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DEVELOPMENT AND EVALUATION OF ELEMENTARY OSMOTIC PUMP TABLETS BEARING ANTIDIABETIC DRUG

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ABSTRACT

An elementary osmotic pump (EOP) system that could deliver Glipizide (GZ) simultaneously for extended periods of time was developed in order to reduce the problems of type 2 non-insulin-dependent diabetes mellitus. In general, poorly water-soluble drugs is not good candidates for elementary osmotic delivery. However, GZ is a water-insoluble drug with a low dose (5 mg) so it is a great challenge to pharmacists to provide satisfactory extended release of GZ. GZ entrapped beta cyclodextrin it enhance the solubility of GZ. In present study, effect of appropriate amount of osmogents, plasticizer, and drug polymer ratio were optimized. One optimized formulation was selected for further evaluation. Different dissolution models were applied to drug release data in order to establish release mechanism and kinetics criteria for selecting the most appropriate model was based on best goodness of fit and smallest sum of squared residuals.

KEYWORDS: *Elementary osmotic pump tablets, Controlled release, β- cyclodextrin, Glipizide.*

• INTRODUCTION

Osmotic pumps are controlled drug delivery devices based on the principle of osmosis. Wide spectrums of osmotic devices are in existence, out of them osmotic pumps are unique, dynamic and widely employed in clinical practice.[1] Osmotic pumps offer many advantages like they are easy to formulate and simple in operation, improved patient compliance with reduced dosing frequency, more consistent and prolonged therapeutic effect is obtained with uniform blood concentration and moreover they are inexpensive and their industrial

adaptability vis-à-vis production scale up is easy.[2] The osmotic pump tablet system for oral administration has advantages such as-

- An osmotic pump tablet has excellent zero-order release kinetics.
- Constant delivery rate and there by reduce risk of adverse reactions.
- Delivery of drugs takes place in solution from which is ready for absorption.
- In – vivo delivery rate can be accurately predicted on the basis of in-vitro data.

The delivery rate from osmotic devices is not influenced by gastric pH and hydrodynamic conditions.[3, 4]

Elementary osmotic pumps are systems for the delivery of a drug in the form of a solution that release the active material at controlled rates. These systems work with the principle of osmosis, osmotic pressure is produced by active material in itself and /or an accompanying osmotic agent. The preparation consists of the core that contains the active material and a semipermeable membrane that coats the core, having an orifice produced by a microdrill in order to release the active material. When the system is in the gastrointestinal tract, fluid enters into the preparation and dissolves the active material in the core. Thus, the pressure formed in the preparation induces a release of the solution at a slow but continuous rate.[4, 5]

Here the aim of study was to formulate a simple EOP prepared with glipizide as a model drug. Glipizide is hypoglycemic agents belonging to the second generation sulphonylurea, derivatives. Generally, they are individually used in the treatment of type II noninsulin dependent diabetes mellitus. Glipizide lowers glucose concentrations by stimulating the release of insulin from pancreatic β-cells. Glipizide has a similarly biological half -life (2-4 h), depending upon the individual and the dose is 2.5 mg two to three times a day.[6,7]

Hence in this glipizide was chosen as a model drug. It was supposed that controlled release of glipizide not only reduces the GI irritation, but also give better therapeutic effect. Also by this study the factors responsible for controlling drug release through the elementary osmotic pump tablets were evaluated.[8, 9]

MATERIALS AND METHODS

Glipizide was received as a gift sample from Micro Lab. (Pondicherry, India). Cellulose acetate obtained from Central Drug House, New Delhi, India. PEG-400, PVP K-30,

Mannitol, β-cyclodextrin, all are also obtained from CDH New Delhi; other chemicals were of analytical grade and used without any further purification.

METHODS

Drug analysis: GZ was analyzed by using UV—Vis double beam spectrophotometer (UV-1700, Shimadzu, Japan) method at λ max 274 nm in pH (1.2) 276 nm in pH (6.8). Calibration curves were prepared in the concentration range 1-10µg/ml. correlation coefficients were found to be R^2 = 0.9963 in pH 1.2, R^2 = 0.9993 in pH (6.8).[10] (Figure 1 shown in this paper).

