ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Kinetic Modeling and Comparison of Invitro Release of Metformin Hydrochloride from Commercially Available Formulations

Jitendra C Shah, and Ashwini Deshpande*

SVKM's NMIMS, School of Pharmacy and Technology Management, Shirpur, Dist. Dhulia, Maharashtra-425405.

ABSTRACT

This research describes that the quantitative analysis of the values obtained in dissolution release tests are easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used. From the theoretical analysis of the occurring process, these mathematic models are derived. In most of the cases the theoretical concept does not exist and some empirical equations have proved to be more appropriate. The dissolved amount of drug is a function of the test time when drug release from solid dosage forms has been described by kinetic models. Some commonly used analytical definitions of the functions are zero order, first order, Hixson-Crowell, Weibull, Higuchi, Baker-Lonsdale, Korsmeyer-Peppas and Hopfenberg models. Other release parameters, such as dissolution time, assay time, dissolution efficacy, difference factor (f1) and similarity factor (f2) can be used to characterize drug release profiles.

Keywords: Drug release kinetic models, model dependent method, model independent method, statistical analysis

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Metformin Hydrochloride is one of the most commonly used drugs in the world. Metformin is an antidiabetic drug which is classified in to the biguanide class. It is the first line drug of choice for the treatment of type 2 diabetes and also particularly in overweight, obese people and with normal kidney function. This drug is officially in Indian Pharmacopoeia (I.P.2010). [1-3]Long-term stability and shelf life of a dosage form determination, and the impact of post-approval changes in the developed process can also be assist by dissolution studies. For the pharmaceutical industry regulatory authorities such as the FDA have implemented guidelines on dissolution testing of solid dosage forms. [4-6] Dissolution tests can provide the ability to differentiate between interbatch inconsistencies within a product and provide a description for in vitro drug release allowing determination of in vivo suitability of the formulation. [7]By the use of dissolution profile comparison and analysis the evaluation of in vitro equivalence between reference and test batches can be conducted. Very often, an in vitro dissolution test is more sensitive and discriminating than an in vivo test. According to a quality assurance point of view, a more discriminative dissolution method is preferred, as the test will indicate probable deviations in the quality of the product before in vivo enactment is affected. [7]For the comparison of invitro dissolution profiles methods can be divided in to three main groups: ANOVA (Analysis of variance) based statistical methods, model-independent and model dependent approaches. ANOVA-based methods can be categorized as one-way ANOVA which measure the difference between the means of two drug release data sets at a single time point of dissolution and multivariate analysis of variance (MANOVA), which measure the difference between the means of two drug release data sets at a multiple time points of dissolution. Most of the studies have shown that the ANOVA-based methods were overly discriminating and because of that it was difficult to distinguish between two dissolution curves. [8-10]The model independent approach allows the profile or profile differences to be translated into a single value allowing a simpler analysis of data. [9-18]Two model-independent techniques are commonly used, ratio tests and fit factors. The commonly used ratio tests include comparison of the mean dissolution times (MDTs), variance of dissolution times (VTs), and the relative dispersion of dissolution times (RDs). [19]Moore and Flanner were introduced the fit factors which are also known as the difference factor f1 and the similarity factor f2.[17]The difference factor f1 Calculate the % difference between the two dissolution curves at each time point And is a measurement of the relative error between two curves. The limit for difference factor f1is from 0-15.Thesimilarity factor f2 is a logarithmic reciprocal square root transformation of the sum of Square error and is a measurement of similarity in the % dissolution between the two curves. The limit for the similarity factor f2 is from 50-100. As the value increases from above 50 then the reference and test products are identical to each other. The similarity factor f2 is gaining admiration due to its recommendation by a number of regulatory authorities as a criterion for the assessment of similarity between dissolution profiles. [11, 20, 21] Model independent approaches directly compare the dissolution data without having to rely on model functions that may prove to be artificial. Model dependent approaches have been used extensively for the representation of dissolution data. [9-11, 13, 21] The approach requires a suitable mathematical function that can be linear or nonlinear to describe the dissolution data. Nonlinear models tend to be more reliable as they predict responses outside the observed

range of data, whereas linear models are linear in their parameters. [14-15]The commonly used models for both linear and nonlinear functions are: Higuchi, Hixson–Crowell, Korsmeyer–Peppas, Weibull, Logistic, zero-order, and first-order. [21] After selection of model, the dissolution profiles are compared and estimated in terms of the model parameters. In the meantime, the mathematical model approach also provides an insight into the drug release mechanism. Although such mathematical models have been used to characterize dissolution profiles, such methods are quite complicated and require caution in their application compared with model-independent methods. [10]As there are many different brands available in the market, there are ample of chances to switchover from one brand to another brand due to the unavailability of the particular brand by prescribers. Now a day's choices for the release rate retarding polymers are more and its choice varies from manufacturer to manufacturer, which may lead to variation in drug's plasma levels. Chances of such switchover from one to another brand by patients without involving prescriber also cannot be overlooked. Though all marketed formulations comply with FDAs requirement, hostile conditions during transportation, unintentional technical difficulties in storage may lead to alteration in release profile. Due to these reasons the rationale of this work was to examine if there are any differences between various commercially available immediate release and sustained release metformin tablets through evaluation of in vitro dissolution profiles using both model-dependent and model-independent approaches. Different brands of immediate-release and sustained release solid dosage form metformin tablets were obtained from commercially available vendors for this study. Dissolution testing was carried out using USP (United States of Pharmacopoeia) Apparatus type2 (paddle) to obtain dissolution profiles of I.R. and S.R. tablets in 900 mL pH 6.8 phosphate buffer with samples taken at 10, 20, 30, 45, and 60 min for immediate release tablets and for sustained release tablets samples taken at 1, 2, 3….10 hours by using the same phosphate buffer pH 6.8 but for initial two hours 0.1N HCL is used. Additional In process quality control tests (IPQC) were also carried out on each brand of metformin tablets, including weight variation, friability test, hardness test and disintegration test for immediate release tablets and same tests are carried out for sustained release tablets except disintegration test according to I.P.2010.

MATERIALS AND METHODS

In this research, five brands of commercially available Immediate Release (I.R.) including one reference and seven brands of Sustained Release (S.R.) including one reference uncoated metformin tablets were obtained from different vendors. Detailed information of the different I.R and S.R. brands of tablets is summarized in Table 1 and 2. The labelled amount of drug substance for each brand is the same (500 mg), as are all of the excipients in the formulations of the different brands. However, there is no detailed information about the excipients used in the different formulations.0.1N HCL and phosphate buffer of pH 6.8 was used as the dissolution medium as specified in the I.P 2010. Phosphate buffer was prepared by mixing 68 g of potassium dihydrogen phosphate (KH_2PO_4) with 9 gm of sodium hydroxide (NaOH) and sufficient distilled water to produce 10 L. Potassium dihydrogen phosphate (KH_2PO_4) and sodium hydroxide (NaOH) were analytical grade and purchased from Rankem laboratories. Metformin hydrochloride was dissolved in the phosphate buffer to make a series of standard

calibration solutions with different concentrations for development of a calibration curve using a UV spectrophotometer at 233 nm.

