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COMPARATIVE IN VITRO STUDIES AND BIOEQUIVALENCE ASSESSMENT OF SOME COMMERCIALLY AVAILABLE METFORMIN HYDROCHLORIDE TABLETS IN VIJAYAWADA

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ABSTRACT

Metformin Hydrocloride tablets prescribed for treatment of non-insulin dependent diabetes mellitus (NIDDM). The aim of the study is to compare the differences in dissolution behavior and asses bioequivalence of some commercially available Metformin Hydrocloride tablets in Vijayawada. The objective is to find out potent generic brand and reduce the cost of treatment for diabetes mellitus with respect to its composition and manufacturer. Eight generic brands manufactured by different companies were evaluated for physicochemical properties, drug content, *in vitro* dissolution studies and compared with each other. The *in vitro* dissolution studies were performed in USP Dissolution Apparatus II using pH 6.8 phosphate buffer solution for 1 hr. The bioequivalence was assessed based on *In vitro* dissolution profile and f1 & f2 factors. *In vitro* dissolution of all the brands was satisfactory and the brand Obimet® shown highest dissolution of 94.49% within 1 hr. The f1 and f2 values were in the range of 2 – 8 and 74 – 93 respectively. It is evident that test products were bioequivalent to the reference product and the brand Obimet® could be used as a best generic substitute which reduce the dose and cost of treatment for diabetes mellitus.

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INTRODUCTION

Nowadays drug's cost increases due to the expensive branded drug and the cost can reduced by substituting cheaper generic drugs. The increase in production and consumption of generic drugs need bioequivalence for therapeutically equivalent to the branded drug. In order to find this, bioequivalent studies are conducted according to the Food and Drug Administration (FDA). Two different formulations of a same drug are bioequivalent when their rate of dissolution and absorption is same. Bioequivalence studies focus on the drug release from the formulation and subsequent absorption into the systemic circulation, which consist of both *in vivo* and *in vitro* studies (Demirturk E, 2006). According to US Pharmacopeia, necessary *in vitro* tests are assay, content uniformity and dissolution studies. The *in vitro* dissolution used to predict the *in vivo* bioequivalence.

Therefore, *in vitro* tests can used to determine bioequivalence of products. The dissolution profile comparison is more precise than others to characterize the drug product. To compare dissolution profiles, two model independent fit factors, the difference factor (f1) and the similarity factor (f2) introduced by Moore and Flanner (1996) as mathematical indices, were used in this study. Metformin Hydrocloride is a biguanide, which used orally in hyperglycemic patients. Nowadays it is widely used in the management and control of non-insulin dependent diabetes mellitus (NIDDM). The oral bioavailability of metformin is 50 – 60% and biological half-life is 1.5 – 1.6 hr (http://www.rxlist.com/glumetza-drug.htm). It is freely soluble in water and has low permeability to cell membranes. Despite of widespread of NIDDM and extensive use of metformin (World Health Organization, 1998), there are no reports on the bioavailability and bioequivalence of the various brands of metformin Hydrocloride tablets in

Vijayawada. Hence, the present study was carried out to investigate *Invitro* study and bioequivalence of metformin Hydrocloride tablets in Vijayawada market.

MATERIALS

Metformin Hydrochloride tablets were purchased from local market at Vijayawada. Metforin was purchased from Yarrow chem Products, Mumbai. NaOH from S.D. Fine Chem. Ltd, Mumbai, HCl and Potassium Dihydrogen Phosphate were obtained from Qualigens Fine chem, Mumbai and all other ingredients used were of analytical grade.

METHODS

Eight brands of antidiabetic tablets containing Metformin hydrochloride as main active ingredient was selected and procured from the local market in Vijayawada. All the brands contained label strength of 500 mg Metformin hydrochlorid. The physicochemical equivalence of eight brands of Metformin hydrochloride tablets was determined through the evaluation of both official and non-official standards. All tests were performed within product expiration dates. The strength of Metformin hydrochloride and other details were given in Table 1.

ANALYTICAL TESTS FOR API

Melting Point Determination: Melting point determination of pure drug Metformin hydrochloride was done; as it is a first indication of purity of the sample. The presence of small amount of impurity can be detected by lowering as well as widening in the melting point range.

