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An approach to develop the controlled drug delivery system for Glipizide

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ABSTRACT

This study presents the development of extended release formulations of glipizide based on osmotic technology. In this study two-layer push pull osmotic tablet system was developed using Carbopol, Sodium chloride, microcrystalline cellulose. The push-pull osmotic tablets consist of two layers, one containing drug along with osmogen and other an osmotic agent and swellable polymer. A semi permeable membrane that regulates water influx in to both layers surrounds the system. After coating, orifice was simply drilled in drug side surface.

This study was intended to study the influence of tablet core variable, including, amount of sodium chloride in drug layer, carbopol 934P amount in push layer and drug layer. Effect of pH, orifice size, agitation intensity, and weight gain by coating on in vitro release was studied.

Keywords: glipizide, carbopol 934P, Sodium chloride, microcrystalline cellulose.

INTRODUCTION

Osmotic devices are most promising strategy based system for controlled drug delivery. They are among the most reliable controlled drug delivery system and could be employed as oral drug delivery systems or implantable device. Osmosis is an aristocratic biophenomenon, which is exploited for development of delivery systems with every desirable property of an ideal controlled drug delivery system. Osmotic system utilizes the principles of osmotic pressure for delivery of drug. [1]

Osmotically controlled oral drug delivery systems (OCODDS) utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is

independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system. [2]

Glipizide, an oral hypoglycemic agent, is one of the most commonly prescribed drugs for the treatment of patients with type II diabetes mellitus. It is practically water-insoluble, but the absolute bioavailability is close to one. Thus, it belongs to class 2 of Biopharmaceutical Classification System (BCS). Glipizide has a relatively short elimination half-life (2–4 hrs), thereby requiring two to three times daily dosing in large number of patients, which often leads to non-compliance. [3, 4]

Thus, there is a strong clinical need and market potential for a dosage form that will deliver glipizide in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance.

MATERIALS And METHOD

1. Preparation of standard curves of glipizide:

Standard curve of glipizide was prepared in phosphate buffer pH 6.8, pH 7.4 and acidic buffer pH 1.2

Procedure:

Stock-1: accurately weighed (10mg) of Glipizide was dissolved in 20 ml of given buffer taken in 100ml calibrated volumetric flask and volume was made up to the mark using given buffer.

From stock-1 0.5 ml solution was withdrawn and diluted up to 10 ml in volumetric flask this gives 5 µ/ml. Similarly 10, 15, 20, 25,30,35,40 µ/ml were prepared by withdrawing 1, 1.5, 2, 2.5, 3, 3.5, and 4, respectively. Absorption of each solution was measured at 276 nm using shimadzu UV-1700 UV/Vis spectrophotometer.

Note: Here given buffer means phosphate buffer pH 6.8, pH 7.4 or acidic buffer pH 1.2

Table 1: Composition of glipizide push pull osmotically controlled release tablets

Ingredients	C1	C2	C3	C4	C5
Drug layer:					
Glipizide	10	10	10	10	10
Carbopol 934P	25	50	75	100	125
NaCl	25	25	25	25	25
MCC	45	45	45	45	45
Mg. stearate	Trace	Trace	Trace	Trace	Trace
Push Layer:					
Carbopol	100	100	100	100	100
MCC	80	80	80	80	80
NaCl	10	10	10	10	10
Mg. stearate	Trace	Trace	Trace	Trace	Trace

2. Preparation of glipizide push-pull osmotic tablets:

Bilayer osmotic tablets were prepared according to formulation given in Table 1. The drug layer was comprised of Glipizide, Carbopol 934 P, NaCl, MCC, and magnesium stearate. All the ingredients weighed accurately and shifted through 60# then mixed properly. The osmotic layer comprise of Carbopol, MCC, NaCl, Magnesium stearate. All the ingredients weighed accurately and shifted through 60# then mixed properly. Bilayer standaed convex tablets having 10 mm diameter and 6-7 kg/cm^2 hardness were prepared. Prepared tablets were evaluated for various parameters.

3. Coating of tablets:

A 6% w/v solution of cellulose acetate in acetone was used as a semi permeable membrane provider. Caster oil was used as a plasticizer. The tablets were warmed to 40 ± 2^{o}C before applying coating solution. (Table 2 contains coating composition).

