 minutes. All the tablets that have been tested are within the limit [11] (Table 2).

Potency Test

Potency of all brands was found within 95.34–103.65%.USP specification for the drugs are equivalent to not less than 95.0 % & not more than 105.0 %. Six brands are within the limit of potency according to the USP specification (Table 1).

Dissolution Test

Dissolution is a test used by the Pharmaceutical industry to characterize the dissolution properties of the active drug, the active drug's release and the dissolution from a dosage formulation. Dissolution testing is used to formulate the drug dosage form and to develop quality control specifications for its manufacturing process. The USP specification of Clopidogrel is not less than 75% of the labeled amount dissolved in 45 minutes [12]. It is seen from the result that all brand of Clopidogrel tablets meet the specification (Table 3).

Time (min)	% of Drug Release								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
0	0	0	0	0	0	0	0	0	0
5	30.92±0.15	34.14±0.39	30.92±0.25	26.34±0.45	26.34±0.23	24.31±0.14	20.89±0.32	24.18±0.23	21.92±0.68
15	49.67±0.12	47.67±0.13	46.45±0.21	39.32±0.43	39.32±0.35	38.32±0.15	40.82±0.64	42.50±0.65	41.37±0.55
30	55.73±0.42	61.81±0.48	53.28±0.25	60.56±0.46	60.56±0.45	63.69±0.55	66.12±0.26	55.67±0.78	61.72±0.44
45	72.01±0.67	75.97±0.42	71.31±0.35	83.12±0.55	83.12±0.46	82.33±0.65	83.64±0.75	79.86±0.67	77.50±0.65
60	96.17±0.53	98.57±0.49	96.06±0.54	92.46±0.43	92.46±0.21	100.47±0.54	96.74±0.45	97.11±0.65	97.03±0.54

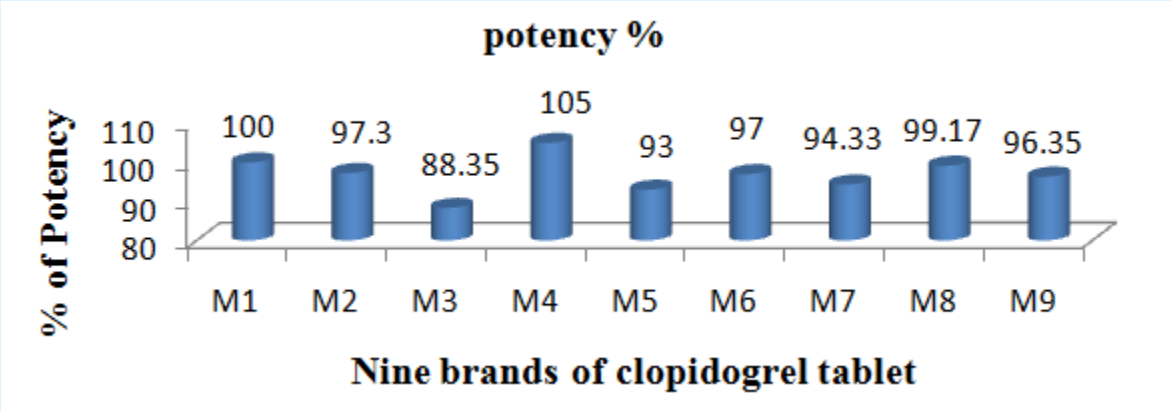

Figure1: Determination of potency of nine brands of clopidogrel tablet.

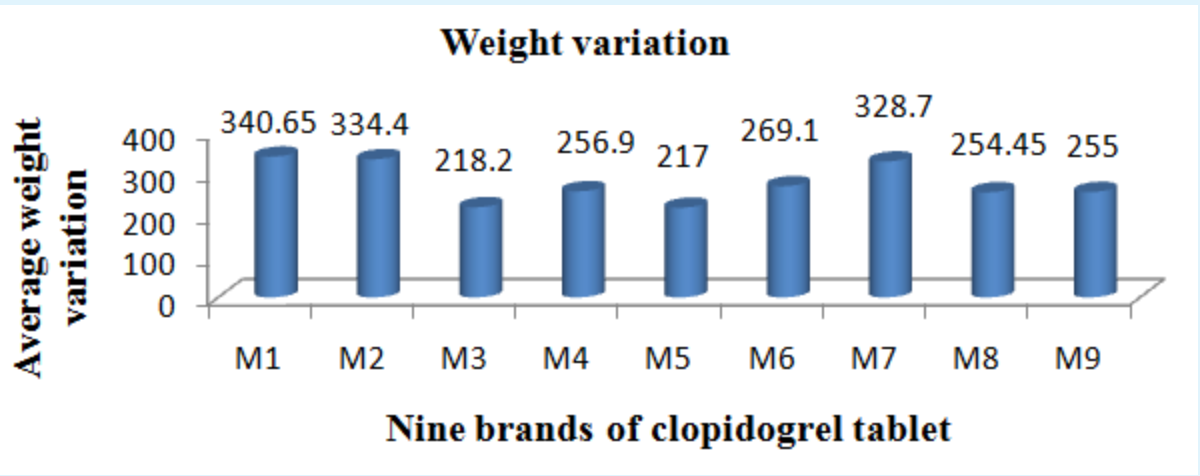

Figure 2: Average weight variation of nine brands of Clopidogrel tablet.

