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Comparative Evaluation of Some Commercial Clopidogrel Tablets Available in Yemen

Bassam Abduh Ali[1]*, Mohammed Gameel Al-haddad[2], Abdullah Ahmed Areqi[3]

1. Department of Pharmaceutics, Faculty of Pharmacy, University of Science and Technology, Taiz Branch, Yemen
2. Department of Pharmaceutics, Faculty of Pharmacy, University of Science and Technology, Hodaidah Branch, Yemen
3. Department of Pharmacology, Faculty of Pharmacy, University of Science and Technology, Hodiadah, Yemen

Corresponding author: Bassam Abduh Ali: Email: bassam00001@yahoo.com

ABSTRACT

Clopidogrel is a medication to reduce the risk of heart disease and taken orally. Quality of drug characterizes the production process and every phamaceutical company strives for it but often it is very difficult to achieve. This study was to investigate quality control parameters of some marketed Clopidogrel tablets. To assess the quality, eight different marketed brands of Clopidogrel 75 mg tablets available in Yemeni market collected from different pharmacies in Hodeida city. Different quality parameters like weight variation, hardness, thickness and friability were determined according to established protocols. Then the in-vitro dissolution test, potency, disintegration time were also carried out. UV-spectrophotometer was used to determine the percentage released and assay at 218 nm. All the brands comply the requirements of Pharmacopoeia as they showed acceptable weight variation range. Friability of all brands was less than 1% and no significant differences in disintegration times as they disintegrated within 15 minutes. In case of dissolution profile, all brands except C6 showed acceptable dissolution time as they released more than 60% of drug in 45 minute. The hardness of only two brands was within the range. All brands also meet the potency specifications. This study suggested that most commercially Clopidogrel tablets in Yemen maintain the quality and comply with the pharmacopeia specifications.

Keywords: Clopidogrel, Physicochemical, Dissolution profile, Potency.

INTRODUCTION

Quality of a product is an important factor in supporting the marketing of commercial drug products as well as patient compliance. Quality assurance processes may range from the performance of simple chemical experiments, which determine the identity and screening for the presence of particular pharmaceutical substance to more complicated requirements of pharmacopoeial monographs. It can be achieved by following some parameters that are specified in the respective monograph of the drug (Hasan *et al.*, 2013). United States of Pharmacopeia and British Pharmacopeia are such two Pharmacopeias that provide the necessary specifications.

Quality is essential for the survival and growth of the organization and customer satisfications. As a result, there will be development of belief on the customer's mind about the product of that company which is an important criterion for the survival and growth of the organization (Nasrin *et al.*, 2011). If the quality of the product is low then there will be increased return of the product from the market and then profitability and customer

loyalty are decreased (Lamba *et al.*, 2010). There are two types of tests, compendial and non-compendial tests (Anderson *et al*., 2009; Yarkala *et al.,* 2012).

Clopidogrel is a novel thienopyridine inhibitor of adenosine diphosphate (ADP)–induced platelet activation as in figure (1). Clopidogrel is a routine component of the clinical management of patients after acute coronary syndrome. It is approved for the reduction of atherosclerotic events in patients with stroke, myocardial infection, cardiovascular disease and acute coronarysyndrome (Yarkala *et al*., 2012).

The objective of this study is to ensure conformity of quality for some different commercially available brands of Clopidogrel tablets in Yemeni market, to ensure the significant difference between expensive and economic product through effectiveness. This study is also conducted to obtain a brief idea about physico-chemical parameters of those brands.

METHODS

Standard Clopidogrel powder was kindly supplied as a gift from Bio-pharm (Yemen). The eight brands Clopidogrel tablets were purchased from different pharmacies in Hodeida city in Yemen.

Recruitment of sample product

The available marketed samples of eight brands (more than 20 tablets of each brand) of Clopidogrel tablet were purchased from different retail pharmacies at Hodeida city in Yemen. These tablets of eight brands were coded as C1, C2, C3, C4, C5, C6, C7 and C8. The samples were checked for their physical appearance, name of manufacturer, batch number, and manufacturing date, expiry date, manufacturing license number and maximum retail price at the time of purchase.

Evaluation of the selected products thickness and diameter measurement

Thickness and diameter of 10 tablets formulations were measured using thickness micrometer (GT.Tools, India) and mostly (2 – 4)mm (Gunda, 2015).

