Int. J. Drug Res. Tech. 2014, Vol. 4 (1), 01-13 ISSN 2277 - 1506

International Journal of Drug Research and Technology

Available online at http://www.ijdrt.com

Original Research Paper

DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE BILAYER MATRIX TABLET OF GLIPIZIDE AND METFORMIN HYDRO CHLORIDE

Rajeev Sharma[1]*, Naresh Kalra1, Rahul Gupta[2] and Rakesh Kumar Jhat[1]

[1]Rajastahn Pharmacy College, Bhankrota, Jaipur, India

[1]Department of Pharmaceutics, Alwar Pharmacy College, MIA Area, Alwar, Rajasthan, India

[2]Department of Pharmacy, Barkatullah University Bhopal, Madhya Pradesh, India

ABSTRACT

The ultimate aim of the present study was to develop sustained release bilayer matrix tablet formulation that contains both glipizide & metformin HCl such that it can provide synergistic effect for the therapeutic Management of diabetes. Bilayer tablet was formulated to develope and determine the sustained release effect of both Glipizide and Metformin Hydrochloride using various polymers as hydroxyl propyl methyl cellulose K15 M, Hydroxy Ethyl Cellulose and Ethyl cellulose etc. at different concentration. The influence of varying the polymer/polymer (w/w) ratio was evaluated. The excipients used in this study did not alter physicochemical properties of the drug, as tested by Fourier transform Infrared Spectroscopy. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity. The in vitro drug dissolution study was carried out using USP 22 apparatus II, paddle method and the release mechanisms were explored. Mean dissolution time and regression values were determined to characterize the drug release rate from a dosage form and helped to indicate the drug release retarding efficiency of the polymer used. Kinetic modelling of in vitro dissolution profiles revealed the drug release mechanism ranges from diffusion controlled to anomalous type.

Keywords: Bilayered tablet, Matrix tablet, Glipizide, Metformin Hydrochloride, Hydroxy Propyl Methyl Cellulose and Ethyl Cellulose.

INTRODUCTION

The patients with type 2 diabetes, if not able to achieve suitable control after about 3 months of dietary modification and increased physical activity, then oral anti diabetics (oral hypo glycaemics) may be tried. The two major classes are the sulfonylureas and the biguanides. Sulfonylureas act mainly by increasing endogenous insulin secretion, while biguanides act chiefly by decreasing hepatic gluconeogenesis and increasing peripheral utilisation of glucose.[1] Chronic hyper glycemia of diabetes mellitus is associated with long-term damage, dysfunction & failure of various organs. Therefore a long lasting treatment is required with proper diet and multi drug therapy. For that, multiple drug dosing can be avoided by preparing sustained release combination drug formulation of glipizide[9] and metformin HCl. As both the drugs are used for the treatment of life threatening disease such as the diabetes by providing the synergistic action[2] by different mechanism such as glipizide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas and metformin HCl improves glucose tolerance in patients with type II diabetes by decreasing the hepatic glucose production, decreasing the intestinal absorption of glucose, and by improving the insulin

sensitivity by increasing peripheral glucose uptake and utilization. Therefore aid in achieving the synergistic effect and better patient compliance. Glipizide is a water insoluble drug with low dose (10 mg) belonging to Bio pharmaceutics Classification System class-II drug[7] while metformin hydrochloride is highly water soluble drug (300mg/ml at 25^0C) with high dose (500 mg), belonging to Bio pharmaceutics Classification System class III.[7] Glipizide is reported to have a short biological half-life (3.4±0.7 h) requiring to be administered in 2 to 3 doses of 2.5 to 10 mg per day.[10] Sustained Release formulations that would maintain plasma levels of drug for 8 to12 hrs might be sufficient for once a day dosing for glipizide. Sustained Release products are needed for glipizide to prolong its duration of action and to improve patient compliance.[11] Glipizide generally undergoes hydrolysis in presence of moisture[3], while metformin HCl is hygroscopic in nature.[4] These properties may affect the stability of both molecules when given in single layer tablet dosage form. Also metformin hydrochloride being highly water soluble drug with high dose (500 mg), leads to difficulty in providing an extended release rate from formulation and there might be problems in controlling the initial burst of drug from such formulation. Thus both of drugs shows incompatibility with each other therefore, there is a substantial need to develop such a system to avoid intimate contact between the two drugs i.e. sustained release bilayer tablet formulation of glipizide & metformin HCl that can overcome all the limitations of both the drugs and for that granules of Glipizide were layered by Polyethylene glycol 6000 while granules of Metformin Hydrochloride by Sterotex NF using melt granulation technique, this technique not only avoid the contact between both of drugs but also increases the solubility profile of glipizide in water.[8] This Sustained release dosage form reduces the frequency of dosing and also aids in reducing the pill burden and thus helps in improving the patient compliance. It also results in less fluctuation of drug in circulating blood level. Most importantly, because of prolonged duration of action, it shall produce a strict control of blood pressure and consequently less hypertension complication[5].

MATERIALS AND METHODS

The different materials used were depicted in table 1.

Formulation of the Bilayer Sustained Release Matrix Tablets

Preparation of granules by melt granulation method

A) Glipizide granules

Weighed quantity of polyethylene glycol 6000 (PEG) was melted on water bath at 60 degree celcius. Then weighed quantity of glipizide were dispersed in melted PEG and stirred continuously for proper homogenize mixing. This semisolid dispersion was cooled at room temperature. Finally, granules of glipizide were passed through sieve 60#. Different ratios of glipizide and Polyethylene glycol 6000 used for Preparation of glipizide granules were depicted in table 2.

B) Metformin hydrochloride granules

Weighed quantity of stereotex was melted on water bath at 63 degree celsius. Then weighed quantity of metformin HCl were dispersed in melted sterotex and stirred continuously for proper homogenized mixing. This semisolid dispersion was cooled at room temperature. Finally, granules of metformin HCl was passed through sieve 44#. Different ratios of metformin HCl and sterotex, for preparation of metformin HCl granules were depicted in table 3.

Characterization of granules

Angle of Repose

The angle of repose is defined as the maximum angle possible between the surface of pile of powder and the horizontal plane. Angle of repose of granules was determined by fixed funnel method, the diameter of the powder cone was measured and angle of repose was calculated using the following equation.[12]

$\tan \theta = h/r$

Where, h = height of the pile;

r = radius of the pile

The tangent of the angle is equal to the coefficient of friction between the particles.

