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DEVELOPMENT OF CORRELATIONS FOR A MONOLITHIC MATRIX SYSTEM CONTAINING GLIPIZIDE

RAZVOJ I KORELACIJE MATRIKS MONOLITNIH SISTEMA KOJI SADRŽE GLIPIZID

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Abstract

The current research work has been embarked upon in an endeavor to formulate and evaluate the monolithic matrix tablets of glipizide for sustained release properties. Besides, this study illustrates the development of a validated *in-vitro in-vivo* correlation (IVIVC) for glipizide dosage forms depicted significantly modified drug release profile. All these formulated tablets containing glipizide and also showed sustained in vitro drug release in 12 hours. The drug release pattern from these tablets was correlated well with Korsmeyer-Peppas model and followed nonfickian diffusion mechanism. Based on the release constraints for sustained release as per USP, the sixteenth formulation (HPMC K4M: EC: Carnauba wax: 50:30:30) was chosen for further *in vivo* studies in rabbits. The values of regression co-efficient of IVIVC (percent drug dissolved versus percent drug absorbed) for marketed formulation and optimized formulations were calculated. The r^2-values for IVIVC of the both formulations were not significantly ($p<0.05$) different from each other. Internal prediction errors of IVIVC, calculated from observed Area under Curve (AUC) and predicted AUC, were less than 10% which authenticate the success of the correlation study. Thus, the current study presents a valid level A IVIVC for glipizide dosage form and may serve as an imperative tool in scale-up process.

Key words
In vitro- in vivo correlation; Glipizide; monolithic matrix drug delivery system.

Ključne reči
in-vitro invivo korelacije, glipizid, sistem monolitnog matriksa otpuštanja leka.

INTRODUCTION

Ample reports underscore that type 2 diabetes mellitus (T2DM) is a global health challenge. The worldwide pervasiveness of diabetes in adults was estimated to be 4.0% in 1995 and may rise to 5.4% by the year 2025. Recent estimates advocate that the number of patients diagnosed with T2DM will become more than double to 300 million before 2025[1].

T2DM is a chronic progressive disorder characterized by defective insulin secretion and increased insulin resistance and hence it requires an intense glycemic control. Glipizide is an oral rapid and short acting anti-diabetic drug from the sulfonylurea class. It is classified as a second generation sulfonylurea, exhibits 2 to 5 hours of half life and 100% bioavailability at regular formulation & 90% in extended release[2]. Besides, glipizide is poorly soluble in water and belongs to biopharmaceutical classification system (BCS) class II, low solubility and high permeability; it has two pka value is 5.9[3]. However, frequent dosing schedule and risk of gastrointestinal symptoms make its dose optimization complicated. In this milieu, we hypothesized that a suitable sustained release glipizide formulation is obligatory to lengthen the presence of the dosage form in the stomach or in the upper small intestine for a desired period of time, until all the drug is released. Also, we presumed that this modified formulation may prolong the drug's duration of action, improve oral bioavailability and curtail the gastrointestinal symptoms.

Over the last three decades, diverse approaches have been pursued to increase the retention of an oral dosage form in the stomach, including matrix systems[4]. Which improve absorption of drugs especially those are absorbed from stomach and small intestine[5]. These systems contain drug with matrix forming agents meant to retain for several hours in the gastro intestinal tract. On contact with the gastric fluid, these systems form a water colloidal gel barrier around their surface and swells. The swelled gel entraps the drug, thereby promoting sustained release. The amount of drug release depends upon the water penetrability and energy required to relax the polymeric chains. The aqueous solubility of the polymers will decide the drug release mechanism.

In the recent years, the concept and application of a mathematical model such as *in vitro-in vivo* correlation (IVIVC) for pharmaceutical dosage forms has been a paramount focus of attention[6]. A regulatory guidance of IVIVC for both immediate and modified-release dosage forms has been developed by the Food and Drug Administration (FDA) to minimize the need for bioavailability studies as part of the formulation design and optimization[7]. IVIVC could also be employed to establish dissolution specifications and to support and/or validate the use of dissolution methods. This is because the IVIVC includes *in vivo* relevance to *in vitro* dissolution specifications.

