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In-vitro Pharmaceutical Quality Control Testing: a Comparative study of Different Brands of Metformin Tablets Available in the Trinidad & Tobago, West Indies

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Abstract

Metformin tablet is used in type-2 diabetes to control the blood sugar level and it is widely available in the Pharmaceutical market of Trinidad. The objective of this study was to compare the quality of the metformin tablet formulations those are locally available in Trinidad & Tobago pharmaceutical market manufactured by various pharmaceutical companies with pharmacopoeia standards. The four popular brands (A, B, C, D) of metformin conventional tablet of 500 mg strength were chosen. The metformin tablets were obtained from government hospital pharmacies as well as from local private pharmacies. To compare the quality of tablet formulations of different brands various official parameters like friability, weight variation, disintegration time, dissolution and drug assay tests were performed as per the pharmacopoeia. The result of all these parameters of different brands were in the pharmacopoeial limits so it could be concluded that marketed pharmaceutical tablets of metformin of these brands are safe, effective and efficacious as well as satisfy quality control limits of pharmacopoeia.

Keywords-Metformin, Friability, Disintegration Time, Dissolution, weight variation, drug assay.

INTRODUCTION

Metformin is a first-line therapy for type 2 diabetes mellitus (T2DM, formerly 'non-insulin-dependent diabetes mellitus'), and is one of the most commonly prescribed drugs worldwide. As a biguanide agent, metformin lowers both basal and postprandial plasma glucose. Chemically it is N,N-dimethylimidodicarbonimidic diamide hydrochloride and it is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula is as shown in Fig 1:

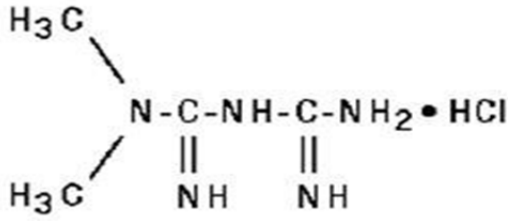

Fig. 1. Metformin hydrochloride chemical structure

The safety, effectiveness and efficacy of pharmaceutical dosage form can be guaranteed when its quality is reliable and to confirm the quality of pharmaceutical dosage form it is required to perform the evaluation tests as per the official books like USP, BP, IP, EP etc [1-5].

For the conventional tablets weight variation, friability, disintegration, dissolution, drug assay, uniformity of contents are the evaluation test those are required to perform to confirm about the quality of tablet.

Friability is the tested for a tablet to see whether the tablet is stable to abrasion or not, it is tested by using Roche friabilator and 1% maximum loss in the weight after friability test is allowed.

Weight variation test is performed to check that the manufactured tablets have a uniform weight. As per USP following limit for the tablets (table 1)

Table 1. Weight variation test limit as per USP

Average weight (mg)	Maximum percentage difference allowed
130 or less	±10
130-324	±7.5
More than 324	±5

Disintegration test is performed to see how much time a tablet takes to break down in to the small particles as this is first step before the drug dissolution in the body. The condition of this test should be same like in the body as this is the part of *In-vivo-In-vitro* correlation.

The dissolution test provide the information about the drug release pattern and it is close proximate to bioavailability so it gives the information about the safety and efficacy of the dosage form. The drug assay study provide the information how much practically available in the given dosage form and after comparing with the theoretical value, a result about the efficacy can be given [5-7].

MATERIALS AND METHODS

Four different brands of metformin hydrochloride tablets were obtained from the Pharmacy of Eric Williams Medical Science Hospital, Mount hope and some from the local private pharmacies. The metformin hydrochloride pure drug powder purchased from the Sigma eldritch and other solvents purchased from the local market of AR grade.

For weighing ADAM AFA-120 LC balance was used. To measure the pH of solutions OAKTON pH meter was used,

Maxi Mix –II was used for mixing purpose, Electrolab EF-2 was used for friability testing, Electolab ED-2L was used for disintegration process, Electolab EDT- 08Lx was used for the dissolution study and for UV-Visible spectrophotometer analysis Agilent 8453 instrument was used.

The different brands of metformin tablets those are available in the Trinidad local market were given their code A, B, C, D.