Bulk density and tapped density

25 g of Metformin hydrochloride granules, 25 g of Glipizide granules were weighed respectively and transferred into a graduated measuring cylinder via a large funnel and the volume of the powder was measured. Tapped volume of the powder was measured by tapping method. The bulk density of the granules is calculated by given formula.

LBD = Wt of Powder / Vol. of Powder

TBD = Wt of Powder / Tapped Vol. of Powder

Compressibility index and Hausner's ratio

The compressibility index and Hausner's ratio have become the simple, fast and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the Hausner's ratio are determined by measuring both the bulk volume and the tapped volume of granules as follows:

$$\text{Compressibility Index} = 100 \times \frac{Vo - Vf}{Vo}$$

$$\text{Hausner's Ratio} = \frac{Vo}{Vf}$$

Preparation of Glipizide/Metformin HCL Bi-Layer Sustained Release Matrix Tablet

The bilayer sustained release tablets were formulated by using direct compression technique. Bilayer tablets were prepared manually by double compression method. First, the die cavity was adjusted for required weight of lower layer and was compressed. Then the compressed lower layer was again pressed into the die cavity, adjusted for required weight of upper layer and compressed to produce bilayer tablet. The composition of glipizide and metformin sustained release layer was depicted in table 6 & 7.

Evaluation of matrix tablets

Size and Shape

The particle size of the granules, Type of tablet press, Production lot sizes, Type of tablet processing, Packaging operations, and Overall production costs influences the size and shape of the tablet. For example, the non-uniform forces during compression and the convex surface may leads to the observance of capping problems which in turn necessitating the use of a slower tablet press or one with pre compression capabilities.[14] The high degree of control over the shape and size is maintained by determining the uniformity in tablet tooling within established specifications.[14]

Tablet Thickness

For the production control, the adequate standardisation of punch and die tooling was done. The thickness was measured by placing 10 tablets in a holding tray and measuring the total thickness within ± 0.01 mm using digital vernier calliper.[15]

Weight/Weight Variation

The actual weight of the tablet is related to the geometry of the die and the position of the lower punch in the die as dictated by the weight adjustment cam. 20 tablets were selected randomly from each batch and average weight was calculated.[14] Then the deviation (as per IP limit ±5% for >500 mg tablet) of individual weights from the average weight was determined.

Hardness

The die fill/compressional force relationship, with uniform tooling, made the tablet hardness a useful tool for physically controlling tablet properties during a production operation.[14] The hardness of the tablets was determined by using Monsanto type hardness tester. For adequate mechanical stability 4-5 kgs/tablet hardness is required.

Friability

A laboratory device known as the Roche Friabilator, was used, This device subjects a number of tablets (n=20) to the combined effects of shock and abrasion by utilizing a plastic chamber which revolves at 25 rpm, dropping the tablets a distance of 6 inches with each

revolution.[14] Normally, a pre weighed tablet sample (Wo) is placed in the Friabilator chamber which is then rotated for 100 revolutions. The tablets were removed from the chamber, dusted, and reweighed (W). Conventional tablets that lose less than 1.0% in weight are generally considered acceptable. When capping is observed during the friability testing, tablets should not be considered acceptable, regardless of the percentage weight loss.

F (%) = [1-Wo/W] X100

Potency and Content Uniformity

The potency of tablets is generally expressed in terms of grams (g), milligrams (mg), or micrograms (µg) of drug per tablet, and is given as the label strength of the product.[14] The usual method of determining potency of tablet products (average assay content) involved the taking of 20 tablets which were powdered and a quantity of the powder containing about 15 mg of Glipizide was taken and was dissolved in 30 ml of methanol with gentle heating on a water bath, and final volume was made up to 50.0 ml using methanol. The 5 ml of the solution was filtered and diluted to 50.0 ml with methanol and the absorbance of the resulting solution was measured at 274 nm using an ultra violet spectrophotometer.[17] The weighed quantity of the 0.1 g of Metformin Hydrochloride was taken from the same 20 powdered tablet sample shaked with 70 ml of water for 15 minutes, diluted to 100.0 ml with water and filtered and again diluted 10.0 ml of the filtrate to100.0 ml with water. Further dilution of 10.0 ml to 100.0 ml with water was done and the absorbance of the resulting solution at the maximum at about 232 nm was determined.[17] Finally the content of Glipizide and Metformin HCL was determined using simultaneous equation method (vierodot's equation) by taking 237 and 798 as specific absorbance for Glipizide and Metformin HCL respectively.[17]

Drug Excipient Compatibility Studies

Fourier transform infrared spectra of Metformin HCl and physical mixture of Metformin HCL and polymers (HPMC K15M and Ethyl Cellulose) were taken, whose spectra was obtained by taking a sample containing 20 mg of Metformin Hydrochloride which was diluted with 20 ml of ethanol, filtered and evaporated to dryness on a water-bath and the residues were dried at 105° for 1 hour.[17] All the characteristic peaks of pure drug were observed in the spectrum of mixture. This indicated that there was not any interaction between drug and polymer.

In vitro drug release studies

The primary objectives of an in vitro dissolution test are to demonstrate that (a) essentially 100% of the drug can be released from the dosage form, and (b) the rate of drug release is uniform from batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective.[14] Drug release studies were determined using USP dissolution apparatus-2 a paddle type (Electrolab, Mumbai, India) instrument operated at 50 rpm at a temperature of 37±0.5ºC. The dissolution media used was 900 mL of 0.1 mol/L HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for next 12 h. Sink condition was maintained for the whole experiment. Samples (10 mL) were withdrawn at regular intervals and the same volume of pre warmed (37±0.5ºC) fresh dissolution medium was added to maintain the constant volume. The samples withdrawn were filtered through a 0.45 µ membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 274nm for Glipizide and at 233 nm for Metformin HCL.

Release kinetics

Different kinetic models (zero-order, first-order, Higuchi's, Korsmeyer's and Hixson Crowell) were applied to interpret the release profile (the order and mechanism of drug release) from matrix system.

First order

(log cumulative percentage of drug released versus time, if the plot is linear then data obeys zero order kinetics)

Log Qt = Log Qo- K1t/2.303

Where, Qt = Amount of drug released in time't'.
Qo = Initial amount of drug concentration in solution.
K1t = First order rate constant.

