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IN VITRO BIOEQUIVALENCE STUDIES OF SIX BRANDS OF SR METFORMIN HCL TABLETS

A. Swathi Annapurna*, P.V. Kamala Kumari , P.T.P.R.S. Srujana, Y.Srinivasa Rao

Vignan Institute of Pharmaceutical Technology, Duvvada, Andhra Pradesh, India

*Corresponding Author E-mail: swathi.kodukula@gmail.com

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ABSTRACT

Pharmaceuticals dosage form efficacy generally depends on their formulation properties and manufacturing methods, hence it is likely that the quality of dosage form may vary. Metformin hydrochloride is an oral anti-diabetic drug used mainly to treat type II diabetes mellitus and available as several brands in the market which make it difficult to select the safe, effective and economic one. The aim of this work was to check, compare and evaluate the quality standards of different brands of Metformin hydrochloride Sustained Release (SR) tablets available in local market of Visakhapatnam, Andhra Pradesh, India. Bio equivalence studies are the commonly accepted methods displaying therapeutic equivalence between two products. This study was conducted to evaluate the bioequivalence between different formulations of Metformin 500mg which are marketed in and around Visakhapatnam, Andhra Pradesh. Test for weight variation, hardness, friability, disintegration time, and dissolution were conducted. The dissolution test was performed at pH 6.8 for all the brands of the tablet. Further all the tablets passed weight variation, hardness, friability and disintegration test as per the pharmacopoeial standards.

INTRODUCTION

The oral route of delivery is the most preferred administration route as it offers one of the safest and most convenient methods of drug administration. So, it is necessary to evaluate the perfect quality maintain of each drug for human health. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems. These immediate release dosage forms have some limitations such as. Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance. The unavoidable fluctuations in the drug concentration may lead to over medication or under medication as the C_{ss} Values fall above or below the therapeutic range. The fluctuating drug levels may lead to precipitation of adverse effects especially for a drug with small therapeutic index, whenever over medication occurs.[1,2] In order to overcome the drawbacks of conventional drug delivery systems, several advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

ORAL CONTROLLED DRUG DELIVERY SYSTEMS[1]: Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of

GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

Pharmaceutical products which are formulated for systemic delivery via the oral route of administration, inspite of the type of delivery (immediate, sustained or controlled release) and the design of dosage form (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) physicochemical, pharmacokinetic and Pharmacodynamics characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed. The main areas of potential challenge in the development of oral controlled drug delivery systems are:-

a) To develop an oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site of action.
b) To modulate the GI transit time so that the drug delivery system developed can reach the target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.
c) If the drug to be delivered is subjected to extensive hepatic first pass metabolism, preventive measures should be taken to either bypass or minimize the extent of hepatic metabolic effect.

Metformin hydrochloride extended-release tablets contain an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (N, N dimethylimidodicarbonimidic diamide hydrochloride) is a member of the biguanide class of oral antihyperglycemics and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents.[3.] Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[4.]The t1/2 was 5.4 hours for metformin hydrochloride extended-release tablets.[5.] Pre-requirement of drug products that should be chemically and pharmaceutically equivalent must be identical in strength, quality, purity, active ingredient release profile and also in the same dosage form, for the same route of administration[6]. Because of the widespread use of this drug, quality control testing should be done for metformin hydrochloride SR marketed products to ensure safety; efficacy; accepted quality; rationality of use to protect public health.[7,8.] The objective of this work was therefore to evaluate the pharmaceutical quality of six different brands metformin hydrochloride SR tablets dispensed in and around Visakhapatnam, Andhra Pradesh, India.

MATERIALS ANDMETHODS

The quality analysis of Metformin hydrochloride SR tablets was studied through the evaluation of weight variation, hardness, friability, disintegration time, dissolution rate, potency study. The study was performed by doing these various test procedures which are the key factor in exploring the quality of the different brands of these tablets.