Coating was done in coating machine. Tablets were put in coating pan and rotate pan. Coating solution was sprayed by spray gun. Hot air supplies and dried the tablets. After coating dry tablets were weighed for percentage weigh gain up to 12 % by following equation.

% weigh gain = (Wt-Wo/ Wo) ×100

Where, Wt = weight of tablet after coating Wo = weight of tablet before coating

Table 2: Coating composition

Ingredients	Quantity
Cellulose Acetate	1.50gm
Castor oil	0.40gm
Acetone	25 ml

4. Evaluation parameters [5]:

4.1 Tablet dosage forms assay:

The Glipizide tablets were tested for their drug content. Five tablets were finely powdered; quantities of the powder equivalent to 10 mg of Glipizide were accurately weighed and transferred to a 100-ml of volumetric flask containing 20ml of Phosphate buffer pH 7.4 mixed thoroughly then volume made up to 100ml with same buffer. And filter. Dilute 10 ml of the resulting solution to 200 ml with Phosphate buffer pH 7.4 and measure the absorbance of the resulting solution at the maximum at 276 nm using Shimadzu-1700 UV/Vis spectrophotometer. The linearity equation obtained from calibration curve as described previously was use for estimation of glipizide in the tablet formulations.

4.2 Weight variation test:

To study weight variation 20 tablets of each formulation were weighed using a Sartorious electronic balance and the test was performed according to the official method.

4.3 Hardness:

For each formulation, the hardness and friability of 6 tablets were determined using the validated Ablet hardness tester and the Roche friabilator (Camp-bell Electronics, Mumbai, India), respectively.

4.4 In-vitro drug release studies:

In vitro study of Glipizide was carried out using USP-2 paddle apparatus. The test conditions were as follows: Tablets which contain about 10 mg of Glipizide were placed in 900 ml of pH 7.4 phosphate buffer medium and temperature maintained at 37 ± 0.5 ^{o}C, the rotation rate of paddle was adjusted to 50 rpm/min. At different intervals, 10 ml of samples were withdrawn and replaced with the same dissolution medium. Filter the withdrawn samples through the whatman filter paper. Measure the absorbance of the resulting solution (dilute if necessary) at the maximum at 276 nm using Shimadzu-1700 UV/Vis spectrophotometer.

4.5 Study on effect of different formulation variables of tablets:

4.5.1 Calculation of theoretical dissolution profile:

The pharmacokinetic parameters of Glipizide were utilized for the calculation of theoretical drug release profile for 12 hours dosage form. The immediate release part for sustained release Glipizide was calculated using equation (4.1) and was found to be 3.5 mg.

$$\textbf{Immediate release part} = (C_{ss} \times V_d) / F \text{ ---------- } \textbf{(4.1)}$$

Where, C_{SS} is steady state plasma concentration, Vd is volume of distribution and F is fraction bioavailable.

$$\textbf{Dose} = \textbf{Immediate release part}[1+ (0.693*t/t_{1/2})] \text{----------} \textbf{(4.2)}$$

Where, t is time up to which sustain release is required and $t_{1/2}$ is half life of drug.

$$\textbf{Dose} = 3.5[1+(0.693*12/3.8)]$$
$$= 11.1\text{mg} (\approx 10\text{mg})$$

Here, the formulation should release 3.5 mg (35 %) of drug in 1 hour like conventional tablet and 0.59 mg (5.9 %) per hour up to 12 h thereafter.

Table 3: Important pharmacokinetic parameters of glipizide [3]

Immediate release part = (Css x Vd) / F ---------- (4.1)

Table 3: Important pharmacokinetic parameters of glipizide [

Pharmacokinetic parameters	**Value**
Fraction of drug absorbed (f)	1
Elimination half-life ($t_{1/2}$)	3.8 h
Terminal disposition rate Constant k_{el}	0.21 h^{-1}
Apparent volume of distribution (V_d)	0.17 l/kg
Minimum effective concentration (C_{ss} min)	20 ng/ml
Maximum effective concentration (C_{ss} min)	300 ng/ml
Clearance (CL)	0.52 $\pm$ 0.18 ml min^{-1} kg^{-1}
.	