Higuchi's (cumulative percentage of drug released versus square root of time, if the plot is linear then data obeys diffusion mechanism)

$Q = \sqrt{D\delta/\tau}\,(2C - \delta Cs)Cst$

Where, Q = Amount of drug released in time't'.
D = Diffusion coefficient of the drug in the matrix.
Cs = Solubility of the drug in the matrix.
δ= Porosity of matrix.
τ= Tortuosity.
t = Time (h)

Peppas Korsmeyer (log cumulative percentage of drug released versus log time)

$At/A\infty = ktn$

Where, k = Constant.
n = Release.
t = Time.
At and A∞= Absolute cumulative amount of drug
released at time 't'.

Zero-order

(cumulative percentage drug release verses time, if the plot is linear then data obeys zero order kinetics with slope equal to Ko)

$Qt - Q0 = K0t$

Where, Qt= Amount of drug release dissolved in time 't'.
Qo= Initial amount of drug concentration in solution.
K0t = Zero order rate constant.

Hixson Crowell (Cube roots of percent releases (Cube root of initial drug
load minus cube root of % drug remaining) are plotted against time (hour) to demonstrate the Hixson Crowell plot).

$M1/3 = Mo1/3 - Kct$

Where, Kc is the cube root dissolution rate constant**.**

Stability Studies

Stability of a pharmaceutical preparation can be defined as the capability of a particular formulation (dosage form or drug product) in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life. The optimized matrix tablets were subjected to stability studies(as per ICH guide lines) at 25°C ± 2°C / 60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH. The products were evaluated for their physical characteristics, drug content, and In vitro drug release profiles over a period of 3 months.

RESULTS AND DISCUSSION

Preformulation Study

Calibration curves of glipizide

Calibration curve of glipizide was carried out in different media such as 0.1 N HCl (pH 1.2) (figure 1) and phosphate buffer (pH 7.5) (figure 2). Absorbance Vs concentration graph was plotted and It was observed that a linear correlation followed between absorbance and concentration, depicting the occurrence of Beer-Lamberts law.

Calibration curves of metformin HCL

Calibration curve of metformin HCl was carried out in different media such as 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.5) (figure 3). Absorbance Vs concentration graph was plotted and It was observed that a linear correlation followed between absorbance and concentration, depicting the occurrence of Beer- Lamberts law.

Characterization & Evaluation of Granules

The optimized glipizide granules (Batch P1 and P2) and metformin HCL granules (Batch S1 and S2) were evaluated for flow properties (Table 4 & 5) such as angle of repose, bulk density, tap density, Carr's index and Hausnner ratio and Particle size distribution (Table 8 & 9). Glipizide is water insoluble drug; hence a hydrophilic carrier such as PEG 6000 was selected for the preparation of granules. Particle size distribution was studied by sieve analysis technique. Granules separated in to different size fraction by sieving for 5min. & the cumulative frequency of retained granules were shown in Table 6&7.

Drug Excipient Compatibility Studies

Fourier - transform infrared (FT - IR) spectra of glipizide & optimized batch P1 were scanned

over the wave number range of 4000 to 400 cm-1. It was observed that glipizide showed prominent peak at 3337, 2941, 1689 & 1159 cm^{-1} bands of NH – stretching, CH- stretching, C=O & SO_2 stretching appeared in the spectra of pure glipizide shown in figure 8.4. FT-IR spectra of glipizide granules (Figure 4) showed similar bands of glipizide at same position indicated that there is no chemical interaction between glipizide and PEG only physical mixing took place in between glipizide & polyethylene glycol. Fourier - transform infrared (FT - IR) spectra of metformin HCl & optimized batch were scanned over the wave number range of 4000 to 400 cm-1. Pure metformin HCl showed prominent bands of functional group at 3371 & 2814 cm^{-1} such as NH_2 stretching & CH_2 stretching In the spectra (figure 5 A) Similar bands also appeared at same position of formulated batch of metformin HCl (figure 5 B) indicated that there is no chemical interaction between metformin HCl & sterotex.

Evaluation of Bi layered Tablet

Tablet characteristics

Bi layered tablets were evaluated for hardness, friability, thickness, weight variation and content uniformity (table 10). All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in house specifications for weight variation, drug content, hardness and friability.

In vitro Drug Release

In vitro release studies of bilayered tablet were carried out in different dissolution media at different scanning wavelength range to determine the release of Glipizide and Metformin HCL separately. The drug release from the batch P1S1 at wavelength range of 274 showed the more sustained release effect of Glipizide as compared to the release effect of batch of P2S2 this effect may be attributed, due to the presesnce of an equal amount of PEG 6000 in P1S1 batch as the flux enhancing nature of PEG 6000 increases the volume of fluid imbibed in to the core. The sustained release effect may also be due to the higher concentration of hydroxyl propyl methylcellulose & hydroxy ethyl cellulose in batch P1S1 as compared to the batch P2S2 as In aqueous media, these polymers swells and forms a gel containing glipizide granules, and drug get diffused through this gel by non fikian type of diffusion & followed zero order release in phosphate buffer (pH 7.5) shown in table 8.14. It was observed that up to 23 %, 45 % , and 70 % drug released at the end of 8 hrs in 0.1 N HCl (pH 1.2), and phosphate buffer (pH 7.5) respectively, this indicated that glipizide has pH dependent release profile. The drug release from the batch P1S1 at wavelength range of 233 showed the more sustained release effect of Metformin HCL as compared to the release effect of batch of P2S2. The sustained release effect may be due to the hydrophobic polymer such as sterotex & ethyl cellulose which forms matrix surrounding the core of the drug & hindered rate of the penetration of solvent into the drug therefore more time required to release the drug through the matrix.

Kinetic analysis of release *data*

The kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations .The data were analyzed by the regression coefficient method and regression coefficient value (r2) of all batches were shown in table 11. In Kinetics study it was observed that drug get released by erosion mechanism through fikian type of diffusion the release mechanism for bilayer tablet of metformin and glipizide, it could be seen that data of metformin obtained from in vitro release was best fitted with Higuchi kinetics while the release of glipizide follow zero order as shown in table 11. Thus compression of glipizide and metformin HCl granules as a bilayer tablet did not alter their release characteristics.

