A Comparative Analysis of Commercial Metformin Tablets

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ABSTRACT

Objective: Five commercial brands were analyzed with respect to their physical characters, chemical content, and drug release. **Methods:** The brands of metformin were randomly selected. All the groups were coded and analyzed. The tablets were examined for their shape, size, weight, and color and the tablets were tested for their friability, disintegration, drug content, and purity using standard procedures. **Results and discussion:** On physical inspection, Brand C 500 was is the smallest and Brand D 500 SR was the largest in size. Brand C 500 was lesser in weight while Brand E XR 500 weighed more. On purity test, all other brands passed the standard for purity. All the brands had loss in weight less than 1% after the friability test. On chemical content examination, variation was seen between the batches as well as the brands. The brands such as Brand A XL 500 and Brand D 500 SR contained the required content. But the brands like Brand C 500 and Brand E XR 500 had only lesser content and failed in the validity test. **Conclusion:** The physical properties of the five brands of metformin tablets were analyzed. Sustained release dosage form was mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time. Apart from the color and shape, the weight and size are very important to improve patients' compliance. It is the duty of the pharmaceutical company to manufacture proper dosage forms to achieve the therapeutic goal.

Keywords: Metformin, physical aspects, sustained release, content, disintegration time

Metformin hydrochloride (MET) is chemically N,N-dimethylimidodicarbonimidic diamide hydrochloride (1, 1-dimethylbiguanide hydrochloride) that acts by decreasing intestinal absorption of glucose, reducing hepatic glucose production and increasing insulin sensitivity (Fig. 1) Metformin is considered as the first-line oral hypoglycemic agent in the treatment of type 2 diabetes mellitus. MET is the drug of choice in obese patients.[1–3] Metformin activates adenosine monophosphate-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance and metabolism of glucose and fats. Activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells. It is an official drug in Indian Pharmacopoeia,[4] British Pharmacopoeia,[5] European Pharmacopoeia,[6] and United States Pharmacopoeia BP.[7]

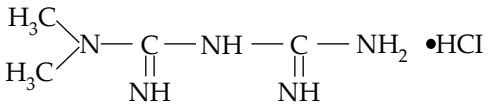

Figure 1. Chemical structure of MET.

Many brands are available for metformin generic in the market. This study was committed to evaluate the quality of the five brands of metformin. The brands having high quality should be equivalent not only in their basic chemical structure and dosage forms but also in their content, purity, friability and dissolution rates.[8]

OBJECTIVE

The study was a single-blind comparative analysis of five brands of metformin tablets and this study intended:

- To evaluate the physical quality in their appearance, purity in their substance, friability on handling, and the content in their preparations.

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- To evaluate the time taken for their dissolution/ release.
- To analyze the observations and make a comparison of the brands.

METHODOLOGY

Five commercial brands of metformin were randomly selected. Metformin brands having label strength of 500 mg were purchased from a retail pharmacy in Chennai. Three batches were taken from each brand. All tests were performed within product expiration dates. The brands were coded (Table 1) and analyzed in the following procedures. The analysts were kept blinded.

The tablets were visually examined for their shape, size, weight and color; the tablets were tested for their purity, friability, and content, and dissolution rates were estimated using standard procedures.

Physical Inspection

The shape and color of the different brands of tablets were examined visually. The size was examined with the help of Vernier caliper. Tablets of each brand were weighed individually using a digital analytical balance (Ohaus Adventure, China).

Purity

Assay to estimate the purity of metformin of the given five brands was carried out using ultraviolet (UV) spectrophotometer method at specific absorbance (232 nm) as per Indian Pharmacopoeia.[8]

Table 1. Coding of Tablets

Brand	Coding	Expiry date	No of tablets
BRAND - A XL 500	GF01	FEB 2014	25
	GF02	APR 2014	25
	GF03	APR 2014	25
BRAND - B SR 500	XM01	FEB 2014	25
	XM02	JAN 2014	25
BRAND - B 500	XM03	NOV 2014	25
BRAND - C 500	GP01	MAY 2015	25
	GP02	JAN 2015	25
	GP03	APR 2015	25
BRAND - D SR	GM01	MAR 2014	25
	GM02	MAR 2014	25
	GM03	MAY 2014	25
BRAND - E XR 500	CP01	JULY 2014	25
	CP02	AUG 2014	25
	CP03	MAR 2012	25

Friability Test

It is the tendency of the tablets to powder, chip, or fragment and this can affect the elegance appearance and consumer acceptance of the tablet, and can also add to the tablet's weight variation or content uniformity problems. Friability is a property that is related to the hardness of the tablet. An instrument called friabilator is used to evaluate the ability of the tablet to withstand rattling in packaging, handling, and shipping.

