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Formulation Development and Assessment of Controlled Release Bilayered Osmotic Tablet Carrying Sulfonylurea Class – Anti Diabetic Agent & Imperative Factors Imparting Significant Impact on Drug Release

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ABSTRACT

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. Cellulose acetate NF (CA-398-10 NF) in a concentration of 8 % w/w for 10.0 mg tablet was optimized as coating polymer and Polyethylene Glycol 3350 NF in a concentration of 0.284%was optimized as pore former for Glipizide tablets. The manufacturing procedure was standardized and found to be reproducible. The values were found to be 7.28 and 72.65 (between T-1 & T-2), 2.37 and 85.69 (between T-1 & T-3**)** and 6.21 and 75.54 (between T-2 & T-3), respectively. One batch of three strengths were charged for stability studies at accelerated condition 40°C/75% RH, and at 25°C/60% RH in proposed pack i.e. HDPE Containers and 3 months stability data was found satisfactory. Thus the objectives envisaged in this study were arrived. Further studies are needed to investigate this formulation for its performance *in vivo* and its bioequivalence with the marketed product, Glucotrol XL. Extended release formulations of glipizide were developed based on push-pull osmotic technology.

KEYWORDS: Osmotic pressure; Glipizide; Polyethylene Glycol 3350; bioequivalence.

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INTRODUCTON

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. Osmotic pumps offer many advantages over other controlled drug delivery system: Easy to formulate and simple in operation, Osmotic system is independent of pH and other physiological parameters to a large extent. Decrease dosing frequency, Reduce rate of rise of drug concentration in blood, Sustained & consistent blood levels within the therapeutic window, Reduce interpatient variability, reduce side effects, Improve patient compliance.

Principle of osmosis:

Osmosis refers to the process of movement of solvent from lower concentration of solute towards higher concentration of solute across a semipermeable membrane. Abbe Nollet first reported osmotic effect in 1748, but pfeffer (1877) had been pioneer of quantitative measurement of osmotic effect. He measured the effect in 1877 by utilizing a membrane, which is selectively permeable to water but impermeable to sugar.

The membrane separated sugar solution from pure water. Pfeffer observed a flow of water into the sugar solution that was halted when a pressure P was applied to the sugar solution. Pfeffer postulated that this pressure, the osmotic pressure π of the sugar solution is directly proportional to the solution concentration and absolute temperature. Van't hoff established the analogy between the pfeffer results and the ideal gas laws by the expression

$$\pi = n_2RT \text{.....(1.1)}$$

where n_2 represents th the molar concentration of sugar (or other solute) in the solution, R depicts the gas constant, and T the absolute temperature.

A number of researchers (Reid, 1966; Hughes,1961) have discussed, modified and brought about more accurate expression of this equation. Another method of obtaining a good approximation of osmotic pressure is by utilizing vapour pressure measurements and by using the expression:

$$\pi = RTln(P_0/P)/v \quad \text{----------(1.2)}$$

where, P_0 = vapour pressure of the pure solvent
P = vapour pressure of the solution
V = molar volume of solvent

As vapour pressures can be measured with less effort than osmotic pressure, this expression is frequently used. Osmotic pressure for soluble solute is extremely high. This high osmotic pressure is responsible for high water flow across semi permeable membrane. The rate of water flow dictated by osmotic pressure can be given by equation:

$$Dv/dt = A\theta\Delta\pi/l \quad \text{--------(1.3)}$$

Where, Dv/dt = water flow across the membrane area A and thickness l with permeability θ. Δπ depicts the difference in osmotic pressure between the two solutions on either side of membrane. This equation is strictly applicable for perfect semipermeable membrane, which is completely impermeable to solutes[1,2,3].

MATERIAL AND METHODS

PREPARATION OF GLIPIZIDE PUSH-PULL OSMOTIC BILAYER TABLETS

Table No 1. Manufacturing Formula for Glipizide extended release tablets 10.0 mg

Sr.No.	Ingredients	Trial 1mg/tab	Trial 2mg/tab	Trial 3mg/tab	Trial 4mg/tab	Trial 5mg/tab	Trial 6mg/tab	Trial 7mg/tab with O.A	Trial 8[$Qty 5000 tablets /Gm]
		1000 tablets							
	DRUG LAYER:								
1	Glipizide USP	10	10	10	10	10	10	10.5	52.5
2	Polyethylene Oxide NF(Polyox WSR N80 NF FP)	70	80	100	125	150	178.1	178.1	890.5
3	Hypromellose USP 5 CPS (Methocel Premium E5LV)	40	30	20	15	10	10	10	50
4	Isopropyl Alcohol USP	#60.00	#30.00	#60.00	#30.00	#30.00	#60.00	#60.00	#300
5	Magnesium Stearate NF	2	2	2	2	2	1.4	1.4	7
6	Microcrystalline cellulose USP	77.5	47.5	67.5	47.5	27.5	**0**	--	0
Average weight of drug layer		**199.5**	**199.5**	**199.5**	**199.5**	**199.5**	**199.5**	**200**	1000