CONCLUSION

The present study of development & evaluation of sustained release bilayer tablet of glipizide & metformin HCl concluded that the Glipizide granules formulated by melt granulation

technique using polyethylene glycol gives uniform granules. The Evaluation study of glipizide granules showed good flow property due to the carrier polyethylene glycol which acts as binding agent and increase flow of granules. The In vitro release study showed sustained release effect due to HPMC K-15 and HEC GM/250 & follow Zero order release (R=0.9897). The study in multimedia showed glipizide had pH dependent solubility. Metformin HCl granules produced by using hydrogenated vegetable oil (Sterotex) through melt granulation technique gives uniform granules. The In vitro release study in multimedia showed sustained release effect due to hydrophobic polymer like sterotex NF and ethyl cellulose. Release obtained follows Higuchi model (R=0.9768) by erosion mevhanism.

Table 1: Material

S. No.	Materials
1	Metformin Hydrochloride
2	Glipizide
3	Hydroxy Propyl Methyl Cellulose (K-15 M)
4	Ethyl cellulose
5	Polyethylene Glycol 6000
6	Sterotex® NF
7	Colloidal Silicon Dioxide
8	Microcrystalline cellulose
9	Cross carmellose sodium
10	Lactose Monohydrate
11	Polyvinyl pyrolidone K-30
12	Iron red oxide
13	Magnesium stearate

Table 2: Different ratios of glipizide and Polyethylene glycol 6000 used for Preparation of glipizide granules

Batch Code	Glipizide : Polyethylene glycol
P1	1:1
P2	1:2

Table 3: Different ratios of metformin HCl and sterotex for preparation of metformin HCl granules

Batch Code	Metformin Hydrochloride : Sterotex
S1	1: 0.5
S2	1: 0.75

Table 4: Characterization of Granules of Glipizide

Batch Code	bulk density (g/cm3 ± SD) *	Tapped density (g/cm3 ± SD) *	Hausner ratio	Carr's index (% ± SD) *	Angle of repose (θ ± SD) *
P1	0.3354±0.0180	0.4254±0.0014	1.12±0.02	10.42±0.02	26.42±1.46
P2	0.3922±0.0224	0.4079±0.0044	1.17±0.02	11.32±0.02	28.66±1.60

*Mean ± S.D. (n=3)

Table 5: Characterization of Granules of Metformin HCL

Batch Code	bulk density (g/cm3 ± SD) *	Tapped density (g/cm3 ± SD) *	Hausner ratio	Carr's index (% ± SD) *	Angle of repose (θ ± SD) *
S1	0.4580±0.0334	0.5324±0.0004	1.52±0.02	12.46±0.02	28.46±1.48
S2	0.4346±0.0460	0.5089±0.0534	1.42±0.02	11.44±0.02	31.22±1.48

*Mean ± S.D. (n=3)

Table 6: Composition of glipizide sustained release layer

Ingredients	**Contents (mg/tablet)**	
	P1 (1:1)	**P2 (1:2)**
Glipizide+ Poly ethylene glycol	35	35
Hydroxy Propyl Methyl Cellulose (K-15 M)	25	18
Hydroxy ethyl cellulose	30	25
Polyvinyl pyrrolidone K-30 (PVP K-30)	20	20
Lactose Monohydrate	37	49
Magnesium stearate	02	02
Iron red oxide	01	01
Total weight	150	150

Table 7: Composition of Metformin Hydrochloride sustained release layer

Ingredients	Contents (mg/tablet)	
	S1 (1:0.5)	S2 (1:0.75)
Metformin Hydrochloride+ stereotex	350	350
Ethyl cellulose	-	150
Hydroxy Propyl Methyl Cellulose (K-15 M)	150	-
Polyvinyl pyrrolidone K-30 (PVP K-30)	50	50
Colloidal Silicon Dioxide	05	05
Microcrystalline cellulose	10	10
Magnesium stearate	05	05
Total Weight	570	570

Table 8: Particle size distribution of optimized batch P1 and P2

Sieve number	Weight retained (gm)	Cumulative Frequency	% Cumulative Frequency
44	0.009	0.009	5.16
60	0.1	0.109	6.26
85	0.145	0.254	14.58
100	0.221	0.475	27.28
100 passed	1.52	1.741	100

Table 9: Particle size distribution of optimized batch S1 and S2

Sieve number	Weight retained (gm)	Cumulative Frequency	% Cumulative Frequency
44	0.009	0.009	0.17
60	0.012	0.021	0.40
85	0.014	0.035	0.66
100	0.5329	0.5679	10.83
100 passed	4.120	4.6879	21.40

Table 10: Tablet Characteristics

Batch	Diameter (mm*)	Thickness (mm*)	Hardness (Kg/cm2*)	Weight variation (gm*)	Friability (%*)	Drug content (%*)
P1S1	12±0.2	15 ± 0.2	5.37±0.5	0.568±0.08	0.39±0.5	92 ± 5
P2S2	12.7±0.2	15.2 ± 0.2	6.01±0.4	0.559±0.08	0.32±0.5	92.4 ± 5

*mean ± S.D. (n =3)

Table 11: Kinetics of drug release study of bilayer tablet of glipizide and metformin HCl

Model	R2 Glipizide in P1S1, P2S2		R2 Metformin HCL in P1S1, P2S2	
	0.1N HCl (pH 1.2)	Phosphate buffer (pH7.5)	0.1N HCl (pH 1.2)	Phosphate buffer (pH7.5)
Zero order	0.7330, 0.6899	0.9965, 0.9843	0.8252, 0.7943	0.7423, 0.7012
First order	0.7741,0.74322	0.9265, 0.9067	0.9913, 0.9781	0.9523, 0.9451
Peppas	0.9227, 0.8954	0.9548, 0.9439	0.9912, 0.9824	0.9748, 0.9673
Hixson Crowell	0.7609, 0.7423	0.9871, 0.9523	0.9699, 0.9594	0.9196, 0.9128
Higuchi	0.9596, 0.9276	0.8587, 0.8432	0.9932, 0.9921	0.9768, 0.9719
n	0.3823, 0.3458	0.7091, 0.5721	0.3985, 0.3827	0.3377, 0.3318
K	2.1925, 2.098	0.8825, 0.8537	7.79, 7.38	9.7704, 9.421