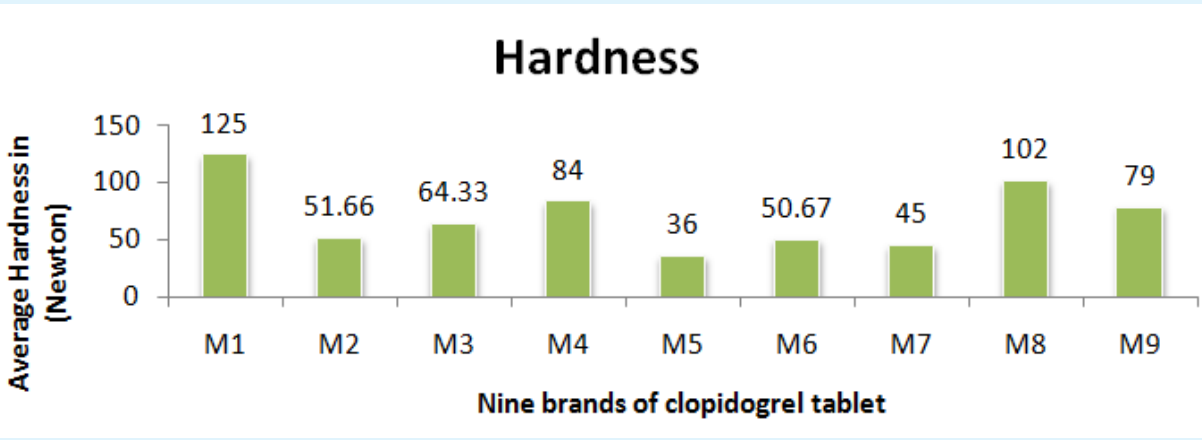

Figure 3: Average hardness of nine brands of Clopidogrel tablet.

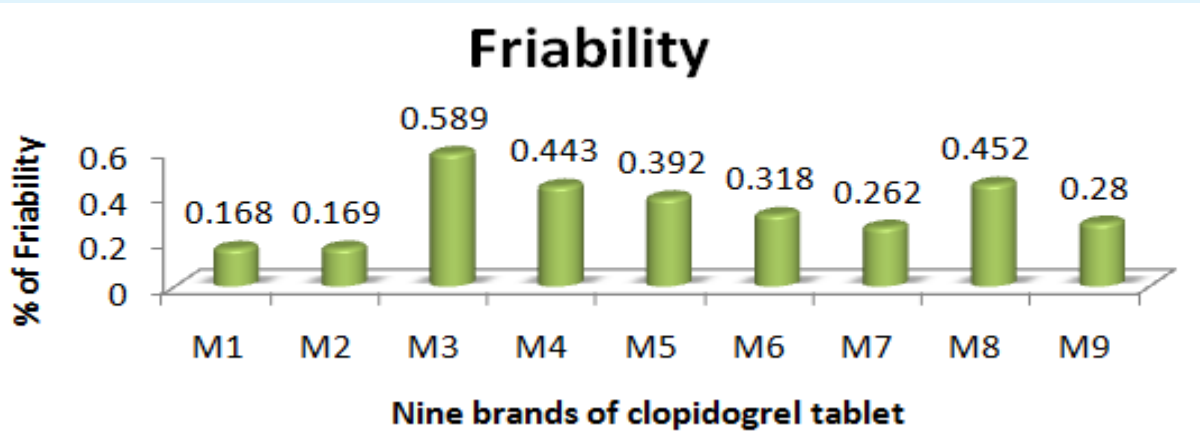

Figure 4: % Friability of nine different brands of clopidogrel tablets.