PUSH LAYER:									
1	Polyethylene Oxide NF(Polyox WSR 303)	50	55	60	75	80	100	100	500
2	Sodium Chloride USP @	5	10	15	25	30	38	38	190
3	Ferric Oxide Red NF	1	1	1	1	1	1	1	5
4	Magnesium Stearate NF	0.5	0.5	0.5	0.5	0.5	1	1	5
5	Microcrystalline cellulose USP	83.5	73.5	63.5	38.5	28.5	**0**	**0**	0
Average weight of push layer		**140**	**140**	**140**	**140**	**140**	**140**	**140**	**700**
Average weight of bi-layer tablet		**340**	**340**	**340**	**340**	**340**	**340**	**340**	**1700**
FOR FUNCTIONAL COATING:									
1	Cellulose Acetate NF(CA-398-10 NF)	29.7	29.7	29.7	29.7	29.7	29.7	*35.64	*178.2
2	Polyethylene Glycol 3350 NF	2.3	2.3	2.3	2.3	2.3	2.3	*2.76	*13.8
3	Acetone NF	#495.00	#495.00	#495.00	#495.00	#495.00	#495.00	*594.00	*2970
4	Methyl Alcohol NF	#55.00	#55.00	#55.00	#55.00	#55.00	#55.00	*66.00	*330
Average weight of functional coated tablet		**371.5**	**371.5**	**371.5**	**371.5**	**371.5**	**371.5**	**372**	**1860**
FOR TOP COATING:									
1	Opadry Blue OY-LS-20921 IH	16	16	16	16	16	16	*19.20	*96
2	Purified Water USP	#117.34	#117.34	#117.34	#117.34	#117.34	#117.34	*140.81	*704.05
Average weight of top coated tablet		**387.5**	**387.5**	**387.5**	**387.5**	**387.5**	**387.5**	**388**	**1940**
FOR PRINTING:									
1	Opacode Black ink S-1-277001 IHT	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

does not remain in the product

- 20 % excess to compensate coating losses.
- $ Reproducible Trial

MANUFACTURING PROCESS:

PRECAUTIONS:

Glipizide being light sensitive material all the manufacturing activities to be done under sodium vapor lamp with Relative humidity NMT 55% and temperature 24 ± 4º C. Glipizide blend, compressed tablets and in-process samples are to be stored in black polybag at all stages of manufacturing till packing stage. It should not be subjected to exposure to direct light. Samples to be preserved in self sealed poly bag.

Table No: 2. Manufacturing Process For Drug Layer

MANUFACTURING PROCESS FOR DRUG LAYER	
1.	Sift Glipizide USP (micronized) and Hypromellose USP using 30 # (600µm) stainless steel sieve.
2.	Sift and collect Polyethylene Oxide NF (Polyox WSR N80 NF FP) using 30 # (600µm) stainless steel sieve.
3.	In a stainless steel container take Isopropyl alcohol USP to be used as a granulating solvent for non aqueous granulation.
4.	Charge in Rapid Mixer Granulator in the following order Glipizide USP, Polyethylene Oxide NF (Polyox WSR N80 NF FP), and Hypromellose USP.
5.	Mix for 10 minutes with impeller at slow speed (75 rpm).
6.	Proceed for non-aqueous granulation using Isopropyl alcohol USP. Set the appropriate parameters on Rapid mixer granulator to execute the following: Initially spray about 20 % + 20 % granulating solvent from step 3 through spraying assembly for uniform spraying and run impeller at slow speed and chopper of RMG off for 1 + 1 minutes. Again spray about 20 % + 20 % granulating solvent from step 3 through spraying assembly for uniform spraying and run impeller at slow speed and chopper of RMG off for 1 + 1 minutes. Rake the content meanwhile using clean paddle. Spray about 20 % remaining granulating solvent from step 3 through spraying assembly for uniform spraying and run impeller at slow speed (75 rpm) and chopper of RMG off for 1 minute. For final mixing, run the impeller and chopper at slow speed (1500 rpm) for 2 minutes.

	Discharge the granules into FBD bowl with impeller speed slow (75 rpm) and chopper slow (1500 rpm). Remove the material adhered to the RMG bowl using stainless steel scrapper into the FBD bowl through discharge valve. Distribute the material uniformly using stainless steel paddle and proceed for drying.
7.	Run the FBD as BLANK at ambient air temperature for 5 minutes without granules.
8.	Dry the wet granules in FBD at an inlet set temperature 25°C. Inlet High temperature alarm 40°C for the cycles of 10 minutes (I st cycle), 15 minutes (II nd cycle), __ minutes (III rd cycle) and __ minutes (IV th cycle) till the LOD is Not more than 2.0 % w/w (Target 1.0 % w/w). Fluid Bed Drier: Blower: 2200-2350 rpm
9.	Sift dried granules through 30 # (600µm) using Vibro sifter and collect it into stainless steel round bins. Transfer sifted granules to stainless steel square bin.
10.	Pre-mix the granules in cage blender for 5 minutes. (13 rpm)
11.	Sift Magnesium Stearate NF using 60 # (250µm) stainless steel sieve.
12.	Add the Magnesium Stearate in cage blender and lubricate for 5 minutes (13 rpm). Close the stainless steel square bin tightly. Check the weight of lubricated granules.
13.	Keep aside the lubricated blend of drug layer in a double black colored poly bag and tightly closed condition until taken up for compression.
MANUFACTURING PROCESS FOR PUSH LAYER	
1.	Mill Sodium Chloride (with 5% extra quantity) through hammer mill (Cadmill) 0.5 mm screen, Impact forward and fast speed and sift through 40 # (425 µm). Weigh actual quantity of Sodium Chloride. Record excess quantity of Sodium chloride discarded in presence of site QA
2.	Sift and collect Polyethylene oxide (Polyox WSR 303) using 20 # (850µm) stainless steel sieve. Sift and collect Ferric Oxide Red using 60 # (250µm) stainless steel sieve.
3.	Charge in cage blender in the following order Polyethylene oxide (WSR 303) NF, Ferric Oxide Red NF and Sodium Chloride USP.
4.	Mix for 15 minutes in cage blender (13 rpm).
5.	Sift Magnesium Stearate NF using 60 # (250 µm) mesh stainless steel sieve.
6.	Add the blend in cage blender and lubricate for 5 minutes (13 rpm) with Magnesium Stearate. Close the stainless steel square bin tightly. Check the weight of blend.