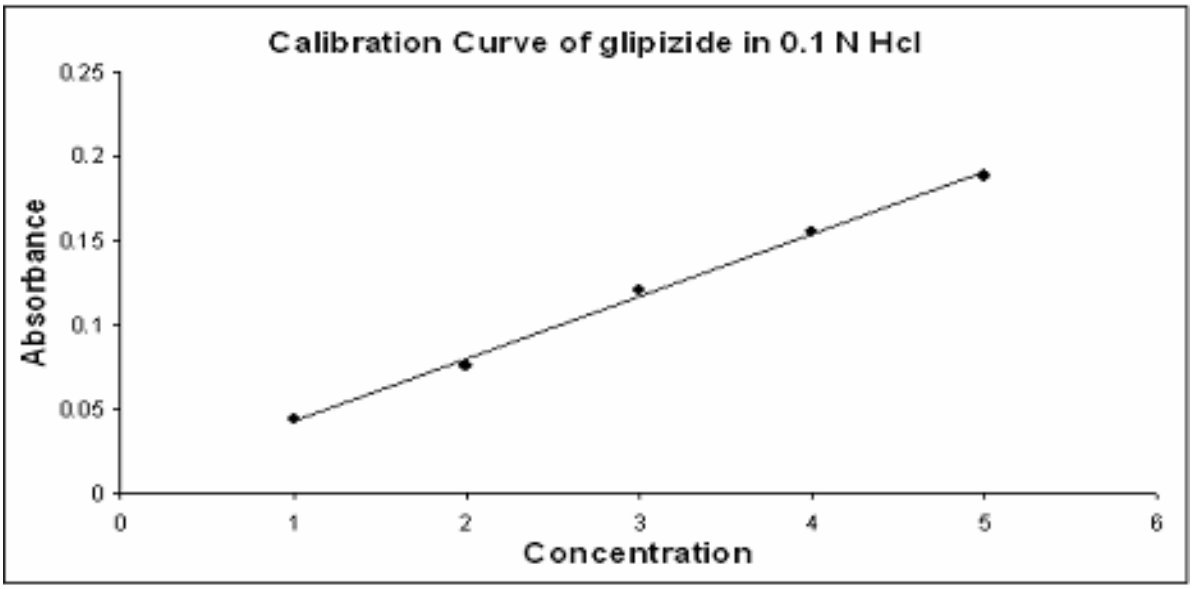

Figure 1: Calibration of Glipizide in 0.1 N HCl (pH 1.2)

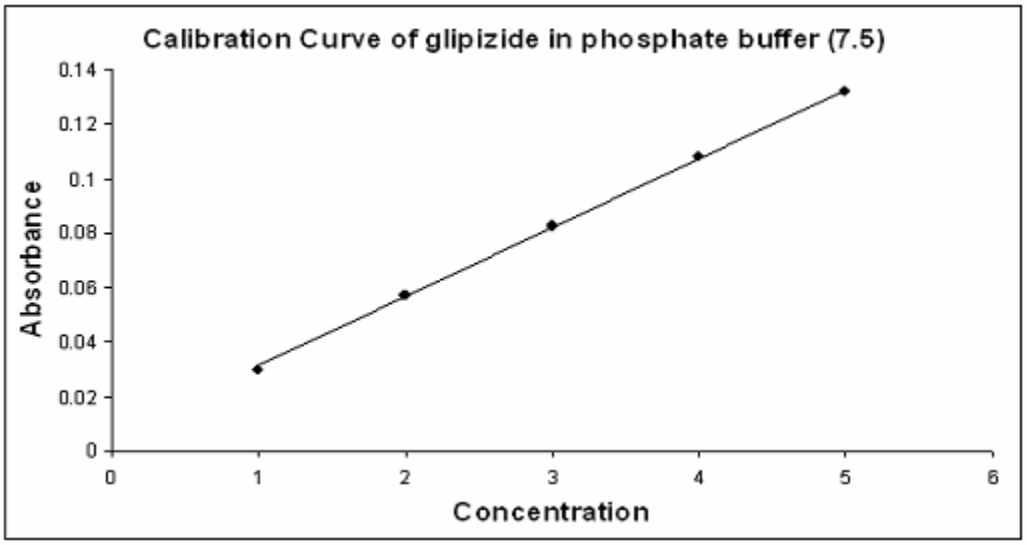

Figure 2: Calibration of Glipizide in phosphate buffer (pH 7.5)

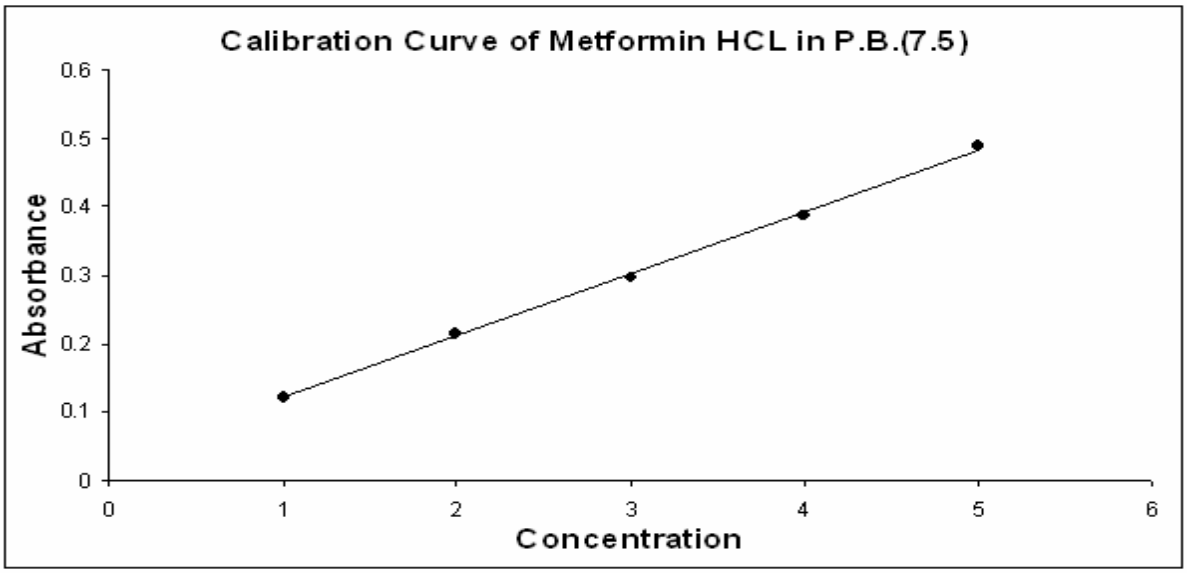

Figure 3: Calibration of metformin HCl in phosphate buffer (pH7.5)

