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PREPARATION OF GLIMEPIRIDE *ALOE BARBADENSIS MILLER* LEAVES MUCILAGE AND POVIDONE CONTROLLED RELEASE MATRIX TABLETS: *IN VITRO* AND *IN VIVO* EVALUATION

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ABSTRACT

The main purpose of the present study was to prepare Glimepiride matrix tablets with *Aloe barbadensis miller* leaves mucilage and Povidone and to study its novelty as a matrix forming polymer for controlled release tablet formulations. Physicochemical properties of the dried powdered *Aloe barbadensis miller* mucilage and Povidone blend, drug-excipient compatibility studies, pre formulation studies, post formulation studies, *in vitro* drug release studies, mathematical modeling of *in vitro* dissolution data and *in vivo* hypoglycemic effects in rabbits were performed. *Aloe barbadensis miller* mucilage was found to have good flow properties, Glimepiride was found compatible with the excipients used. The granules were found to have good flow properties and *in vitro* drug release pattern. The mathematical modeling proved that the release of drug from the formulations followed zero order release. The reduced hypoglycemic actions were maintained for prolonged time in *in vivo* hypoglycemic studies. All these values were found to be satisfactory. The data revealed that the dried *Aloe barbadensis miller* mucilage and Povidone combination can be used as a matrix forming polymers for making controlled release matrix tablets.

KEYWORDS: Glimepiride; *Aloe barbadensis miller;* Povidone; matrix tablets; *in vitro; in vivo;* controlled release.

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INTRODUCTION

The mucilage of *Aloe barbadensis miller* leaves clinically and experimentally proved anti-diabetic activity[1] and release retardant activity in the present study. Glimepiride is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus. It belongs to sulfonyl urea drug class. Glimepiride is a weak acid with PKa of 6.2. Glimepiride is practically insoluble in water and acidic environment but highly permeable (class 2) according to the Biopharmaceutical classification System (BCS) [2]. The oral absorption is uniform, rapid and complete with nearly 100% bioavailability. The normal dose[3] of Glimepiride is 1to2 mg. The pharmacokinetics and dosage schedule supports once daily controlled release formulations for Glimepiride for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance[4]. The main objective of present research is to design controlled release tablets of Glimepiride using *Aloe barbadensis miller* leaves mucilage and Povidone combination and to evaluate both *in vitro* and *in vivo* parameters.

MATERIALS AND METHODS

Materials

Glimepiride was a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. *Aloe barbadensis miller* leaves were collected from plants growing in local areas of Anantapur, India. The plant was authenticated at the Botany Department of Sri Krishnadevaraya University, Anantapur, India. Povidone, Micro crystalline cellulose (Avicel) and Magnesium stearate were procured from SD Fine chemicals (Mumbai, India). All other chemicals used were of AR grade and deionized water was used throughout the experiment.

Extraction and Characterization of Mucilage

The fresh *Aloe barbadensis miller* leaves were collected and washed with water. Incisions were made on the leaves and left over night. The leaves were crushed and soaked in water for 5–6 h, boiled for 30 min and left to stand for 1h to allow complete release of the mucilage into the water. The mucilage was extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The so precipitated mucilage was dried in an oven at 40^0C, collected, ground, passed through a # 80 sieve and stored in desiccator at 30^0C & 45% relative humidity till use[5, 6]. The so obtained mucilage was purified and characterized as per procedures describe in official books.

Drug-Excipient Compatibility Studies

The drug-excipient compatibility testing was performed by Differential Scanning Calorimetric (DSC) analysis using Thermal Analysis instrument (DSC 60, Shimadzu, Japan). The Fourier Transform Infrared (FTIR) spectrums were recorded using FTIT spectophotometer (Hitachi-270-30 IR spectrophotometer, Japan).

Preparation of Matrix Tablets

Controlled release Glimepiride matrix tablets with *Aloe barbadensis miller* leave mucilage and Povidone were prepared by using different drug: mucilage ratios. *Aloe barbadensis miller* leaves mucilage and Povidone were used as matrix formers, while microcrystalline cellulose as a diluent and Magnesium stearate as a lubricant. All ingredients used were passed through a # 100 sieve, weighed and blended. Wet granulation technique was adopted in preparing the granules and compressed by using 10 mm flat faced punches[7]. The formulae of different matrix tablets were shown in Table 4.