Weight variation test: The purpose of this test is to verify the uniformity of each batch which ultimately reflect the drug content uniformity in all the formulation batches. The test was performed as per the official procedure, 20 tablets were randomly selected and weighed individually and also average weight was calculated. The difference between average and individual weight was calculated, further % weight variation was calculated and compare with the USP limits [5-8].

Friability test: This test is usually performed to check possible wear and tear loss in the tablet during the transportation and this is closely related to tablet hardness. It is usually performed in the Roche Friabilator. Randomly 10 tablets were selected and their initial weight (W1) was recorded and after that these weighed 10 tablets were placed in the friabilator and the friabilator was operated for four minutes at 25 rpm speed and 100 revolutions, the tablets were weighed again (W2) and the percent loss (Friability) was then calculated by using following formula

$$\% \text{ Friability} = \frac{(W1 - W2)}{W2} * 100$$

The official permissible limit for friability is 1% [5-8].

Disintegration test: Disintegration is the process of breaking the tablet in to the small granules and it is prior step of drug dissolution and it is the part of *In-vitro- In vivo* correlation so the disintegration test determine the time required to breaking the tablet and pass all the particle from mesh size 10. USP disintegration apparatus (Electolab ED-2L) containing six glass tubes was used for the purpose. The disintegration test was performed as USP and to determine the disintegration time, one tablet of metformin was placed in each tube and the basket rack is positioned in a 1L beaker containing distilled at 37±2°C temperature. The instrument was operated with a motor driven device with 28-32 cycle/min frequency. When all the particles from all the six tubes passed from the tube mesh to the outer beaker that time was noted as disintegration time after that the average time was noted and this process was repeated for all four different brands of metformin tablets. For the uncoated tablet the disintegration time limit is 15 minutes [8-10].

Dissolution test: Dissolution test is close proximate to the bioavailability this is the reason it is required to perform to confirm drug release pattern of the dosage form as well as efficacy of dosage form. This test is the part of *In-vitro-In-vivo* correlation so all the parameters of this test was set as per the *In-vivo* condition of human body. The dissolution test was performed by using Dissolution Tester-USP (Electrolab EDT- 08Lx) of type 2. To determine drug release 900 ml of phosphate buffer, pH 6.8 was used as dissolution medium. The 5, 10, 15, 30, 45, 60 minutes were set as a sampling time. The dissolution medium was heated up to 37±0.5°C by an auto heater. One tablet was put into all six baskets and stirred immediately at 100 revolutions per minute (rpm). After specified time intervals the 5 ml solution was withdrawn, diluted it with fresh solvent and the amount of dissolved metformin was determined from UV-Visible spectrophotomter (Agilant 8453) by taking absorbance at the wavelength of maximum absorbance at about 233 nm in comparison with a standard metformin solution in the same medium (Phosphate buffer pH 6.8). By measuring the absorbance, the percentage (%) of drug release was calculated [5,6]

Drug Assay: This is required to confirm that the labelled amount of drug is available in the given dosage form. To perform this test ten metformin tablets were selected randomly and crushed them in the mortar and powder was made. The equivalent powder containing about 10 mg drug was taken in the beaker and dissolved in 100 ml of distlled water. The mixture was made uniform by the help of Maxi Mix-II instrument. About 1 ml solution was taken, diluted it upto 10 mL and absorbance at the wavelength of maximum absorbance at about 233 nm by measured by the help of UV-Visible spectrophotomter. The available amount was calculated by using the standard calibration curve [5, 6, 10]

RESULT AND DISCUSSION

After the randomly selection of tablets the weight variation, friability, drug assay, disintegration and dissolution test were performed as per the United States Pharmacopoeia procedures [5].

The result of weight variation of twenty randomly selected tablets are given in table 2 &3 and figure 2.

As per the USP the weight variation limit for the tablet which is having the weight equal or more than 324 mg is 5 % and the given results shown that all the twenty randomly selected tablets (average weight is more than 324 mg) of all four brands are having weight variation less than 5 % which proves that the four brands (A, B, C, D) of metformin tablets those are available in the Trinidad pharmaceutical market passed the official weight variation test.