7.	Keep aside the lubricated blend of push layer in a double poly bag and tightly closed condition until taken up for compression as per parameters mentioned below.
COMPRESSION	
1.	**10 mg strength:** Set the compression machine for the bilayer tablets with pre-checked 9.5 mm diameter dies and punches, the punches should be round, shallow concave and plain on both sides.
2.	Take the stainless steel square bin containing the granules ready for compression to compression cubicle.
3.	Load the drug layer granules in front hopper and push layer granules in rear hopper
4.	Use a 20 # stainless steel sieve above the front hopper and load the drug layer granules
5.	Set the machine with loading of drug layer granules and set weight of drug layer first. After setting of drug layer set weight of bilayer tablet by adjusting weight of push layer.
6.	Set the machine speed and start the compression machine and set the compression parameters of tablets as per the parameters mentioned in compression set-up parameters. Compression machine speed: 25 rpm: (Maximum) 15-25 rpm Target speed 18 -22 rpm[4,5].

Physical Properties of Glipizide and Granules of Tablet Batches

Angle of repose

The angle of repose of glipizide and granules was determined by the funnel method (Reposogram). The accurately weighed drug or tablet blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation[6,7.]

$$\theta = \tan^{-1} h / r$$

Where, h = the height of the powder cone, r = the radius of the powder cone

Bulk Density

Loose bulk density (LBD) and tapped bulk density (TBD) were determined. Glipizide was passed through 20 sieve to break the clumps, if any. Accurately weighed 10 g of the drug was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 500 times from a distance of 14 $\pm$ 2 mm. The tapped volume (V_a) was measured to the

nearest graduated unit. The tapping was repeated for 750 times.

Again the tap volume was measured to the nearest graduated unit. The same procedure was followed for granules of the tablet. The LBD and TBD were calculated in g/ml using following formula;

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index (Carr's Index) The compressibility of the drug and granules was determined by the Carr's compressibility index.

Carr's index (%) = [(TBD – LBD) x 100] / TBD

Table No 3. Flow property of blend depending upon Compressibility index

Compressibility Index (%)	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
> 35	Very poor

Hausner Ratio: The Hausner ratio of the drug and granules was determined by following equation,

Hausner ratio = (TBD/LBD)

Evaluation of Coated Tablets

Percentage weight gain: From the batch of glipizide tablets, 25 core tablets were randomly selected subjected to coating. The initial weight of 25 uncoated tablets was recorded. After period of coating, spraying of coating solution was stopped and allowed to drying for 10–15 min, in the coating pan at 45 ^{O}C to remove the majority of solvent moisture. The weight of 25 coated tablets was recorded. The percent weight gain was calculated. Samples were collected for predetermined weight gain (approximately).

Dimensions: Thickness and diameter of coated tablets were measured using vernier calipers.

Content Uniformity Test: The glipizide tablets were tested for their drug content. Twenty tablets were finely powdered; quantity of the powder equivalent to 15 mg of glipizide was accurately weighed and transferred to a 50 ml of volumetric flask. 30 ml of methanol was added to this flask

and mixed thoroughly. Heat the mixture gently on water bath and cool then make up the volume with methanol. The solution was filtered. Dilute 5 ml of the resulting solution to 50 ml with methanol and measure the absorbance of the resulting solution at λ_{max} 276 nm[8,9,10].

Hardness Test: "Hardness factor", the average of the six determinations, was determined of coated tablets and reported. The force is measured in kilograms per centimetre square.

In vitro Drug Release: Dissolution (By HPLC): The dissolution of Glipizide from Glipizide Extended Release tablets is performed as per USP II (Paddle) apparatus, with analysis of the dissolution aliquots by HPLC.

Apparatus:

1. Suitable liquid chromatograph equipped with a UV detector capable of operating at 225nm, sample injection system of 50µl capacity, data acquisition system or integrator.
2. HPLC column- C18, 15cm, 3.9mm, 4µ particle size or equivalent.
3. HPLC mobile phase filtration system incorporating 0.45µ membrane filter.
4. Standard laboratory equipment.
5. Rotating paddle apparatus (USP II) e.g. Electrolab TDT.
6. Suitable 0.45µ PVDF syringe filter.

Reagents:

1. Purified water for Dissolution.
2. Purified water for HPLC use.
3. Acetonitrile, HPLC grade.
4. Working standard of Glipizide.
5. Monobasic potassium phosphate.
6. Sodium hydroxide.

Table No:4. Preparation details:

Dissolution media	**0.2N sodium hydroxide:** Prepared by dissolving 8g of sodium hydroxide in 1000mL water.
Mobile phase buffer	**Buffer pH 7.5 SIF without Pancreatin:** Weigh about 6.8g of Monobasic potassium phosphate in 1L volumetric flask & dissolve it in sufficient amount of water. Adjust the pH to 7.5 with 0.2N sodium hydroxide. Dissolve and dilute to volume with water. Dissolve about 6.8 g of Monobasic potassium phosphate in sufficient amount

Mobile phase	of water. Dilute with water to 1000 ml and filter through 0.45µm nylon filter. Prepare a filtered and degassed mixture of phosphate buffer and Acetonitrile in the ratio of (60:40 v/v) respectively.

Table No 5. Dissolution parameters:

Dissolution Medium	pH 7.5 SIF without Pancreatin (900mL)
Dissolution Volume	900 mL
Apparatus	Type II paddle
Speed	50 RPM
Temperature of Dissolution Medium	37°C ± 0.5°C
Time point	4, 8 & 16 hrs

The model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. Comparison of the dissolution profiles of the prepared tablets with innovator product drug release profile was carried out[11,12,].

Hixson-Crowell Cube Root Law Model: To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data were also plotted in the Hixson-Crowell Cube Root Law,

$$W_0^{1/3} - W_t^{1/3} = K_{HC}\, t$$

Where, W_0 = the initial amount of the drug in the tablet, W_t = the amount of drug remain in the dosage form, K_{HC} = the dissolution rate constant

Higuchi Model: Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media, and the equation is,

$$Q_t = K_H.\, t^{1/2}$$

Where, Q_t = Amount of drug released in time t, K_H = Higuchi dissolution constant

Reproducibility: The reproducibility of the manufacturing procedure was confirmed by preparing two repeat batches (batch size of 5000 tablets each strength) of the final optimized formulation on two different occasions. The tablets were evaluated for dissolution as the rest of the parameters were

proved to be reproducible and compared with tablets of the earlier batch.