Identification of Pure Drug: FTIR spectroscopy was used for identification of pure drug Metformin hydrochloride.

Determination of λ_{max}: An accurately weighed 10 mg of Metformin hydrochloride was transferred in a 100ml volumetric flask. To the flask phosphate buffer was added in small proportion so as to dissolve Metformin hydrochloride. The volume was made up to 100ml with phosphate buffer pH 6.8 to get a concentration of 100µg/ml ((Imad H and Ahmed BJ., 2010). 20µg/ml solution of Metformin hydrochloride was prepared in dilution. The resulting solution was scanned in UV-Vis spectrophotometer from 400- 200nm to determine the λ_{max}.

Calibration of Standard Curve: Accurately weighed 100 mg of Metformin hydrochloride was dissolved in 100 ml of pH 6.8 phosphate buffer solution. The resultant solutions were having concentration of 1000 µg/ml (1 mg/ml). 1 ml of this solution was further diluted up to 100 ml with 6.8 pH phosphate buffer to give a solution of Concentrations 10 µg/ml. Appropriate aliquots were pipetted out from the stock solution in to a series of 10 ml volumetric flasks. The volume was made up to the mark with 6.8 pH phosphate buffer to get a set of solutions having the concentration range of 0, 2, 4, 6, 8 and 10 µg/ml for Metformin hydrochloride. Absorbance of the above solutions was measured at 232 nm ((Imad H and Ahmed BJ., 2010), a calibration curve of absorbance against concentration was plotted, and the regression equation and correlation coefficient was determined.

INVITRO EVALUATION OF TABLETS

The physicochemical equivalence of eight brands of Metformin hydrochloride tablets were determined through the evaluation of both official and non-official standards according to the USP pharmacopoeia including uniformity of weight, friability, hardness, disintegration, dissolution rate and drug content (Osadebe PO and Akabogu A., 2004).

Visual Inspection: The shape and color of the different brands of tablets were examined visually.

Thickness & Diameter: Three tablets from each brand were used for thickness determination. Thickness & diameter of each tablet was measured in mm using Vernier Calipers (Mitutoyo Dial, Mitutoyo, Japan). The mean and standard deviation values were calculated and reported.

Hardness Test: The crushing strength of the tablets was determined using hardness tester (Lab India). Sample tablets (10) of each brand were taken, a tablet was placed between the spindle of the Lab India hardness tester machine until the tablet breaks and the pressure required to break the tablet was then read off the machine and recorded (Arcot RC, Chan J, *et.al.,* 2011).

Friability Test: Twenty tablets of each brand were weighed and subjected to abrasion using a Roche friabilator at 100 revolutions for 4 min (Aulton ME., 2002). The tablets were dedusted and weighed again then percent of weight loss was recorded. The friability of the tablets were then calculated using the following expression

% Friability = [(Initial weight – Final weight)/Initial weight]×100

Weight Uniformity: Total20 tablets from each brand were weighed individually using a digital analytical balance. The average weight was determined and the percentage (%) deviation of the individual tablets from the mean was determined (Aulton ME., 2002).

$$\% \text{ Weight variation} = \frac{(\text{Average weight} - \text{Individual Weight})}{\text{Individual Weight}} \times 100$$

Disintegration Test: Tablet disintegration was determined at 37 °C using (Lab India) disintegration apparatus. The disintegration time of randomly selected six tablets of each brand was determined in distilled water (Aulton ME., 2002). The disintegration time was taken to be the time no granule of any tablet was left on the mesh.

Drug content estimation: Ten tablets from each brand was finely powdered and powder equivalent to 100 mg of Metformin was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of phosphate buffer (pH 6.8). The flasks were shaken thoroughly to get uniform solution. The volume made up to the mark with phosphate buffer solution and filtered. One ml of the filtrate after suitable dilution was subjected for the estimation Metformin content at 232 nm using a double beam UV-visible spectrophotometer (Pamula RB, Surender G, *et.al.,* 2010).

Each reading was carried out in triplicate and the average Metformin content in each brand was calculated.

Dissolution Test: The rotating paddle method (USP apparatus II) was used to study the drug release from 6 tablets of each brand. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at 37^0C ± 0.5^0C, at a rotational speed of 100 rpm. Ten ml samples were withdrawn at intervals over the period of 1 hr and the volume was replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed for Metformin after appropriate dilution by UV spectrophotometer at 232 nm. The percentage of drug released is calculated using the given formula **(**Gray VA and Grady LT., 1997).