Procedure

Twenty tablets were weighed and subjected to abrasion using a tablet friability tester (Veego Instruments Corporation, Mumbai, India) at 25 revolutions per minute (rpm).

- Weigh 20 tablets altogether = W1
- Put these tablets in the friabilator and adjust the instrument at 100 rpm (i.e., 25 rpm for 4 min)
- Weigh 20 tablets (after friability) = W2
- Friability (% loss) = W1 − W2 % W1 × 100

Chemical Content Determination

This is used to determine whether the individual content of the tablets are within the limits set with reference to the average content of the sample.

Metformin powder is weighed in amounts of 0.1, 0.2, 0.3, 0.4, 0.5, and 0.75 mg. Each sample was dissolved separately in 1 mL of 0.2 M HCl and shaken up for 5 min. Five milliliters of 10^{-5} M $KMnO_4$ was then added, warmed in a water bath at 50°C for 10 min, and cooled for 3 min before 2 mL of 10^{-4} M methylene blue and 100 mL of distilled water was added. Five milliliters aliquot of the final volume was taken for each weight. The absorbance of the resulting solutions was determined at 663 nm. The procedure was applied to the five brands of metformin employed in the study.

Dissolution Rate Determination

In vitro dissolution rate is an important tool to predict the *in vivo* bioavailability and bioequivalence and to decide on interchangeability.[9] As per Food and Drug Administration guidance for highly soluble drugs, a single-point dissolution test specification of 85% in 60 min or less is sufficient as a quality control test for uniformity between different batches.[10] Similarly, as per the European Medicines Agency (EMA) guidance, when more than 85% of the active substances are dissolved

within 15 min, it is sufficient as a quality control test for uniformity between different batches.[11,12]

For this reason, dissolution testing of solid oral drug products has emerged as one of the most important control tests for assuring product uniformity and batch-to-batch equivalence.[13] Therefore, any dosage forms having good dissolution rate is considered to be having good quality and is an important part of good manufacturing practice.[14] Before performing dissolution test, six serially diluted solutions of pure metformin with the concentration of 0.3125 to 10 µg/mL were prepared from a stock solution and a standard curve was drawn. The curve was linear between 0.3125 and 10 µg/mL. The dissolution test was undertaken using USP apparatus II (Erweka DT6R, Gemini BV, The Netherlands) with the rate of 100 rpm at 37°C on six tablets of each brand. The dissolution medium was 900 mL phosphate buffer (pH = 6.8). To draw dissolution profile, 5 mL of dissolution samples were withdrawn at different time intervals up to 60 min and replaced with the same volume of prewarmed dissolution medium. Subsequently, samples after 100-fold dilution were assayed by UV spectrophotometer at an absorbance wavelength of 232 nm. The concentration of each sample was determined from a calibration curve (Fig. 2).

Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1,000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 in 0.1; 1,000 mL.

Apparatus II: 100 rpm, for tablets labeled to contain 500 mg.

Time: 1, 3, and 10 hours.

Procedure: Determine the amount of MET ($C_4H_{11}N_5$·HCl) dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a 0.45-m hydrophilic polyethylene filter and suitably diluted with *Medium.* Calculate the amount of MET, in percentage, released at each time point by the formula as follows:

$$\frac{C \times (A_u / A_s) \times (V - V_s) + (C_{60} \times V_s) + (C_{180} \times V_s)] \times 100}{L}$$

where C is the concentration of the standard solution in mg/mL; A_u and A_s are the absorbances of the solution under test and the standard solution, respectively; V is the initial volume of *medium* in the vessel, in mL; V_s is the volume withdrawn from the vessel for previous samplings, in mL; C_{60} is the concentration of MET in the *medium* determined at 1 h, in mg/mL; C_{180} is the concentration of MET in the *medium* determined at 3 h, in mg/mL; 100 is the conversion to percentage; and L is the tablet label claim in mg.