Stability Study: R&D batches of three strengths were charged for stability studies at accelerated condition 40°C/75% RH, and at 25°C/60% RH in proposed pack for marketing i.e. HDPE Containers and 3 months stability data was found satisfactory[13,14.]

RESULTS AND DISCUSSION

UV spectroscopy scanning of glipizide in PBS pH 6.8

The standard stock solution was prepared as per the method described in methodology and scanned by UV-Visible spectrophotometer.The UV absorption spectrum of glipizide showed peak at 276.0 nm against reagent blank and is same as literature value. This method had shown reproducibility (R^2 = 0.999) and Beer Lambert law was obeyed in the range of 10 to 35 µg/ml.

Table No 6. Standard curve of glipizide in phosphate buffer (pH 7.4) at 276 nm

Sr.No.	Concentration (mcg/ml)	Absorbance			AverageAbsorbance
		1	2	3	
1	0	0	0	0	0
2	5	0.145	0.144	0.145	0.145
3	10	0.254	0.256	0.255	0.255
4	15	0.362	0.36	0.364	0.362
5	20	0.469	0.468	0.47	0.469
6	25	0.615	0.625	0.617	0.615
7	30	0.771	0.772	0.772	0.772
Absorbance = Concentration * 0.0248 + 0.0022, Co-efficient = 0.9951					

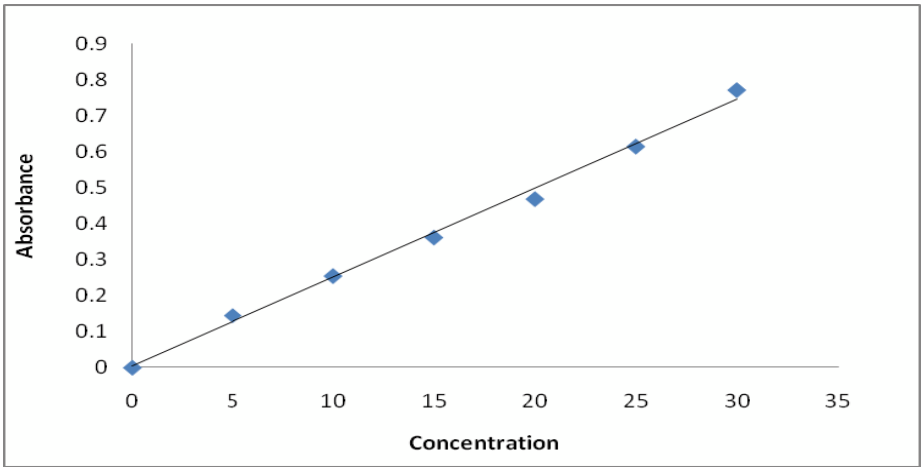

Figure No 1. Calibration curve of Glipizide in Phosphate buffer pH 7.4

EVALUATION

Evaluation of powder flow properties:

Table No 7. Values of pre- compressive parameters.

FORMULATION CODE	Angle of repose	Loose Bulk density (g/ml)	Tapped Density (g/ml)	Hausner's factor	Carr's Index (%)
T1	25.71	0.49	0.55	0.9	9.25
T2	24.22	0.49	0.54	0.89	10.9
T3	26.94	0.5	0.53	0.9	9.09
T4	29.12	0.5	0.56	0.9	7.4
T5	27.62	0.5	0.57	0.94	5.66
T6	26.94	0.5	0.53	0.9	9.09
T7	24.22	0.49	0.54	0.89	10.9
T8	29.12	0.5	0.56	0.9	7.4

PREFORMULATION STUDIES

The following preformulation studies were performed for glipizide and excipients.

Melting Point: Melting point of glipizide was determined by capillary tube method and it was found to be 208 ± 1.27 ^{o}C. This value is same as that of the literature citation 208-209 ^{o}C.[68]

Drug Excipients Compatibility Study

FT-IR Study: FT-IR studies were carried out for pure drug alone and along with excipients. The results are summarized as follows. A FT-IR spectrum of pure glipizide is shown in the Figure 06 and peaks are listed in the Table 8. Similarly FT-IR spectra of glipizide in combination with excipients and in optimized formulation are shown in Figures 5-8. The peaks given in the Table 8 can be considered as characteristic peaks of glipizide. These peaks were not affected and prominently observed in FT-IR spectra. This indicates that there is no interaction between glipizide and excipients and the drug was compatible with the formulation components.

Table No 8: FT IR Interpretation of Glipizide

Group	Wave number
N-H str	3325.28-3251.48
C-H str	2943.84-2855.47
C=O str	1686.83
C=N str	1651.47
N-F df	1443.98
Ar H	605.98