Drug-Solubility Study: The binding constants between Glipizide and β-cyclodextrin were determined using the phase-solubility method. Excess Glipizide was added to water (20 mL) containing different concentrations of β-cyclodextrin, and shaken at 37^0C for 5 days. Then the filtered solutions were analyzed by high-performance liquid chromatography (HPLC) after dilution with the mobile phase. The glipizide was fractionated on a hypersil ODS column (15 cm × 4.6 mm, ID with 5 µm packing material) with detection at 276 nm using a mobile of methanol-water (60:40, with 0.2% acetate acid). The intrinsic solubility of Glipizide and the binding constants with β-cyclodextrin were calculated using least squares regression analysis as suggested by Higuchi and Connors.[11]

Preparation of Inclusion Complexes

Solid complexes were prepared using different ratios of Glipizide and β-cyclodextrin. The ratios were calculated on a molecular basis, and the following proportions were prepared: 1; 1, 1; 2, 1:6, 1:10, 1:20. The complexes were made by the kneading method and the effect of the kneading time on the complexation was also investigated. The results show that after 3 hr the kneading time has little effect on the complexation. So glipizide and different molar quantities of β-cyclodextrin were wetted in a molar with 50% methanol until a paste was obtained and mixed for 2 hr. Then, these pastes were left to air dry for one night and finally mildly ground and stored under vacuum in desiccators for 5 days. The product was sieved through a 0.247-mm mesh[11]

Preparation of Core tablets

The basic tablet formulation and the varying range of all chemicals are listed in Table 1. Core tablets of glipizide were prepared by wet granulation method. Inclusion complex of glipizide was mixed with all the excipient except, magnesium stearate and talc, all were manually blended, then the blend was granulated with ethanol and resulting wet mass was passed

through 16 mesh sieve and dried it in hot air oven at 50-60^{0}C for sufficient time (15-20 min). After this granules were passed through 22 mesh sieve. These granules were then manually blended with magnesium stearate and talc, the resulting granules were then compressed into tablets using calibrated single stroke punching machine.

Coating and drilling of the formulations

The core tablets were coated in a pan coater (laboratory model made of stainless steel). Cellulose acetate as semi-permeable membrane and PEG 400 as plasticizer were used in coating solution (Table-2). The core tablets were coated in coating pan and initially pan was rotated at low speed and heated air was passed on the tablet bed. Then the speed of pan coater was increased and coating solution was manually sprayed over the surface of tumbling tablets with a spray gun. The manual coating procedure was done by intermittent spraying and drying. The coated tablets were dried overnight at 50^{0}C to remove solvent. A 0.50 mm orifice was micro drilled manually by a sharp needle on one side of tablet.[5]

Micromeritic properties of powder blend

Loose Bulk density (Db), tapped density (Dt), percentage compressibility (PC), hausners ratio (HR), and the angle of repose (AR) of powders were determined (Table3). Db and Dt were determined by USP method I using a tapped density tester.[12] Angle of repose by fixed funnel method. PC and AR were calculated using equation (1) and (2)

% Compressibility = (Dt-Db) /Dt ×100---------- (1)

Angle of repose (θ) = $\tan^{-1}$ (h/r) ---------- (2)

Evaluation of physicochemical parameters of core and coated tablets

The blend was evaluated for flow properties like, % compressibility and angle of repose. The hardness of core tablets were evaluated by Monsanto hardness tester (n=10). Friability of core tablets was carried on a Roche Friabilator for which 20 accurately weighed tablets were used. The core and coated tablets were also evaluated for weight variation, thickness and diameter. The average orifice diameter of the OP_3 was determined microscopically (n=20) using a pre calibrated ocular micrometer (Table 4). Effect of various variables like PEG-400 concentration, membrane thickness, orifice size, pH of release media and agitation rate were studied on drug release.[7]