IN VITRO BIOEQUIVALENCE ASSESSMENT

The *in vitro* dissolution used to predict the *in vivo* bioequivalence. Therefore, *in vitro* tests can used to determine bioequivalence of products. The dissolution profile comparison is more precise than others to characterize the drug product. A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles. The difference factor (f1) calculates the percent (%) difference between the two curves at each point and is a measurement to the relative error between the two curves:

$$f1 = \{[\Sigma n=1\ n \mid Rt - Tt \mid]/ [\Sigma t=1\ n\ Rt]\}*100$$

Where *n* is the number of time points, Rt is the dissolution value of the reference batch at time t, and Tt is the dissolution value of the test batch at time t.

The similarity factor (f2) is the logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f2 = 50 \bullet \log \{[1+ (1/n) \Sigma t=1n (Rt - Tt)2]-0.5\bullet100\}$$

For the curves to be considered similar, f1 values should be close to 0, and f2 values should be close to 100. Generally, f1 values up to (0-15) and f2 values greater than 50 (50-100) ensures sameness or equivalence of the two curves and thus, of the performance of the test and reference products **(**Moore JW, Flanner HH., 1996).

RESULTS AND DISCUSSION

ANALYTICAL TESTS FOR API

Melting Point Determination: After performing capillary method melting point of Metformin HCl found in range of 226 - 230^OC. The presence of small amount of impurity can detect by widening in the melting point range.

Identification of Pure Drug: FT - IR spectroscopy was used to determine the functional group present in the pure drug sample. The FTIR spectrum of pure Metformin HCl has shown the characteristic peaks at 3393.51, 3370.66, 3173.92, 1630.84, 1571.05, 1486.18, 1447.60 and 1418.67 cm^{-1}. The absorption bands between 2800 and 3200 $cm^{-1}$was indicates presence of – NH stretching of amine groups. The wave numbers observed at 1486.18, 1447.60 and 1418.67 may be assigned to the C - H bendings respectively. IR spectrum of Metformin HCl is as follows:

Determination of λ_{max}: The Metformin HCl in pH 6.8 phosphate buffer was scanned in UV - Vis spectrophotometer from 400 – 200 nm to determine the λmax. The λmax was found to be at 232 nm, so the calibration curve of Metformin HCl was developed at this wavelength.

Calibration of Standard Curve: The standard curve of Metformin HCl was done by using pH 6.8 PBS as the medium and the maximum absorbance was found at 232 nm. The standard graph was constructed by making the concentrations of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml solutions. The absorbance of solutions was examined under UV - visible spectrophotometer at an absorption maximum of 232 nm. The standard graph was constructed by taking the absorbance on Y - axis and concentrations on X - axis. The standard calibration curve of Metformin HCl in pH 6.8 PBS was shown in *Fig 2*. Drug concentration and absorbance followed linear relationship the curve obeyed Beer - Lambert's law and the correlation coefficient value (R^2) is 0.999.

INVITRO EVALUATION OF TABLETS

Visual Inspection: Eight brands of marketed Metformin hydrochloride tablets were visually inspected for colour and shape, the qualities was summarized in Table 4.2. All the tablet brands have shown white colour, capsule shape with biconcave surfaces; whereas the Glycomet® and Gluformin® tablets have shown white colour, round shape with flat surfaces. The brands Glyciphage® Obimet® and Okamet® tablets have shown white colour, capsule shape with biconvex surfaces.

Thickness & Diameter: Thickness and diameter uniformity of tablets are necessary not only for consumer requirements but also for packaging. ± 5% variation is permissible. The thickness and diameter values of the all branded tablets were within limit.

Hardness Test: The hardness of the tablets is an essential criterion in the determination of the ability of the tablets to resist chipping, abrasion or breakage under conditions of storage, transportation and handling. Using Labindia hardness tester, the strength of the tablets was tested. All the tablet brands passed this non-official test according to USP specifications (4-6 kg). The hardness of the tablet was found to be 4.25 – 5.98 kg/cm^2. Brand Okamet® required the least pressure before fracture while brand Glyciphage ® required highest pressure.

