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Research Article

FORMULATION DEVELOPMENT STUDIES OF BILAYER TABLET GLIPIZIDE: A NOVEL AND EVOLUTIONARY APPROACH IN THE TREATMENT OF DIABETES.

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ABSTRACT

Objective:The aim of present study is to formulate glipizide sustained release (SR) and immediate release (IR) bilayer matrix tablet by different concentration of Hydroxypropyl methylcellulose (HPMC) and Ethyl Cellulose (EC) to control the release pattern.
Method:The sustained release layer of glipizide was prepared by using different grades of HPMC like, HPMC K-100, HPMC K-50 and Ethyl Cellulose along with other excipients by wet granulation technique. The immediate release layer of glipizide was prepared by Lactose and Sodium starch glycolate by wet granulation Method.
Result:The powders were evaluated for their flow properties and the finished tablets were evaluated for their physical parameters. The both immediate release and sustained release layers of glipizide were characterized by FT-IR and in vitro dissolution studies. The drug release study of glipizide was evaluated using USP-II paddle type dissolution apparatus. The release rate of glipizide in immediate release layer was studied for 1h in pH 7.4 phosphate buffer media and that of glipizide in sustained release layer was studied for 10 h in pH 7.4 phosphate buffer media.
Conclusion:From the six batches F3 batch showed good release behaviour 91.92% of drug is released over 10 hours and r^2 value is 0.977 in zero-order kinetics. Glipizide is a poorly water soluble (BCS class 2) antidiabetic drug. Due to the poor water solubility of this drug, its bioavailability is dissolution rate-limited. Total four trial batches of each drug have been manufactured to optimize and develop a robust and stable formulation, the stability studies of the products also comply with ICH guideline

Keywords: Bilayer tablets, Glipizide, HPMC, Sustained release, Wet granulation.

INTRODUCTION

Oral route is the most commonly employed route of drug administration. Although different route of administration are used for the delivery of drugs, oral route remain the preferred mode. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product. Even for sustained release systems the oral route of administration has been investigated the most, because of flexibility in dosage forms design that the oral route offers [1]. With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non toxic for an extended period of time [2].

Bi-layer tablet concept has long been utilized to develop sustained released formulation. Such tablet has a fast releasing layer and may contain one (bi-layer), to sustain the drug release. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state as the release from sustaining layer.

Glipizide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets [3]. Extrapancreatic effects also may play a part in the mechanism of action of oral sulfonylurea hypoglycaemic drugs. Glipizide is rapidly and completely absorbed following oral administration in an immediate release dosage form. The absolute bioavailability of glipizide was 100% after single oral doses in patients with type 2 diabetes. Beginning 2 to 3 hours after administration of glipizide extended-release tablets, plasma drug concentrations gradually rise reaching maximum concentrations within 6 to 12 hours after dosing. Glipizide is eliminated primarily by hepatic biotransformation: less than 10% of a dose is excreted as unchanged drug in urine and feces; approximately 90% of a dose is excreted as biotransformation products in urine (80%) and feces (10%). The mean terminal elimination half-life of glipizide ranged from 2 to 5 hours after single or multiple doses in patients with type 2 diabetes [4].

Materials and methods

Glipizide and HPMC50were obtained as gift sample from StadmedPvt. Ltd, Kolkata. Sodium starch glycolate, Lactose monohydrate, Magnesium stearate and HPMCK100were obtained as gift sample from Merck specialties Private Limited. Ethyl cellulose was obtained as gift sample from Lobachem private limited, Mumbai. All other chemicals/reagents used were of analytical grade.

Potency Calculation of Active Pharmaceutical Ingredients: Actual quantity of Active drug required per tablet, Potency = ((label claim X 100)/ Effective assay) X (100/ (100 – Water content))

Method

Method of preparation of bi-layer tablets

Preparation of drug loaded two different layers of tablet-

Batch wise distribution of ingredients is shown in table 1.