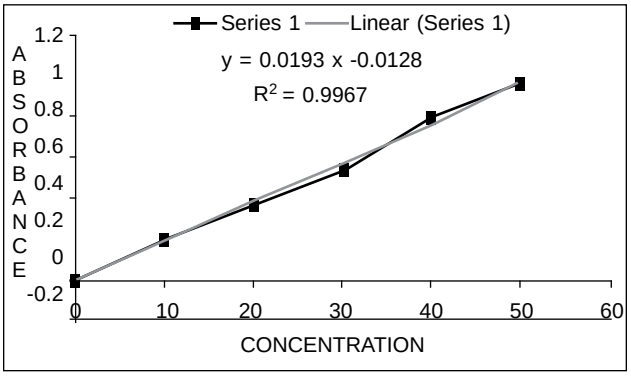

Figure 2. Calibration curve.

RESULTS AND DISCUSSION

Physical Inspection

The different brands of metformin tablets were examined in their physical aspects, namely, shape, size, weight, and color, and the details are given in table 2.

Size of the Tablets

The size of the tablets is above 0.50 cm in all the brands except Brand C 500 having only the size around 0.323 ± 0.003 cm, being the smallest. The size of the Brand D 500 SR is 0.71 cm, being the largest of the brands examined. There is no significant difference between batches of the brands. The size of dosage forms determines the compliance of the patients.

Weight of the Tablets

The weight of the tablets are in the range of 0.75-0.85 g except the Brand C 500 having only 0.55 g and being lesser in weight, while the Brand E XR 500 weighs more (0.85 g) among the brands examined. There is no significant difference between batches of the brands.

Purity

A tablet will usually contain active ingredient and vehicle matter. This study is conducted to identify the actual percentage of concentration of active ingredient of a single tablet of these five brands.

The purity assay showed that the five different brands contained different concentrations of the pure chemical and are found to be chemically not equivalent (Table 2). One of the batches of Brand B SR 500 (XM01), another one of Brand C 500 (GP01), and one more of Brand E XR 500 (CP02) contained only 85%, 86%, and 85% of the ingredient, respectively, and these batches failed

Table 2. Physical Aspects

Brand	Coding	Shape	Size Avg (cm)	Weight	Color	Friability %	Drug content (mg)	Purity (%w/w)	Purity result
Brand A XL 500	GF01	Capsule shape with convex face	0.62	0.75	White	0.133	550	110	PASS
	GF02	Capsule shape with convex face	0.61	0.75	White	0.133	540	108	PASS
	GF03	Capsule shape with convex face	0.615	0.756	White	0.133	501	100	PASS
Brand B SR 500	XM01	Capsule shape with flat face and bevel edges	0.50	0.75	White	0.133	425	85	FAIL
	XM02	Capsule shape with flat face and bevel edges	0.506	0.75	White	0.136	550	110	PASS
Brand B 500	XM03	Capsule shape with convex face	0.52	0.75	White	0.268	474	95	PASS
Brand C 500	GP01	Capsule shape with concave face and bevel edges	0.32	0.55	White	0.225	431	86	FAIL
	GP02	Capsule shape with concave face and bevel edges	0.323	0.55	White	0.256	511	102	PASS
	GP03	Capsule shape with concave face and bevel edges	0.326	0.55	White	0.133	469	94	PASS
Brand D 500 SR	GM01	Oval shape	0.64	0.71	White	0	512	102	PASS
	GM02	Oval shape	0.653	0.70	White	0	519	104	PASS
	GM03	Oval shape	0.653	0.70	White	0	484	97	PASS
Brand E XR 500	CP01	Capsule shape with convex face	0.536	0.85	White	0.618	550	110	PASS
	CP02	Capsule shape with convex face	0.53	0.85	White	0.458	426	85	FAIL
	CP03	Capsule shape with convex face	0.533	0.85	White	0.133	462	92	PASS

the validity test of 90% concentration. All other brands passed the validity test.