Hence, it is crucial to achieve the ultimate goal of formulating clinically effective matrix delivery system of glipizide for effective control of T2DM. In this regard, the present work was designed to address the following objectives: preparation of monolithic matrix tablets, evaluation of *in vitro* drug release pattern to match the target release profile. Subsequently, the *in vivo* studies were conducted to develop and validate an *in vitro-in vivo* correlation (IVIVC) for glipizide delivery system.

MATERIALS AND METHODS

1. Materials

Glipizide (99.3% purity) was received as a gift sample from Aurobindo Pharma Ltd. (Hyd, India). Hydroxy propyl methyl cellulose K4M (HPMC K4M), ethyl cellulose (EC), carnauba wax, sodium carboxy methyl cellulose (SCMC), microcrystalline cellulose (MCC) and magnesium stearate (Mg. stearate) were purchased from Yarrow chemicals Ltd. (Mumbai, India); De-ionized double-distilled water was used throughout the study. All other chemicals and solvents were of analytical grade and used without further purification and purchased from RFCL Ltd. (Mumbai, India). Bath sonicator was used for degassing (PCI analytics, Mumbai, India). LWL precision instrument was used for sample weighing (Contech, Mumbai, India). Elico® pH meter was used for pH adjustment. Ten station rotatory tablet punching machine was used for compression of tablets with 8 mm flat shaped punch (Chamunda Pharma, Mumbai, India).

2.Formulation of monolithic matrix drug delivery system

Accurately weighed drug and optimized black gram powder (80#) used as diluents, HPMC K4M, EC, SCMC and MCC were mixed by geometric mixing in a laboratory blender until the homogenization was attained. Followed by the addition of liquefied carnauba wax at 60°C, the proper mixing was ensured until the uniform damp mass was formed and screened on 22#. Then, the screened granules were dried at 45°C. Granules were tabletted by using 8 mm flat shaped punch and die set in 10-station rotary punching machine at a compression force of 5 tons. Before compression, the dried granules were lubricated by the addition of magnesium stearate. Formulation table can see in Table 1.

3. In vitro drug release study

Dissolution studies were conducted by using USP dissolution test apparatus II (paddle) and a 900 ml of 0.1N HCl (pH 1.2) was used as a dissolution medium for first 2 hrs and followed by phosphate buffer pH 6.8, maintained at 37±0.5°C, 50 rpm; aliquots of 1 ml were withdrawn at 0.5, 1, 2, 4, 6, 8, 10, 12 hours and the same volume of a fresh dissolution medium was replaced. Then, the aliquots were diluted to 10 ml, further analyzed and the relative concentrations were found by using best fitting of the least square regression analysis of peak area versus concentration.

4. In vivo study

The animals used for *in vivo* experiments were New Zealand white female rabbits (2.5 - 3.0 kg). The animals were kept under standard laboratory conditions, temperature at 25±1°C and relative humidity (55±5%). The animals were housed in polypropylene cages, each per cage, with free access to standard laboratory diet (Lipton feed, Mumbai, India) and water at *ad libitum*. The study was approved by the Institutional Animal Ethical Committee (IAEC) (license no: 1035/ac/09/IAEC/ IV-23/BCOP/2012.). The rabbits were fasted for 24 hrs before drug administration but allowed to free access of water. The animals were divided randomly into three groups (n=6) and under random study design, first group of the animals were treated as control, second group received, one uncoated marketed tablet formulation (10 mg of glipizide) and third group received, one optimized formulation (F16) corresponding to a dose of 10 mg glipizide. All the formulations were administrated by the oral gavages.

About 2 ml of blood sample was collected through the peripheral ear vein at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hrs after the administration. Samples were transferred immediately into heparin containing test tubes. After centrifugation at 5000 rpm for 30 minutes, plasma samples were harvested and stored at -20°C until analysis.