Friability Test: The friability test is mostly important criteria for uncoated tablets to examine that the tablets have a good withstand strength for transportation, packaging, shipping and coating. All the tested brands in this study are uncoated tablets. The friability was tested for these tablets for all brands. The friability was less than 1 % for all the brands, which is an indication of good mechanical resistance of the tablet.

Weight Uniformity: Tablets were subject to weight variation study for uniformity of weight. All brands showed different mean weight which indicates the use of different excipients in the different brands. The weight of the tablet varied between 524 ± 0.16 to 714 ± 0.98 mg for all the tablet brands.

Table 1. Composition of Commercial Tablets

BrandName	Metformin HCl (mg)	Manufacturer	Batch No.	Mfg – Exp Date
Elmet (Reference)	500	Micro labs LTD	MEAS0010	2015-2019
Glycirite	500	MHS pharmaceuticals Pvt.Ltd	TPGT-0033	2016-2018
Okamet	500	Cipla LTD	E760753	2016-2019
Glyciphage	500	Franco-Indian pharmaceuticals.LTD	GA16099	2016-2019
Obimet	500	Abbott India Ltd	ADB0220	2016-2019
Elcephase	500	Elder Pharmaceuticals Ltd	AL6069	2016-2019
Glycomet	500	USV Pvt.Lmtd	28012523	2016-2019
Gluformin	500	Abbott Limited	SKB0056	2016-2018

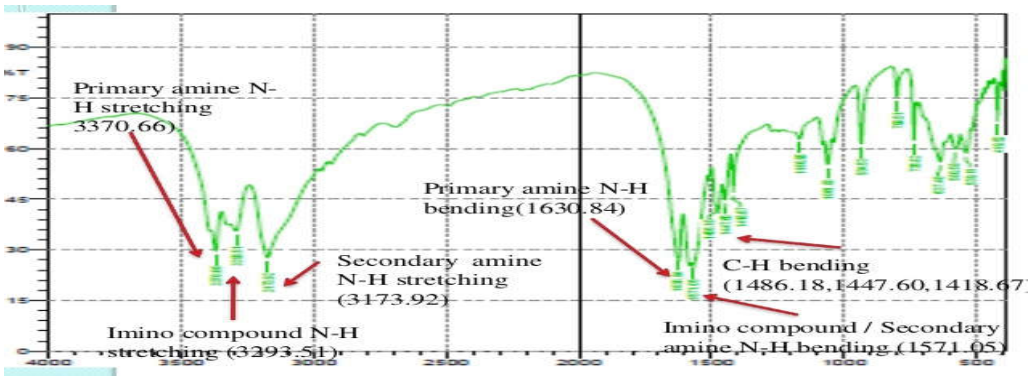

Fig 1. IR Spectra of Memantine HCl

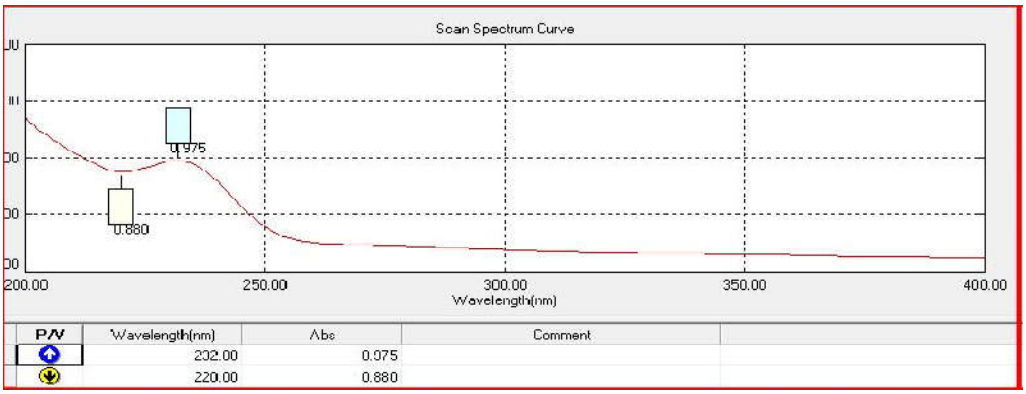

Fig. 2. λ_{max} of Memantine HCl

Table 2. Standard Calibration Curve of Metformin HCl

Sr. No	Concentration (µg/ml)	Absorbance in phosphate buffer (pH6.8)
1	0	0.00
2	2	0.1563
3	4	0.2901
4	6	0.4199
5	8	0.5801
6	10	0.7184