Friability Test

The difference in weight loss before and after the friability test is analyzed. If it is to be declared as stable preparation for handling and transport, it must be less than or equal to 1%. The friability is expressed as the loss of mass and it is calculated as a percentage of loss of weight in the initial weight.[15] All the brands are having the weight loss less than 1% after the friability test. But among the batches of the brands examined, Brand A XL 500 have no significant difference within their three batches. The batch of Brand B SR 500 coded as XM03 has higher friability. It is because of being conventional or short-acting dosage form. The brand, Brand D 500 SR, has no weight loss in friability test and it is a very stable dosage form of the brands examined. The batches of Brand E XR 500 coded as CP01 and CP02 have got higher friability than code CP03.

Chemical Content

We examined only the tablets having concentration of 500 mg of metformin. A wide range of variations is

seen in the contents of the tablets. The variation is seen between the batches as well as the brands. A brand should contain 90% of the substance (450–550 mg) to clear the validity test. The brands such as Brand A XL 500 and Brand D 500 SR contain the required content. But the brands like Brand C 500 and Brand E XR 500 had only lesser content and failed the validity test. The content is also not uniform among batches (Fig. 3).

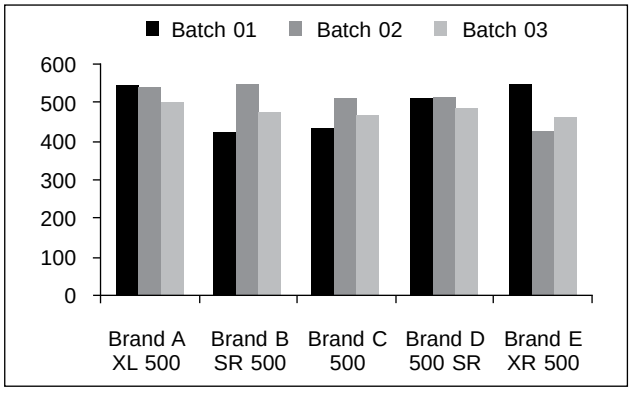

Figure 3. Drug content in milligrams per tablet.

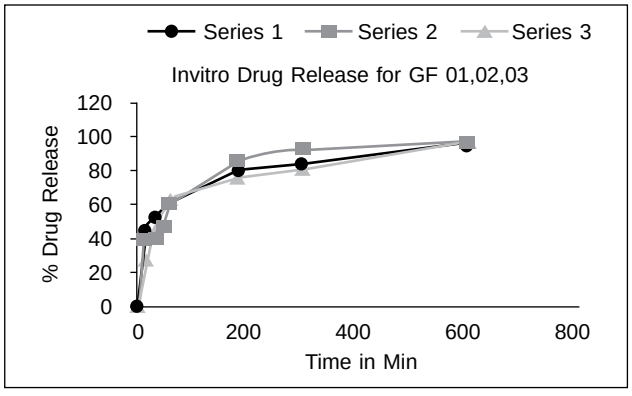

Figure 4. Release of Brand A.

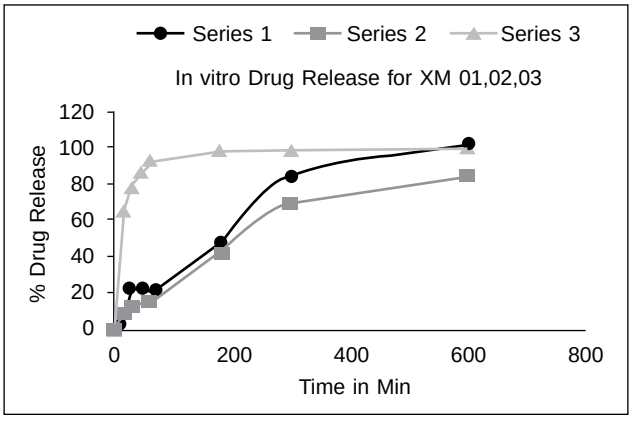

Figure 5. Release of Brand B.