5. Analysis of release data

Glipizide content from powder mixture, matrices and *in vitro* dissolution study samples were measured by spectrophotometric (Shimadzu UV-1601, Shimadzu Corporation, India) method developed in both buffers (IP 1996) over an analytical range of 1–50 $\mu g ml^{-1}$ at 276 nm. An HPLC prominence Class-VP 2.0 (Shimadzu, India) was used for method development and validated for quantification of glipizide in rabbit plasma samples. Analysis was performed on thermoscientific Hypersil BDS, 5µ particle size, C18 column at 1.0 ml/min flow rate with 70:30 v/v mixture of acetonitrile: 10mM KH_2PO_4 buffer pH 3 as mobile phase (MP) at 254 nm.

6. Drug release kinetics

To scrutinize the mechanism of drug release from glipizide matrix tablets, the data obtained was fitted to mathematical equations of different kinetic models such as zero-order (cumulative amount of drug release versus time)8, first-order (log cumulative percentage of drug remaining versus time)[9], Higuchi (cumulative percentage of release versus square root of time)[10] and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) models[11].

$$F = kt \quad \text{---------- (1)}$$

$$\ln F = kt \quad \text{---------- (2)}$$

$$F = kt^{0.5} \quad \text{---------- (3)}$$

$$F = kt^{n} \quad \text{---------- (4)}$$

Table 1. Composition of all formulations

Formulation code	HPMC K4M (mg)	EC (mg)	Carnauba wax (mg)	SCMC (mg)	MCC (mg)	Diluent	Mg stearate (mg)	Total weight (mg)	Method
1	-	30	30	-	50	50	8	168	Wet
2	-	30	30	-	50	50	8	168	Direct
3	-	50	10	-	50	50	8	168	Wet
4	-	50	10	-	50	50	8	168	Direct
5	50	-	30	-	50	50	8	188	Wet
6	50	-	30	-	50	50	8	188	Direct
7	30	-	10	-	50	50	8	148	Wet
8	30	-	10	-	50	50	8	148	Direct
9	-	-	30	50	50	50	8	188	Wet
10	-	-	30	50	50	50	8	188	Direct
11	-	-	10	30	50	50	8	148	Wet
12	-	-	10	30	50	50	8	148	Direct
13	30	30	30	10	50	50	8	208	Wet
14	30	30	10	10	50	50	8	188	Direct
15	50	50	30	10	50	50	8	248	Wet
16	50	30	30	10	50	50	8	228	Direct

7.Development of IVIVC and its internal validation

The data obtained from *in vitro* dissolution tests and bioavailability studies were used to develop IVIVC. For novel drug products, dissolution is the essential screening tool to select the formulation for clinical trials. Correlations were developed by plotting the fraction of drug dissolved and fraction of drug absorbed in vivo along an identical and time scale to 12 hrs. Fraction of drug absorbed and percentage of drug absorbed were computed from the following equations respectively.

$$F_t = C_t + K_{el} x AUC_{0-t} \text{ ---------- (5)}$$

$$\%absorption = [F_t / K_{el} x AUC_{0-t} / AUC_{0-\infty}] x 100 \text{ ---(6)}$$

Where, C_t = plasma drug concentration at time t, K_{el} = elimination rate constant. Its value used in this equation was obtained from marketed formulation. AUC_{0-t} = area under the concentration time curve from time 0 to t, $AUC_{0-\infty}$ = area under the concentration time curve from time 0 to infinity.

A graph was plotted between percentage drug absorbed and dissolved for all formulations and regression analysis was also performed. IVIVC was considered good if the value of regression coefficient was not different from one. The predictability of developed IVIVC was assessed by its internal prediction error (%) of C_{max} (maximum plasma drug concentration) or AUC, calculated by following formula:

$$\text{Percent Prediction Error} = [(AUC_{Cobserved} - AUC_{predicted}) / AUC_{observed}] \times 100 \text{ ------ } \mathbf{(7)}$$

According to the FDA guidelines, an IVIVC is predictive if the internal prediction error for a formulation is not more than 15% for AUC and C_{max} and the internal prediction error across formulations is not more than 10% for AUC and C_{max}.

8. Statistical Analysis

Statistical analysis was done using SPSS statistical package. Student's t-test was used to determine the statistically significant differences between the results. Results with p-values <0.05 were considered statistically significant.