In-vitro release studies: Drug release *in vitro* was studied using USP XXIII dissolution apparatus (rotation speed at 50 r/min, 900 ml of phosphate buffer pH 6.8 as the dissolution

medium at 37°C ± 0.5°C). During the release test, 5 ml samples were withdrawn at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 9.0 10, 11, 12 and 24 h and filtered through a 0.45 µm filter. An equal volume of fresh dissolution medium at the same temperature was added. The amount of glipizide was determined by measuring the absorbance at 276.0 nm using UV-Vis spectrophotometer (Shimadzu 1700, Japan). This study was done in triplicate manner.

Drug content uniformity testing

Glipizide content present in osmotic pump tablets was determined by weighing accurately one tablet and crushed it in 100 ml of methanol. The sample was shacked for 30 min and filtered. The solution after filtration was analyzed by UV-Vis spectrophotometer at 276 nm, after appropriate dilutions with methanol.[6]

Scanning electron microscopy studies

To study the nature of membrane surface of developed osmotic pump tablets, both and after dissolution studies, electron microscopic method was used. The samples for SEM were prepared by placing semi-permeable membrane on a both side adhesive tape stuck to a stub. Gold palladium coating on the prepared stub was carried out by using Sputter coater (POLARON model SC- 76430). The thickness of coating was $189A^0$.

The coated stubs were randomly scanned under Electron microscope (LEO-430, UK).

Kinetic modeling of drug release: Dissolution data of the optimized and other formulations of glipizide elementary osmotic pump tablet was fitted to various mathematical models (zero-order, first order and Higuchi) in order to describe the kinetics of drug release. (Table6).

Study the effect of release media and agitation rate on drug release profiles

To study the effect of dissolution media on drug release and to assure a reliable *in-vitro* performance, release studies tests of the optimal formulation(OP3) were performed in 0.1 N hydrochloric acid solution (pH 1.2), phosphate buffer pH 6.8 and phosphate buffer pH 7.4 at 37± 0.5°C. The samples were taken out at predetermined intervals and analyzed after filtration by UV spectroscopic method at 276 nm for glipizide. The results are shown in figure 3.

Drug release from osmotic pumps to a large extent is independent of agitation intensity of the release media.[6] To study this parameter, release studies of the optimized formulation was

performed at different agitation intensity 50, 100 and 150 rev/min. in USP-1 basket type dissolution apparatus. All samples were withdrawn at predetermined intervals and analyzed after filtration by UV (UV-1700 Shimadzu, Japan) at 276 nm for glipizide. (Shown in figure4).

Accelerated stability studies

Stability studies were done according to ICH and WHO guidelines. The prepared osmotic pump tablets containing glipizide (OP3) was selected for stability study on the basis of *in-vitro* drug release, weight variation test, hardness and drug content. The selected tablets of glipizide (OP3) sealed in aluminum packaging coated inside with polyethylene, and various replicates were kept in the humidity chamber maintained at 40^0C and 75% RH for 6 months. At the end of studies, samples were analyzed for the drug content, *In -vitro* dissolution and other physicochemical parameters. The observation of accelerated stability is presented in table7.

RESULTS AND DISCUSSION

Micromeritic properties of powder blend

As shown in Table 3, the powders of prepared formulations were evaluated for Db, Dt , PC, HR and angle of repose. The Db and Dt of formulations ranged from 0.18+_.07 to 0.20+_0.007 and 0.24+_.012 to 0.25+_0.015 respectively. The PC and HR of powders of formulations ranged from15.10+_2.7 to25.0+_1.9. Angle of repose ranged from 19.7+_1.8 to 22.5+_1.5. As such all the results obtained indicate that the formulated powders match the compressibility and flow properties satisfactory.