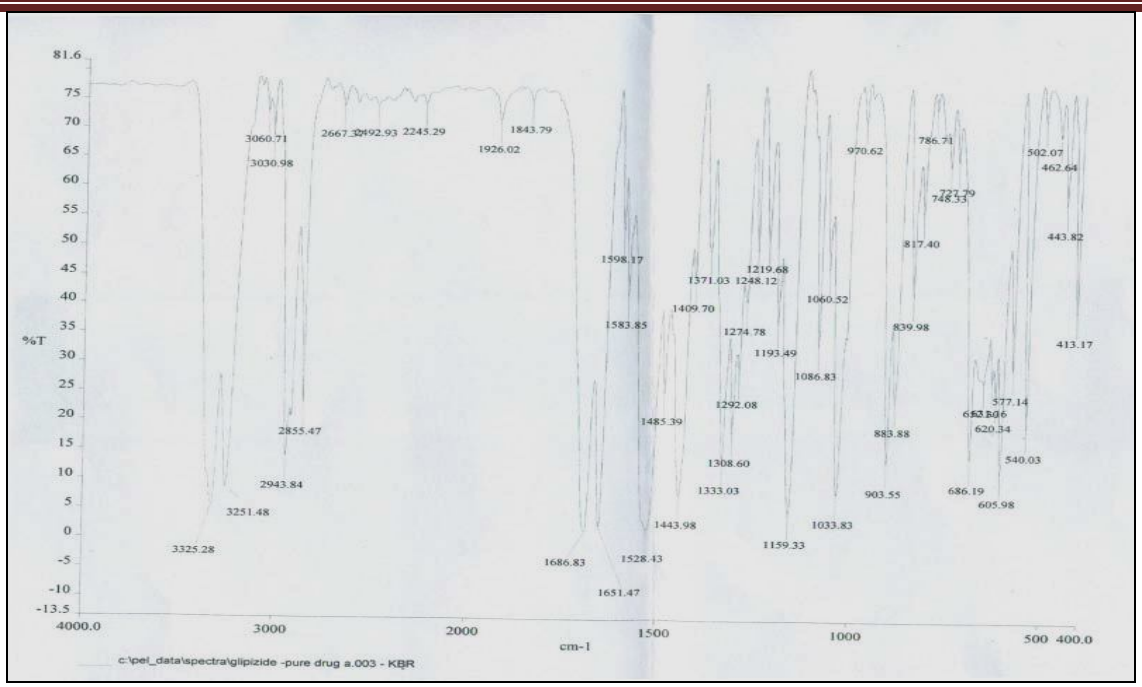

Figure No 2 . FT IR Interpretation of Glipizide

DSC Studies:

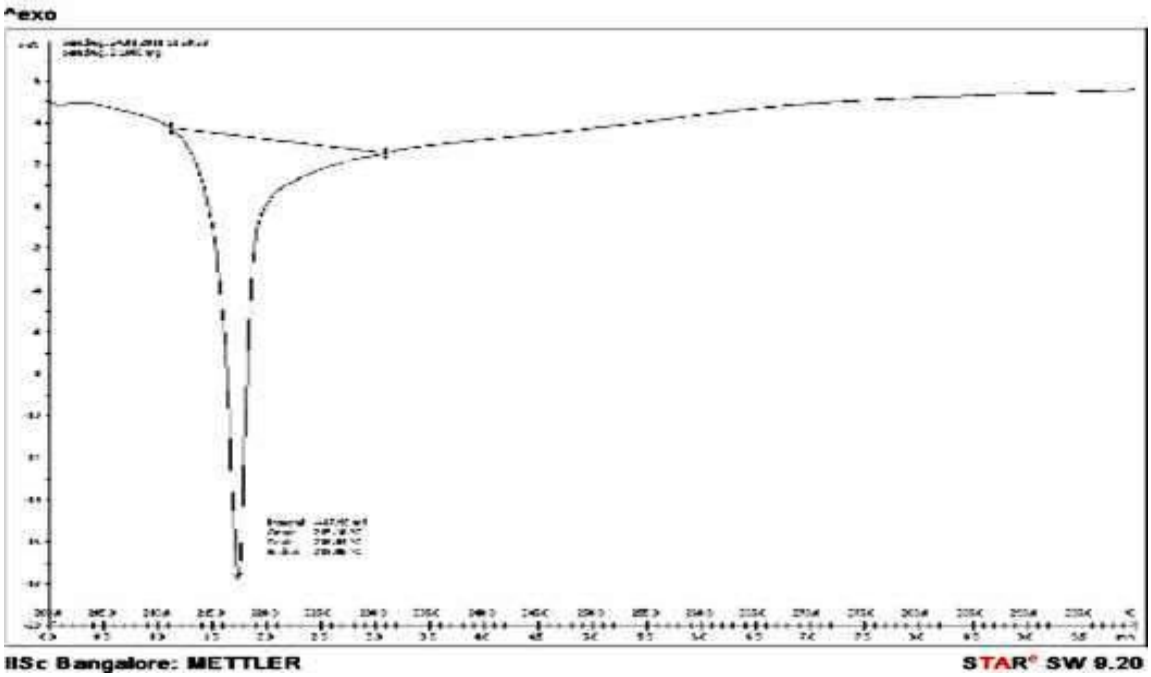

Figure No 3. DSC thermogram of glipizide pure drug.

Table No 9. Drug release profile of T1 –T8 for Glipizide extended release tablets 10.0 mg

TIME (hour)	Limits	T1	T2	T3	T4	T5	T6	T7	T8
		1000 tablet batch size						Reproducible	Reproducible 5000 Tablet
0	0	0	0	0	0	0	0	0	0
4	Between 5% and 30%	50.02	40.26	35.48	30.14	25.26	20.16	19.65	16.01
8	Between 35% and 65%	89.25	75.65	65.24	60.19	56.47	50.34	49.36	49.6
16	Not less than 80%	102.59	99.56	99.25	98.59	98.16	98.25	97.15	97.05