The friability test was conducted in Roche friabilator by using 10 tablets, the results of all different brands are given in the tablet 4 and figure 3.

The results of friability test shows that all the four brands of metformin tablets are under the pharmacopoeia limits (1%) means all these brands of metformin tablets those are available in Trinidad pharmaceutical market are having good strength and can tolerate the shocks during transportation handling of these tablets.

The disintegration test was performed in the distilled water at 37 ±2°C in the Electrolab ED-2L instrument. The results of all four brands are given in table 5 and figure 4.

The results of disintegration test shows that the disintegration time of all four different brands of metformin tablet is less than 10 minutes which is less than the standard disintegration time (15 minute) for uncoated tablet that proves all these brands of metformin tablet passes the quality control limits as per the pharmacopoeia. The brands C disintegration time is about 2 min 38 sec means it disintegrates very fast so it might be possible that the drug from this brands will be available very fast for absorption as well as the onset of time will be very less.

To confirm the amount of metformin drug in the tablet drug assay was performed for all four different brands, the results are given in the table 6 and figure 5.

The results of drug assay of four different brands of metformin tablets shows that amount of metformin drug available in all these formulation is near to 100 % means drug are available as per their stated value and the dosage form is in stable form. Out of all these brands the brands D is having lowest amount (93.23%) as compare to others but it is in therapeutic window so no chance of under and over pharmacological action.

The dissolution study was performed to see the drug release pattern in the four different brands of metformin tablets. The dissolution data of multipoint study are given in table 7 and figure 6.

The results of dissolution study shows that all four brands releases about 95 % % drug within one hour. Among all four brands the brand c releases the highest amount of drug even in the 10 minute it release about 87% drug so onet of action is fast as well as the time required to reach the maximum concentration is very less as compare to other brands. The results says all the brands of metformin tablet available in the Trinidad complies the drug release profile parameters as per the pharmacopoeia.

Table 2. Weight variation test of four different brands of metformin tablets

Tablet No	Brand A	Brand B	Brand C	Brand D
	% Weight variation	% Weight variation	% Weight variation	% Weight variation
1	0.0375	1.1305	-3.417	1.5105
2	-1.5225	-1.3515	-0.136	-1.9855
3	0.8325	-0.8585	3.281	0.1805
4	0.0075	-1.4025	-0.748	0.2375
5	0.1275	0.6715	2.567	0.1615
6	-0.1725	-0.9095	1.377	-0.8075
7	1.8825	0.2805	0.119	-1.3015
8	-0.1125	0.5015	1.938	-0.7125
9	-1.4175	-0.5525	-2.465	-0.4275
10	-0.8475	-0.4845	-0.884	-0.4845
11	0.7125	1.3685	2.193	1.7765
12	0.9975	-0.6715	-1.003	2.2135
13	0.0675	-0.7905	0.153	-0.8075
14	0.3825	2.4735	-1.666	-0.4085
15	-0.3075	-3.0685	-0.544	0.0665
16	-1.2975	2.5585	2.601	1.1685
17	0.5925	-0.9435	0.884	-0.2755
18	0.4725	0.9095	-1.734	-0.5035
19	1.6275	0.1445	0.986	-0.4275
20	0.1425	-1.5385	0.221	-0.6935