- Glipizide+HPMC sifted through sieve no 40.
- The sifted materials were hand mixed in a polythene bag.
- The mixed materials were granulated using granulating solution of starch pest, weighted the 10mg starch powder and dissolve in hot 100 ml distilled water and continuously stirring. The mixture was mixed thoroughly to get a damp mass, passed through sieve no8.
- The above granules were air dried for 15 mins and finally dried in hot air oven at 45^0 C-50^0 C till load was<2%.
- Then it is passed through sieve no20.
- After that it is passed through sieve no30.
- Then these were checked for their pre- compression properties. Compression stage

- The prepared and dried granules were transferred to compression stage. The obtained granules were mixed with magnesium stearate as a lubricant.

Preparation of tablet by wet granulation method

The tablet machine is set 9mm die-punch.
First the sustained release layered accurately weighted and filled in die and one single or precompression punches are created.
Then the immediate release layered accurately weighted and filled vacant space of die properly.
Then the seconded compressions or final compressions are created.
The compression forces are maintained properly.

Powder characterization [5-7]

Angle of repose

Angle of repose was determined by using funnel method. The granules were poured from funnel that can be raised vertically until a maximum cone height 'h' was obtained. Then the diameter of the powder cone was measured and the angle of repose was calculated using the following equation. $\theta = \tan^{-1}(h/r)$ [8].

Bulk density and Tapped density [9, 10].

Bulk density of powder blend for glipizide tablet

Bulk Density Apparent bulk density was determined by placing pre-sieved granules into a graduated cylinder and measuring the volume and weight as it is. The bulk density is calculated by using following formula. Bulk density = Weight of powder / volume of packing.

Tapped density

A quantity of 2 gm of powder from each formula was introduced into a 10 ml measuring cylinder. After a initial volume was observed, the cylinder was allow to fall under its own weight on the hard surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in the volume was noted. The tapped density was calculated by using following formula. Tapped density = weight of powder / tapped volume of packing.

Compressibility index of powder blend for glipizide tablet

Compressibility index Compressibility index of granules was determined by Carr's compressibility index. Carr's index: [(TBD – LBD) x 100]/ TBD.

Hausner ratio of powder blends for Glipizide tablet

Hausner ratio was determined by using the ρ_B is loose bulk density and pt is tapped bulk density. Hausner ratio is greater than 1.25 is considered to be an indication of poor flow ability. Hausner ratio = ρ_T / ρ_B

Evaluation of tablets [11, 12].

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined values are reported [13].

Weight variation

Twenty tablets were randomly selected from each batch and average weightwas calculated.

Then individual tablet were weighted and individual weight was compared with an average weight.

Thickness

Twenty tablets were randomly selected from each batch and their thickness was measured by using vernier calliper. Thickness of three tablets from each batch was measured and mean was calculated [14].

Friability [15]

Roche friabilator was used for the purpose. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution tablets were deducted and reweighed. Compressed tablets should not lose more than 1% of their weight. Values are reported. The percentage friability was measured using the formula, $\% F = \{1-(Wo/W)\} \times 100$

Determination of maximum wavelength of glipizide in phosphate buffer (pH 7.4)

Glipizide was accurately weighed and dissolved in 10m. Mol phosphate buffer of pH 7.4 to prepare a stock solution of 1mg/ml. The stock solution was further diluted to 10mcg/ml with diluents (10m.Mol phosphate buffer of Ph7.4), then the diluted solution was scanned for maximum absorbance in UV double beam spectrophotometer (shimandzu1700) in the range of 190 to 400 nm, using 10m.Mol phosphate buffer of pH 7.4 as blank. The λmax was found to be 276 nm.

Drug – Polymers interaction study

DSC of the Glipizide and excipients to study the interaction between components

The DSC study of Glipizide in formulation indicating that there was no interaction between the drug-excipients, which is shown in figure 3 and 4.

FTIR spectroscopy of the Glipizide and excipients to study the interaction between components

The FT-IR spectrum of Glipizide in formulation indicating there was no interaction between the drug-excipients. They were scanned over a wave number range of 4000 cm^{-1} to 400 cm^{-1} using FTIR (Perin Elmer, USA, Model: Spectrum one, Version A) is shown in figure 1and 2.