Table 1: Metformin I.R. tablet used in the test

Brand	Dosage (mg)	Appearance
A (Reference Product)	500	White Circular with one side on indented line with written Glu and on other side plain
B (Test)	500	White Circular with one side on indented line and on other side USV
C (Test)	500	White oblonged with one side on indented line and on other side Glyciphage
D (Test)	500	White Circular with indented line on one side and plain on other side
E (Test)	500	White oblonged with indented line

Table 2: Metformin S.R. tablet used in the test

Brand	Dosage (mg)	Appearance
A (Reference)	500	White oblonged and plain on both surface
B (Test)	500	White oval with plain on both side
C (Test)	500	White Circular with plain on both side
D (Test)	500	White oblonged with indented line
E (Test)	500	White oblonged and plain on both surface
F (Test)	500	White oblonged and plain on both surface
G (Test)	500	White oval and plain on both surface

Dissolution Testing

In vitro dissolution was carried out via USP Apparatus type 2 (paddle) at a speed of 100 rpm in 900 mL of dissolution medium (pH 6.8 Phosphate buffer) maintained at 37 ± 0.5 °C using a water bath fitted with a variable speed stirrer and heater. Selection of 100- rpm rotation speed was based on the I.P. 2010 guideline. Samples (5 ± 0.1 mL) were taken manually at 10, 20, 30, 45, and 60 min for I.R tablets and 1,2,3……10 hours for S.R. tablets and replaced with an equal volume of fresh medium to maintain a constant dissolution volume. The samples were filtered and dilution is carried out by taking 0.1 ml and diluted up to 10 ml with the same phosphate buffer, and the absorbance was measured at 233 nm using a UV spectrophotometer. The drug concentration determined by the calibration model was used to calculate the total mass of the drug released in the medium.

In this work, the dissolution profiles are represented as the cumulative percentages of the amount of drug released at each sampling interval. Each profile is the average of six individual tablets.

ISSN: 0975-8585

Tablet Weight variation, Disintegration, Friability, and Hardness Tests

Weight variation test is carried out according to I.P 2010. This test include the twenty tablets are taken, weigh individually and the overweight and underweight tablets are discarded to reject the batch. If two tablets are not according to the specification then not to reject the batch. The limits are described in the Table 3.

Table 3: Weight variation specification according to I.P 2010

Average weight of tablets	Maximum % difference allowed
<80	± 10 %
80-250	± 7.5 %
>250	± 5 %

The disintegration test was carried out as stated in the I.P. 2010, in which one dosage unit was placed in each of the six tubes of the basket with a tablet on the top of the disc. Phosphate buffer at pH 6.8 was used as the immersion fluid at 37 °C. The specification states that all of the uncoated tablets should disintegrate within 15 min. The end point was determined when there were no particles or granules remaining on the disc.

The friability test method was adapted from that in the Indian Pharmacopoeia. The I.P. 2010 method states that 10 tablets or weight of ≥6.5 gm are rotated in the friability drum at 25 RPM for 4 min.

In the hardness test, six tablets were taken individually and determined by using a Monsanto hardness tester. When the device was started, the vice gradually applied force onto the tablet until it split, and the force at which this occurred was recorded.

Model-Independent Methods

Model-independent approaches produce a single value from a dissolution profile, providing direct comparisons of the dissolution data. Consequently the results do not depend on the selection of the specific parameter for fitting data but on the chosen sampling time in the calculation. Model-independent approaches include ratio tests and fit factors. In this study fit factors have been used for the calculation.

Fit factors include a difference factor $f1$ and a similarity factor $f2$.[3-4] The difference factor $f1$ calculate the % difference between the two curves at each time point and is a measurement of the relative error between two curves which is given by,

$$F1 = [(\sum^{n}_{t=1}(Rt - Tt)/ (\sum^{n}_{t=1}Rt)] \times 100$$

Where Rtand Tt are the percent drug dissolved of the reference and test products, respectively, at each sample point i.

The similarity factor *f*2 is a logarithmic reciprocal square root transformation of the sum of square error and is a measurement of similarity in the % dissolution between the two curves which is given by

$$F2 = 50 \times \log [(1 + (1 + (1/n) \sum^{n}_{t=1}(Rt - Tt)^{2})^{-0.5} \times 100]$$

Model Dependent Methods

Model dependent methods are established on different mathematical functions, which describe the dissolution profile. Once an appropriate function has been designated, the dissolution profiles are estimated depending on the derived model constraints. The nonlinear regression module of Statistical 5.0 was used to determine the suitable drug release kinetic model describing the dissolution profile. In non-linear regression analysis the Quasi-Newton and Simplex methods minimized the least squares. The model dependent approaches included zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Baker-Lonsdale, Weibull, Hopfenberg, Gompertz, Non-conventional order 1, Non-conventional order 2, Reciprocal powered time and regression models.

Zero-order model

Dosage forms that do not disaggregate and release the drug when the drug get slowly dissolved and can be represented by the equation:

$$Q_0 - Q_t = K_0 t \text{.....Eq. 3}$$

Rearrangement of equation (3) yields:

$$Q_t = Q_0 + K_0 t \text{.....Eq.4}$$

Where,

Q_t =the amount of drug dissolved in time *t,*

Q_0 = the initial amount of drug in the solution (most times, Q_0= 0) and K_0 is the zero order release constant expressed in units of concentration/time.

Plot: Cumulative amount of drug released versus time to study the release kinetics of drug.

Application: In some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc. this model is generally used. [22]

First order model

To describe absorption and elimination of some drugs, this model has been used, although it is difficult to conceptualize this mechanism on a theoretical basis. First order kinetics can be expressed by the equation:

$$dC/dt = -KC \text{.....Eq. 5}$$

Where ***K***is first order rate constant expressed in units of time-1.

Equation (5) can be expressed as:

$$\log C = \log C_0 - Kt / 2.303 \quad \text{.....Eq. 6}$$

Where C_0= the initial concentration of drug, k = the first order rate constant, and t = time.

Plot: The data obtained are plotted as log cumulative percentage of drug remaining *vs*. time which would yield a straight line with a slope of -K/2.303.

Application: Those containing water-soluble drugs in porous matrices for that this model has been preferred. [23]

Higuchi model

To describe drug release from a matrix system was proposed by Higuchi in 1961 was the first example of a mathematical model. Initially it was considered for planar systems, and then it was extended to porous systems and different geometrics. This model is based on the hypotheses that (i) in the matrix, initial drug concentration is much higher than drug solubility; (ii) only in one dimension (edge effect must be negligible), drug diffusion takes place; (iii) system thickness is grater then the drug particles; (iv) dissolution and matrix swelling are negligible; (v) drug diffusivity is constant; and (vi) in the release environment, perfect sink conditions are always attained. Accordingly, model expression is given by the equation:

$$f_t = Q = A\sqrt{D(2C - C_s)\,C_s\,t} \quad \text{.....Eq.7}$$

Where Q = the amount of drug released in time t per unit area A,
C = the drug initial concentration, *Cs* = the drug solubility in the matrix media and
D = the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance.