RESULTS AND DISCUSSION

1. Physical properties of the compressed matrix tablet system

The tablets of glipizide were prepared by wet granulation technique using HPMC (K4M), carnauba wax and ethyl cellulose. The weight variation and thickness of all the formulations were found to be within limits. Hardness of the tablets was found to be between 6.2 to 7.4 kg/ cm^2. The friability was below 1% for all the formulations, indicating good mechanical resistance of the tablets. The drug content varied between 98.56 to 90.20 % in all tablets with low standard deviation indicating the content uniformity of the prepared batches. All other physical properties can see in Table 2.

2. In vitro drug release study

To analyze the mechanism of drug release from these glipizide formulations, the *in vitro* dissolution data were fitted to various mathematical models like zero order, first order, and Higuchi and Korsmeyer-Peppas models. The results of the curve fitting into these aforementioned mathematical models were given in Table 3. The *in vitro* drug release for optimized formulation and marketed formulation were depicted in Figure. 1. HPMC K4M on exposure to water becomes hydrated, swells and forms a gel layer around the tablet, exibiting a sustained release effect[12].

Hydroxy ethyl cellulose is slowly soluble in water, but the degree of hydration of matrices is higher, relates to diffusion. Drug release mechanism by EC was mostly by Non-Fickian diffusion mechanism. Higher the concentration of carnauba wax, slower the release of dosage form. The cumu-

Table 2: Physical properties of the compressed matrix systems

Formulation Code	Angle of Repose (°)	Bulk Density (g/cm3)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's ratio (%)	Hardness (Kgf/cm2)	Friability (%)	Drug content (%)	Swelling index (%)
1	28.38±0.02	0.38±0.23	0.51±0.60	26.23±0.51	1.35±0.30	6.5±0.12	-0.10±0.02	92.23±0.20	24.19±0.10
2	24.22±0.12	0.39±0.05	0.53±0.32	25.60±0.51	1.34±0.06	6.7±0.10	-0.05±0.02	98.25±0.02	19.01±0.12
3	25.25±0.01	0.38±0.55	0.51±0.50	26.23±0.62	1.35±0.06	6.8±0.15	-0.36±0.01	90.56±0.20	28.22±0.20
4	24.02±0.01	0.34±0.20	0.47±0.25	27.96±0.25	1.38±0.10	7.4±0.52	-0.09±0.10	98.23±0.62	19.23±0.14
5	24.22±0.31	0.37±0.51	0.51±0.62	26.43±0.64	1.35±0.06	7.6±0.51	-0.24±0.02	94.52±0.62	24.69±0.52
6	25.26±0.36	0.38±0.51	0.51±0.16	26.23±0.03	1.35±0.02	7.0±0.52	-0.02±0.05	98.62±0.65	20.16±0.52
7	24.36±0.36	0.36±0.56	0.49±0.62	27.07±0.52	1.37±0.03	6.2±0.02	-0.04±0.05	96.62±0.01	26.31±0.12
8	24.58±0.63	0.37±0.31	0.51±0.50	26.43±0.23	1.35±0.06	7.0±0.06	-0.02±0.05	94.52±0.62	20.57±0.41
9	24.35±0.63	0.41±0.51	0.55±0.56	24.89±0.02	1.33±0.21	5.6±0.06	-0.12±0.06	98.56±0.45	24.73±0.95
10	25.31±0.61	0.39±0.13	0.53±0.50	25.64±0.10	1.34±0.21	7.4±0.05	-0.11±0.05	90.20±0.51	19.01±0.95
11	25.28±0.23	0.35±0.34	0.49±0.54	27.28±0.02	1.37±0.20	4.0±0.03	-0.04±0.04	98.62±0.84	17.93±0.75
12	25.37±0.65	0.36±0.92	0.49±0.73	27.07±0.01	1.37±0.01	7.4±0.06	-0.15±0.05	98.52±0.95	21.92±0.62
13	25.38±0.65	0.37±0.16	0.51±0.90	26.43±0.03	1.35±0.01	6.9±0.05	-0.02±0.09	98.51±0.95	18.51±0.74
14	25.00±0.63	0.36±0.51	0.49±0.86	27.07±0.06	1.37±0.05	5.8±0.01	-0.15±0.06	96.54±0.41	17.54±0.51
15	26.31±0.51	0.40±0.05	0.53±0.54	24.88±0.05	1.33±0.05	6.3±0.03	-0.07±0.09	94.62±0.62	26.11±0.56
16	26.33±0.52	0.39±0.56	0.53±0.93	26.19±0.06	1.35±0.62	7.3±0.12	-0.28±0.06	97.12±0.84	22.81±0.47