Precompressional parameters

Precompressional parameter of I.R. and S.R layers granules results were compared in the table 2 in range between angle of repose (22.41 to 26.56), compressibility index between (14.285 to 23.809) respectively. Bulk density and tapped density between (0.3 to 0.36) gm/cc and (0.37 to0.44) gm/cc respectively. The result showed in table 2 indicates good flow property and compressibility.

Postcompressional parameters

The thickness of the tablets was ranged from 5.01mm to 5.21mm. The hardness and percentage friability of the tablets of all formulation remained in range of 6.23 to 6.76 and 0.32 to 0.82 respectively. Drug content was ranged from 98.18% to 99.97%. The result is depicted in table 3. The disintegration test for immediate release layer is determined using the disintegration test apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of phosphate buffer of Ph7.4 maintained at 37 ±2°C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

In vitro drug release study

In vitro drug release study was performed using dissolution apparatus USP type II paddle method with a stirring speed 50 rpm at 37^0 C ± 0.5 in 900 ml of 7.4 pH phosphate buffer up to 24 hr. The samples were collected at per selected time intervals with replacement of equal volume of dissolution media. The absorbance of collected samples was measured spectrophotometrically at 276 nm which is shown in table 4 to 9 and figure 5 to 8.

Stability Studies (ICH Geneva 2003): The optimized formulation was subjected for two month stability study according to ICH guidelines. The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at room temperature 40ºC / 75% RH for 2 months and evaluated for their permeation study.

Drug Content

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 15mg of glipizide was taken and

dissolved in 30 ml of methanol with gentle heating on a water bath, cool and add sufficient amount of methanol is added to produce 50 ml. filter and dilute to 5 ml of the filtrate to 50ml with methanol. The absorbance was measured spectrophotometrically at 276 nm after suitable dilution that shows in table 3.

RESULT AND DISCUSSION

Table 1: Batch wise distribution of the ingredients

	Ingredients	F1	F2	F3	F4	F5	F6
Immediate release layer	Glipizide (mg)	4	4	4	4	4	4
	Lactose (mg)	66	66	66	66	66	66
	Sodium Starch Glycolate(mg)	25	25	25	25	25	25
Sustained release layer	Glipizide (mg)	6	6	6	6	6	6
	HPMC K-100 (mg)	40	------	35	-----	30	-------
	HPMC K-50 (mg)	-------	40	-------	35	-------	30
	Ethyl Cellulose (mg)	108	108	113	113	118	118
	Magnesium Stearate (mg)	1	1	1	1	1	1
	Total weight of the tablet (mg)	250	250	250	250	250	250

Table2: Precompressionalparameters of bilayer tablets of Glipizide IR and SR

SL NO	Formulation	Angle ofrepose	Bulk density gm/cc	Tapped density gm/cc	Carr's Index	Hausners ratio
1	F1	24.37±1.732	0.3±0.006	0.37±0.002	18.918±0.13	1.23±0.002
2	F2	26.39±0.093	0.36±0.007	0.42±0.05	14.285±0.10	1.17±0.09
3	F3	23.61±2.312	0.32±0.001	0.42±0.07	23.809±0.17	1.31±0.09
4	F4	22.41±1.025	0.360±0.043	0.44±0.09	18.181±0.21	0.73±0.04
5	F5	26.56±1.884	0.310±0.021	0.39±0.03	20.512±0.28	1.26±0.02
6	F6	25.21±1.992	0.330±0.006	0.4±0.09	17.05±0.19	1.21±0.03

Table 3: Postcompressional parameters of bilayer tablets of Glipizide IR and SR

Batch no	Hardness kg/ Cm^2± SD, n=6	Friability ±SD, n=10	Weight variation n=20	Thickness(mm) ± SD, n=6	Drug content(%), (±SD), n=3
F1	6.28±0.01	0.32±0.01	1.91	5.13±0.02	99.70±0.45
F2	6.76±0.36	0.76±0.01	1.20	5.06±0.02	98.18±0.85
F3	6.23±0.01	0.82±0.01	1.77	5.15±0.02	98.81±0.83
F4	5.36±0.35	0.49±0.01	2.15	5.18±0.02	99.04±0.45
F5	6.54±0.36	0.39±0.01	1.95	5.01±0.02	99.97±0.55
F6	6.41±0.36	0.59±0.01	2.34	5.21±0.02	98.88±0.62