Table 4: Theoretical dissolution profile of glipizide

Time in min	Cumulative percentage release
0	0
60	35.0
120	40.9
180	46.8
240	52.7
300	58.6
360	64.5
420	70.4
480	76.3
540	82.2
600	88.1
660	94.0
720	99.9

4.5.2 Comparison of dissolution profiles by similarity factor f_2: [6, 7]

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 value is 50 to 100.

The dissolution profiles of products were compared using a similarity factor (F_2). This similarity factor is calculated by following formula,

$$f_2 = 50 \times \log \{[1+ (1/n) \Sigma_{J=1}^{n} | R_j - T_j |^2]^{-0.5} \times 100 \}$$

When n is the number of dissolution time and R_j and T_j are the reference and test dissolution values at time t. Two dissolution profiles are considered similar when the F_2 value is 50 to 100.

4.5.3 Effect of sodium chloride:

To study the effect of sodium chloride and to assure a reliable performance of developed formulation, first drug release study of optimize formulations were conducted. Then changes the amount of sodium chloride in drug layer of optimize formulations and again drug release study was carried out in pH 7.4 phosphate buffer.

4.5.4 Effect of carbopol 934P amount on push layer:

To study the effect of carbopol 934P amount on push layer and to assure a reliable performance of developed formulation, drug released study of optimize formulation were conducted. Then changing the carbopol 934P amount in push layer of optimize formulations drug release study was carried out in pH 7.4 phosphate buffer

4.5.5 Effect of pH:

To study the effect of pH release study of optimize formulations were conducted in different pH. The release media was 0.1N HCL i.e. pH1.2, phosphate buffer (pH 6.8), phosphate buffer (pH

7.4). Digital pH meter Digium Electronics Hyderabad was used to measure the pH of buffer medium.

4.5.6 Effect of weight gain:
To study the effect of weight gain of the coating on drug release, optimum batch of glipizide were coated as a per procedure described in 4.2.3.1. So as to get tablets with different weight gains (10, 12 and 14% w/w).

4.5.7 Effect of orifice size:
To study the effect of orifice size on drug release, optimum batch of glipizide were mechanically drilled so as to get tablets with different orifice size. Orifice size was measured by traveling microscope. Take a tablet fix it to a clamp in horizontal position. Focus the traveling microscope to the orifice of the tablet. When viewed through the eye piece note the reading of vertical scale.

RESULTS AND DISCUSSION:

5.1: Standard curve of glipizide in phosphate buffer pH 7.4 at 276 nm:

Sr. No.	Concentration (mcg/ml)	Absorbance
1	0	0
2	5	0.145
3	10	0.255
4	15	0.362
5	20	0.469
6	25	0.615
7	30	0.772
y=0.024x R^2 = 0.995		

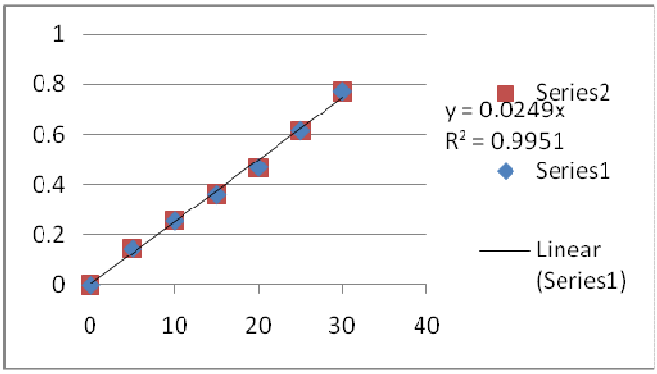

Figure 1: Calibration curve of Glipizide in Phosphate buffer pH 7.4

5.2 Standard curve of glipizide in phosphate buffer pH 6.8 at 276 nm:

Sr. No.	Concentration (mcg/ml)	Absorbance
1	0	0
2	5	0.142
3	10	0.246
4	15	0.355
5	20	0.452
6	25	0.595
7	30	0.742
y= 0.024x		
R^2 = 0.995		