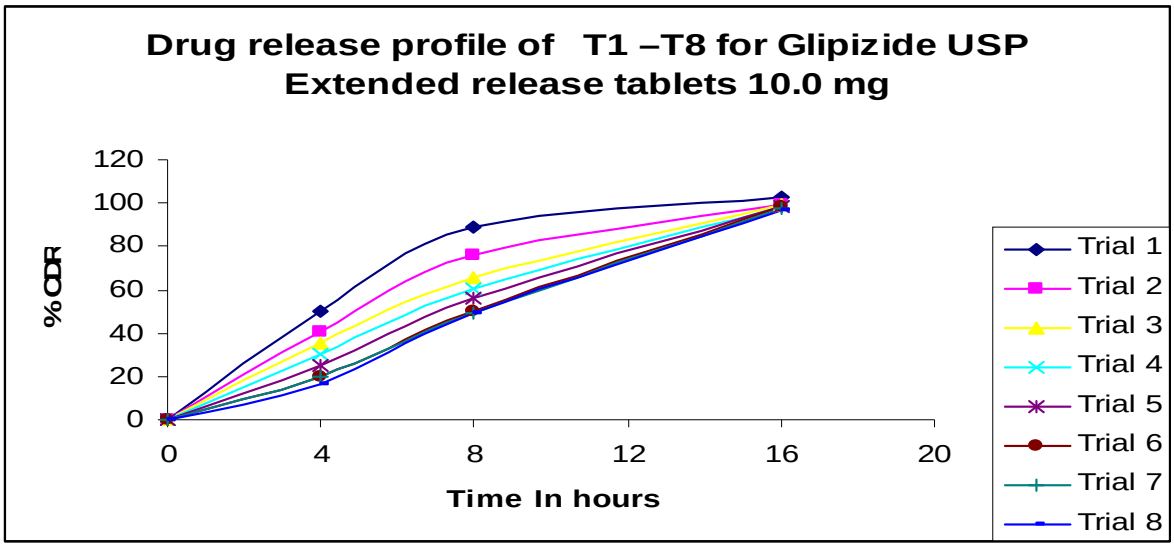

Figure No 4. Drug release profile of T1 –T8 for Glipizide extended release tablets 10.0 mg

Effect of % Weight Gain: To study the effect of weight gain by coating on drug release, core tablets of glipizide of the batch T-7 were coated with Functional coating so as to get tablets with different weight gain (% w/w). Release profile of glipizide from these formulations is shown in Figure 33, 34. It is clearly evident that drug release decreases with an increase in weight gain of the coating membrane. No bursting of tablet was observed during the dissolution in any formulation.

Table No 10. In vitro release of Glipizide 10 mg. from the tablets of batch T-7) with different weight gain

Glipizide 10.0 mg			
Hours	**6 % Coating**	**8 % Coating**	**10 % Coating**
0	0	0	0
4	26.65 ± 1.36	19.65 ± 0.61	14..28 ± 1.52
8	65.184 ± 3.64	49.36 ± 3.74	45.25 ± 2.56
16	102.98 ± 0.86	97.15 ± 1.04	95.57 ± 0.81

*Each value was an average of three determinations

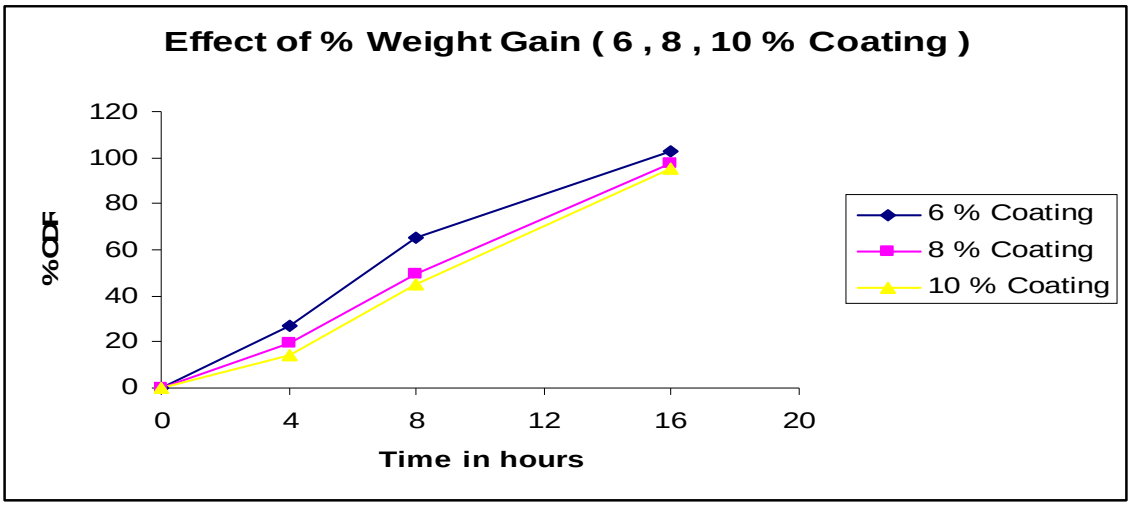

Figure No 5. In vitro release of Glipizide 10 mg. from the tablets of batch T-7) with different weight gain.

Figure No 6. Photograph of the Glipizide tablets of the optimized batch PGB 2001 (10.0 Mg)

Figure No 7. Photograph of the Glipizide tablets of the optimized batch PGB 2001 (5.0 Mg)

Figure No 8. Photograph of the Glipizide tablets of the optimized batch PGB 2001 (10.0 Mg)

KINETICS OF IN VITRO DRUG RELEASE

Table No 11. Kinetic data for Glipizide

Glipizide 10.0 mg Tablet USP (PGB 2001)				
Hours	KINETIC DATA FOR GLIPIZIDE			
	% CDR	Log Percent drug released	Percent drug unreleased	Log Percent drug unreleased
0	0	0	100	2
4	19.65	1.293	80.35	1.904
8	49.36	1.693	50.64	1.704
16	97.15	1.987	2.85	0.458

Table No 12. Comparison of orders of *in vitro* release of Glipizide from tablets of batch PGB 2001 (10.0 Mg)

Formulation	*In vitro* release of Glipizide in 7.5 SIF Regression equations	
	Zero order	First order
PGB 2001 (10.0 Mg)	y = -6.1769x + 101.7	y = -0.0992x + 2.2108
	R2 = 0.9969	R2 = 0.8946