Table 4: zero order drug release rate (SR layer)

Time in hour	Cumulative % of drug release					
	F1	F2	F3	F4	F5	F6
1	44.81	44.42	59.17	58.98	62.04	53.7
2	50.74	46.95	59.55	59.94	66.07	54.77
3	51.13	48.45	60.13	64.15	66.45	59.94
4	52.28	49.21	68.94	65.49	71.24	61.28
5	55.72	52.28	71.43	65.87	74.11	63.19
6	55.92	54	76.22	67.79	75.07	63.96
7	65.68	61.09	79.66	72.58	80.81	66.64
8	69.7	61.85	88.85	74.30	84.83	68.75
9	75.26	71.81	90.58	81.96	86.37	77.75
10	79.66	74.87	91.92	82.34	86.75	79.66

Table 5: First order drug release rate (SR layer)

Time in hours	log Cumulative % of drug release					
	F1	F2	F3	F4	F5	F6
1	1.651	1.647	1.772	1.770	1.792	1.726
2	1.705	1.671	1.774	1.777	1.820	1.738
3	1.708	1.685	1.779	1.807	1.822	1.777
4	1.718	1.692	1.838	1.816	1.852	1.787
5	1.746	1.723	1.853	1.818	1.869	1.800
6	1.747	1.732	1.882	1.831	1.875	1.805
7	1.817	1.785	1.901	1.860	1.907	1.823
8	1.843	1.791	1.948	1.870	1.928	1.837
9	1.876	1.856	1.957	1.913	1.936	1.890
10	1.901	1.874	1.963	1.915	1.938	1.901

Table 6: Higuchi model of drug release rate (SR layer)

Squre root of time	Cumulative % of drug release					
	F1	F2	F3	F4	F5	F6
1	44.81	44.42	59.17	58.98	62.04	53.7
1.414	50.74	46.95	59.55	59.94	66.07	54.77
1.732	51.13	48.45	60.13	64.15	66.45	59.94
2	52.28	49.21	68.94	65.49	71.24	61.28
2.236	55.72	52.28	71.43	65.87	74.11	63.19
2.449	55.92	54	76.22	67.79	75.07	63.96
2.645	65.68	61.09	79.66	72.58	80.81	66.64
2.828	69.7	61.85	88.85	74.30	84.83	68.75
3	75.26	71.81	90.58	81.96	86.37	77.75
3.162	79.66	74.87	91.92	82.34	86.75	79.66

Table 7: Koresmeyer-peppas model of drug release rate (SR layer)

Log of hour	Log Cumulative % of drug release					
	F1	F2	F3	F4	F5	F6
0	1.651	1.647	1.772	1.770	1.792	1.726
0.301	1.705	1.671	1.774	1.777	1.820	1.738
0.477	1.708	1.685	1.779	1.807	1.822	1.777
0.602	1.718	1.692	1.838	1.816	1.852	1.787
0.698	1.746	1.723	1.853	1.818	1.869	1.800
0.778	1.747	1.732	1.882	1.831	1.875	1.805
0.845	1.817	1.785	1.901	1.860	1.907	1.823
0.903	1.843	1.791	1.948	1.870	1.928	1.837
0.954	1.876	1.856	1.957	1.913	1.936	1.890
1	1.901	1.874	1.963	1.915	1.938	1.901

Table 8: Zero-order drug release rate (IR layer)

Time in hours	Cumulative % of drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.166	14.74	23.26	11.29	18.57	14.97	16.08
0.333	15.89	27.40	15.70	19.34	17.42	17.61
0.5	17.04	31.02	36.57	26.04	19.34	25.27
0.666	34.28	38.68	55.53	30.06	34.28	41.94
0.833	42.13	40.40	56.87	39.25	56.49	45.57
1	44.81	44.42	59.17	58.98	62.04	53.30

Table 9: First order drug release rate (IR layer)