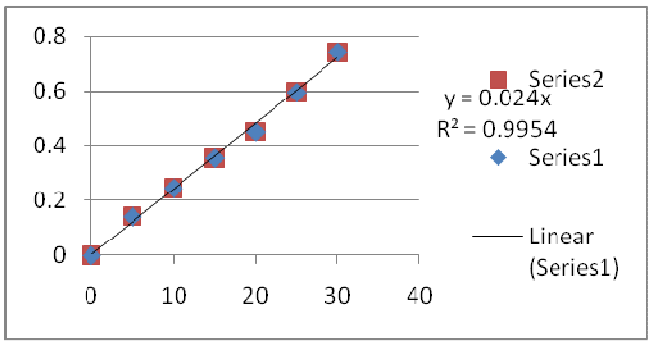

Figure 2: Calibration curve of Glipizide in Phosphate buffer pH 6.8

5.3 Standard curve of glipizide in 0.1 N HCl at 276 nm:

Sr. No.	**Concentration** (mcg/ml)	Absorbance
1	0	0
2	5	0.127
3	10	0.223
4	15	0.351
5	20	0.467
6	25	0.546
7	30	0.693
8	35	0.763
y=0.022x		
R^2 = 0.997		

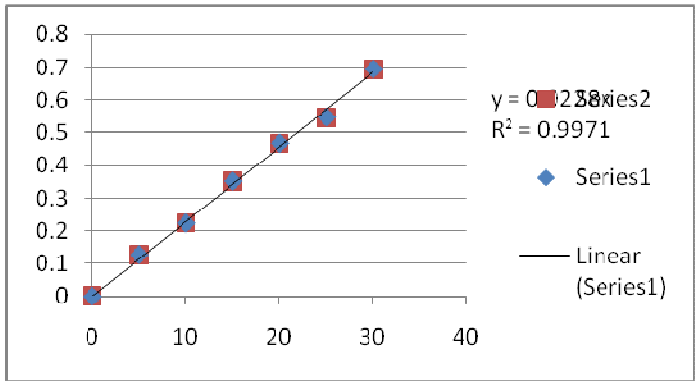

Figure 3: Calibration curve of Glipizide in 0.1 N HCl

5.4 Pre-compression parameters:

Code	Parameters				
	Angle of	Bulk	Tapped	Carr's	Hausner
C1	32.38±0.13	0.36±0.02	0.43±0.02	16.48±0.13	1.21±0.01
C2	27.52±0.28	0.35±0.02	0.40±0.04	16.08±0.04	1.19±0.01
C3	26.39±0.19	0.39±0.00	0.49±0.01	18.41±0.11	1.23±0.02
C4	27.67±0.16	0.34±0.01	0.41±0.01	15.43±0.15	1.22±0.01
C5	28.62±0.21	0.39±0.01	0.48±0.00	16.10±0.05	1.17±0.02

5.5 Post compression parameters:

Table 4.8: Characteristics of glipizide osmotic tablets containing carbopol 934P as expanding agent

Batch code	Hardness (kg/cm^2)	Weight variation (mg)	Uniformity of content (%)
C1	6.4	294.6	92.5
C2	6.2	320.5	98.6
C3	6.3	344.6	99.4
C4	6.2	369.8	96.4
C5	6.3	395.8	93.2

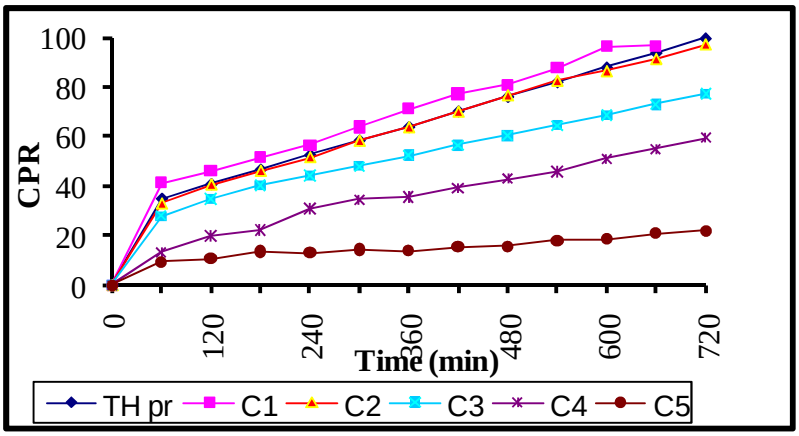

Figure 4: Dissolution profile of batches C1 to C5 & theoretical profile

Figure 4. Clearly depicts the effect of carbopol 934P on the in vitro release profile of Glipizide. It has revealed that the polymer concentration has the significant effect on the drug release profile.