Evaluation of physicochemical characteristics of core and coated tablets

As shown in Table 4 and 5, the results of thickness of core and coated tablets ranged from 6.05+_00.28 to7.12+_0.02mm and 5.58+_0.16 to 7.39+_.07mm respectively. The drug content uniformity ranged of drug for GZ 97.5+_0.2 to 99.6+_0.77 indicating a uniform content in the formulations. Thus all prepared tablets in this study meet the USP requirements for weight variation test. The hardness and friability of core tablets ranged from 5.16+_0.08 to 5.22+_0.17kg//cm^2 and0.24 to 0.6 percent respectively. The final comparison revealed that the prepared core and coated tablets were superior in hardness accompanied with very negligible amount in percentage weight loss.

Influence of coating on drug release

The prepared core formulations were manually coated with coating solution by dip coating technique (0.07to0.26 mm thickness of coating. PEG-400 is used as plasticizer and also to enhance the physicochemical property of cellulose acetate membrane. The surface of coated tablets had a smooth and uniform appearance. (Shown in figure5).

Influence of orifice size on release rate

The drug release profile was recorded for different orifice size 0.5 to 1.5 mm. results of release study indicate that no significant difference 0.5mm exists in release profiles however with orifice size 1.5 mm some what rapid release was noted. (Shown in figure6).

Influence of different dissolution media and rotation rate on drug release profile

The release profile of optimal formulation in different dissolution media was recorded. Release rate for all were found almost similar, observed in release rate on application of PCP Disso-V2-08**.**

The release rate at 50 rpm, 100 rpm, and 150 rpm were analyzed by PCP Disso-V2-08. It can be concluded that as drug release was independent of agitation rate from osmotically controlled system. (Shown in figure4).

In vitro drug release and kinetics of drug release

The In vitro release was performed for 3 hrs in acidic buffer (pH 1.2) and followed by 18 hrs in phosphate buffer (pH6.8) and (pH7.4). The optimal formulation releases 98.62% at 18 hrs. The criteria employed to select the best fit model was the one with the highest correlation coefficient determination (Table 6). The best – fit model was found to be zero order form optimized formulation. The selection criteria for the best model were based on goodness of fit of the data and residual sum squares. The release of GZ from osmotic pump tablets followed non-Fickian mechanism.

Drug- excipient interaction studies

The drug excipient interaction studies were carried out by employing IR Spectroscopic technique. The IR absorption peaks of GZ at 2937.81, 1689.50 and 884.01 cm^{-1}. The spectra of the optimized formulation showed the IR absorption peaks almost similar to those of the mixture of GZ and excipient thus indicating that no chemical interaction occurred between drug and the excipients used. (Figure2).

Accelerated stability studies

The prepared osmotic pump tablets were selected for stability study on the basis of In vitro dissolution profile and their physical properties. The osmotic pump tablets were investigated at 40^0C/75% RH in aluminium foil packaging for 6months (Table7.). It was found that osmotic pump tablets were stable under these storage conditions for at 6 months. It could be concluded `that the developed that the developed product is stable and no measureable degradation product was observed.

Table 1- Formula for different batches of core formulation

Table 4.6: Formula for different batches of core formulation							
INGREDIENTS (mg per tablet)	**FORMULATION CODE**						
	OP1	**OP2**	**OP3**	**OP4**	**OP5**	**OP6**	**OP7**
Glipizide	5	5	5	5	5	5	5
β-cyclodextrin	100	100	100	100	100	100	100
Mannitol	50	75	150	200	100	100	100
Lactose	100	100	100	100	50	100	150
PVP K-30	20	20	20	20	20	20	30
Magnesium stearate	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5
Total weight of the tablet	285	310	385	435	285	335	395

Table 2. Composition of coating solution and membrane thickness

Coating layer code	**Coating Material**		**Coating Thickness (mm)**
	PEG-400 in acetone (%w/w)	**Cellulose acetate (%w/w)**	
CL0	0	40	0.075
CL1	7	40	0.12
CL2	12	40	0.19
CL 3	24	40	0.23
CL4	50	40	0.29