Except when the total depletion of the drug, this relation is valid during all the time in the therapeutic system is achieved. The drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the expression is given by equation (8), to study the dissolution from a planar heterogeneous matrix system:

$$f_t = Q = \sqrt{\frac{D\delta}{\tau}(2C - \delta C_s)\,C_s\,t} \quad \text{.....Eq. 8}$$

Where D = the diffusion coefficient of the drug molecule in the solvent, δ = the porosity of the matrix, τ = the tortuisity of the matrix and Q, A, Cs and have the meaning assigned above. Tortuisity is defined as the dimensions of radius and branching of the pores and canals in the

matrix. In a general way it is possible to simplify the Higuchi model as (generally known as the simplified Higuchi model) [24]

$$f_t = Q = K_H \times t^{1/2} \text{.....Eq. (9)}$$

Where, K_H = the Higuchi dissolution constant.

Plot: cumulative percentage drug release versus square root of time is plotted.

Application: To describe dissolution of drug from several types of modified release pharmaceutical dosage forms, transdermal systems and matrix tablets with water soluble drugs this relationship can be used.

Korsmeyer – Peppas model

To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer Peppas model and the equation derived is as:

$$M_t / M_\infty = Kt^n \text{..... (10)}$$

WhereM_t / M_∞ = a fraction of drug released at time t, k = the release rate constant and n = the release exponent. The n value is used to characterize different release for cylindrical shaped matrices.

For the case of cylindrical tablets, 0.45 ≤n corresponds to a Fickian diffusion mechanism, 0.45 < n <0.89 to non-Fickian transport, n = 0.89 to Case II (relaxation) transport, and n >0.89 to super case II transport. To find out the exponent of *n* the portion of the release curve, where M_t / M_∞< 0.6 should only be used. [25]

Plot: log cumulative percentage drug release versus log time, to study the release kinetics, data obtained from in vitro drug release studies were plotted.

Hixson Crowell

Hixson and Crowell (1931) suggest that the particles regular area is proportional to the cube root of its volume. They derived the equation:

$$W_0^{1/3} - W_t^{1/3} = \kappa t \text{..... Eq. (11)}$$

Where, $W_0$is = initial amount of drug in the pharmaceutical dosage form,
W_t = remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface-volume relation. The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets.

ISSN: 0975-8585

Plot: Cube root of drug percentage remaining in matrix versus time, to study the release kinetics, data obtained from in vitro drug release studies was plotted. [26]

Application: This model is mainly applicable to that if the tablet dimensions diminish proportionally, where the dissolution occurs in planes that are parallel to the drug surface, in such a manner that the initial geometry.

Akaike Information Criterion (AIC)

AIC is good for prediction AIC is an asymptotically efficient model selection criterion. AIC is used to test the applicability of the release models. The Akaike Information Criterion is a measure of goodness of fit based on maximum possibility. When comparing several models for a given set of data, the model associated with the smallest value of AIC is regarded as giving the best fit out of that set of models. The AIC will give appropriate values when used to compare models with same weighing scheme. [3] This AIC can be calculated by following equation.

$$AIC = n * \ln (WSSR) + 2 * P$$

Where, n = number of dissolution data points
WSSR = weighed of sum of square residues
P = number of parameters in the model

RESULTS

Tablet Weight variation, Disintegration, Friability, and Hardness Tests for Immediate Release (I.R) tablets (As per I.P.2010)

Weight variation test:

Table 4: Weight variation test results of five brands of I.R tablets

Brand name	Weight variation (mg)
A (Reference Product)	596.66±5 (591.66 – 601.66)
B (Test)	600.9±5 (595.9- 605.9)
C (Test)	545.3±5 (540.3 - 550.3)
D (Test)	656.6±5 (651.6 - 661.6)
E (Test)	517.8±5 (512.8 – 522.8)

Disintegration test:

Table 5: Average disintegration times of six tablets for each brand

Brand name	Disintegration time	Standard Deviation (SD)
A (Reference Product)	6 min 42 sec	1.21
B (Test)	5 min 30 sec	0.84
C (Test)	6 min 21 sec	0.82
D (Test)	5 min 28 sec	0.84
E (Test)	6 min 10 sec	1.03

Friability test:

Table 6: Friability Test results of I.R tablets based on Avg. of six tablets

Brand name	Friability (%)	SD
A (Reference Product)	0.18	0.008
B (Test)	0.69	0.008
C (Test)	0.27	0.005
D (Test)	0.61	0.007
E (Test)	0.38	0.008

Hardness test:

Table 7: Hardness Test results of I.R tablets based on Avg. of six tablets

Brand name	Hardness ($kg/m^{2)}$	SD
A (Reference Product)	12.8	0.08
B (Test)	11.1	0.08
C (Test)	12.1	0.08
D (Test)	11.2	0.08
E (Test)	11.9	0.08

Tablet Weight variation, Friability, and Hardness Tests for Sustained Release (S.R) tablets (As per I.P.2010)

Weight variation test:

Table 8: Weight variation test results of seven brands of S.R tablets

Brand name	Weight variation (mg)
A (Reference)	959.05±5
B (Test)	707.3±5
C (Test)	703.3±5
D (Test)	754.3±5
E (Test)	845.9±5
F (Test)	701.4±5
G (Test)	857.3±5

ISSN: 0975-8585

Friability test:

Table 9: Friability Test results of S.R tablets based on Avg. of Six tablets

Brand name	Friability (%)	SD
A (Reference)	0.52	0.008
B (Test)	0.63	0.008
C (Test)	0.56	0.007
D (Test)	0.66	0.006
E (Test)	0.59	0.007
F (Test)	0.57	0.007
G (Test)	0.58	0.007

Hardness test:

Table 10: Hardness Test results of S.R tablets based on Avg. of six tablets

Brand name	Hardness (kg/m$^{2)}$	SD
A (Reference)	15.7	0.08
B (Test)	14.5	0.08
C (Test)	15.6	0.08
D (Test)	14.2	0.08
E (Test)	15.3	0.08
F (Test)	15.5	0.08
G (Test)	15.5	0.08