Collection of Sample: There are about more than forty products of metformin hydrochloride SR tablets in India. Six different available brands were collected from the local retail markets (Visakhapatnam). About thirty tablets of each brand were collected for the analysis. All brands of metformin hydrochloride SR contain 500 mg per tablet. The samples were properly checked for their physical appearance, the name of the manufacturer, batch number, and date of manufacturing, date of expiration, and manufacturing license number at the time of purchase. The information about the sample of the different brands of metformin hydrochloride SR tablets was given in table 1.

Reagents, instruments and equipments used: Distilled water, phosphate buffer (pH 6.8), Monsanto hardness tester (Elite Scientific & equipments), test tubes, basket

rack, standard motor drive device (speed motor),Roche friabilator (Elite Scientific & equipments),USP dissolution apparatus (M/s Lab India (Model- DS 8000); Whatman filter paper (10 mesh); Pipette; Volumetric flask; UV-visible spectrophotometer (Elite Scientific & equipments), constant temperature bath (37±0.5^{0}C), volumetric flask.

Evaluation test for Tablets[9]

Determination of weight variation of tablets: Ten tablets of each brand of metformin hydrochloride were taken and weighed individually with the mentioned an analytical balance. The average weight and the percent deviation of the tablets for each brand were calculated[10, 11]. Then % of weight variation is calculated by using the following formula is given below: Percentage weight variation= (average weight – individual weight)/ individual weight x 100 %

Determination of hardness of the tablets: Tablet hardness is defined as the force required breaking a tablet diametrically. A tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded[12]. Hardness is also termed as the Tablet Crushing Strength. Devices used to measure the hardness were Monsanto tester, tester, Schleuniger tester. Hardness of the tablets was observed by the use of Monsanto hardness tester. Monsanto tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deduced from it. The acceptable range of hardness or crushing strength of tablet is 4 to 7 kg-f (kilogram of force). During the study, the hardness of all tablets was determined using Monsanto Hardness Tester[13]. Ten tablets of each brand were taken and the hardness of the tablets was determined.

Determination of Thickness: Tablet thickness should be controlled within a ± 5% variation of a standard value. Any variation in tablet thickness within a particular lot of tablets or between manufacturer's lot should not be apparent to the unaided eye for consumer acceptance of the product. Thickness of the tablets was calculated by the use of Vernier calipers. Desired thickness was calculated to be 3.5 to 4 mm.

Determination of friability of the tablets: The friability test has also close relation with tablet hardness and is necessary to evaluate the capability of the tablet to withstand abrasion in packaging, handling, and shipping[14] The laboratory friability tester subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets a distance of 6 inches with each revolution. Normally, a preweighed tablet is placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Tablets that lose less than 0.5 to 1% of their weight are generally considered acceptable. When capping is observed on friability testing, the tablet should not be considered for commercial use, regardless of the percentage of loss seen. Friability of the tablets was calculated by the use of Roche friabilator. Friability should be less than 1%.[15] Percentage friability= {(Initial weight- Final weight)/ Initial weight} x100

Dissolution rate test of tablets: Generally, dissolution is the process of a solid drug to undergo solution, which affects the rate of drug absorption under standardized conditions of liquid or solid interface, temperature, and solvent composition [16]. This quality assurance type drug release pattern during a certain period of time is important for the perfect activity of a medicine in an internal organ of a human body in a definite Time17. Dissolution test for each brand of metformin hydrochloride SR tablet was carried out by USP dissolution type apparatus. Dissolution rate of the each brand of tablets was determined using 8 compartment dissolution test apparatus using paddle stirrer at 50 rpm and at a temperature of 37± 0.5^{0}C .Phosphate buffer Ph 6.8 (900ml) was used as dissolution fluid. One tablet (500mg) was used in each test. Samples of dissolution fluid (5ml) were withdrawn at intervals 0.5,1,2,3,4,5,6,7,8,9,10,11,12 hours. A

fresh 5ml of dissolution fluid was replaced to maintain sink condition. Each of the withdrawn samples was filtered and filtrate diluted. The absorbance was measured at 232nm.The concentration was determined against Standard solution of Metformin Hydrochloride in the same medium. Each dissolution experiment was run in triplicate and percentage of dug release is calculated using the formula. The obtained data was denoted (Table 4) and (figure1).