Table3. Micromeritic properties of powder blend

Table 4.11: Comparative study of various granules characteristics.					
Formulation	**Angle of repose (*Θ*)**	**Bulk density (gm/ml)**	**Tapped density (gm/ml)**	**Hausner,s ratio (H_R)**	**Compressibility %**
OP1	21.7±1.8	0.20±.07	0.21±.012	1.23±.024	19.10±2.7
OP2	19.7±2.3	0.17±.04	0.23±.016	1.40±.029	22.8±2.4
OP3	18.7±1.9	0.18±.06	0.26±.015	1.28±.023	23.0±2.1
OP4	22.5±1.5	0.19±.07	0.22±.014	1.36±.031	21.0±2.7
OP5	19.7±1.7	0.20±.06	0.21±.017	1.31±.025	29.8±2.3
OP6	20.4±2.6	0.17±.08	0.22±.016	1.29±.023	19.0±1.9
OP7	19.5±2.4	0.20±.05	0.21±.011	1.29±.025	21.6±2.8

***Mean**±SD n=3 (All values are the average of three determinations)

Table 4. Physicochemical properties of all prepared core formulations

S. No.	Parameter	Formulation code						
		OP1	OP2	OP3	OP4	OP5	OP6	OP7
1	Tablet weight (mg), (n=20) Core tablets Coated tablets	285.5±.76 294.7±1.7	310.7± .52 331.1±1.8	385.7± .54 399.5±2.5	435.9±.21 479.1±1.8	285.5±.76 314.7±1.7	335.4±.65 359.5±2.5	395.8±.14 419.8±0.4
2	Highest (%)deviation	0.518	0.478	0.304	0.360	0.387	0.272	0.636
3	Hardness of core tablets (n=10)	5.16±0.08	5.2±0.12	5.42±0.10	5.1±0.20	5.22±0.17	5.12±0.20	5.16±0.30
4	Diameter (mm), n=20 Core tablets Coated tablets	13.23±.02 13.49±.07	15.34±.02 15.65±.06	13.28±.05 13.57±.04	13.35±0.3 13.76±0.7	13.24±.03 13.64±.05	13.19±.04 13.44±.05	12.09±0.3 12.48±0.5
5	Thickness (mm), n=20 Core tablets Coated tablets	6.05±.28 6.13±.16	7.12±.02 7.39±.07	6.21±.007 6.43±0.05	6.07±.04 6.46±.03	6.27±.075 6.38±.17	6.21±.02 6.49±.04	5.23±.11 5.58±.07
6	Friability (%)	0.012	0.034	0.185	0.279	0.294	0.189	0.239
7.	% Drug content GL.	97.53±0.2	98.3±0.21	98.6±0.14	99.6±0.77	95.7±0.14	96.5±0.20	99.8±0.16
8	Orifice diameter (mm) (n=20)	0.50±.016	0.51±.017	0.52±.01	0.53±.01	0.51±.02	0.53±.01	0.50±.01

Table 5. Physicochemical properties of optimized formulation (OP3)

	Coating layer code	Thickness* (mm)	Hardness* (kg/cm^2)	Weight variation* test (%)	Friability (%)	Drug content* (%)	Drug release* (%)
Optimized formulation (OP3)	CL0	6.21±.007	5.42±0.10	917.7± .54	0.247	98.46±0.18	57±1.45
	CL1	6.34±.011	5.42±0.10	917.7± .54	0.247	98.46±0.18	69.6±1.01
	CL2	6.45±.016	5.42±0.10	917.7± .54	0.247	98.46±0.18	86±1.07
	CL3	6.72±.127	5.42±0.10	917.7± .54	0.247	98.46±0.18	98±0.101
	CL4	6.97±.117	5.42±0.10	917.7± .54	0.247	98.46±0.18	99.47±0.11

Mean ±SD, n=3 (All values are the average of three determinations).

Table6. Correlation coefficient values obtained from In vitro release data of optimized formulation

Regression coefficient (R)			
Zero-order	First-order	Higuchi	Hixon-crowell
R^2	R^2	R^2	R^2
0.9769	0.8763	0.9563	0.9690

Table7. Accelerated stability studies of optimized formulation.