Calibration curve of API (metformin HCL) in 0.1 N HCL and pH 6.8 buffer

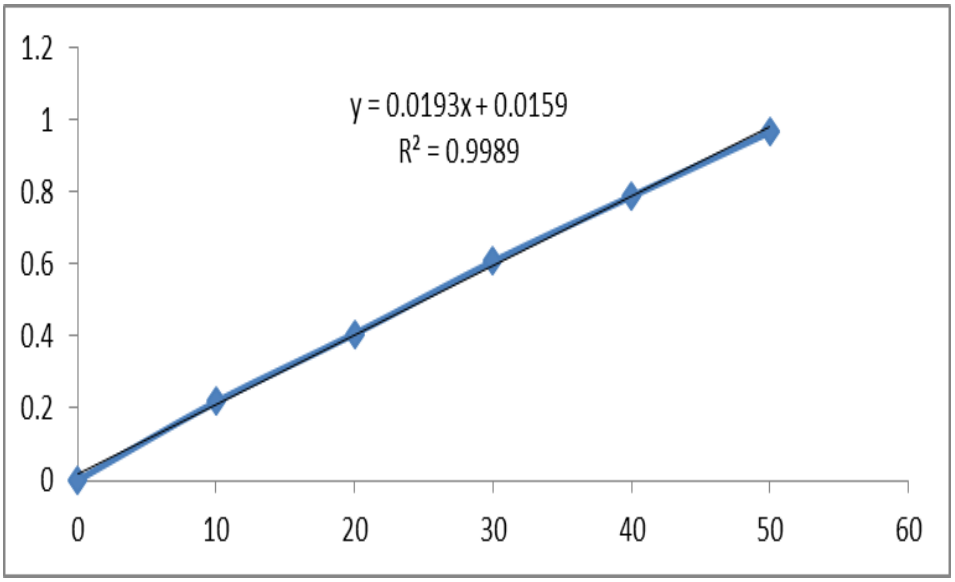

Figure 1: Linearity curve of Metformin HCL in 0.1 N HCL

ISSN: 0975-8585

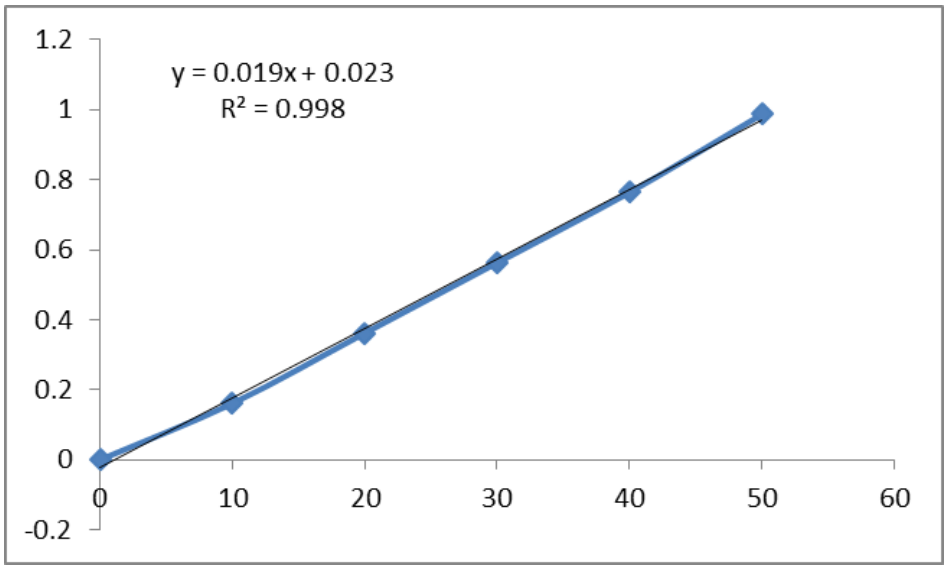

Figure 2: Linearity curve of Metformin HCL in pH 6.8 buffer

In Vitro Dissolution Tests for I.R tablet

Table 11: Dissolution data and their statistical properties of I.R tablets

Time (Min)	Brands	% CDR	%RSD
10	A (Reference)	66.91	5.39
	B (Test)	72.21	2.06
	C (Test)	64.82	5.34
	D (Test)	63.83	4.11
	E (Test)	66.08	3.11
20	A (Reference)	84.69	2.58
	B (Test)	85.16	2.68
	C (Test)	79.53	5.06
	D (Test)	80.01	2.56
	E (Test)	81.07	1.86
30	A (Reference)	91.93	1.01
	B (Test)	92.31	1.74
	C (Test)	89.11	2.60
	D (Test)	88.41	1.62
	E (Test)	91.02	2.07
45	A (Reference)	91.84	0.89
	B (Test)	92.80	1.30
	C (Test)	92.70	1.12
	D (Test)	91.82	0.81
	E (Test)	98.04	2.82
60	A (Reference)	92.80	1.21
	B (Test)	92.41	0.91
	C (Test)	94.09	1.66
	D (Test)	93.19	1.65
	E (Test)	92.80	1.34

ISSN: 0975-8585

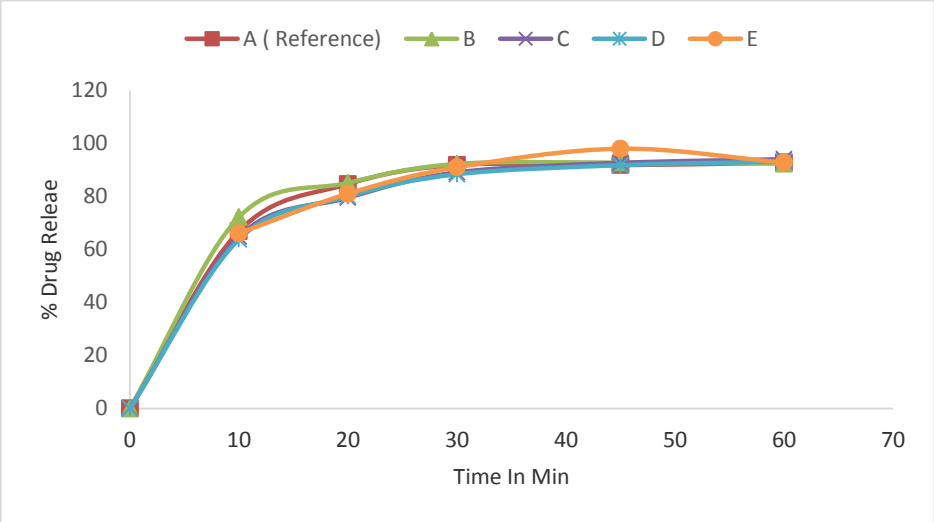

Figure 3: % Drug Release Versus Time in min of five brands of I.R tablets

Model Independent Methods (Fit Factors)

Table 12: F1 and F2 calculation for four brands of I.R tablets

S. No.	Brand Name	F1 (Difference)	F2 (Similarity)
1	A (Reference)/ B (Test)	0.61 %	97.25 %
2	A (Reference)/ C (Test)	2.80 %	76.90 %
3	A (Reference)/ D (Test)	2.38 %	77.57 %
4	A (Reference)/ E (Test)	2.97 %	73.51 %