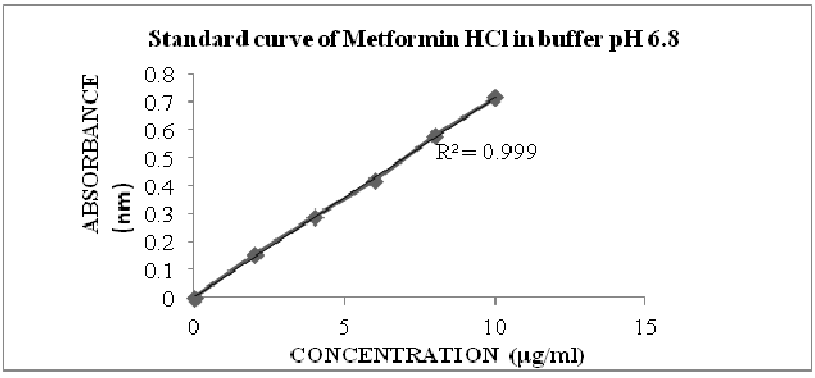

Fig 3. The Standard Calibration Curve of Metformin HCl

Table-3: Visual Inspection of Metformin HCl Tablets

Brand Name	Colour	Shape	Surface Property
Melmet (Reference)	White Colour	Capsule	Biconcave
Glycirite	White Colour	Capsule	Biconcave
Okamet	White Colour	Capsule	Biconvex
Glyciphage	White Colour	Capsule	Biconvex
Obimet	White Colour	Capsule	Biconvex
Elcephase	White Colour	Capsule	Biconcave
Glycomet	White Colour	Round	Flat
Gluformin	White Colour	Round	Flat

Table 4. Thickness & Diameter of Metformin HCl Tablets

Brand Name	Thickness (mm)	Diameter (mm)
Melmet	5.44 ± 0.002	7.96 ± 0.006
Glycirite	5.21 ± 0.001	7.95 ± 0.005
Okamet	4.89 ± 0.005	6.93 ± 0.002
Glyciphage	4.85 ± 0.006	7.97 ± 0.001
Obimet	5.00 ± 0.001	8.24 ± 0.004
Elcephase	5.20 ± 0.002	7.99 ± 0.002
Glycomet	4.08 ± 0.003	12.48 ± 0.001
Gluformin	3.96 ± 0.004	12.40 ± 0.003

Table 5. Hardness of Metformin HCl Tablets

Brand Name	Hardness (Kg/Cm^2)
Melmet	5.61 ± 0.02
Glycirite	4.58 ± 0.13
Okamet	4.45 ± 0.05
Glyciphage	5.98 ± 0.06
Obimet	4.25 ± 0.12
Elcephase	5.95 ± 0.11
Glycomet	4.32 ± 0.23
Gluformin	4.68 ± 0.09

Table 6. Friability of Metformin HCl Tablets

Brand Name	% Friability
Melmet	0.31 ± 0.001
Glycirite	0.22 ± 0.004
Okamet	0.21 ± 0.003
Glyciphage	0.22 ± 0.001
Obimet	0.94 ± 0.007
Elcephase	0.84 ± 0.005
Glycomet	0.67 ± 0.003
Gluformin	0.21 ± 0.002

Table-7: Weight Uniformity of Metformin HCl Tablets

Brand Name	Mean Weight (mg)	% Variation
Melmet	640 ± 0.017	0.156 ± 0.002
Glycirite	714 ± 0.042	0.563 ± 0.011
Okamet	524 ± 0.023	0769 ± 0.003
Glyciphage	560 ± 0.043	1.785 ± 0.012
Obimet	636 ± 0.027	0.625 ± 0.004
Elcephase	712 ± 0.025	3.188 ± 0.015
Glycomet	592 ± 0.033	0.338 ± 0.003
Gluformin	594 ± 0.022	0.677 ± 0.002

The variation in weight was within the range of ± 5% complying with pharmacopoeial specification.