Hardness test

The crushing strength of the tablet was measured using automatic hardness tester (LIH-1, USA). At first 10 tablets were picked randomly from 20 tablets. Force has been applied with the screw thread and spring until the tablets has been fractured (Kamal, 2012).

Friability test

Friability test to evaluate the ability of tablet to withstand abrasion during packaging, handling & transporting. Twenty Clopidogrel tablets were taken randomly & weighted together. Clopidogrel tablets were then placed into the friability tester (PTF 10E,Germany), subjected to 100 rpm for 1 minute (25 rpm for 4 minutes) and were re-weighted. The loss of weight indicates the friability and the percent of weight loss was calculated (Gomez *et al*., 2004).

Weight variation test

For each brand, 20 tablets were randomly and weighted individually using an analytical balance and the average weights were then determined (Chouhan *et al*., 2016).

Disintegration test

The disintegration test is carried out in an apparatus (PTWS 100D, Germany) containing a basket rack assembly with six glass tubes of 7.75 cm in length and 9 mm in diameter, the bottom of which consists of a (#10) mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml phosphate buffer PH=6.8 which is maintained at 37±2 °C. Six tablets were placed in each of the tubes and

the time required for complete passage of tablet fragments through the mesh was considered as the disintegration time of the tablet (Gibson, 2001; Monographs, 2002).

Potency test

Dissolve an accurately weighed quantity of Clopidogrel reference in 0.1 N HCl to get 0.0075 mg/ml solution of Clopidogrel determined λ_{max} (Rao *et al.,* 2014). Then 4 tablets of Clopidogrel were grinded and then transferred 75 mg ,add about 100 ml of 0.1 N HCL and stir for about 20 minutes to dissolve , filter the solution and diluted and then absorbance was measured at 218 nm (Suhas *et al.,*2011). The percentage of drug content was calculated according to standard calibration curve (Cazedey *et al.,* 2012).

Dissolution and drug release

The experimental conditions are, medium is phosphate buffer solution pH 6.8, apparatus is paddle method (USP apparatus I, Erweka TD6R, Germany) and the temperature is kept constant 37± 2ºC. Dissolution test was carried out using 900ml of phosphate buffer solution at a paddle speed of 50 rpm for 45 minutes. The samples (5 ml) were taken at 0, 5, 15, 25, 35 and 45 minutes interval, filtered and diluted suitably; it was replaced by same amount of the fresh medium each time. Absorbance of the resulting solution was measured 218 nm against phosphate buffer solution pH 6.8 as a blank. The amount of released drug was calculated using standard calibration curve (USP, 2004).

Data analysis

All determinations and calculation in the study were carried out with the use of a Microsoft Excel 2010.

RESULTS AND DISCUSSION

Thickness and diameter

Thickness of the tablet is inversely proportional to hardness i.e. increase in the thickness decrease hardness & *vice versa*. Very thick tablet affects packaging either in blister or plastic container. In general, thickness and diameter are controlled within 5 percent of average value (USP, 2004). So, from the results of the thickness of the different tablet brands it was observed that all the tested tablets had deviation less than 5% and they were uniform in their thickness and acceptable limit (Table I) and (Figures 2 and 3).

Hardness test

If the tablet is too hard, it may not disintegrate in the required period and if it is too soft, it will not withstand the handling during subsequent processing such as coating or packaging and shipping operations (*Gupta KA et al., (2010)*. Hardness was monitored using an automatic tablet hardness tester and the results were tabulated (Table I) and (Figure 4). Hardness range specification is (5-8) kgs (USP, 2016). Only three brands C1, C3 and C6 fulfill the specification of this test by the average value of hardness (5.87 ± 0.229), (5.86 ± 0.366) and 4.87 ± 0.531 respectively that were within the acceptable range.

Friability test

The USP specification for friability test is 1% (Nushrat *et al*., 2017). It was monitored that eight different brands of Clopidogrel tablets were in accordance with guideline (Table I) and (Figure 5).