Table 3. In vitro release kinetics for glipizide matrix delivery system

Formulation code	Zero order		First order		Higuchi		Korsmeyer-peppas		Drug release mechanism
	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Diffusion exponent (n)	
1	0.963	5.2385	0.9925	-0.0417	0.9983	20.1198	0.9962	0.4379	Fickian
2	0.9433	6.4525	0.9812	-0.0751	0.9936	25.1825	0.9863	0.4542	Non-Fickian
3	0.9527	5.5356	0.9843	-0.0496	0.9952	21.4254	0.9963	0.4131	Fickian
4	0.9531	8.1586	0.5959	-0.0647	0.7449	19.1139	0.676	0.2723	Fickian
5	0.9408	8.2023	0.5912	-0.0724	0.7385	19.3344	0.6527	0.2506	Fickian
6	0.9354	5.0274	0.9822	-0.0413	0.9929	19.7722	0.9977	0.3828	Fickian
7	0.9407	6.6375	0.9373	-0.108	0.9915	25.9183	0.9943	0.3719	Fickian
8	0.9315	6.6061	0.9021	-0.137	0.9876	25.9495	0.993	0.3346	Fickian
9	0.9626	4.9356	0.9902	-0.0367	0.9982	18.9618	0.9965	0.4726	Non-Fickian
10	0.9406	6.2708	0.9778	-0.0759	0.9925	24.5157	0.9947	0.3848	Fickian
11	0.5856	4.2163	0.9857	-0.1119	0.7309	19.4971	0.626	0.2282	Fickian
12	0.936	6.2266	0.9808	-0.0772	0.9914	24.4352	0.9971	0.358	Fickian
13	0.9397	6.4636	0.9726	-0.0891	0.9925	25.2936	0.9968	0.3649	Fickian
14	0.9364	6.0171	0.9879	-0.0668	0.9917	23.6104	0.9964	0.3618	Fickian
15	0.9504	4.4599	0.9813	-0.0309	0.9947	17.294	0.982	0.4997	Non-Fickian
16	0.9378	6.3496	0.9787	-0.0623	0.9899	24.8301	0.9913	0.52	Non-Fickian

lative % drug release of optimized formulation was fitted to Higuchi (cumulative % drug release vs. square root of time) and Korsmeyer-Peppas (log cumulative percentage drug release Vs. log time) models. The ''n'' value was found to be 0.46±0.04 with good correlation coefficient ''r'' i.e. 0.99. The ''n'' value indicates that the release of glipizide from matrix tablets follows the Fickian diffusion behavior.

3. Study of interactions of polymers

The retardation of drug release was observed in the order of carnauba wax > HPMC K4M > EC in interactions as depicted in the normal plot. All the variables showed a significant effect individually in all formulations (95% confidence, $\alpha = 0.05$). The carnauba wax was more retardant to release the drug and EC has a negative standardized effect.

Studies show that more sodium carboxy methyl cellulose incorporation may lead to quicker burst release. HPMC K4M polymer on continuous hydration by the time caused polymeric chains relaxation, and was found to swell within less time than the swelling time of EC polymer.

4. Pharmacokinetic analysis

The plasma concentration of glipizide after administration of marketed and matrix formulations were shown in Figure. 6. The pharmacokinetic parameters including Cmax, tmax, elimination rate constant, half-life, AUC_{0-t} , $AUC_{0-\infty}$, $AUMC_{0-t}$, $AUMC_{0-\infty}$, and MRT (mean residence time) were given in Table 4. The elimination half-life was extended from 2.7 to 4.53 hours for marketed and optimized formulation respectively. The mean residence time of the dosage forms showed extension to 7.45 from 2.81 hrs, thus highlighting the sustained action in the body. The continuous drug release may improve absorption of the drug in gastrointestinal area and thereby contributes to better bioavailability[13].