Disintegration Test: The observed disintegration times for all the brands of Metformin hydrochloride investigated was less than the 15-min limit prescribed by the official pharmacopeia. All tablets of the different generic brands passed the disintegration test. The fastest disintegrated tablets were brand of Obimet® while the slowest one was brand Elcephase®. The various brands could have employed different disintegrants to improve the penetration of aqueous liquids.

Table 8. Disintegration time of Metformin HCl Tablets

Brand Name	Disintegration Time (minutes)
Melmet	6.46 ± 0.31
Glycirite	5.80 ± 0.27
Okamet	5.28 ± 0.22
Glyciphage	8.07 ± 0.32
Obimet	4.58 ± 0.18
Elcephase	8.45 ± 0.32
Glycomet	5.06 ± 0.14
Gluformin	5.51 ± 0.24

Drug content estimation: The weight variation test is clearly not sufficient to assure uniform potency of tablets. The potency of tablets is expressed in terms of label strength of the product. Results achieved from analysis of active ingredient in all brands exhibit in table 4.8. As USP specified, the content should not be less than 95% and not more than 105% of abeled amount. Results in table 4.8 indicate that all products stayed on the acceptable limits.

Table 9. Drug content estimation of Metformin HCl Tablets

Brand Name	Drug content (%)
Melmet	96.12 ± 0.61
Glycirite	96.54 ± 0.22
Okamet	98.24 ± 0.32
Glyciphage	97.20 ± 0.71
Obimet	98.12 ± 0.15
Elcephase	99.60 ± 0.34
Glycomet	98.23 ± 0.14
Gluformin	98.04 ± 0.24

Dissolution Test: In the present investigation, the release of Metformin hydrochloride from all tablet brands was immediate release and the percent of drug released at 45mins was more than 70% as shown in Figure 4.4 & 4.5. The results obtained from this study revealed that all the brands passed the USP general specifications standard for conventional tablets. The cumulative percentage release in pH 6.8 PBS for all the brands was recorded and the reference Melmet® showed 89.66% drug release in intestinal fluid for 60 minutes, while the brand Obimet® showed higher drug release, respectively 94.49% within 60 minutes. The higher drug release from these brands was possible may be due to presence of higher concentration of the disintegrant.

IN VITRO BIOEQUIVALENCE ASSESSMENT

The percentage dissolution values of all tablet brands used to calculate the f1 and f2 factors. The dissimilarity (f1) and similarity factor (f2) was found between 2 – 8 and 74 - 93. Similarity factor (f2) showed greater than 50 and dissimilarity factor (f1) showed less than 15 for all brands, represented closeness between two profiles. The higher the f2 values, the more similar the dissolution profiles, so the values cited in

Table-10: % Drug Release of Metformin HCl Tablets

Time (min)	Average % Drug Release							
	Melmet	Glycirite	kamet	lyciphage	Obimet	Elcephase	Glycomet	Gluformin
10	40.91	39.92	45.69	31.25	48.54	30.15	40.92	39.69
20	58.31	52.42	59.92	44.65	63.21	43.65	52.62	50.92
30	74.20	76.20	78.15	67.70	79.57	66.70	75.20	71.15
45	84.31	86.32	86.55	78.61	89.63	77.61	87.32	80.55
60	89.66	91.54	92.89	85.11	94.49	84.11	92.54	90.89