RESULTS AND DISCUSSION

Weight variation: The weight of ten different brands of metformin hydrochloride SR tablets was determined with the help of an electronic balance and the observed results have been included in the table below (Mean values ± SD, n=20). According to the BP, for the average weight of tablets (mg) are 80 or less the maximum percentage differences allowed ±10 and for the limit 80-250 mg, the percentage difference should be ±7.5 and more than 250mg this should be ±5. Besides, according to USP, for the average weights of tablets (mg) are 130 or less, 130-324 and more than 324 the maximum percentage difference should be ±10, ±7.5, ±5 respectively [7]. From the experiment results (table 3), it was obvious that weight variation limit values of all branded tablets were within maximum limit differences and no abnormality has occurred.

Hardness, Thickness and friability of tablets: Hardness is one of the most important physical features for evaluating tablet. It may affect tablet friability, disintegration time and bioavailability. Too hard tablets may result in a decrease in the release of the drug. Monsanto hardness tester was used to measure the hardness of 6 different brands (Mean values ± SD, n=10), Thickness (n=10), friability (Mean values ± SD, n=3), The observed results are shown that all different brands of tablets hardness limit 2.75-5.35 kg-f. (Table 4). In the study, it was found that all the brands of metformin hydrochloride sustained release tablets passed the test of hardness and had acceptable crushing strength. Hardness of B5 has more compared to all other brands. It may either due to using different granulation techniques or using different excipients. All the tablets of six brands have even thickness. B1&B2 have 1.6mm thickness. B5&B6 have 1.5mm thickness. B3& B4 have 1.45 & 1.58mm thickness respectively. Besides, the friability of the tablets which is determined using friabilator was found between 0.280–0.990% (Table 4) This indicates an impressive and accepted result.

Calibration curve of Metformin: An U.V. spectrophotometric method based on the measurement of absorbance at λmax 232nm in phosphate buffer of pH 6.8 was used for estimation of Metformin hydrochloride. Before performing dissolution test, ten serially diluted solution of reference standard (Metformin hydrochloride) and a standard solution curve drawn. The curve was linear between concentration range 10-50 µg/ml. Mean peak absorbance was plotted against the concentration to form the calibration curve. The regression equation was established.

Calculation of dissolution test on tablets: The process by which drug dissolves out of a dosage form and is made available for absorption from the gastrointestinal tract. The outcomes of the in vitro release of branded tablets were shown in table 5 and figure 3. The % of drug release for all the six brands of tablets at 5 th hour is more than 44.5% and at 8th hour 66.83% respectively. It indicates the drug released from all the tablets is controlled and also there is no dose dumping of drug. At the end of 12 th hour all brands of tablets released more than 92% of drug. The R^2 values of zero order of all brands was more than 0.967 and R^2 values of first order of all brands was less than 0.797.The R^2 values of zero order of individual brands are greater than R^2 values of first order. It indicates that the drug release follows zero order. The mechanism of drug release is diffusion controlled because R^2 values of Higuchi plot are higher than R^2 values of peppas. The dissimilarity and similarity (f1 & f2) taking B3 as reference (Innovator) product. All the five brands have f2 values more than 50. The dissimilarity values of all brands are less than 15. It indicates that all brands are having similar dissolution profiles as that of reference product. B5 & B6 have f2 values more than 80 which indicate the

dissolution profile is nearer to identical of the reference product.