Time in hours	Log Cumulative % of drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.166	1.168	1.368	1.052	1.268	1.157	1.206
0.333	1.201	1.392	1.195	1.286	1.241	1.245
0.5	1..231	1.491	1.563	1.415	1.286	1.402
0.666	1.535	1.587	1.744	1.477	1.535	1.622
0.833	1.624	1.606	1.754	1.593	1.751	1.658
1	1.651	1.647	1.772	1.770	1.792	1.726

Table10: Kinetic assessment of release data

	Zero order		First order		Higuchi kinetics		Koresmeyer Peppas model	
Formulation	r^2	k_0	r^2	k_1	r^2	k_h	r^2	k_{kp}
F1	0.938	7.52	0.382	1.651	900	25.19	0.931	1.901
F2	0.926	7.48	0.375	0.187	0.884	23.67	0.926	1.874
F3	0.977	8.67	0.364	0.196	0.897	29.07	0.925	1.963
F4	0.946	8.23	0.326	0.191	0.806	26.04	0.904	1.915
F5	0.967	9.19	0.318	0.193	0.823	27.43	0.908	1.938
F6	0.937	7.96	0.338	0.190	0.832	25.192	0.911	1.901

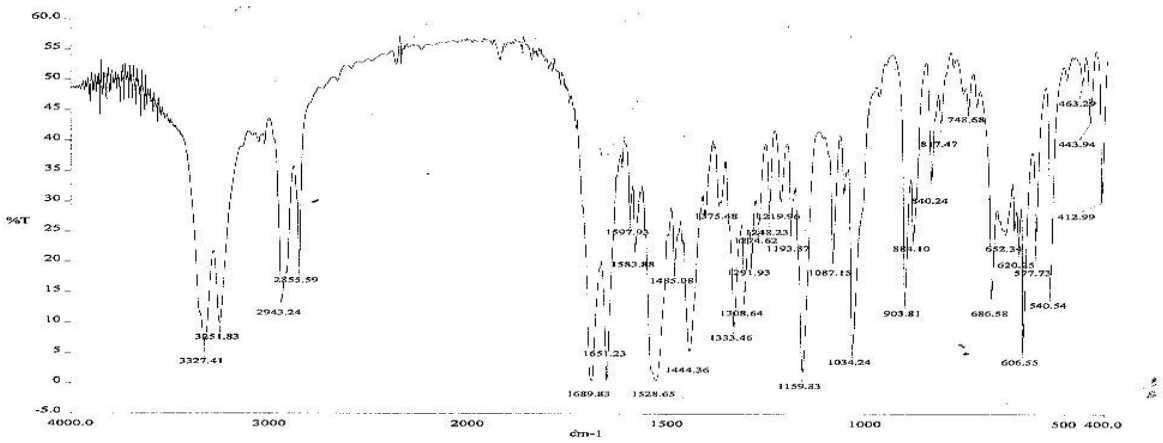

Fig. 1: FTIR of Glipizide

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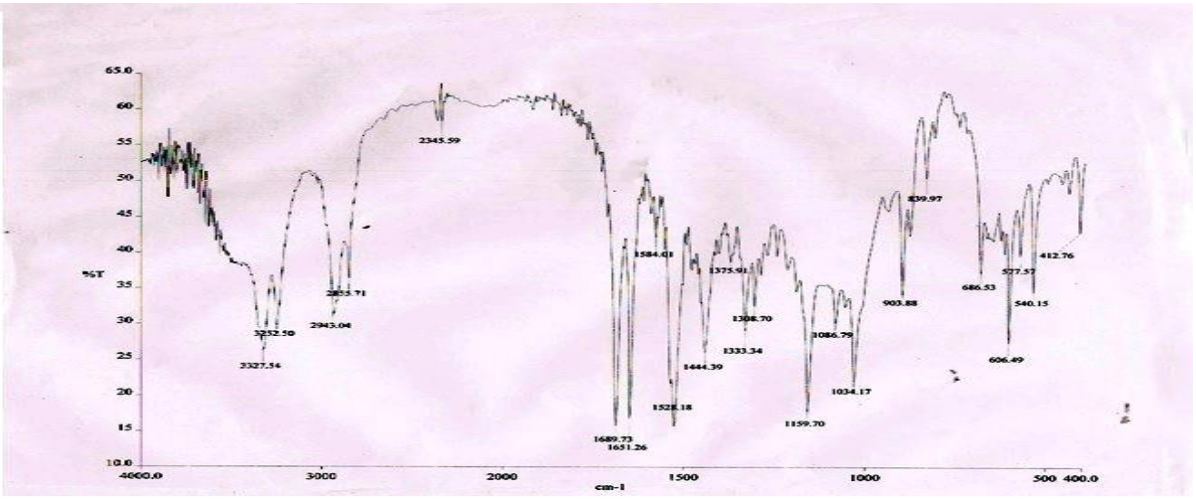