The increased values were observed for t_{max}, half-life, AUC_{0-t} , $AUC_{0-\infty}$, $AUMC_{0-t}$, $AUMC_{0-\infty}$, and MRT in the optimized formulation when compared to marketed formulation, except for Cmax, elimination rate constant. The enhanced absorption of glipizide, observed in the present study may be attributed to the improved nature of the designed formulations.

5. IVIVC for glipizide matrix delivery system

Fig. 7 & 8 show the values of regression co-efficient of IVIVC (percent drug dissolved versus percent drug absorbed) for marketed and optimized matrix formulations. The r^2-values for IVIVC of the both formulations were not significantly ($p<0.05$) different from one. Our observations suggest that the internal prediction errors of IVIVC, calculated from observed Area under Curve (AUC) and predicted AUC, were less than 10%. Hence, the current study displays a level-A correlation for glipizide matrix drug delivery system and may serve as a surrogate of human bioequivalence studies[14].

CONCLUSION

The current study infers that an *in vitro-in vivo* correlation has been established for glipizide matrix delivery systems and successfully optimized. The in vitro drug release was found to follow Fickian diffusion mechanism. This delivery system could prolong plasma concentrations in stagnant levels so that we can overcome the side effects associated with a conventional formulation on long term monotherapy. Furthermore, this IVIVC study could be an imperative tool in the drug scale-up and initial US-FDA approval processes pertaining to the glipizide matrix formulation.

Table 4. Comparison of pharmacokinetic parameters for marketed and optimized formulations

Pharmacokinetic parameters	Marketed product	Optimized formulation
Cmax (ng/ml)	34.88 ± 0.77	29.09 ± 0.89
Tmax (h)	1.00 ± 0.4	4.00 ± 0.5
Elimination rate constant (h^{-1})	0.39 ± 0.01	0.15 ± 0.01
Half-life (h)	2.77 ± 0.04	4.53 ± 0.2*
AUC_{0-t} (ng*h/ml)	107.34 ± 1.53	236.08 ± 12.13
$AUC_{0-\infty}$ (ng*h/ml)	108.73 ± 1.52	245.01 ± 12.51
$AUMC_{0-t}$ (ng*h^2/ml)	302.35 ± 5.48	1761.11 ± 99.78
$AUMC_{0-\infty}$ (ng*h^2/ml)	322.6 ± 6.46	2034.03 ± 131.49
MRT (h)	2.82 ± 0.03	7.46 ± 0.12*

*Results are expressed as (mean ±SD, n=6). *p<0.05.*

Figure 1. In vitro drug release for glipizide matrix formulation (optimized) and marketed formulation (Immediate Release)

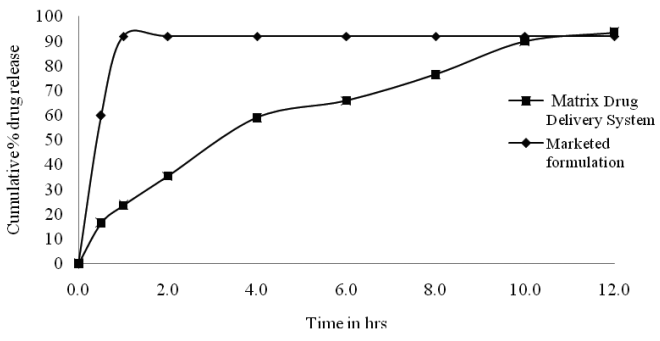


Figure 2. Mean plasma drug concentration-time curves of marketed and matrix formulations