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. Weight variation test was done to check the uniformity of contents and active ingredients so that a uniform product can be guaranteed with an elegant appearance. The tested tablets showed uniformity of weight except brand C3 and C7 that were out the within the compendia limit

Table I. Hardness, Friability, Thickness and Diameter results of different brands of Clopidogrel tablets

Tablet code	Hardness (Kg) ±SD	Friability (%) ±SD	Thickness (mm) ±SD	Diameter (mm) ±SD
C1	5.87 ± 0.229	0.045 ± 0.029	4.48 ± 0.028	8.65 ± 0.006
C2	3.39 ± 0.114	0.067 ± 0.102	3.19 ± 0.065	8.08 ± 0.022
C3	5.86 ± 0.366	0.036 ± 0.019	4.65 ± 0.182	10.31 ± 0.045
C4	2.91 ± 0.316	0.371 ± 0.102	3.12 ± 0.020	7.89 ± 0.042
C5	3.66 ± 0.135	0.198 ± 0.097	2.56 ± 0.056	6.56 ± 0.016
C6	4.87 ± 0.531	0.061 ± 0.076	4.33 ± 0.101	8.22 ± 0.043
C7	2.09 ± 0.312	0.380 ± 0.110	2.06 ± 0.023	8.21 ± 0.049
C8	3.71 ± 0.396	0.082 ± 0.068	4.47 ± 0.022	8.64 ± 0.011

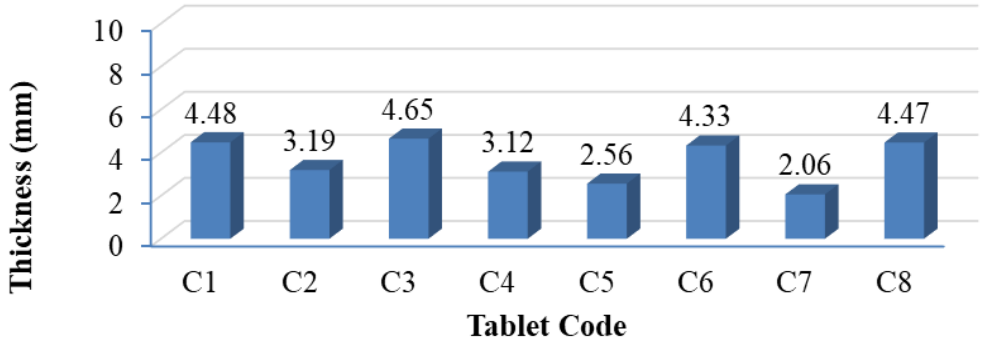

Figure 2. Thickness measurements of different brands of Clopidogrel tablets

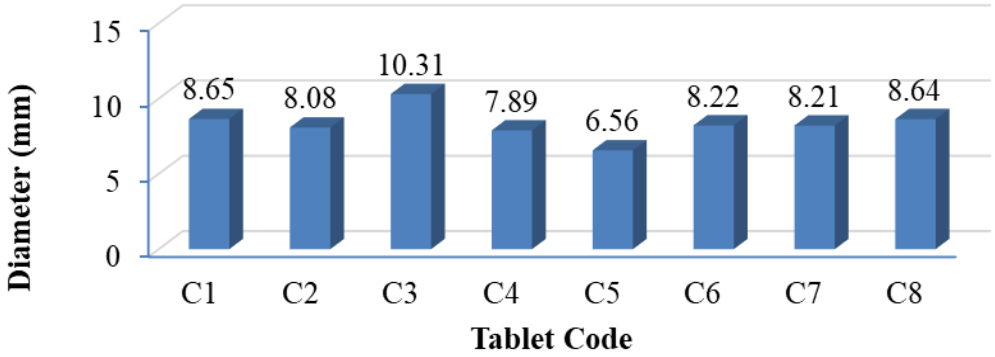

Figure 3. Diameter measurements of different brands of Clopidogrel tablets

according to USP specifications (Table II) and represented in (Figure 6) (*Kishore et al.,* 2013).