Fig. 2: FTIR of Glipizie+HPMC K 100CPS

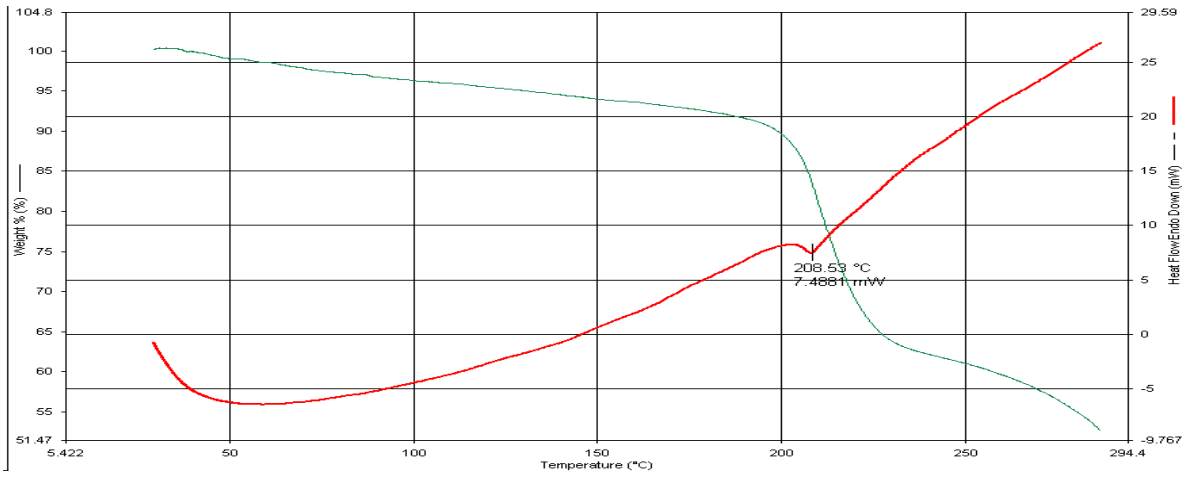

Fig.3: DSC study of glipizide

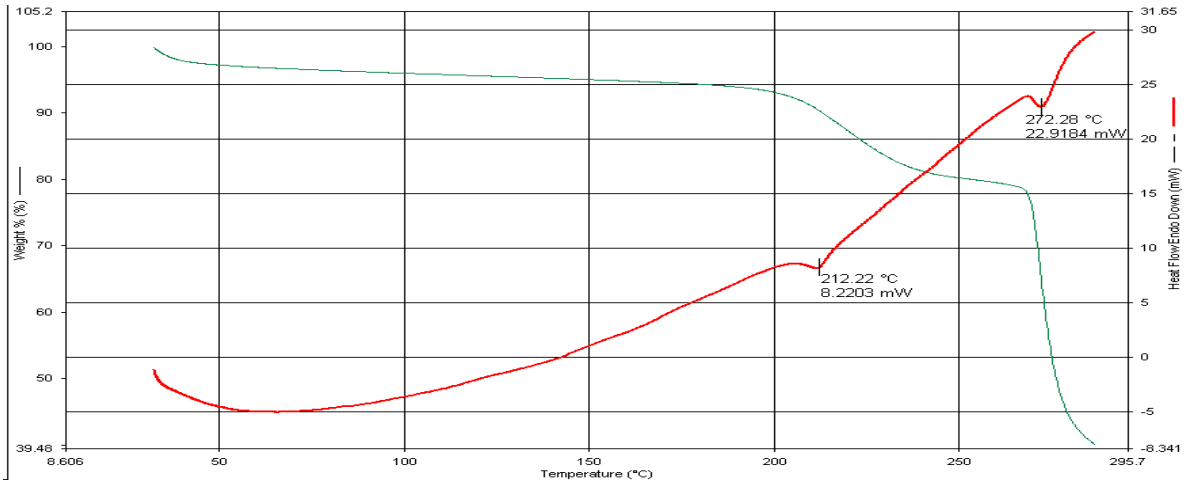

Fig.4: DSC study of glipizide+ HPMC K100CPS