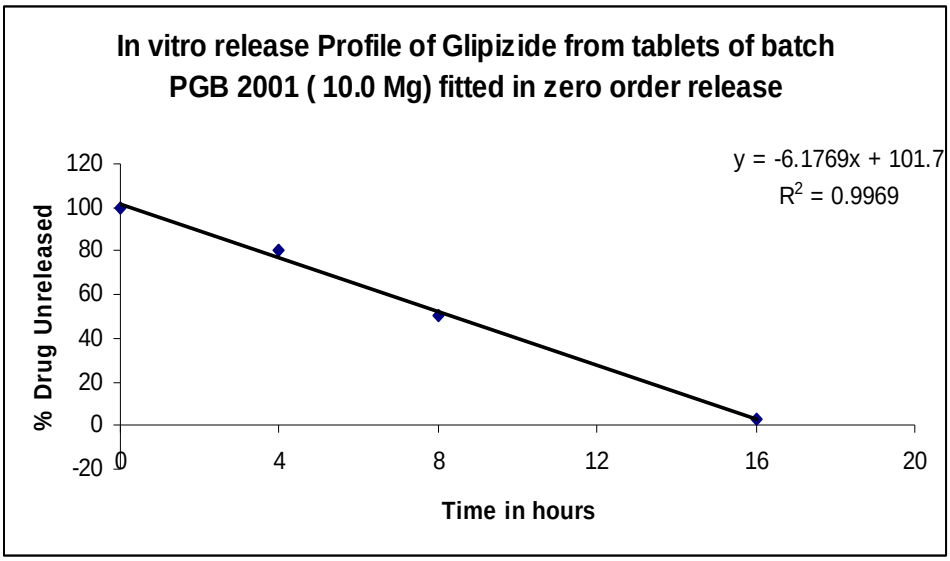

Figure No 9. *In vitro* release profile of Glipizide from tablets of batch PGB 2001 fitted in zero order release.

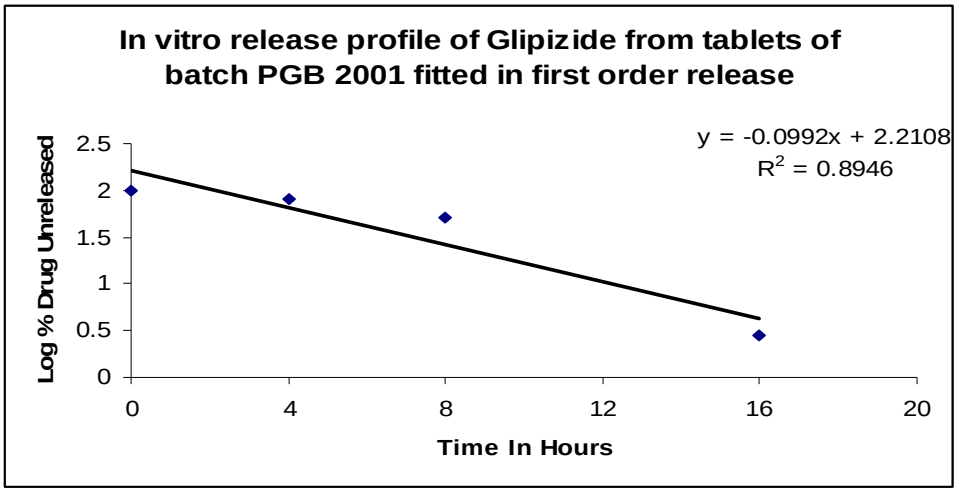

Figure No 10. *In vitro* release profile of Glipizide from tablets of batch PGB 2001 fitted in zero order release.

RELEASE MECHANISMS

To study the release mechanisms of glipizide the data of *in vitro* drug release was verified using Higuchi's model and Hixon-Crowell cube root law models.

Table No 13: Regression equations of *in vitro* release of Glipizide from the tablets of PGB 2001 (10.0 Mg)

Formulation	*In vitro* release of Glipizide in 7.5 SIF Regression equations	
	Higuchi's model	Hixon-Crowel model
PGB 2001 (10.0 Mg)	y = 23.601x - 10.501 R2 = 0.8841	y = 0.0541x - 0.0128 R2 = 0.9986

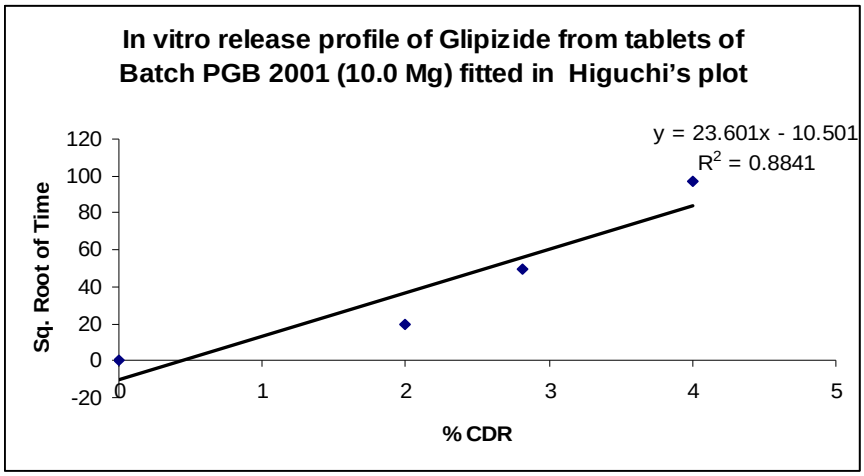

Figure No 11: *In vitro* release profile of Glipizide from tablets of batch PGB 2001 (10.0 Mg) fitted in Higuchi's plot

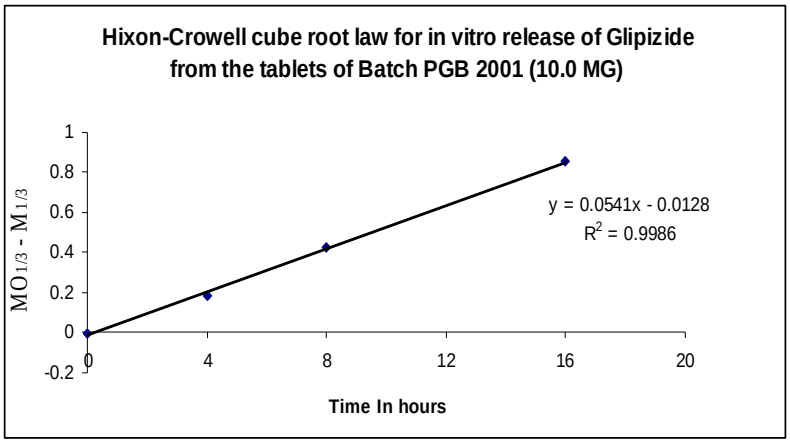

Figure No 12: Fitting of the Hixon-Crowell cube root law for *in vitro* release of Glipizide from the tablets of batch PGB 2001 (10.0 Mg)