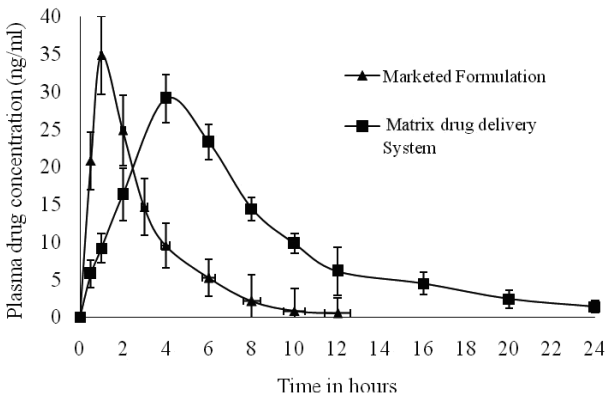


Figure 3. In vitro-in vivo correlation of glipizide marketed formulation

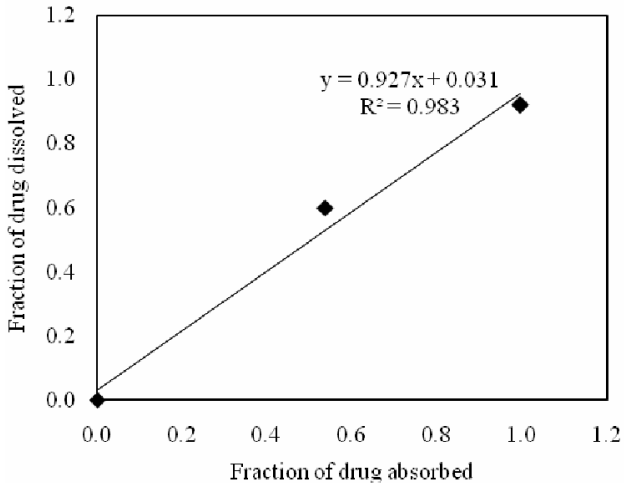
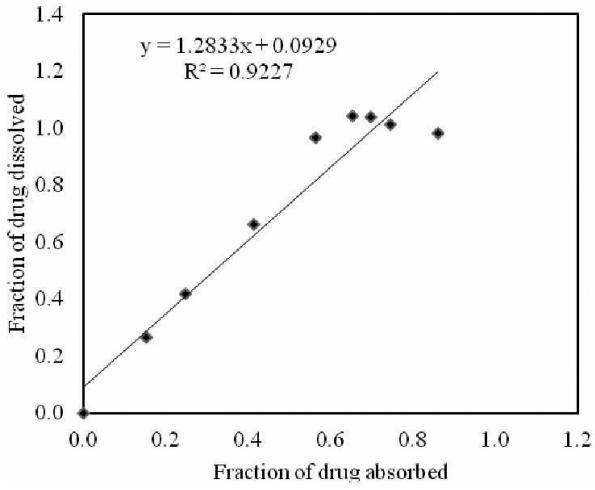


Figure 4. In vitro-in vivo correlation of glipizide matrix delivery system



Apstrakt

Ovo istraživanje je nastalo kao rezultat potrebe da se formuliše i evaluira monolitne matriks tablete glipizida sa svojstvom produženog oslobađanja. U ovoj studiji je prikazano razvoj i validaciju *in-vitro in-vivo* korelacije (IVIVC) za opisane dozirane oblike glipizida sa značajno izmenjenim profilom oslobađanja leka. Sve formulacije tableta sadrže glipizid i takođe pokazuju produženo in-vitro oslobađanje leka u toku 12 sati. Oslobađanje leka iz ovih tableta je dobro koreliralo sa Korsmeyer-Peppas-ovim modelom i sledilo non-Fickian-ove difuzione mehanizme. Na osnovu ograničenja oslobađanja za produženo otpuštanje po propisu USP, 16. formulacija (HPMC K4M: EC: Karnauba vosak: $NaHCO_3$ 50:30:30:25) je izabrana za dalja in vivo istraživanja na kunićima. Izračunate su vrednosti regresionih koeficijenata IVIVC (procenat rastvorenog leka u odnosu na procenat apsorbovanog leka) za komercijalnu i optimizovanu formulaciju. Vrednosti r^2 za IVIVC obe formulacije nisu se međusobno značajno razlikovale ($p<0,05$). Interne greška predviđanja IVIVC, koje su izračunate na osnovu površine ispod krive (AUC) i predviđene AUC, bile su manje od 10%, što potvrđuje uspešnost rezultata korelacione studije. U ovom istraživanju prikazan je validni nivo A IVIVC za dozirane oblike glipizida i može biti snažan alat u scale-up procesu.

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