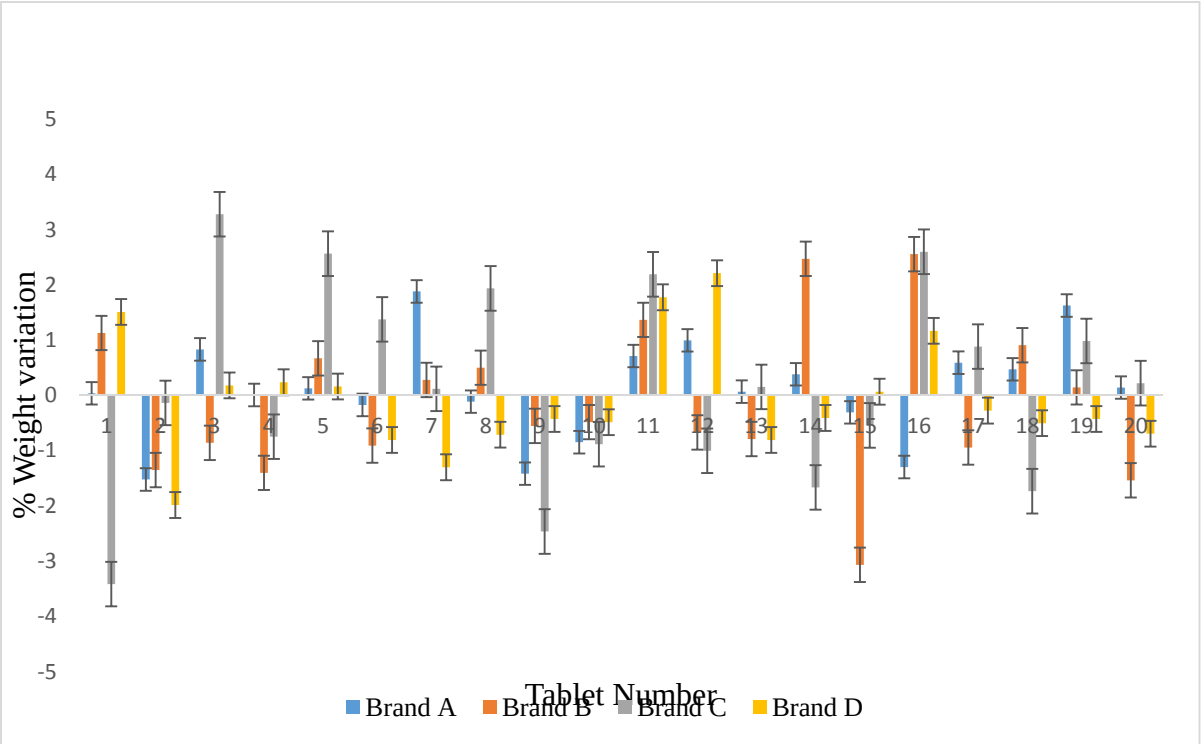

Fig. 2. Weight variation test of four different brands of metformin tablets

Table 3. Weight variation of different brands of metformin tablets

	Brand A	Brand B	Brand C	Brand D
Average Weight ± SD	655.99 ± 5.92 mg	602.71 ± 7.98 mg	602.30 ± 10.35 mg	533.95 ± 5.36 mg
Average % Weight variation	0.11 %	0.13%	0.19%	0.08%

Table 4. Friability test of four different brands of metformin tablets

Brand	A	B	C	D
% Friability ± SD	0.03 ± 0.019	0.02 ± 0.004	0.03 ± 0.004	0.02 ± 0.004

Table 5. Disintegration test of four different brands of metformin tablets

Brand	A	B	C	D
Disintegration Time ± SD(Minute)	9.59 ± 0.22	7.58 ± 0.23	2.38 ± 0.13	7.15 ± 0.07