Condition		$40^0 \pm 2^0$/75% RH±5% RH						
Sampling period		0 month	1st month	2nd month	3rd month	4th month	5th month	6th month
Parameter Evaluated (3)	color	white	white	white	white	white	white	white
	Drug content %	99.27±0.59	98.15±0.27	98.17±0.36	97.11±0.16	97.02±0.36	97.11±0.13	97.02±0.25

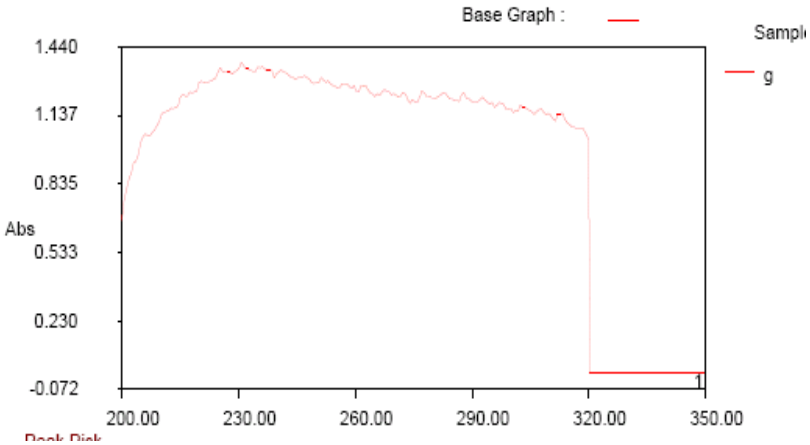

Figure1. UV Scanning Curve of Glipizide

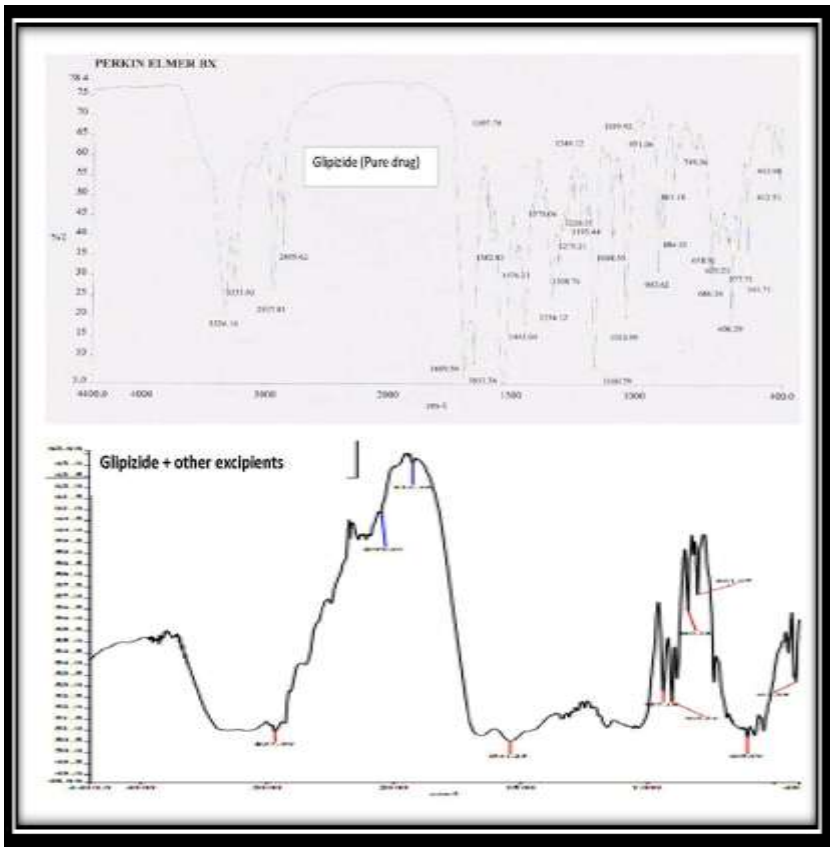

Figure2. FTIR of a) Pure drug (Glipizide) b) Mixture of Glipizide and Other excipient