Disintegration test

Disintegration test is very important for tablet because the dissolution rate of drug depends on it, which ultimately affect the rate of absorption of drug (Kumar *et al*., 2013). 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, the specification of disintegration time requirements 5 to 30 minutes (Table II) and (Figure 7), it was noticed that all the tablets

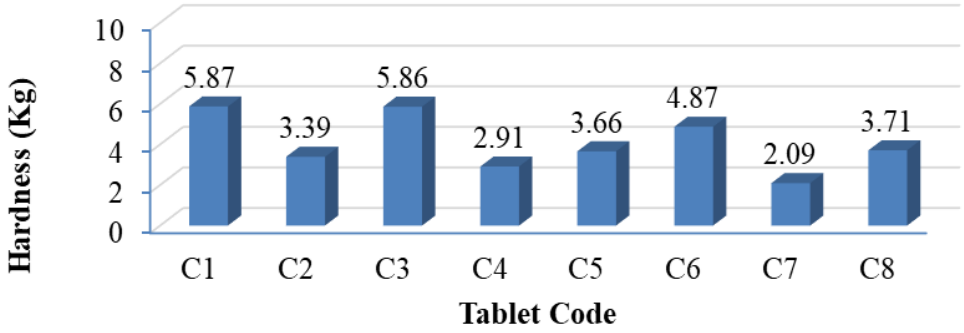

Figure 4. Hardness data of different brands of Clopidogrel tablets

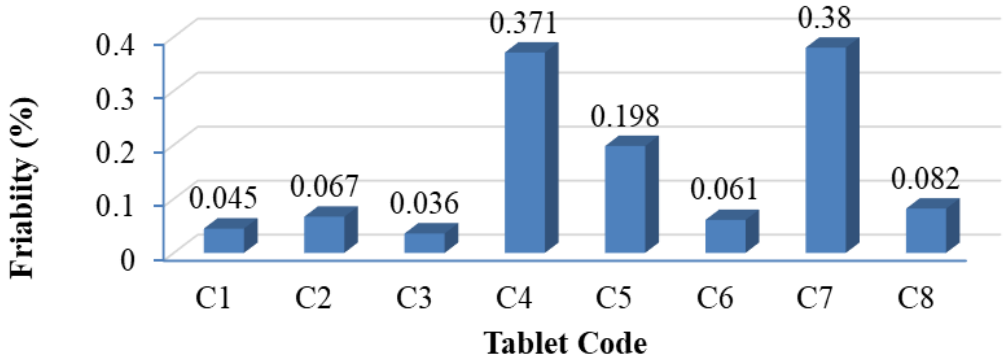

Figure 5. Friability data of different brands of Clopidogrel tablets

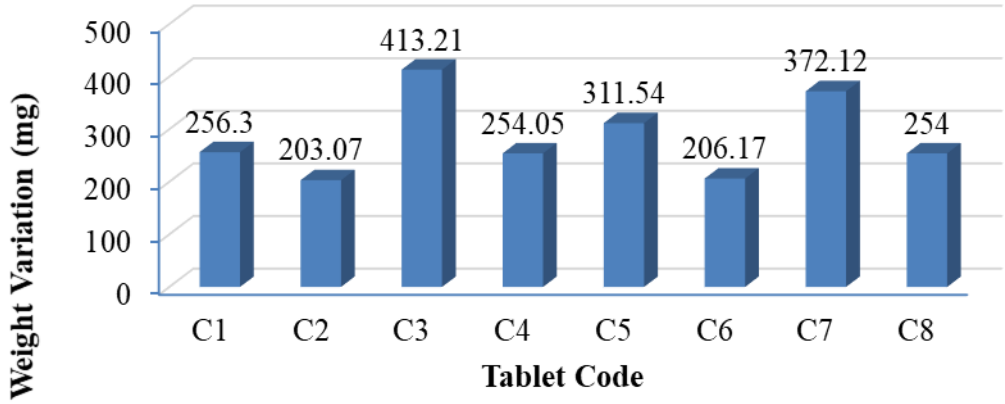

Figure 6. Weight variation of different brands of Clopidogrel tablets

of different brands that have been tested are within the limit.