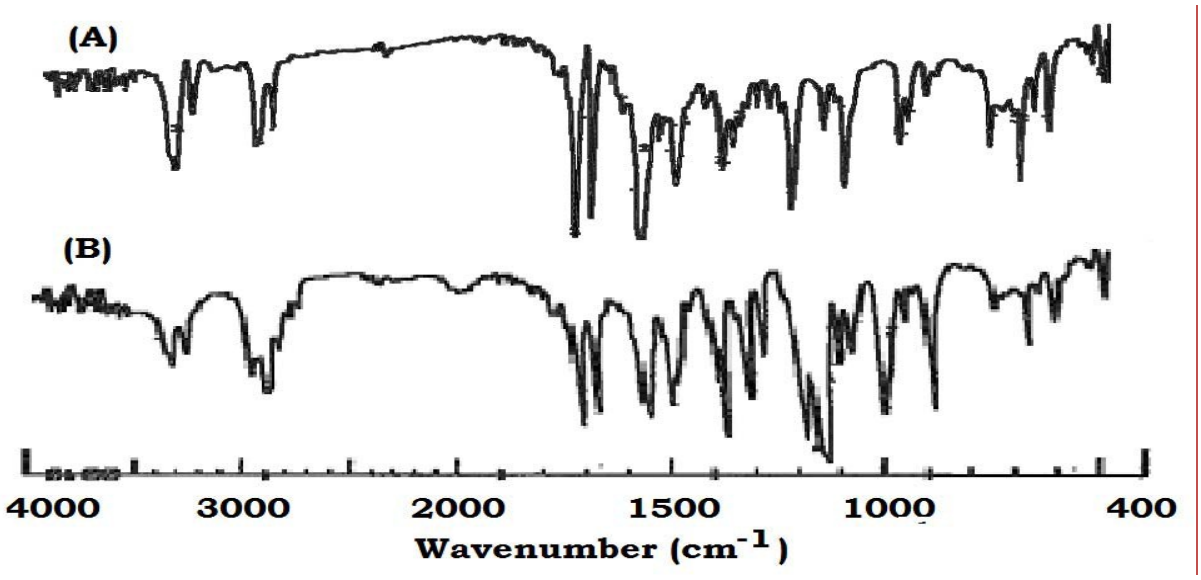

Figure 4: FTIR spectra of (A) Pure glipizide and (B) Glipizide+PEG 6000 granules (batch P1)

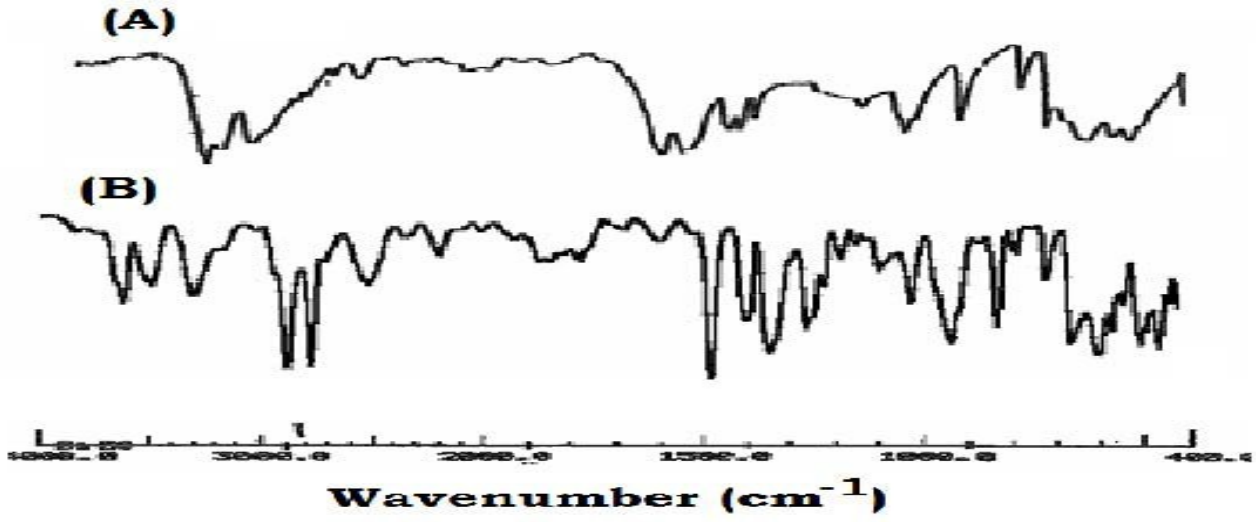

Figure 5: Infrared spectra of (A) pure metformin HCl and (B) Metformin granules prepared by using sterotex

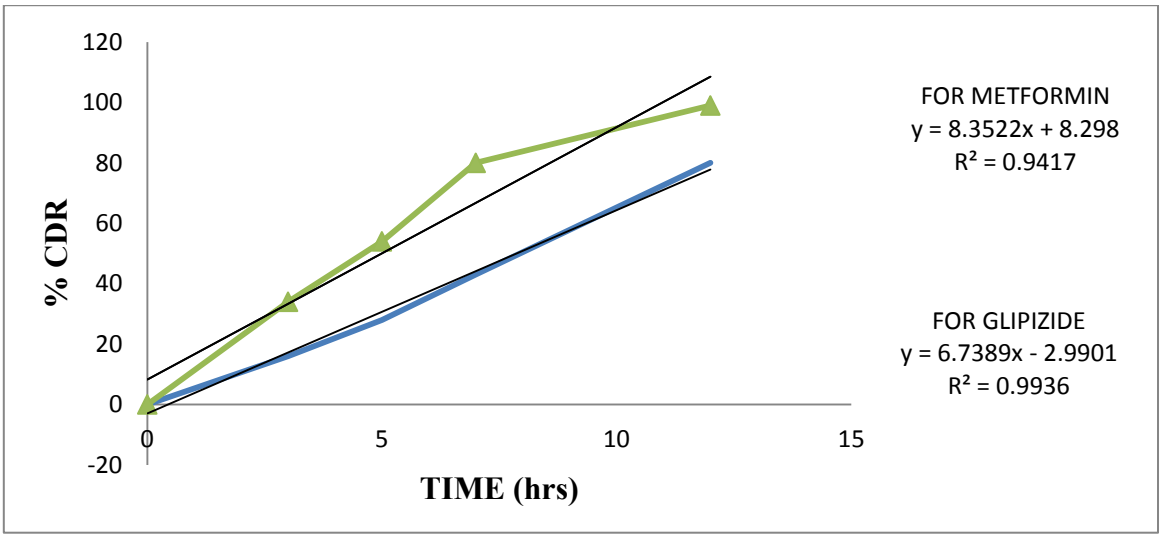

Figure 6: Zero order plot of release kinetics of Glipizide (Blue line) and Metformin HCL (Green line) from bilayer matrix tablets