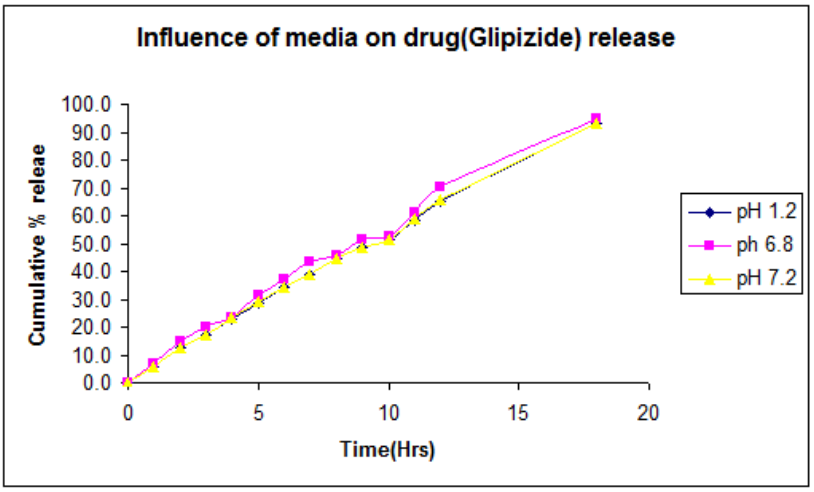

Figure3. Effect of media on Glipizide release profile.

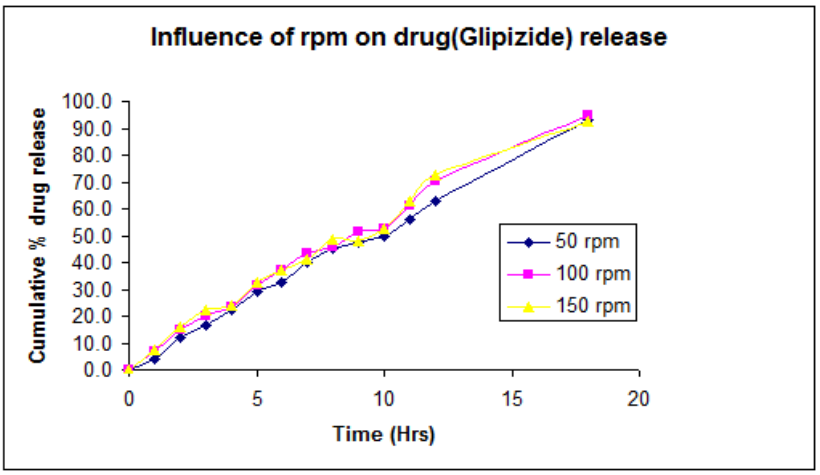

Figure4. Influence of agitation rate on Glipizide release profile.

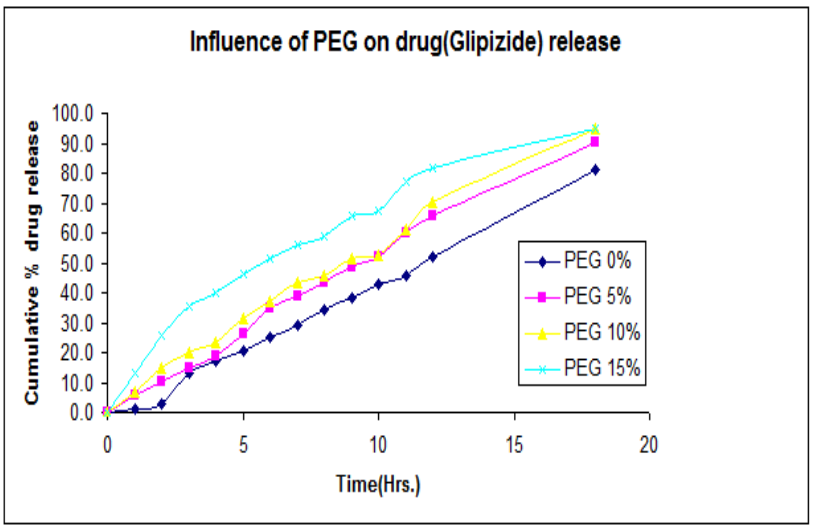

Figure5. Effect of PEG400 level on Glipizide release profile.