In Vitro Dissolution Tests for S.R tablet

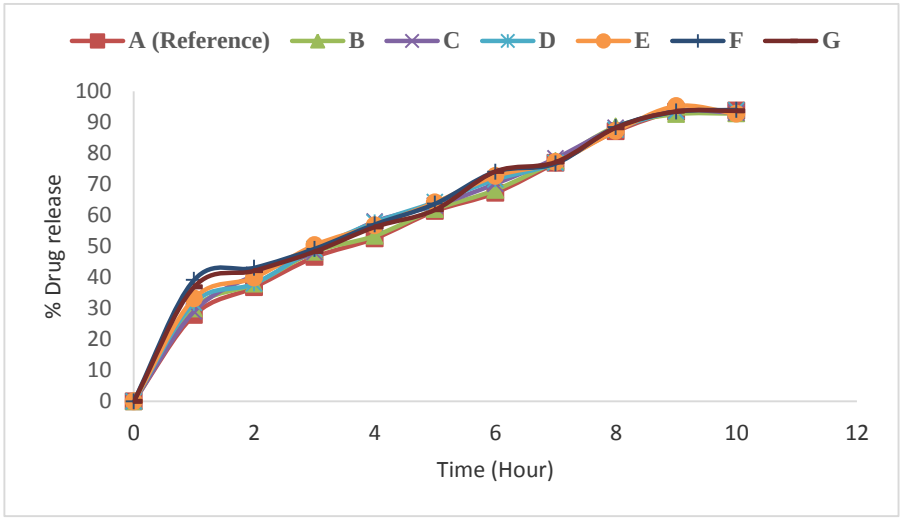

Figure 4: % Drug Release Versus Time in Hour of seven brands of S.R tablets

ISSN: 0975-8585

Table 13: Dissolution data and their statistical properties of S.R tablets

Time (Hour)	Brands	% CDR	%RSD
1 In 0.1 N HCL	A (Reference)	27.83	3.71
	B (Test)	29.96	4.71
	C (Test)	29.02	5.69
	D (Test)	31.81	4.50
	E (Test)	33.21	4.02
	F (Test)	39.12	3.19
	G (Test)	36.88	2.95
3 In pH 6.8 buffer	A (Reference)	46.52	1.48
	B (Test)	48.20	2.47
	C (Test)	48.11	1.73
	D (Test)	49.19	2.11
	E (Test)	50.38	1.70
	F (Test)	49.18	1.91
	G (Test)	48.28	2.36
	G (Test)	93.51	0.88
10 In pH 6.8 buffer	A (Reference)	93.73	1.07
	B (Test)	92.82	0.76
	C (Test)	93.05	0.76
	D (Test)	93.85	1.39
	E (Test)	92.78	0.96
	F (Test)	93.98	1.51
	G (Test)	93.68	1.04

Model Dependent Methods

Different Kinetic Models and Release order for the Seven Brands of Metformin Tablets Based on the Average of Six Tablets

Zero order (% CDR (Cumulative Drug Release) *versus* Time)

Table 14: CDR *versus* Time for seven brands of S.R tablets

Time (min)	A (Ref.)	B	C	D	E	F	G
0	0	0	0	0	0	0	0
60	27.83	29.96	29.02	31.81	33.21	39.12	36.88
180	46.52	48.2	48.11	49.19	50.38	49.18	48.28
600	93.73	92.82	93.05	93.85	92.78	93.98	93.68

ISSN: 0975-8585

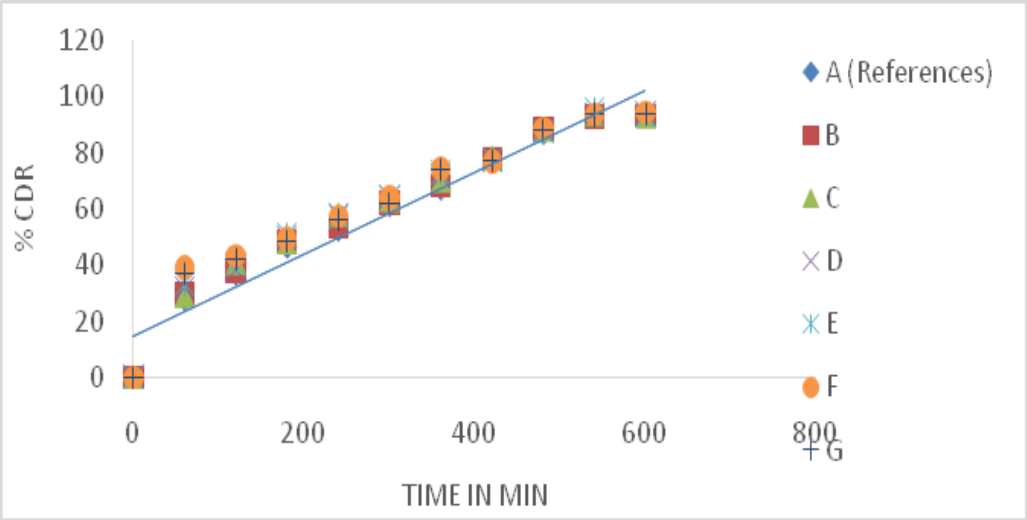

Figure 5: Zero order release kinetics for seven brands of S.R tablets

Table 15: Linearity (R^2) and AIC of zero order for S.R tablets

Brands	Linearity	AIC
A (Reference)	R^2 = 0.9561	43.6802
B (Test)	R^2 = 0.9452	46.3176
C (Test)	R^2 = 0.9377	48.0872
D (Test)	R^2 = 0.9369	45.3356
E (Test)	R^2 = 0.9289	46.5333
F (Test)	R^2 = 0.9122	43.7799
G (Test)	R^2 = 0.9222	45.0296

First Order (Log % CDR Remaining *versus* Time)