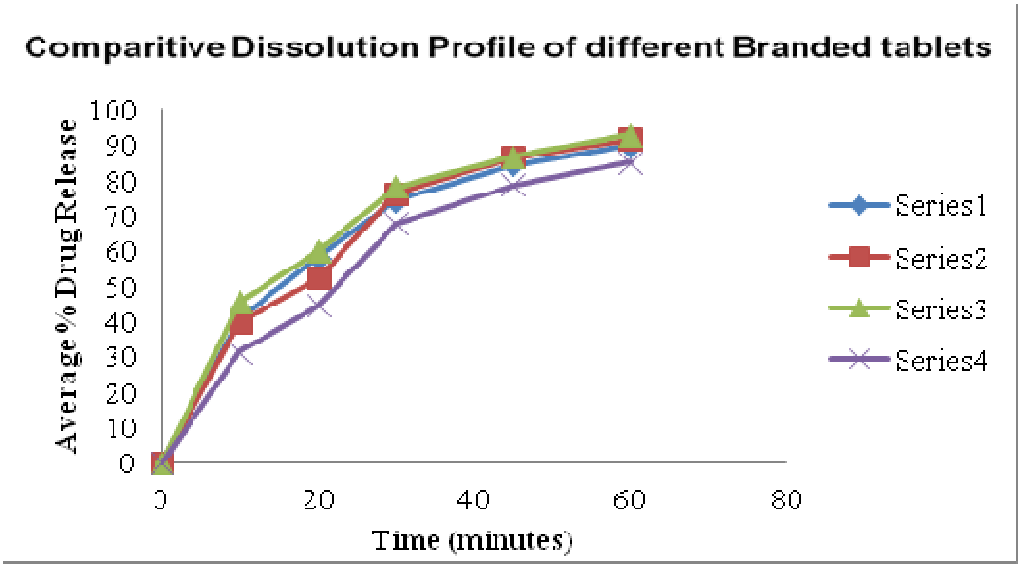

Fig. 4. Comparative Dissolution profile of Brand 1 – 4

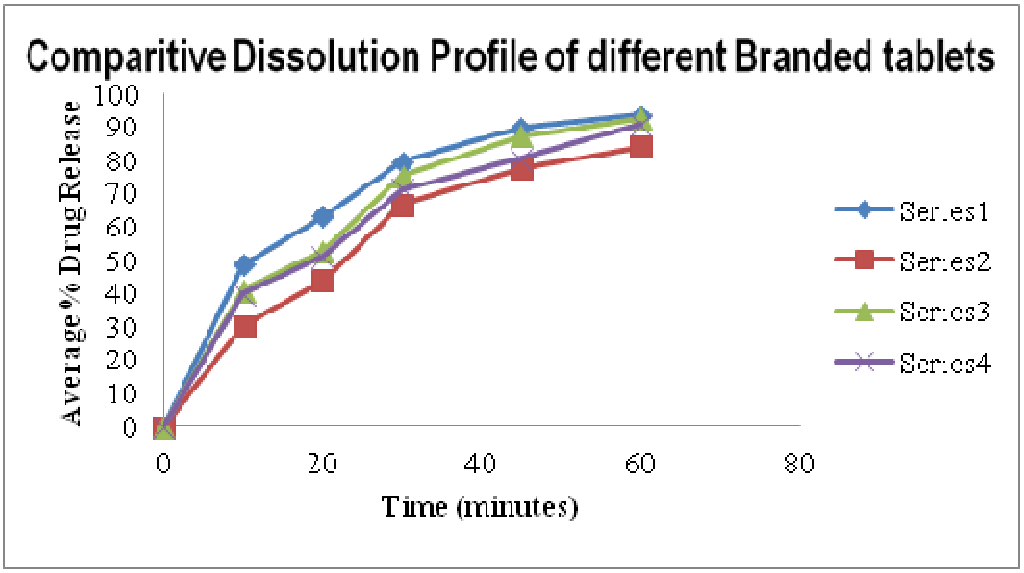

Fig.5. Comparative Dissolution profile of Brand 5 - 8

Table 11. *Invitro* Bioequivalence assessment using f1 & f2 factors

Brand Name	f1 value	F2 value
Melmet (Reference)	0	100
Glycirite	6	85
Okamet	4	90
Glyciphage	7	75
Obimet	2	93
Elcephase	8	74
Glycomet	4	89
Gluformin	6	84

Table 4.10 shows that Obimet ® is the most similar local product to the reference product Melmet®. The similarity factor f2 was 93 and difference factor f1was only 2.

Conclusion

Bioequivalence studies are the commonly accepted methods displaying therapeutic equivalence between the products. The *in vitro* bioequivalence studies can predict the *in vivo* bioequivalence and to save time & cost. *In vitro* dissolution of all the brands was satisfactory and the brand Obimet® shown highest dissolution of 94.49% within 60 minutes. The f1 and f2 values were in the range of 2 – 8 and 74 – 93 respectively. Therefore it is evident that test products were bioequivalent to the reference product. The brand Obimet ® is the most similar local product to the reference product Melmet®. The similarity factor f2 was 93 and difference factor f1was only 2. So Obimet® could be used as a best generic substitute which reduces the dose and cost of treatment for diabetes mellitus.

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