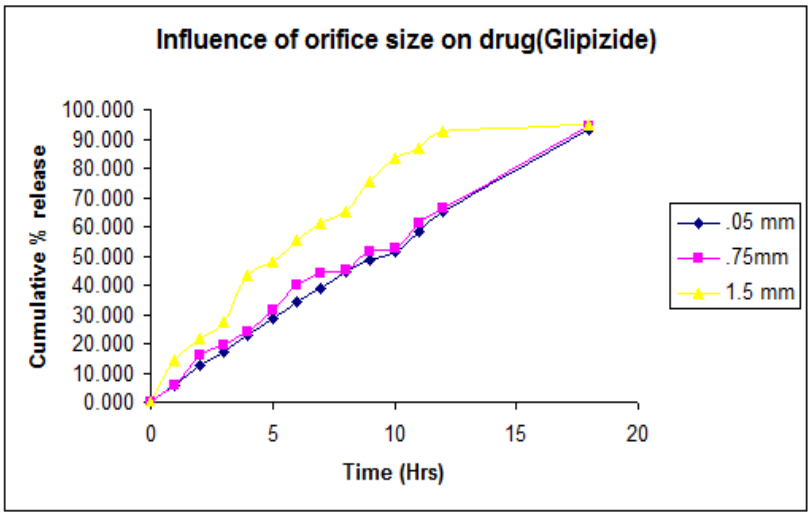

Figure6. Influence of orifice diameter on Glipizide release profile.

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REFERENCES

1. Bhatt, P. Osmotic Drug Delivery Systems for Poorly Soluble Drugs. The Drug Delivery Companies Report Autumn/Winter 2004.
2. Garg, S.; Verma, R.K. Development and evaluation of osmotically controlled oral delivery system of glipizide. European J. Pharmaceutics and Biopharmaceutics. 2004; 57: 513-525.
3. Garg, S.; Verma, R.K.; Mishra, B. Osmotically controlled oral drug delivery. Drug Dev. Ind. Phar. 2000; 2: 695-708.
4. Garg, S.; Verma, R.K.; Krishna, D.M. Formulation aspects in the osmotically controlled oral drug delivery systems. J. Control Release. 2002; 79: 7-13.
5. Kumar, P.; Mishra, B. Development and biopharmaceutical evaluation of extended release formulation of tramadol hydrochloride based on osmotic technology. Acta pharma. 2009; 59: 15-30.
6. British pharmacopoeia, 2003; CD –ROM; Vol, I: Monograph Article 5.
7. Aly, M.; Qato, M.; Ahmad, M. Enhancement of the Dissolution Rate and Bioavailability of Glipizide through Cyclodextrin Inclusion Complex. Pharmaceutical Technology. June 2003; 54-62.

8. Gan. Y.; Pan, W.; Wei, M.; Zhang, R. Cyclodextrin complex tablets for glipizide delivery. Drug Dev. Ind. Lloijuyjoy1234aaPhar. 2002; 28: 1015–1021.
9. Kumar, P.; Mishra, B. Studies on Elementary Osmotic Pump Tablets of Naproxen Sodium. Acta Pharmaceutica Turcica. 2004; 46: 35-41.
10. Bhargava, S.; Agrawal, G.P. Preparation and Characterization of Solid Inclusion Complex of Cepodoxime Proxetil with β-Cyclodextrin. Current Drug Delivery. 2008; 5: 1-6.