Potency test

The percentage content of Clopidogrel tablet should comply with the specification because very highly potent drug may give toxic effect and very less potent drug may give sub-therapeutic effect. Potency of all brands was found within 85.34 ± 0.03 – 130.05 ± 0.02 %. USP specification for the drugs are equivalent to not less than 95.00 % and not more than 105.00 %. Only three brands are within the limit of potency according to the USP specification that were C1, C5 and C6

Table II. Weight variation, Potency and Disintegration time of different brands of Clopidogrel tablet

Tablet code	Weight variation (mg) ± SD	Potency (%)±SD	Disintegration time (min) ± SD
C1	256.30 ± 4.17	96.10 ± 0.05	13.30 ± 1.19
C2	203.07 ± 3.32	130.05 ± 0.02	5.42 ± 0.24
C3	413.21 ± 6.77	107.21 ± 0.07	2.14 ± 0.77
C4	254.05 ± 3.65	85.34 ± 0.03	6.21 ± 0.92
C5	311.54 ± 6.62	96.21 ± 0.06	8.06 ± 1.33
C6	206.17 ± 5.91	103.87 ± 0.09	2.45 ± 0.56
C7	372.12 ± 5.89	112.04 ± 0.10	7.22 ± 1.04
C8	254.00 ± 4.29	115.11 ± 0.03	12.01 ± 1.17

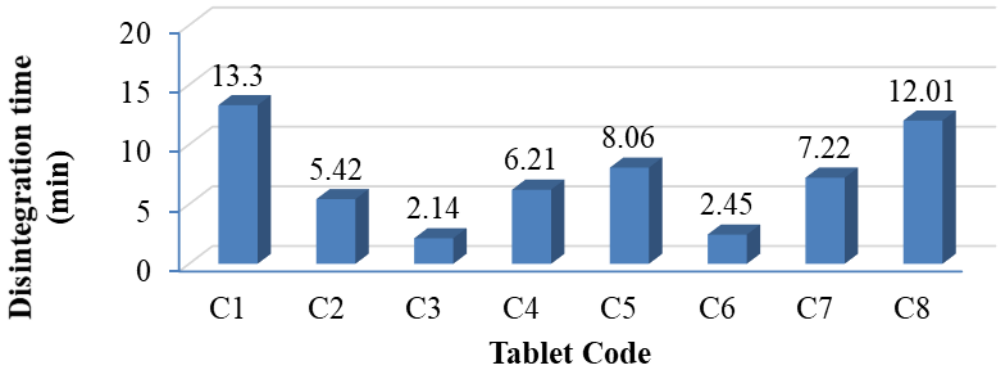

Figure 7. Disintegration time of different brands of Clopidogrel tablets

as observed (Table II) and (Figure 8).

Dissolution test

The drug release study is a measure of the amount of the drug released into the dissolution medium over time. This study gives an idea of amount of drug available for absorption after oral administration

The results of the in vitro release of branded tablets (Table III) and (Figure 9). By the end (45 minutes) of the in-vitro release test, the percentage drug released for brands C1, C2 , C3, C4, C5, C6, C7, and C8 was found to 104.01, 75.21, 88.53, 65.00, 72.00, 39.56, 60.06 and 115.00 % respectively. The USP specification of Clopidogrel is not less than 60% of the labeled amount dissolved in 45 minutes.

The results obtained from the study revealed that all the brands released the drug more than 60% except C6 that not passed this test.

Table IV showed the rank order of branded tablets according to quality control tests. From this table the brands of Clopidogrel tablets can be arranged in a descending manner as shown.

CONCLUSION

All the tested brands of Clopidogrel 75 mg tablets complied with the official quality specifications. By comparing the quality results, the best brand was C1 while C7 was the worst. Clopidogrel tested tablet have uniform weight and also sufficient physical stability to maintain physica

Table III. In vitro release profile for different brands of Clopidogrel 75 mg tablets

Time (min)	Percent of drug release (%) ±SD							
	C1	C2	C3	C4	C5	C6	C7	C8
0	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00
5	30.21± 0.54	13.74± 1.23	19.93± 1.12	15.09± 0.76	18.05± 1.05	06.06± 1.13	14.93± 0.87	25.07± 0.32
15	52.51± 2.17	28.56± 3.21	35.45± 2.45	28.42± 0.55	35.12± 2.73	17.94± 1.09	25.08± 0.65	65.76± 0.54
25	73.37± 3.90	45.23± 0.98	52.67± 0.87	38.21± 0.34	40.42± 1.05	22.08± 2.11	37.11± 1.21	86.33± 0.34
35	89.61± 2.13	62.05± 3.09	71.32± 1.43	46.06± 0.21	57.23± 0.87	30.43± 1.97	45.43± 3.08	97.06± 2.06
45	104.01± 0.12	75.21± 0.22	88.53± 0.34	65.11± 0.98	72.90± 0.97	39.56± 0.70	60.06± 2.06	115.00± 0.03