5.6 In vitro drug release studies:

Table 4.9: In vitro drug release study of glipizide preliminary batches.(cum % drug release)

Time in hr	Theoretical profile	C1	C2	C3	C4	C5
0	0	0	0	0	0	0
1	35	41.29	32.95	27.87	13.35	9.36
2	40.9	46.16	40.65	34.78	19.74	10.56
3	46.8	51.66	46.16	40.28	22.3	13.56
4	52.7	56.43	51.66	44.32	30.74	13.13
5	58.6	63.93	58.26	47.99	34.41	14.23
6	64.05	71.24	63.77	52.39	35.51	13.87
7	70.4	77.31	70.01	56.43	39.18	15.33
8	76.3	81.01	76.61	60.47	42.85	15.7
9	82.2	87.62	82.48	64.5	45.74	17.9
10	88.1	96.43	86.35	68.54	50.93	18.64
11	94	96.79	91.29	72.94	54.96	20.84
72	99.9		97.16	77.35	59.37	21.94

5.7 Selection of best batch:

The selection of the best batch depends on percentage drug release, and similarity factor f_2 value. The f_2 value of batches C1, C2, C3, C4, and C5 were 66.58, 88.80, 52.90, 33.41, and 22.22 respectively. In vitro release of batch C2 was near to the theoretical release profile and f_2 value was 88.80 that were more than other batches. So, the batch C2 is selected for further study.

5.8 Influence of tablets formulation variables on glipizide release rate:

5.8.1 Influence of sodium chloride amount on drug release rate:

To study the influence of NaCl amt on glipizide release rate, drug layer was incorporated with different amount of Nacl. Figure 5 showed that release rate increased significantly as the increase of NaCl amount from 10mg to 30mg. no significant difference is observed between 30 to 50.

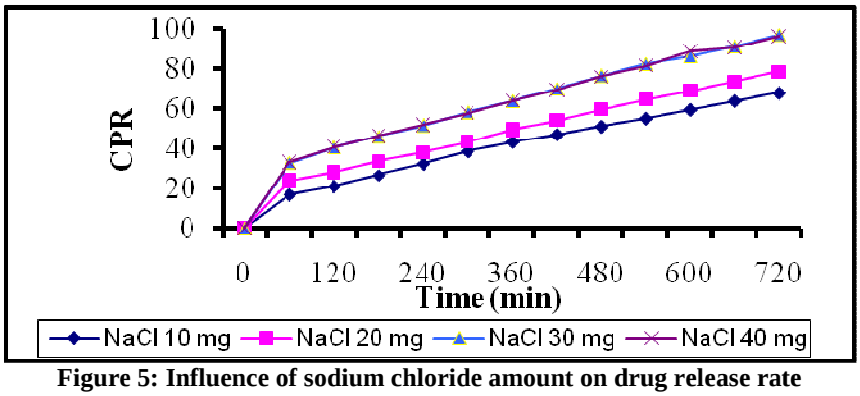

Figure 5: Influence of sodium chloride amount on drug release rate

5.8.2 Influence of carbopol amount on push layer:

To study the influence of carbopol 934P amount on glipizide release rate drug layer was studied by incorporating different amount of carbopol 934P. Figure 6. Showed that release rate increased significantly as the increase of carbopol 934P amount from 50mg to 100mg. When we increase amount of carbopol more than 100 coating of tablet was ruptured.