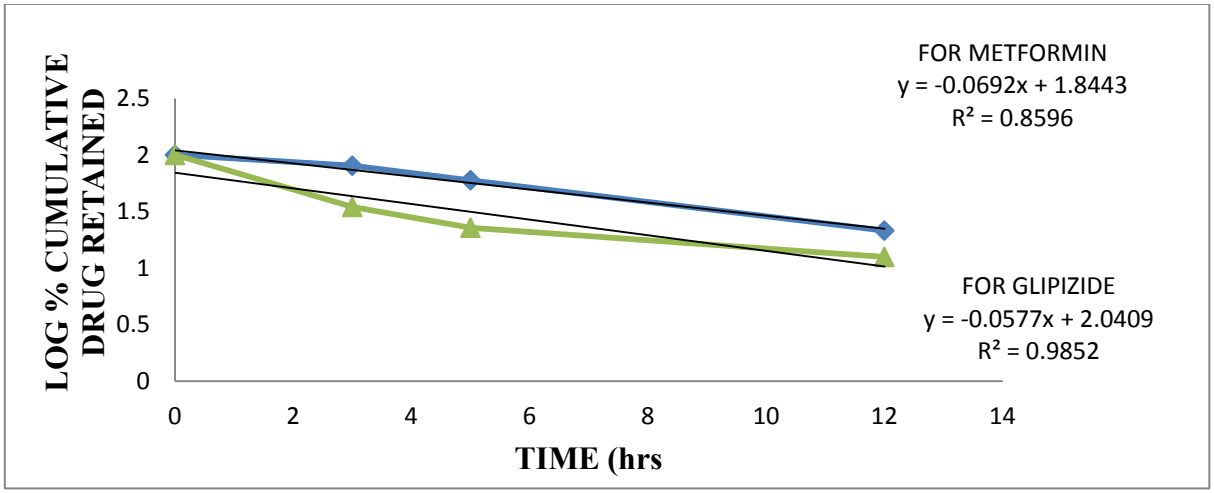

Figure 7: First order plot of release kinetics of glipizde (Blue line) and Metformin HCL (Green line) from bilayer matrix tablets

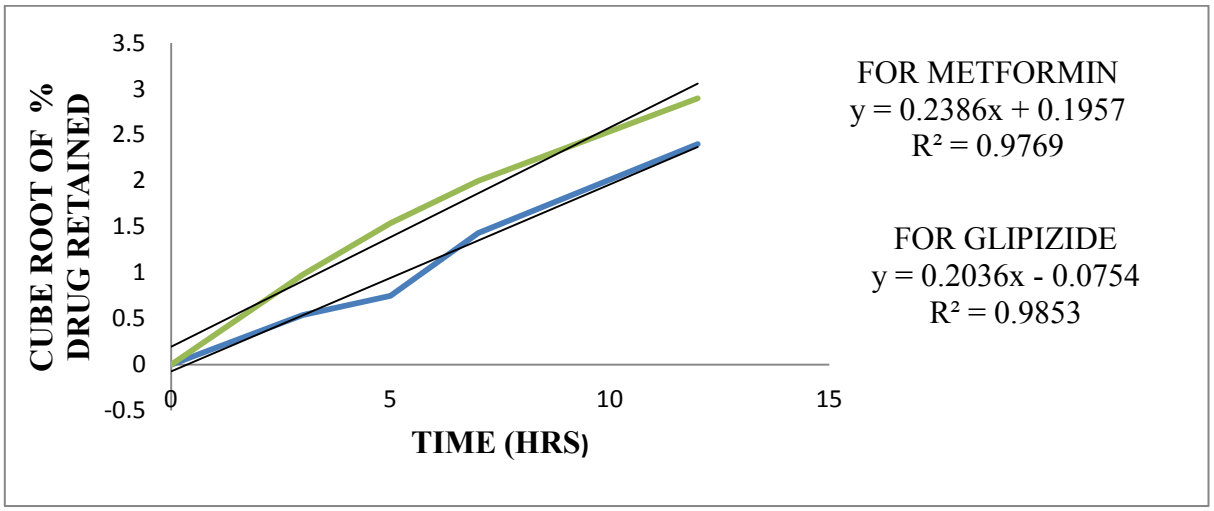

Figure 8: Hixson Crowell plot of release kinetics of glipizde (Blue line) and Metformin HCL (Green line) from bilayer matrix tablets

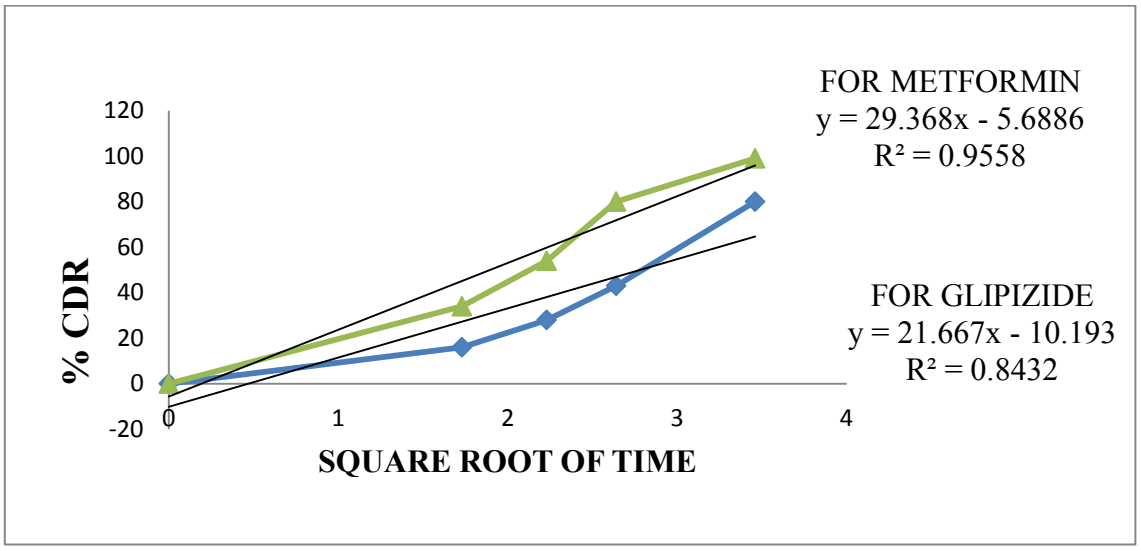

Figure 9: Higuchi plot of release kinetics of Glipizide (Blue line) and Metformin HCL (Green line) from bilayer matrix tablets