Table IV. Rank order of branded tablets according to quality control tests

Test	C1	C2	C3	C4	C5	C6	C7	C8
Weight variation	3	1	8	2	7	6	5	4
Thickness	4	6	8	1	5	7	3	2
Diameter	1	4	7	5	3	6	8	2
Hardness	1	6	2	7	5	3	8	4
Friability	2	4	1	7	6	3	8	5
Disintegration	8	3	1	4	6	2	5	7
Dissolution	2	4	3	6	5	8	7	1
Total rank order	21	28	30	32	37	35	44	25
Conclusive rank order	1	3	4	5	7	6	8	2

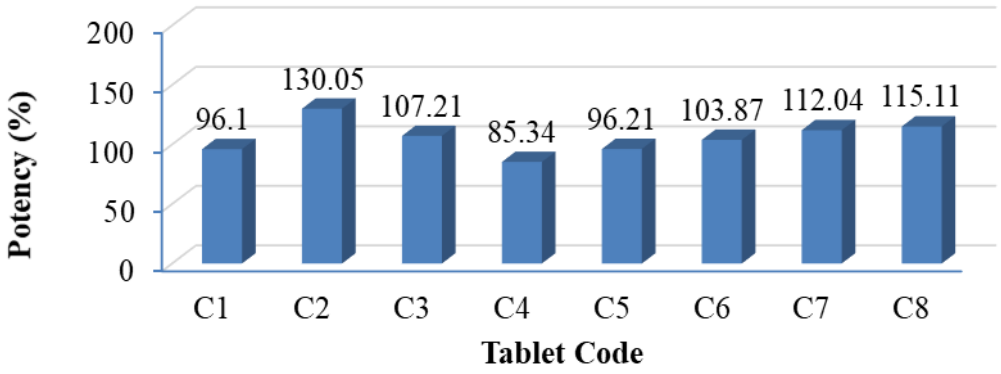

Figure 8. Potency of different brands of Clopidogrel tablets

integrity over time and they will also be capable of with standing the stiffness of mechanical shock confrontation in its production, packaging, shipping and dispensing. It also concluded that all most products passed the pharmacopeial specifications with different levels.

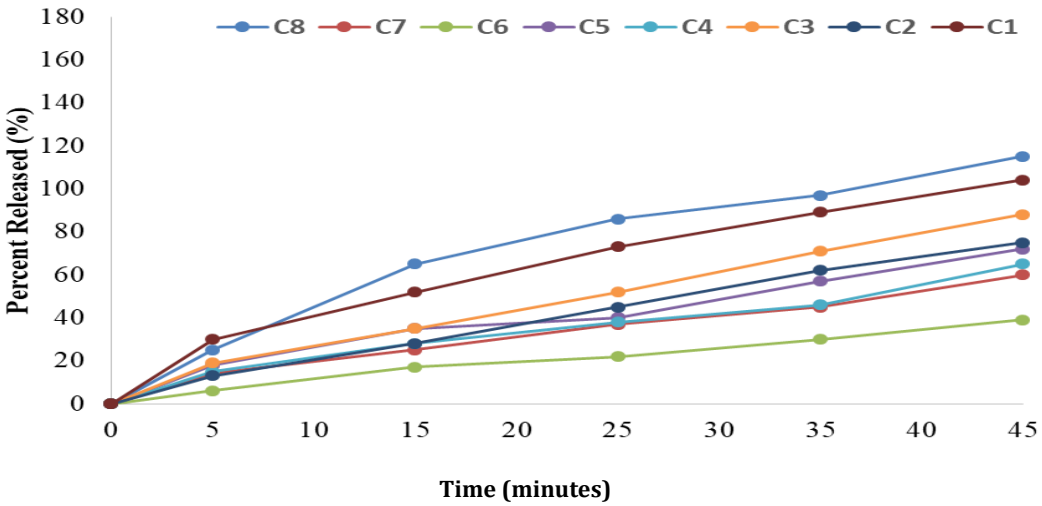

Figure 9. In vitro release profile for different brands of Clopidogrel 75mg tablets

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