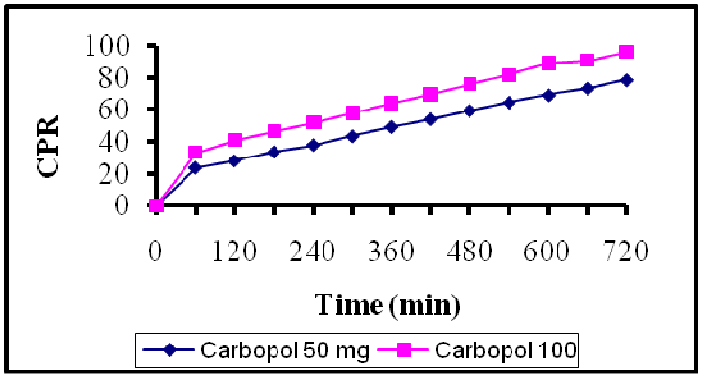

Figure 6: Influence of carbopol amount on push layer

5.8.3 Effect of pH:

To study the effect of pH and assure a reliable performance of developed formulation independent of pH, release study of optimize formulation were conducted according to pH change method. The release media was 0.1N HCL, phosphate buffer (pH 6.8), phosphate buffer (pH 7.4). There is no significant difference observed in glipizide release rate in different pH medium. (Figure 7)

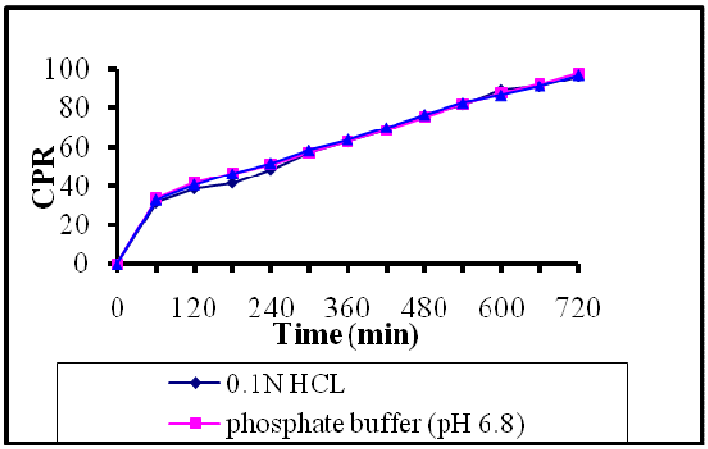

Figure 7: Effect of pH

5.8.4 Effect of weight gain:

To study the effect of weight gain of the coating on drug release, core tablets of glipizide were coated so as to get tablets with different weight gain (10, 12, 14% w/w). Release profile of glipizide from these formulations is shown in fig 8**.** It clearly shows that drug release decrease with an increase in weight gain of membrane. No bursting of tablet was observed during the dissolution in any formulation.

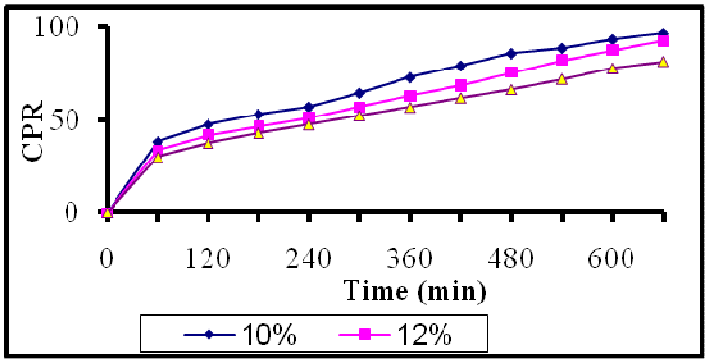

Figure 8: Effect of weight gain by coating

5.8.5 Effect of orifice size on drug release:

To study the effect of orifice size on drug release optimize tablets were mechanically drilled in different orifice size (0.2mm, 0.3mm, 0.5mm). Release profiles of this formulation are shown in Figure 9. It shows that drug release increases with increase in orifice size.