Table 1. Different brands of Metformin HCL SR tablets

Brand Code	Brand	Batch No	Mfg date	Expiry date	Mfg Lic No.	Manufacturer
B1	Glycomet	28012315	08/2016	07/2018	MNB/06/291	USV Private Limited
B2	Gluconorm	J603554	11/2016	10/2018	JK/01/7-08/123	Lupin Limited.
B3	Glyciphage	M16121	08/2016	07/2018	388	Franco-Indian Remedies Private Limited
B4	Metsmall	E600907	08/2016	07/2018	MNB/11/837	Dr. Reddy's Laboratories
B5	Gluformin XL	5KB0054	05/2016	04/2018	M/605/2012	Swiss garniergenixian Sciences
B6	Exermet	F160349	10/2016	09/2019	72/LIA/LL/2010	Cipla Limited

Table 2: Average weight of different brands of diclofenac sodium tablets

Brands	Weight variation± S.D
B1	0.723±0.02
B2	0.688±0.01
B3	0.853±0.006
B4	0.681±0.014
B5	0.763±0.017
B6	0.703±0.011

Table 3: Hardness, Thickness and friability of different brands of metformin hydrochloride SR tablets

Brands	Hardness(kg/cm^2)	Thickness(mm)	Friability (%) ± S.D
B1	4.90±0.21	1.60	0.527±0.008
B2	4.75±0.42	1.60	0.280±0.009
B3	2.75±0.26	1.45	0.99±0.040
B4	2.85±0.47	1.58	0.290±0.010
B5	5.35±0.24	1.50	0.536±0.050
B6	4.65±0.41	1.50	0.426±0.020

Table 4. Calibration curve value of Metformin HCL

Concentration	Absorbance
0	0
10	0.18
20	0.373
30	0.566
40	0.759
50	0.952

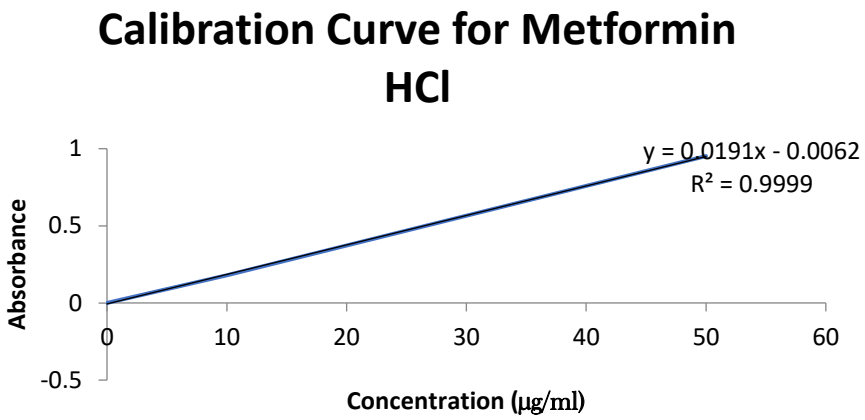

Figure 1 Calibration Curve for Metformin HCl

Table 5. *In-vitro* drug release profiles of different brands of Metformin Hydrochloride