Table 6. Drug assay of four different brands of metformin tablets

Brand	A	B	C	D
% Drug	96.22 ± 0.06	99.46 ± 0.24	100.71 ± 1.31	93.23 ± 0.47

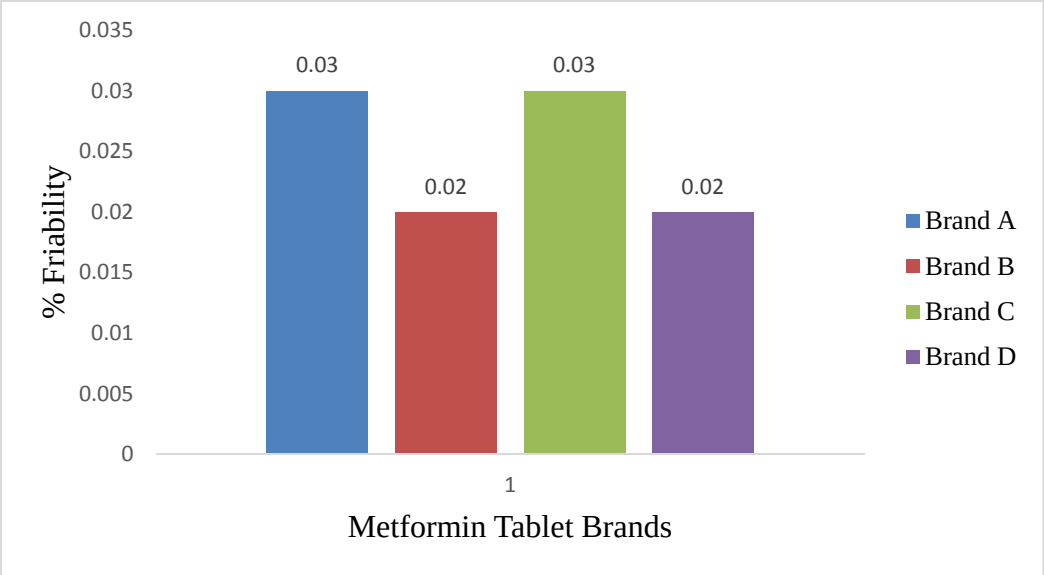

Fig. 3. Friability of four different brands of metformin tablets

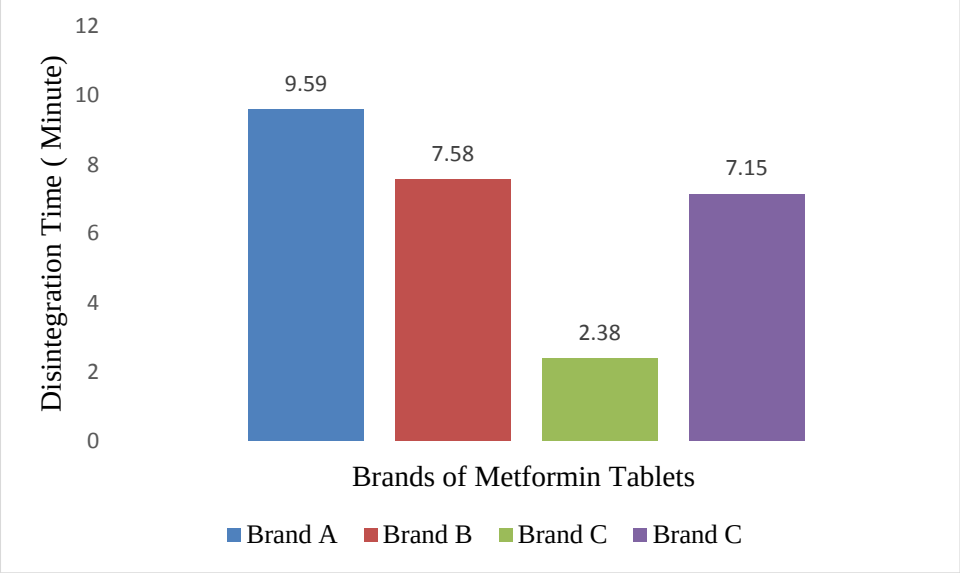

Fig. 4. Disintegration time of four different brands of metformin tablets

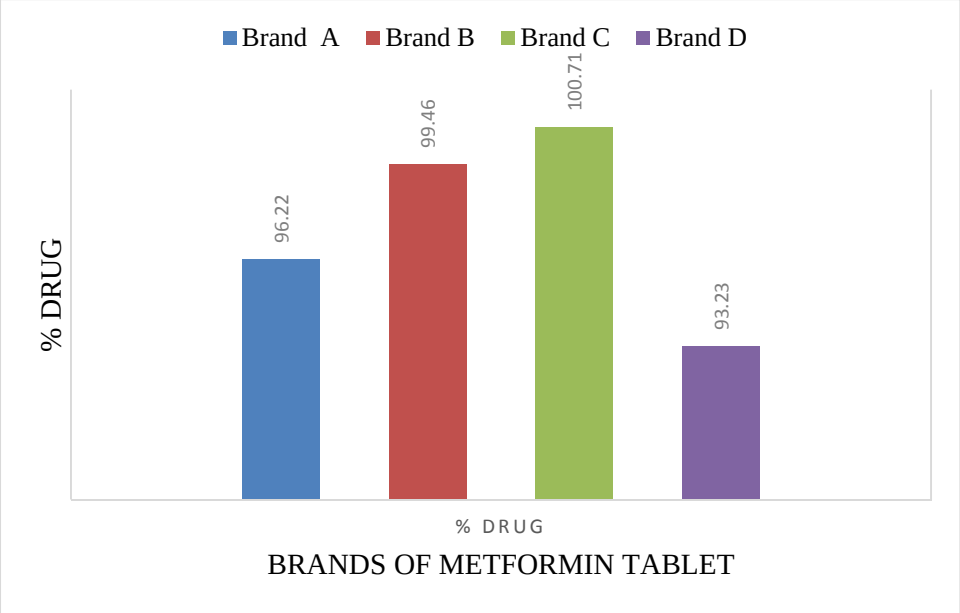

Fig. 5. Drug assay of four different brands of metformin tablet

Table 7. Dissolution study of four different brands of metformin tablets

	Time (Min)	5	10	15	30	45	60
Brand A	Amount of Drug (mg)	69.79	101.91	279.99	404.65	474.56	418.78
	Cumulative% drug release	13.96	20.38	56.00	80.93	94.91	83.76
Brand B	Amount of Drug (mg)	251.57	395.35	415.01	424.11	471.68	416.36
	Cumulative% drug release	50.31	79.07	83.01	84.82	94.34	83.27
Brand C	Amount of Drug (mg)	245.90	437.39	444.51	449.01	464.02	494.66