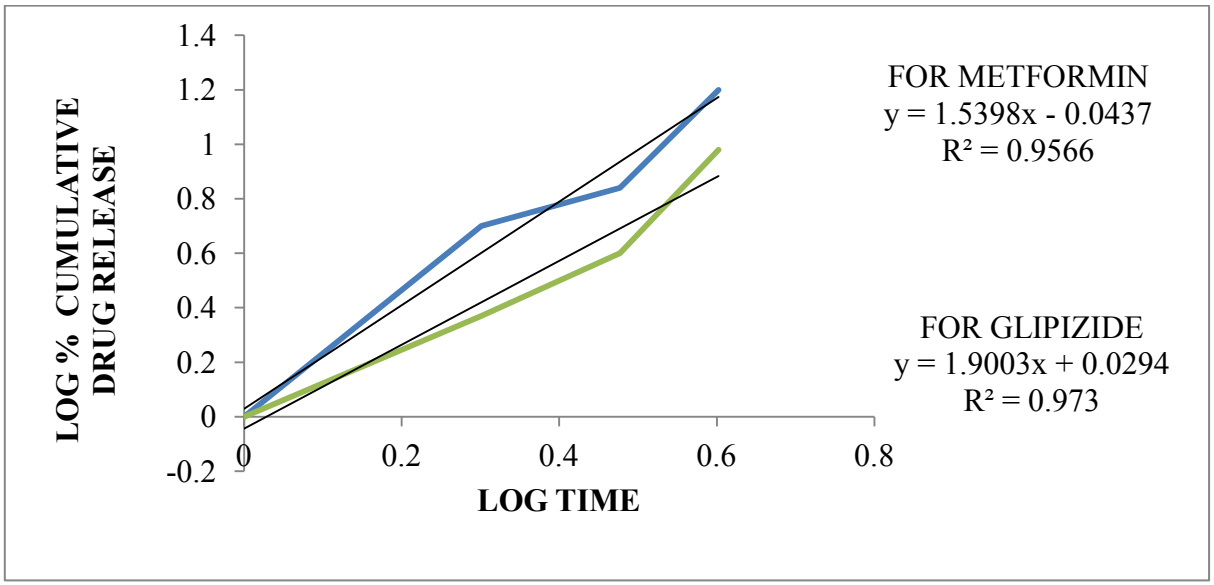

Figure 10: Korsmeyer plot of release kinetics of Glipizide (Blue line) and Metformin HCL (Green line) from bilayer matrix tablets

REFERENCES

1. Sweetman, Sean C (2009), "***Martindale: The Complete Drug Reference***", 36rd Ed., Vol. I, The Pharmaceutical Press, London, 431.
2. Kumar, Vijai; Morris Plains, NJ; Mcguffy and Kevin, Scott (2003), "Directly compressible extended-release matrix formulation for metformin hydrochloride", ***United States Patent***, 6524618.
3. Eswaran, Krishnan lyer (2006), "Oral composition for treatment of diabetes", ***United States Patent***, 0134206A1.
4. Timmins, Peter ; Dennis, Andrew B; Vyas and Kiren, A (2002), "Biphasic controlled release delievery system for high solubility pharmaceuticals & method", ***United States Patent***, 64755521 B1.
5. Gangji, AS; Cukierman, T; Gerstein, HC;Goldsmith, CH and Clase, CM (2007), "A systematic review and meta-analysis of hypo glycemia and cardiovascular events: a comparison of glipizide with other secretagogues and with insulin" , ***Diabetes Care***, 30, 389-394.
6. Sweetman Sean, C (2009), "***Martindale: The Complete Drug Reference***", 36rd Ed., Vol. I, The Pharmaceutical Press, London, 441.
7. Lipinski, CA; Lombardo, F; Dominy, BW and Feeney, PJ (2001), "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings", ***Adv. Drug Deliv. Rev***, 46, 3–26.
8. Passerini, N; Albertini, B; Gonzalez-Rodriguez, ML; Cavallari, C and Rodriguez, L (2002), "Preparation and characterization of ibuprofen-poloxamer 188 granules obtained by melt granulation", ***Eur. J. Pharm. Sci.***, 15, 71–78.
9. Jamzad, S and Fassihi, R (2006), "Development of controlled release low dose class II drug-glipizide", ***Int J Pharm***, 312, 24-32.
10. Patel, JK; Patel, RP; Amin, AF and Patel, MM, (2005), "Formulation and evaluation of glipizide microspheres" , ***AAPS Pharm Sci Tech***, 6, 49-55.
11. Chowdary, KPR and Rao, YS, (2003) , " Design and in vitro and in vivo evaluation of mucoadesive microcapsules of glipizide for oral controlled release" , AAPS Pharm Sci Tech, 4, 1-6.
12. Cooper, J and Gunn, C (1986), "***Powder Flow and Compaction (Tutorial Pharmacy)***", New Delhi, CBS Publishers and distributors, 211-33.
13. Divya, AK; Kavitha, M; Rupesh, Kumar; Dakshayani, S and Jagadeesh Singh, SD (2011), "Bilayer tablet technology: An overview" ,***JA Pharma Sci***. , 01 (08), 43-47.
14. Lieberman Herbert, A; Lieberman, HH; Leon, Lachman and Joseph B, Schwartz (1990), "Pharmaceutical Dosage Forms: Tablets", ***Informa Healthcare***, 2, 318-335.
15. Martin, A (2001), "***Micromeritics In: Physical Pharmacy***", 4th Ed., Philadelphia, Lippincott Williams & Wilkins, 423-52.
16. Banker, GS and Anderson, NR, (1986), "***The Theory and Practice of Industrial Pharmacy***", 3rd Ed., Philadelphia, Lea& Febiger, 293-45.
17. (1996), "***The Pharmacopoeia of India***" New Delhi, Controller of Publication, 2, 550 & 741.
18. Defang, O and Shufang, NL (2005), "In vitro and in vivo evaluation of two extended release preparations of combination metformin and glipizide", ***Drug Dev Ind Pharm***, 31, 677-85.
19. Chein, YW (1997), "***Novel Drug Delivery Systems***", 2nd Ed., New York, Marcel Dekker Inc., 1-42.