Brands	Drug release (%)
B1	93.6
B2	96.7
B3	94.2
B4	95.4
B5	92.5
B6	93.6

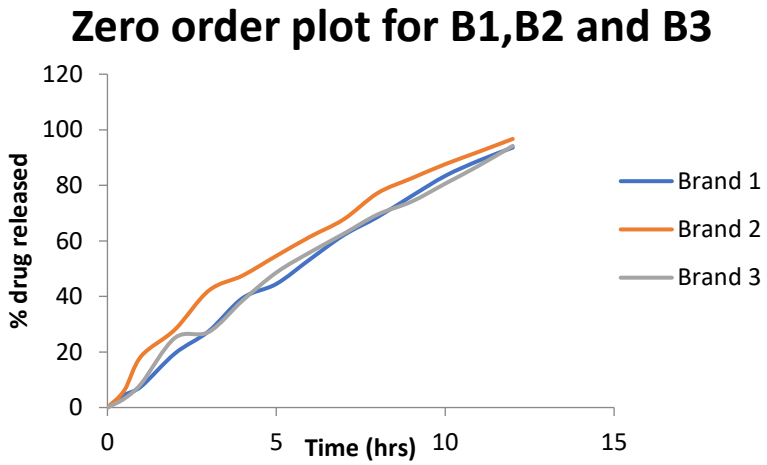

Figure 2 Zero order Plot for B1, B2 and B3

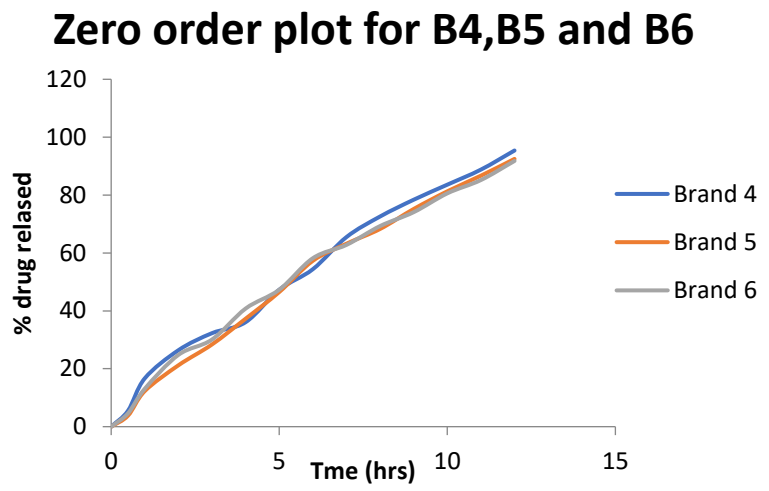

Figure 3 Zero order Plot for B4, B5 and B6

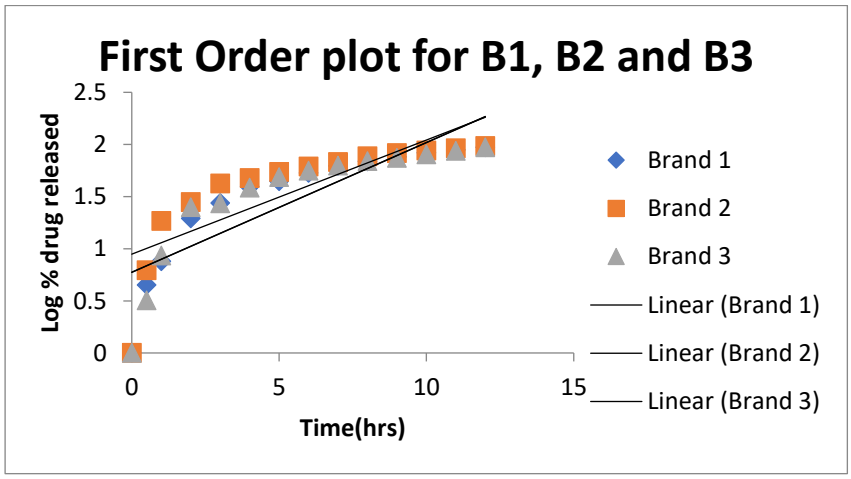

Figure 4 First order Plot for B1, B2 and B3

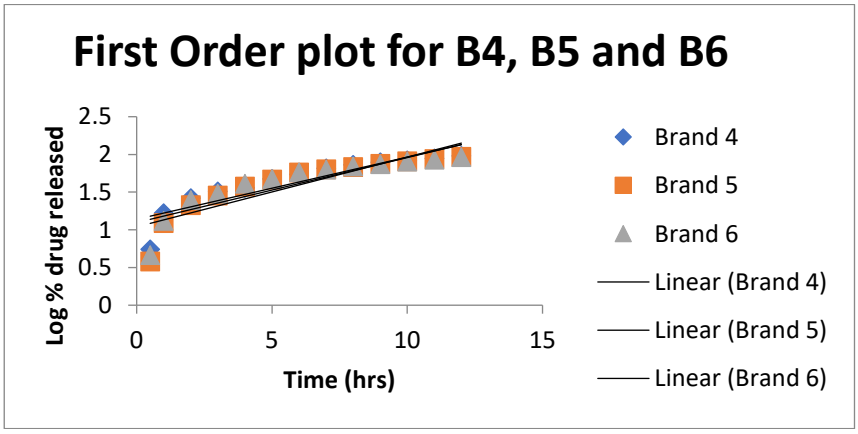

Figure 5 First order Plot for B4, B5 and B6

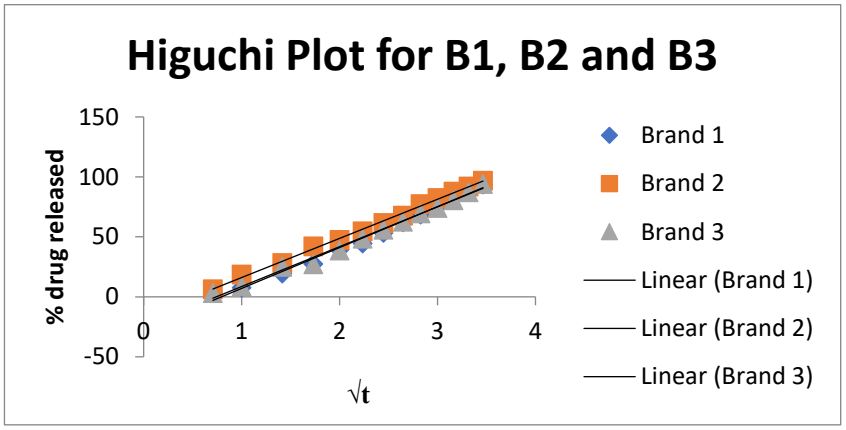

Figure 6 Higuchi Plot for B1, B2 and B3

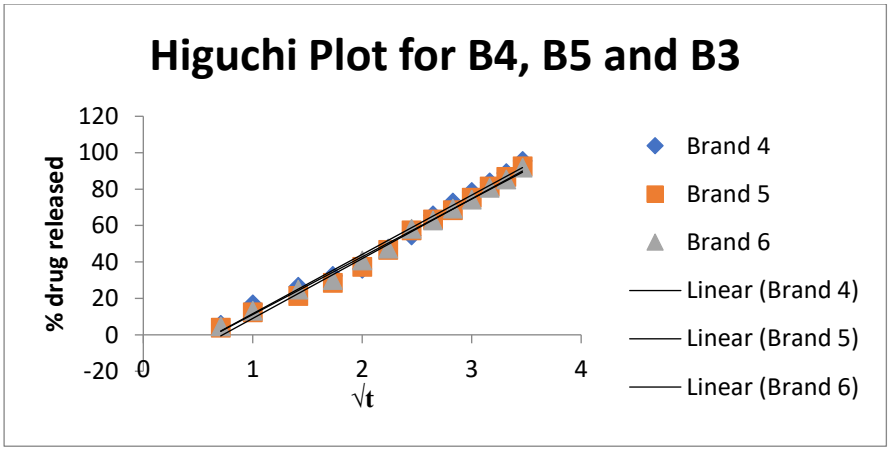

Figure 7 Higuchi Plot for B4, B5 and B6

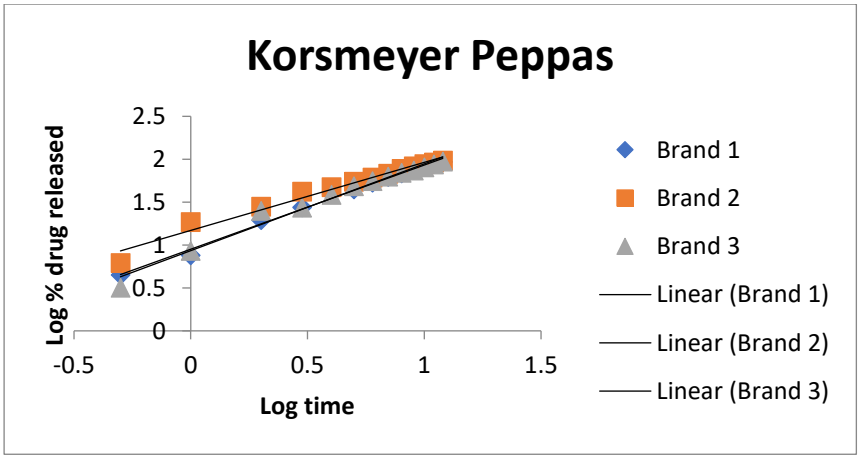

Figure 8Korsmeyer Plot for B1, B2 and B3

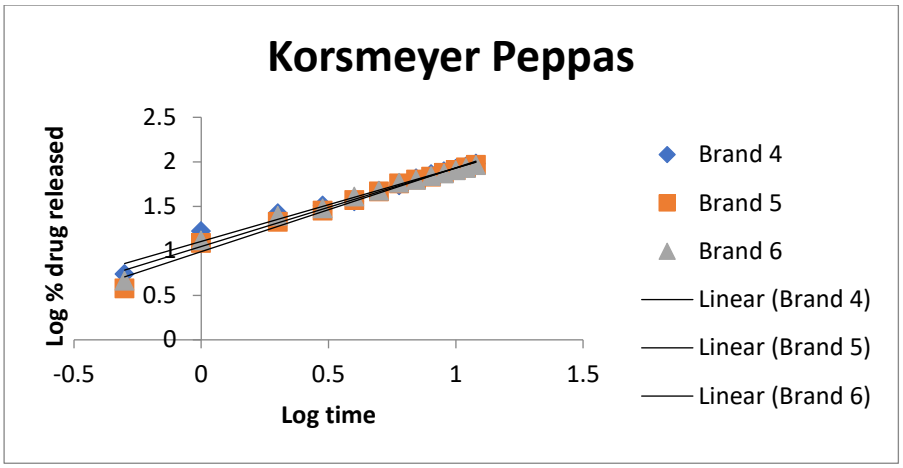