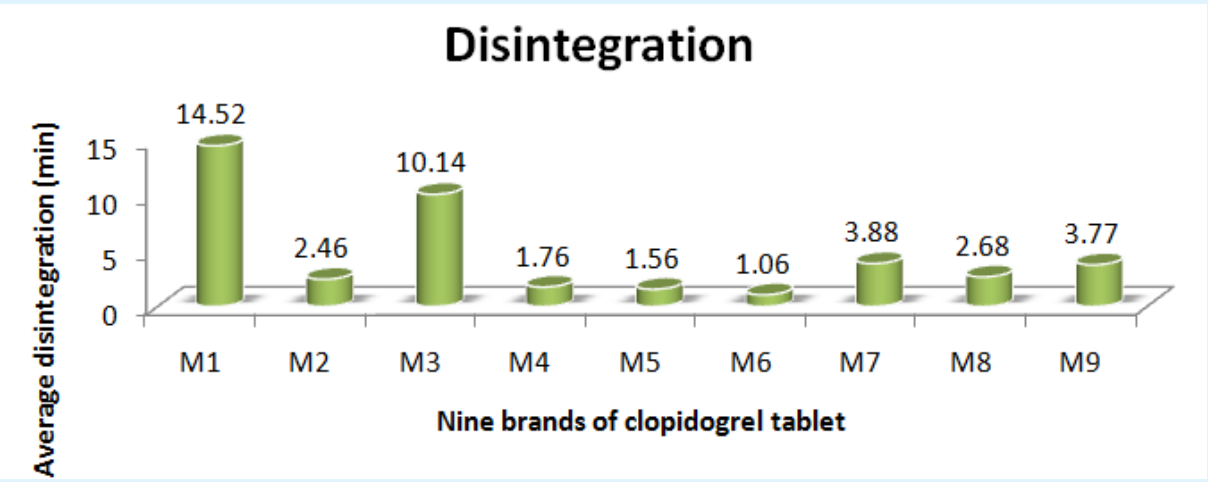

Figure 5: Disintegration time of nine different brands of clopidogrel tablets

Time (min)	% of Drug Release								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
0	0	0	0	0	0	0	0	0	0
5	30.92±0.15	34.14±0.39	30.92±0.25	26.34±0.45	26.34±0.23	24.31±0.14	20.89±0.32	24.18±0.23	21.92±0.68
15	49.67±0.12	47.67±0.13	46.45±0.21	39.32±0.43	39.32±0.35	38.32±0.15	40.82±0.64	42.50±0.65	41.37±0.55
30	55.73±0.42	61.81±0.48	53.28±0.25	60.56±0.46	60.56±0.45	63.69±0.55	66.12±0.26	55.67±0.78	61.72±0.44
45	72.01±0.67	75.97±0.42	71.31±0.35	83.12±0.55	83.12±0.46	82.33±0.65	83.64±0.75	79.86±0.67	77.50±0.65
60	96.17±0.53	98.57±0.49	96.06±0.54	92.46±0.43	92.46±0.21	100.47±0.54	96.74±0.45	97.11±0.65	97.03±0.54

Table 3: Average drug release (%) of nine different brands of clopidogrel tablets.

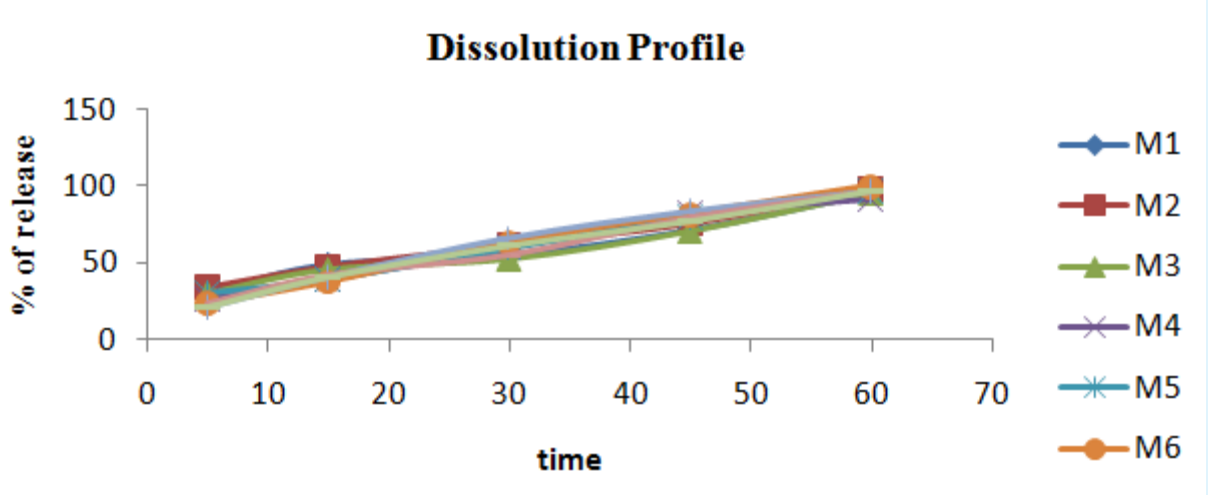

Figure 6: Dissolution profile of nine different brands of clopidogrel tablets.

Conclusion

Overall quality of a pharmaceutical product depends on control of impurities, presence of therapeutic agent that developed potency, safety and efficacy of the drug. A quality product gives not only better therapeutic efficacy but also gives consumer satisfaction and increases its market demand. In the current industrial practice, to compare with the multi brand generic molecules and to provide enough therapeutic activity of the dosage form, *in-vitro* tests play a significant role. In this study we discussed about some quality test such as weight variation, hardness, friability, disintegration time, potency and dissolution test for clopidogrel tablet. Clopidogrel tested tablet have uniform weight and also sufficient physical stability to maintain physical integrity over time and they will also be capable of withstanding the stiffness of mechanical shocks confrontation in its production, packaging, shipping and dispensing.

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