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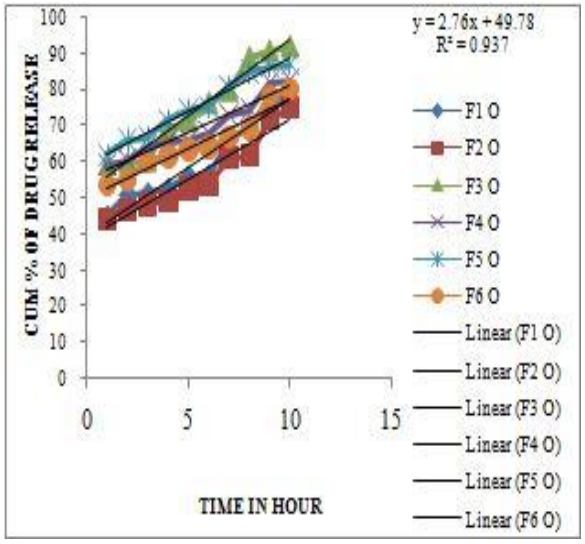


Fig.5: zero order for SR layer

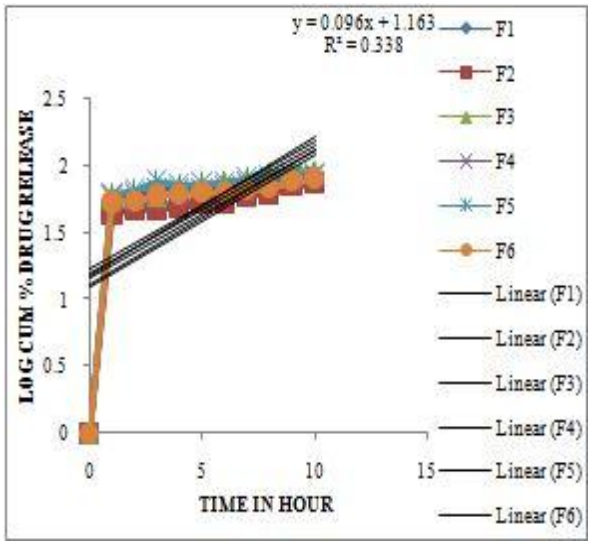
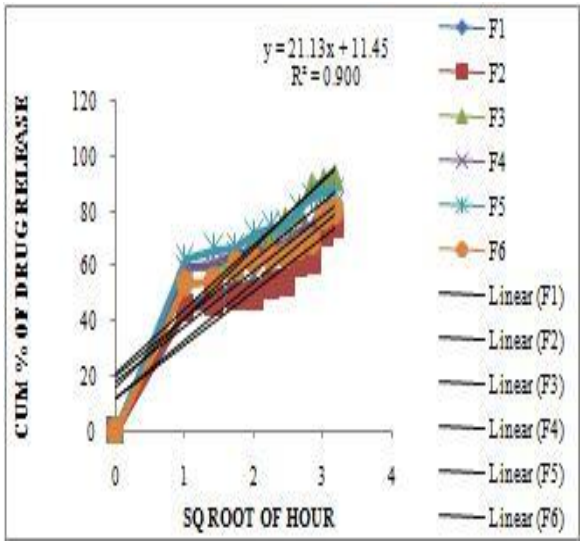