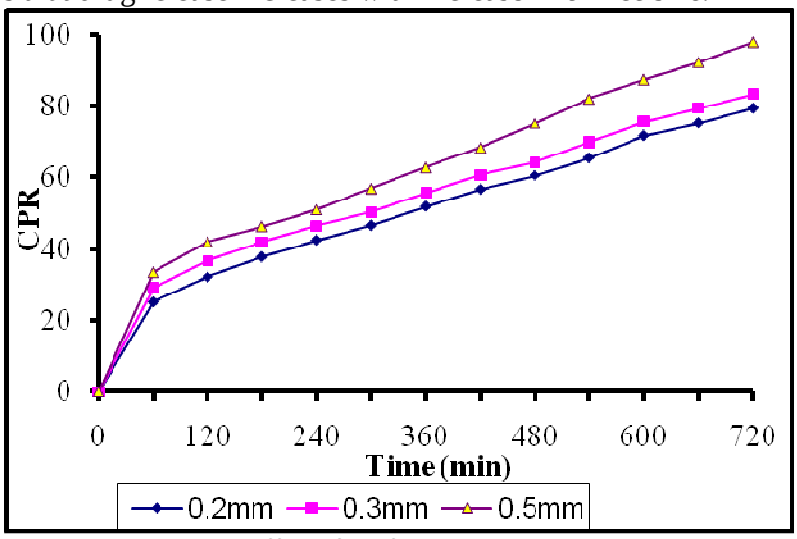

Figure 9: Effect of Orifice size on drug release:

Figure 10:View of initial tablet

Figure 11: View of tablet after 12 hr

6. Stability study of glipizde osmotic push pull tablets:

The stability of Glipizde osmotic push pull tablets were observed after 3 months at room temperature and normal humidity conditions. Initially and after 3 months post-formulation parameters and dissolution rate was measured. The results of stability study are given in Table 6.1, 6.2 and Figure 12.

6.1 Characterization of tablets:

Table 6.1: Characteristic of glipizide osmotic push pull tablets

Initial			3 month		
Hardness (Kg/cm^2)	**Weight variation (mg)**	**Uniformity of content (%)**	**Hardness (Kg/cm^2)**	**Weight variation (mg)**	**Uniformity of content (%)**
6.2	349.1	98.6	6.2	349	98.4

Table 6.2: Stability study of glipizde osmotic push pull tablets

Time (min)	CPR	
	Initial	3 month
0	0	0
60	32.95	33.31
120	40.65	41.02
180	46.16	46.53
240	51.66	52.03
300	58.26	57.90
360	63.77	64.14
420	70.01	69.64
480	76.61	76.25
540	82.48	81.75
600	86.35	89.09
660	91.29	90.93
720	97.16	96.43

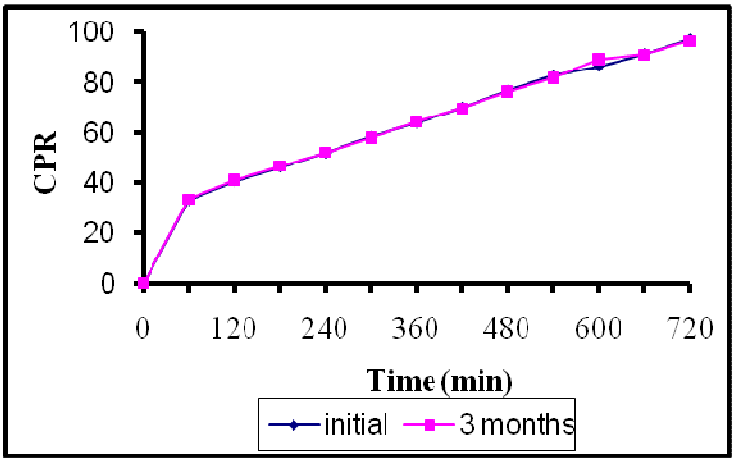

Figure 12: Stability study

CONCLUSION

Extended release formulations of glipizide were developed based on push-pull osmotic technology. The release rate increased significantly as the increase of sodium chloride amount from 10mg to 30mg, no significant difference could be observed between 30 to 50. The release rate increased significantly as the increase of carbopol 934P amount from 50mg to 100mg in push layer. When we increase amount of carbopol 934P more than 100 coating of tablet was ruptured. Drug release was inversely proportional to the coating thickness, but directly proportional to the orifice size. When we increase the coating thickness from 10 to 12 and then 14% w/w it was decrease in drug release rate. The release from developed formulations was independent of pH and agitation intensity of release media, assuring the release to be fairly independent of pH and hydrodynamic condition of body. The manufacturing procedure was standardized and found to be reproducible. Developed formulations were found to be stable after 3 month of storage.

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