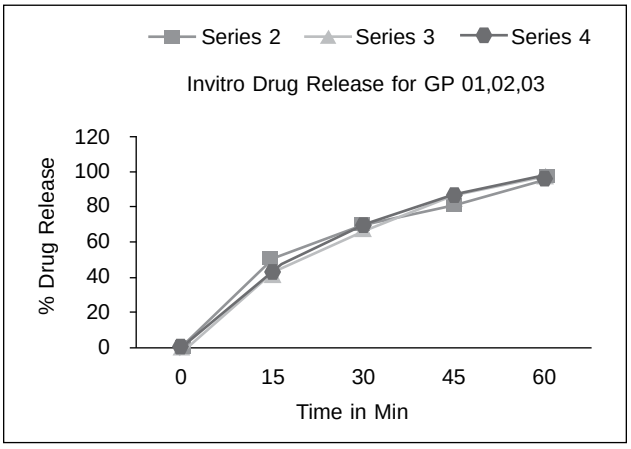

Figure 6. Release of Brand C.

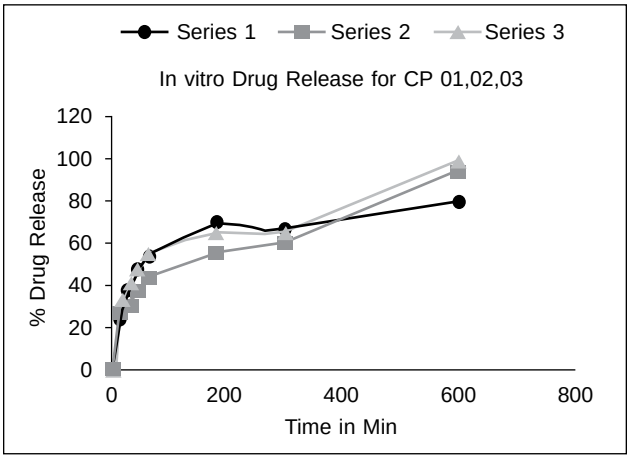

Figure 7. Release of Brand E.

Dissolution Rate

Dissolution or release of the contents is more than 10 h in all brands of sustained dosage forms. But the release in case of Brand B 500, batch XM03, and all the batches of Brand C 500 is in 60 min because of their conventional or short-acting dosage forms. Brand A XL 500 released more than 90% of their contents in 10 h and it is sustained release dosage form as shown in (Fig. 4).

Two batches (XM01, XM02) of Brand B SR 500 took 10 h to release 83%-100% of its contents, but one batch (XM03) being short acting had taken 60 min to release more than 90%. This shows that the long-acting forms are suitable for less frequency in administration of drugs and improves patients' compliance (Fig. 5).

Brand C 500 had taken only 60 min for 94%-97% release as a short-acting form (Fig. 6).

Brand D 500 SR being sustained release form released 86%-92% 10 h (Fig. 7). Brand E XR 500 had release time of 10 h for 80%-99% of their contents (Fig. 8).

MAIN LIMITATIONS OF THE STUDY

Dissolution test *in vitro* will preconceive the *in vivo* behavior of a drug. But the real bioavailability and bioequivalence of the products can be concluded only *in vivo* studies. The human gastrointestinal tract with its own nature and various other factors affect its activity, the generalization of dissolution conditions, and thus results of this study is not aptly applied. *In vivo* and *in vitro* comparison studies are required to confirm findings in this study.[9]

CONCLUSION

The physical properties of five brands of metformin tablets were analyzed and results were presented. Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Economy and greater patient compliance are other advantages of sustained release preparations. Apart from the color and shape, the weight and size are very important to improve patients' compliance. It is the duty of the pharmaceutical company to manufacture the dosage forms sustaining more rattling in handling, to have more shelf life, and to supply the drugs in pure form with recommended content. This only will achieve the therapeutic goal.

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Gaining Weight Losing Strength Versus Losing Weight Gaining Strength

When we gain weight, we must acquire more strength and when we lose weight, we must lose the strength. This is a fundamental principle.

If we gain weight and feel weak, it is a disease and when we lose weight and gain strength, we are recovering from the disease. One is not supposed to gain more than 5kg of weight after the age of 20 years. Any weight gain after that will only be due to accumulation of fat, which leads to insulin resistance.

Insulin resistance does not allow food to convert into energy. In the state of insulin resistance, whatever you eat is converted into fat. As it is not converted into energy so you feel weak. When you reduce insulin resistance by drugs or walking, the metabolism becomes normal and whatever you eat gets converted into energy and you start gaining strength.

Source: eMedinewS Dec 28, 2013