Fig.6: First order for SR layer



. **Fig.7: Higuchi model for SR layer**

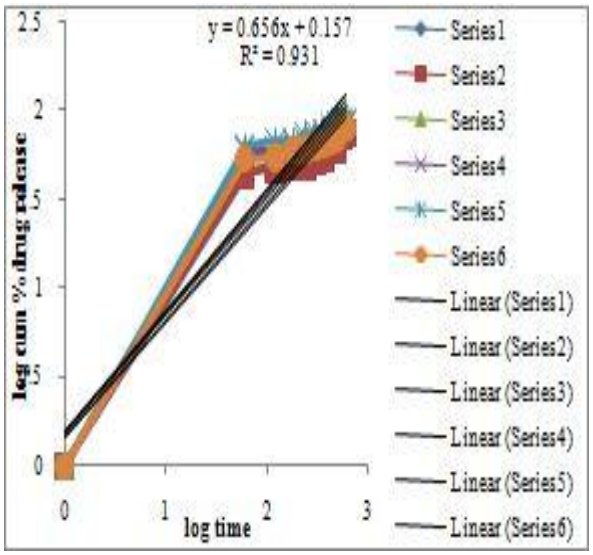


Fig.8: Koresmeyer-peppas model for SR layer

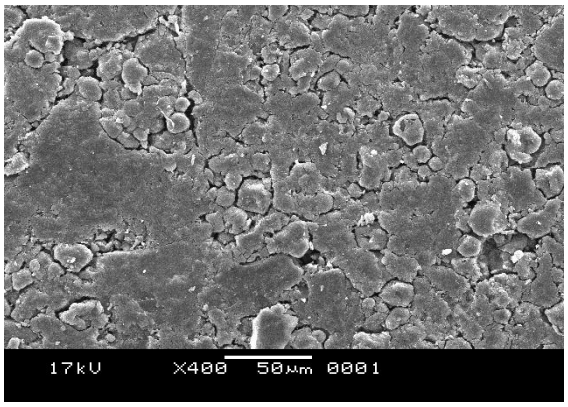


Fig.9: SEM of formulation before dissolution

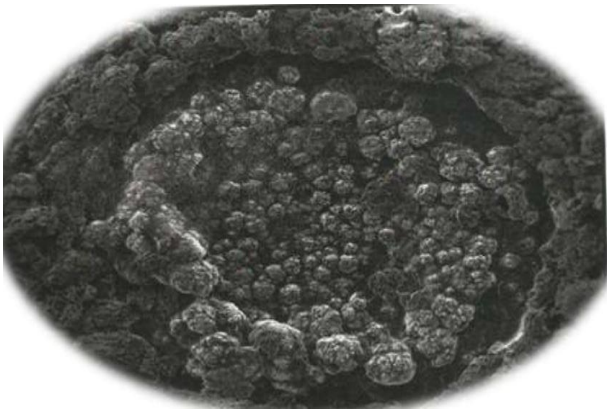


Fig.10: SEM after dissolution

DISCUSSION

For the purpose of above research project, six batches of glipizide (a drug for type-2 diabetes) were prepared in form of bilayer matrix tablets (batch no- F1, F2, F3, F4, F5, F6) using different grades and ratio variation of polymer mainly HPMC (K100, 50CPS) and Ethyl cellulose and out of the above batches, the batch no F3 showed good release behaviour 91.92% of drug are released over 10 hours and when the kinetics study of all batches were compared. All the batches followed mainly zero-order kinetics and batch no-F3 showed the r^2 value 0.977 in zero-order kinetics. In course of formulation all the six batches had immediate release of 40% drug within 1 hour and rest 60% of the drug followed sustained release pattern with optimize drug polymer ratio. From the batch no-F1, F2, F4, F5 F6 also showed good release behaviour over 10 hours.

The SEM study of the batch F3 before and after dissolution also showed good release behaviour shown in figure 9 and 10.

CONCLUSION AND FUTURE SCOPE

Based on the above study, it can be concluded that Glipizide, a conventional drug for type 2 diabetes can be successfully formulated in the form of bilayer matrix tablet by optimizing drug polymer ratio using different grades of common polymers like HPMC, Ethyl cellulose etc. This is basically done to improve bioavailability of the drug and better therapeutic compliance. The sustained layer of the drug showed steady state release behaviour over a prolonged duration of time which may reduce dose related side effects. In future, natural biodegradable polymers can be used to improve therapeutic efficacy of the drug and further minimizing side effects.

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