Figure 9 - Korsmeyer Plot for B4, B5 and B6

Table6.R^2 Values

Brands	Zero Order	First Order	Higuchi	Peppas
B1	0.992	0.736	0.987	0.993
B2	0.967	0.626	0.997	0.971
B3	0.985	0.708	0.991	0.976
B4	0.986	0.797	0.982	0.976
B5	0.987	0.776	0.99	0.982
B6	0.981	0.769	0.994	0.981

Brands	f1	f2
B1	0.911672	79.297
B2	11.4376	56.1689
B4	3.95448	72.0147
B5	0.178042	81.5579
B6	1.09858	82.4541

Table 7 Similarity and Dissimilarity Values

CONCLUSION:

SR 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 SR preparations. Compared to the *in vivo* BE tests, conventional in vitro studies are less complicated, fast, economic and useful quality control tool and evaluate more directly drug absorption than *in vivo* bioequivalence studies. It can be concluded that all the available brands in local region of Visakhapatnam, Andhra Pradesh, India are having within the specified quality range and can be interchange of found and on compliance due to cost issue. The results have shown that all the tested brands satisfied the I. Pre requirements in terms of uniformity of weight, friability, hardness and dissolution. According to present study patients can be safely switch from one brand to an another but with consulting with possibility of some minor GIT complication that can occur after the treatment with new alternative drug.

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