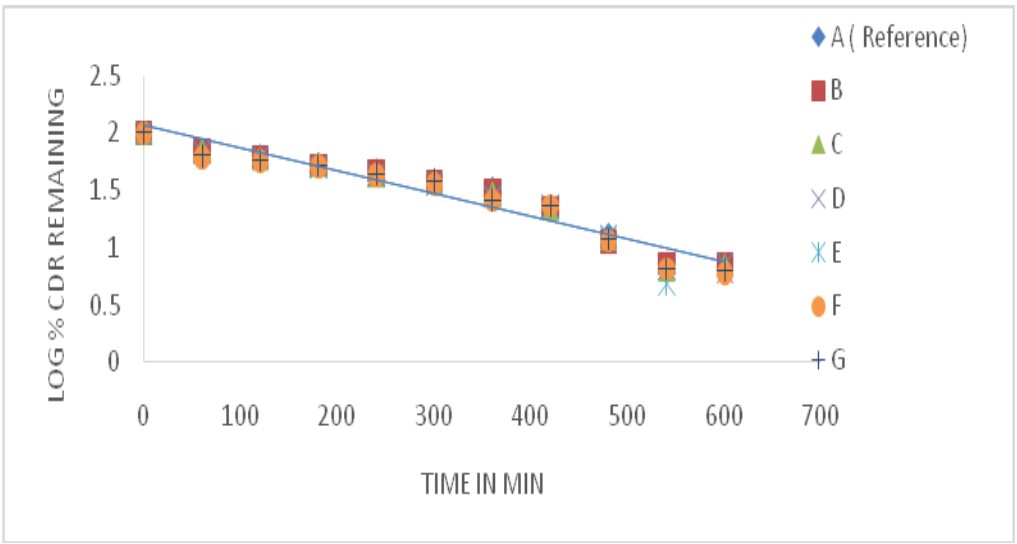

Figure 6: First order release kinetics for seven brands of S.R tablets

ISSN: 0975-8585

Table 16: Log % CDR Remaining *versus* Time for S.R tablets

Time	A (Ref.)	B	C	D	E	F	G
0	2.000	2.000	2.000	2.000	2.000	2.000	2.000
60	1.858	1.845	1.851	1.834	1.825	1.784	1.800
180	1.728	1.714	1.715	1.706	1.696	1.706	1.714
600	0.797	0.856	0.842	0.789	0.859	0.780	0.801

Table 17: linearity (R^2) and AIC of first order for S.R tablets

Brands	Linearity	AIC
A (Reference)	$R^2 = 0.9323$	62.4660
B (Test)	$R^2 = 0.9431$	62.1070
C (Test)	$R^2 = 0.9429$	63.7717
D (Test)	$R^2 = 0.9436$	62.0341
E (Test)	$R^2 = 0.9146$	61.0592
F (Test)	$R^2 = 0.9371$	54.9258
G (Test)	$R^2 = 0.9381$	56.9807

Higuchi Model (%CDR *versus* Square Root of Time)

Table 18: %CDR *versus* Square Root of Time for S.R tablets

S.R. Of Time	A (Ref.)	B	C	D	E	F	G
0.00	0	0	0	0	0	0	0
7.75	27.83	29.96	29.02	31.81	33.21	39.12	36.88
13.42	46.52	48.2	48.11	49.19	50.38	49.18	48.28
24.49	93.73	92.82	93.05	93.85	92.78	93.98	93.68

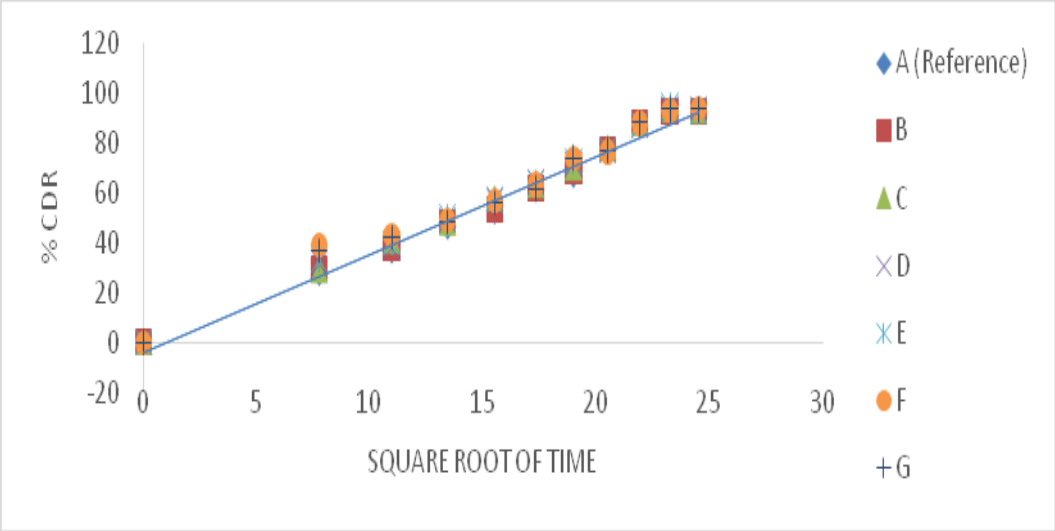

Figure 7: Higuchi model release kinetics for seven brands of S.R tablets

ISSN: 0975-8585

Table 19: Linearity (R^2) and AIC of Higuchi model for S.R tablets

Brands	Linearity	AIC
A (Reference)	R^2 = 0.9855	56.5816
B (Test)	R^2 = 0.9868	53.3567
C (Test)	R^2 = 0.9924	48.0028
D (Test)	R^2 = 0.9923	47.0130
E (Test)	R^2 = 0.9905	47.8466
F (Test)	R^2 = 0.9827	54.3815
G (Test)	R^2 = 0.9837	53.0697

Korsmeyer – Peppas Model (Log % CDR *versus* Log Time)

Table 20: Log % CDR *versus* Log Time for S.R tablets

Log Time	A (Ref.)	B	C	D	E	F	G
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1.778	1.445	1.477	1.463	1.503	1.521	1.592	1.567
2.255	1.668	1.683	1.682	1.692	1.702	1.692	1.684
2.778	1.972	1.968	1.969	1.972	1.967	1.973	1.972

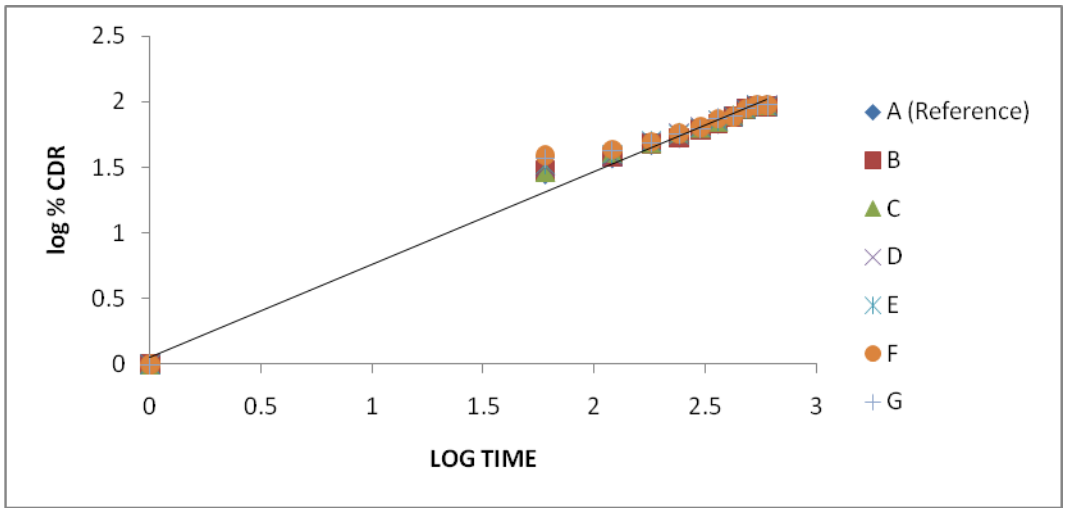

Figure 8: Korsmeyer Peppas model release kinetics for seven brands of S.R tablets