	Cumulative% drug release	49.18	87.48	88.90	89.80	92.80	98.93
Brand D	Amount of Drug (mg)	279.29	401.44	402.92	423.02	439.94	474.51
	Cumulative% drug release	55.86	80.29	80.58	84.60	87.99	94.90

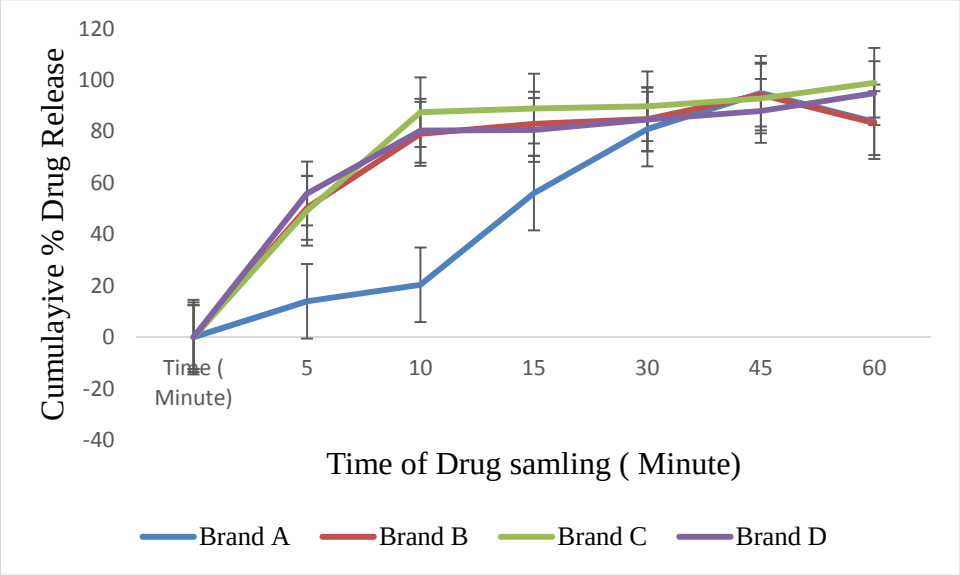

Fig. 6. Drug release study of four different brands of metformin tablets

CONCLUSION

The quality control evaluations of four different brands of Metformin tablets those are available in pharmaceutical market of Trinidad were assessed by this study. The values were compared with the standards. This study showed that all four brands (A, B, C, D) of metformin tablets meet the pharmacopoeia specification of different parameters. The results of various quality control parameters for tablets like weight variation, friability, disintegration time, drug assay and dissolution study all are in the pharmacopoeia limits.

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