REPRODUCIBILITY

The f_1 and f_2 values were calculated from model independent pair wise approach and are as shown in the Table 14. Data for the *in vitro* release of Glipizide from the tablets of the batch T-7 & T-8 (10.0 Mg) and reproducible batches in 7.5 SIF without Pancreatin are shown in the Table 14.

Table No 14: Data for the *in vitro* release of Glipizide from the tablets of the batch T-6 and reproducible batches T-7 & T-8 (10.0 Mg) batch in 7.5 SIF without Pancreatin.

Glipizide 10.0 mg Tablet USP			
Dissolution Media pH 7.5 SIF without Pancreatin			
Hours	T6	T -7	T -8
	Successful Batch	First Reproducible	Second Reproducible
	50 RPM		
	% CDR	% CDR	% CDR
0	0	0	0
4	20.16	19.65	16.01
8	50.34	49.36	49.6
16	98.25	97.15	97.05

* Each value was an average of three determinations

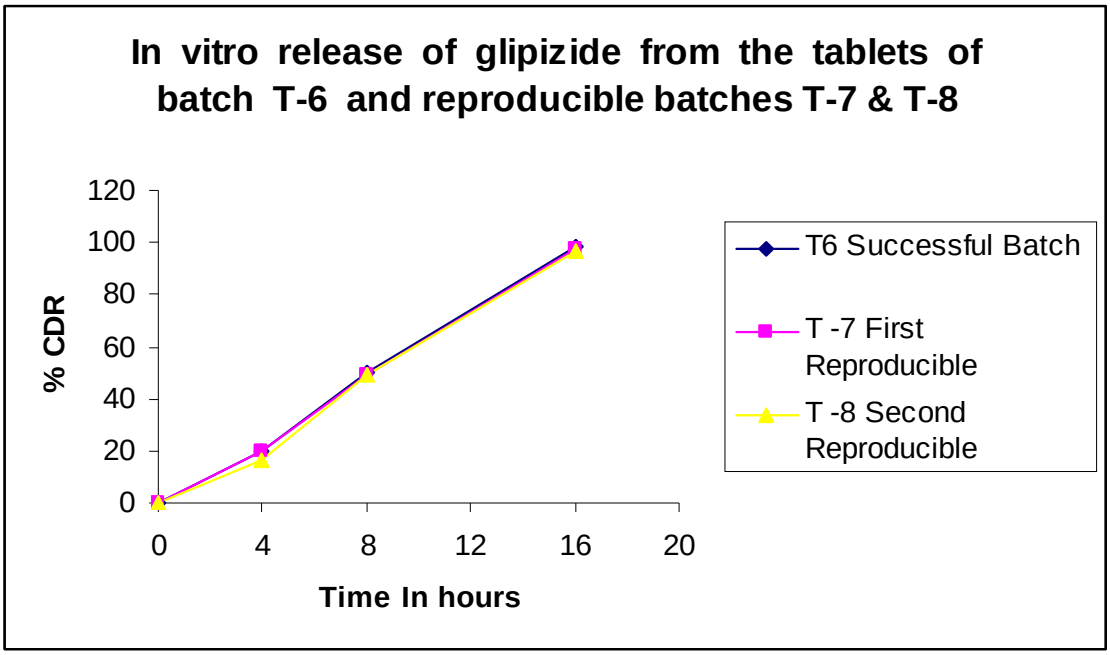

Figure No 13: I*n vitro* release of Glipizide from the tablets of the batch T-6 and reproducible batches T-7 & T-8 (10.0 Mg) batch in 7.5 SIF without Pancreatin.

CONCLUSION

Extended release formulations of Glipizide were developed based on push-pull osmotic technology.Glipizide extended release tablets 10 mg was successfully developed using DMF grade API sourced from A.M.S.A., Italy and Excipients. Granulation, compression, functional coating, laser drilling and top coating and dissolution, potency and impurity profile parameters were satisfactory and consistent from batch to batch even when different lots of drug substance were used. The Exhibit batches will be subjected to stability studies at accelerated condition i.e. 40°C/75% RH, and real time condition 25°C/60% RH. The study shall be continued as per ICH guidelines to confirm the expected shelf life of 2 years (24 months) or more at the specified storage conditions in the primary packing of induction sealed HDPE container fitted with CRC caps. From the FT-IR spectra and thermal analysis (DSC), the interference was verified and found that Glipizide did not interfere with the excipients used. Core tablets of Glipizide trial T-6 were successfully prepared by wet granulation using Polyethylene Oxide NF, Sodium Chloride USP, Hypromellose USP 5 CPS, respectively. *In vitro* release profile of optimized formulation of Glipizide tablets PGB 2001was found to be similar to that of marketed innovator product (Glucotrol XL). The f_1 and f_2 values for the comparison of release of drug from the formulation PGB 2001with the marketed innovator drug release profile were found to be 4.28 and 81.37, respectively. Drug release was directly proportional to the initial level of pore former, but inversely related to the membrane weight. The manufacturing procedure was standardized and found to be reproducible. For Glipizide 10 mg tablet. The values were found to be 8.28 and 71.37 (between T-6 & T-7), 2.37 and 86.72 (between T-6 & T-8**)** and 6.21 and 74.44 (between T-7 & T-8), respectively.

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