Table 21: linearity (R^2) and AIC of Korsmeyer Peppas model for S.R tablets

Brands	Linearity	AIC
A (Reference)	R^2 = 0.9913	48.2025
B (Test)	R^2 = 0.9878	50.0151
C (Test)	R^2 = 0.9886	43.9030
D (Test)	R^2 = 0.9857	45.7882
E (Test)	R^2 = 0.9827	49.1304
F (Test)	R^2 = 0.9717	56.1374
G (Test)	R^2 = 0.9758	55.5994

ISSN: 0975-8585

Hixon - Crowell Model (Cube Root of % Drug Remaining *versus* Time)

Table 22: Cube Root of % Drug Remaining *versus* Time form S.R tablets

Time	A (Ref.)	B	C	D	E	F	G
0	0.000	4.642	4.642	4.642	4.642	4.642	4.642
60	3.915	4.122	4.140	4.085	4.057	3.934	3.982
180	5.646	3.728	3.730	3.704	3.675	3.704	3.726
600	8.434	1.929	1.908	1.832	1.933	1.819	1.849

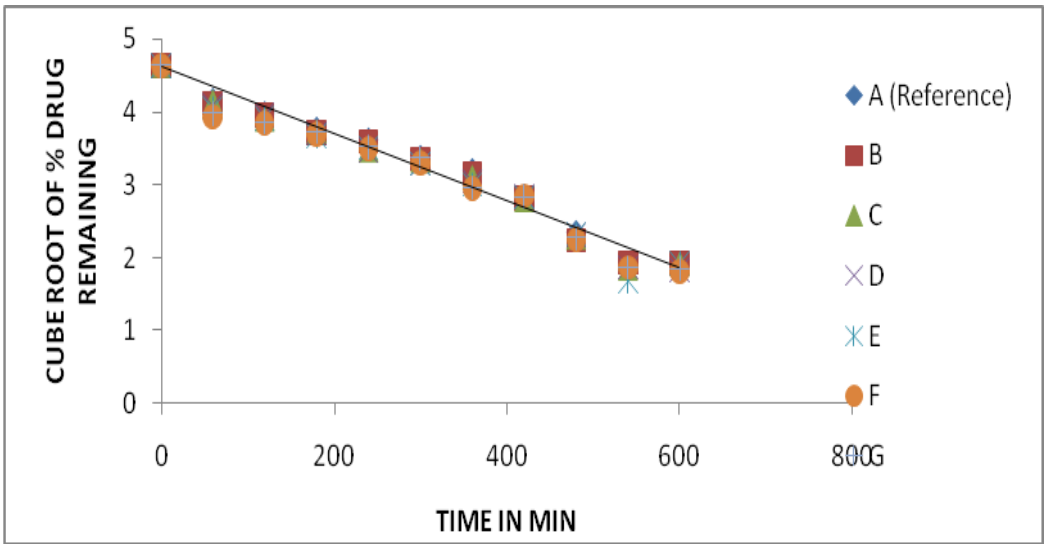

Figure 9: Hixon- Crowell model release kinetics for seven brands of S.R tablets

Table 23: linearity (R^2) and AIC of Hixon- Crowell model for S.R tablets

Brands	Linearity	AIC
A (Reference)	R^2 = 0.998	56.1931
B (Test)	R^2 = 0.998	56.5872
C (Test)	R^2 = 0.998	58.5359
D (Test)	R^2 = 0.998	56.6475
E (Test)	R^2 = 0.963	56.0891
F (Test)	R^2 = 0.998	50.2904
G (Test)	R^2 = 0.998	52.2016

DISCUSSION

Tablet Weight variation, Disintegration, Friability, and Hardness Tests for I.R and S.R tablets (As per I.P.2010)

Weight variation test:

All the brands including reference are obtained within the specification according to I.P.2010.

No brands were observed in overweight and underweight.

Hardness Test

It is shown that the I.R. brand A and C require the greatest force to break them whereas tablets B ,D, and E require approximately only a third of the force of brand A and C tablets for them to break. From the test results above, it is clear that the five brands of metformin tablets can be classified into two groups, brands A and C or brands B, D, and E tablets, in which both groups have similar physical properties. It is known that the compression force during a tableting process plays an essential role on the overall properties of the products, such as tablet disintegration rate, friability, and hardness. It is therefore concluded that the compression forces used during the manufacturing processes for brands A and C are likely to be significantly higher than those used for brands B, D and E.

Similarly for S.R tablet it is shown that brand B and D require the least force to break them whereas tablets A, C, E, F, G require approximately only a third of the force of brand B and D tablets for them to break. From the test results above, it is clear that the seven brands of metformin tablets can be classified into two groups, brands B and D or A, C, E, F and G tablets, in which both groups have similar physical properties. It is known that the compression force during a tableting process plays an essential role on the overall properties of the products, such as friability and hardness. It is therefore concluded that the compression forces used during the manufacturing processes for brands B and D are likely to be significantly lower than those used for other brands.

These both tests were performed to check any differences in weight which ultimately affects the contents of API in dosage form and to check the effect of hardness on the disintegration time of the tablet. The results of these tests (Table no 4, 7, 8) revealed that all brands (as these are commercially available formulations) comply with the Pharmacopoeial standards.

Disintegration test:

The results (Table no 5) show that all of the tablets disintegrated quickly (within 7 min) thereby complying with the I.P specification in which six immediate-release tablets must disintegrate within 15 min using a standard disintegration apparatus. Brands like A (Reference), and C have equal disintegration times, whereas those of brands B, D and E are having similar disintegration time. Brands A and C tablets took twice as long to disintegrate as those of brands like B, D and E .This might be due to the different types of disintegrants used by manufacturers.

Friability Test

Brands like A and C are similar, whereas the weight loss from brands like B, D and E is almost twice than that of A and C. These results (Table no. 6) are complementary to the results of hardness and disintegration tests.

Similarly for S.R tablets Brands like A, C, E, F and G are similar, whereas the weight loss of brands like B and D is almost twice then that of other brands. (Table no 9)

In Vitro Dissolution Tests for I.R tablet

All drugs complied with the dissolution specification stated in the IP that after 45 min, 85% of the drug should be released. The profiles in Figure 3 exhibit four stages of dissolution. The greatest percentage of drug dissolved in the shortest time (i.e., approximately 70% of the drug dissolved within 10 min) was at the initial step. Between 10 and 20 min, approximately 15% more of the drug dissolved, therefore the total percentage of drug dissolved at this time is around 85%. The third step between 20 and 30 min shows a further 10% of drug dissolved. In general, the profiles reached a peak at 45 min where there is the highest percentage of dissolved drug (around 95%). After 45 min, the graphs level off to a plateau up to 60 min with very little change in percentage of drug dissolved. It was surprising that none of the brands was 100% dissolved. The profiles in Figure 3 clearly show that brand B has a very similar dissolution profile to the reference brand A. Quantitative analyses of the dissolution profiles have been carried out using the model independent methods.

Model In dependent Methods

From the calculation of F1 (difference) and F2 (similarity) factor B brand is much more similar to the reference brand A when compared to other test products. As per the specification of F2 all brands are observed within the range.

In Vitro Dissolution Tests for S.R tablet

All dosage forms complied with the dissolution specification stated in the IP that after 10 hour >80% of the drug should be released. The profiles in Figure 4 exhibit three stages of dissolution. The greatest percentage of drug dissolved after the longer period of time (i.e., approximately 93% of the drug dissolved within 10 hour). In 1 hour approximately 27-40 % drug dissolved. In 3 hours 46-51 % of drug dissolved. In general, the profiles reached a peak at 8 hour where there is the highest percentage of dissolved drug (around 93%). After 8 hour, the graphs level off to a plateau up to 10 hour with very little change in percentage of drug dissolved. It was surprising that none of the brands was shown 100% dissolution profile. The profiles in Figure 4 clearly show that brand B and C has a very similar dissolution profile to the reference brand A. Quantitative analyses of the dissolution profiles have been carried out using the model dependent methods.

Model Dependent Methods

Zero order (% CDR *versus* Time)

As per the calculation of AIC (Akaike information criteria), all brands are showing equal results when comparing to reference product as well as with each brand. From this it can be declare that all brands are showing diffusion mechanism and fall under Zero order.

First Order (Log % CDR Remaining *versus* Time)

As per the calculation of AIC (Akaike information criteria), all brands are showing equal results when comparing to reference product as well as with each brand. But when comparison is carried out with the zero order AIC, it can be declare that the Zero order is having less AIC. So all brands fall into Zero order release.

Higuchi Model (%CDR *versus* Square Root of Time)

As per the calculation of AIC (Akaike information criteria), all brands are showing similar results when comparing to reference product as well as with each brand. But when comparison is carried out with the Hixon Crowell and Korsmeyer Peppas model of all the brands only F brand is having less AIC.

Korsmeyer – Peppas Model (Log % CDR *versus* Log Time)

As per the calculation of AIC (Akaike information criteria), all brands are showing similar results when comparing to reference product as well as with each brand. But when comparison is carried out with the Hixon Crowell and Higuchi model of all the brands, four brand A, B, C, and D showing the less AIC.

Hixon - Crowell Model (Cube Root of % Drug Remaining *versus* Time)

As per the calculation of AIC (Akaike information criteria), all brands are showing similar results when comparing to reference product as well as with each brand. But when comparison is carried out with the Higuchi and Korsmeyer Peppas model of all the brands, only two brands E and G showing less AIC. It can also be declare that all brand in the Zero order, First order, Higuchi, Korsmeyer Peppas and Hixon Crowell model showing the diffusion mechanism.

CONCLUSION

Results of the present research led us to conclude that different polymers used in the dosage form by manufacturer and pH of the dissolution media plays a vital role in describing the in-vitro drug release and to predict in-vivo performance of the immediate release (I.R) and sustained release (S.R) dosage formulations. The I.R and S.R formulation showed brand to brand variations. Tablets that disintegrated showed fast release compared to other brands and

decreased the reproducibility. From this observation it can also be concluded that it would be dangerous for a patient to consume the broken tablet. Results also revealed that shifting from one formulation to another formulation is not advisable as the release of API is different because of the different polymers have been used in the formulation by different manufacturers. By using the mathematical model and software application the best fit model can be selected which will help formulator to design different formulae.

REFERENCES

[1] Indian Pharmacopoeia. Government of India. Ministry of Public Healthcare and Family welfare. 2010, 1: 161, 187-193. 2: 1658-1660.
[2] Olubukola O, Tayo F, Moshood O, Bolajoko A. Dissolution Technol 2012; 51-55.
[3] Deshapnde A., Deshpande S., Lokhandwala H. Int J Pharm Bio Sci 2013; 4(2): 717 – 726, 2013.
[4] Lokhandwala H., Deshapnde A., Deshpande S. Int J Pharm Bio Sci 2013; 4(1): 728 – 737.
[5] Maggio RM, Castellano PM, Kaufman TS. Eur J Pharm Sci 2008;34(1): 66–77.
[6] Dissolution Testing of Immediate Release Solid Oral Dosage Forms; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 1997.
[7] O'Hara T, Dunne A, Butler J, Devane J. Pharm Sci 1998; Technol. Today1(5): 214–223.
[8] Yuksel N, Kanik AE, Baykara T. Int J Pharm 2000; 209(1–2): 57–67.
[9] Polli JE, Rekhi GS, Augsburger LL, Shah, VP. J Pharm Sci 1997; 86(6): 690–700.
[10] Costa FO, Sousa JJ, Pais S, Formosinho, SJ. Control Rel 2003;89(2): 199–212.
[11] Costa P. Int J Pharm 2001;220 (1–2): 77–83.
[12] Sathe PM, Tsong Y, Shah VP. Pharm Res 1996; 13(12): 1799– 1803.
[13] Adams E, Coomans D, Smeyers–Verbeke, J.; Massart, D. L. Int J Pharm 2001;226(1–2): 107–125.
[14] Adams E, Coomans D, Smeyers–Verbeke J, Massart DL. Int J Pharm 2002;240:1–2, 37–53.
[15] Pillay V, Fassihi RJ. Control Rel 1998; 55 (1): 45–55.
[16] Shah VP, Tsong Y, Sathe P, Liu JP. Pharm Res 1998; 15(6): 889–896.
[17] Moore JW, Flanner HH. Pharm Tech 1996;20(6): 64–74.
[18] Pinto JF, Podczeck F, Newton JM. Chem Pharm Bull 1997; 45(1): 171–180.
[19] Ocaña J, Frutos G, Sánchez P. Chemometr Intell. Lab 2009; 99 (1): 49–56.
[20] SUPAC–MR: Modified Release Solid Oral Dosage Forms, Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation; Guidance for Industry; U.S.Department of Health and Human Services,Food and Drug Administration, Center for DrugEvaluation and Research (CDER), U.S. GovernmentPrinting Office: Washington, DC, 1997.
[21] Costa P, Sousa Lobo JM. Eur J Pharm Sci 2001;13 (2): 123–133.
[22] Hopfenberg HB, Paul DR., Harris FW. American Chemical Society, Washington, DC. 1976; 26–31.
[23] Narsimhan B, Mallapragada SK, Peppas NA. John Wiley & Sons. 1999; 921-935.

[24] Higuchi T. J Pharm Sci 1963; 52: 1145–1149.
[25] Hixson AW, Crowell JH. Ind Eng Chem 1931 23: 923–93.
[26] Korsmeyer RW, Gurny R., Doelker E, Buri P, Peppas NA. Int J Pharm 1983; 15: 25–35.