Evaluation of Tablets

Swelling Behavior of Matrix Tablets

F-1, F-2, F-3, F-4 and F-5 formulations were subjected to swelling behavior studies. One tablet from each formulation was kept in a Petri dish containing phosphate pH 7.4. At the end of 2 h, the tablet was withdrawn, kept on tissue paper and weighed, repeated for every 2 h till the end of 12 h[8]. The % weight gain by the tablet was calculated by the equation 1:

$$S.I = \{(M_t - M_0) / M_0\} X 100 \quad (1)$$

Where, S.I = Swelling Index, M_t = Weight of tablet at time 't' and M_0 = Weight of tablet at time 0.

Physical Properties of Tablets

The formulated tablets were tested for uniformity in thickness[9], uniformity in weight[10], hardness[11] and friability[12] flow properties[9, 13] and uniformity in drug content as per official procedures.

***In vitro* Drug Release Studies**

Release of Glimepiride from the matrix tablets was studied in 900 ml phosphate buffer (pH 7.4) using United States Pharmacopoeia (USP) 8-station Dissolution Rate Test Apparatus (Model Electro lab, TDT- 06T, Mumbai, India) with 50 rpm paddle speed and 37 ± 0.5^0C. A sample of Glimepiride matrix tablets (2 mg of Glimepiride) was used in each test. Samples of dissolution fluid were withdrawn and filtered (0.45 µm) at different time intervals and were assayed at 230 nm for Glimepiride content using a UV/visible double-beam spectrophotometer (Elico SL 210, Mumbai, India). The *in vitro* drug release studies were conducted in triplicate (n = 3). To analyze the mechanism of drug release from the prepared formulations, the data obtained from *in vitro* release studies were subjected to, Zero order[14], first order[15], Higuchi[16], Korsmeyer Peppas[17] and Hixson Crowell's models[18].

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) (JSM 5610 LV SEM, JEOL, Datum Ltd., Japan) of tablet (F5) was performed before and different intervals of dissolution. The morphological characters of these scans were compared to hypothesize the mechanism of drug release.

***In Vivo* Study**

Normal healthy rabbits weighing 1.5 to 2.0 kg each were used for the *in vivo* studies. The Institutional Animal Ethics Committee's approval was obtained before the commencement of the study. The study was conducted as per standard institutional guidelines. Two groups of rabbits with 5 in each were fasted 12h before the study[19]. Before the administration of drug, a blood sample was taken from the marginal ear vein of each rabbit (control). The blood glucose levels of the collected samples were determined using the glucose oxidase method. Pure Glimepiride and matrix tablets Glimepiride were administered orally to each group. A dose of 160 µg/kg of Glimepiride was administrated in a form of suspension for each rabbit. Blood samples were collected at regular intervals of time (at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24h) and analyzed for blood glucose levels with glucose oxidase method.

Accelerated Stability Studies of Optimized Matrix Tablets

The promising formulation was tested for a period of 3 months at different temperatures of 40^0C with 75% RH, for their drug content[20].

RESULTS

The extracted mucilage was in brownish yellow in colour with a characteristic odour. The mucilage was slowly soluble in water produces hage viscous solution. The percentage yield was 23 ±2.173%. The Average particle size was found to be 165.15±10.265µm. The weight loss on drying was 4.20±2.573, the mucilage was charred at 220±4.52^{0}C and the bio burden was minimal. All the physical properties were represented in Table 1. The chemical properties of the mucilage were shown in Table 2. The angle of repose of extracted mucilage was found to be 27.0±0.05^0 indicates the powdered mucilage has excellent flow properties. The bulk densities of the dried mucilage were utilized for calculating the compressibility index which was 21.6±0.02%, which indicates fair compression properties which were improved by the addition of magnesium stearate in the formulation. The flow properties of *Aloe barbadensis miller* leaves mucilage was shown in Table 3.

The DSC scan of Glimepiride showed a short endothermic peak at 215.50^{0}C. The thermo gram of formulated matrix tablets with *Aloe barbadensis miller* leaves mucilage and Povidone showed an endothermic peak of drug at 215.68^{0}C indicating a slight change in terms of shifting towards the lower temperature. The DSC thermo gram of Glimepiride and the formulated matrix tablet blend were shown in Figure 1 and 2. The FTIR spectrum of Glimepiride and the matrix tablets of Glimepiride were showed in Figure 3, 4 and 5. The characteristic bands 3344.3, 2900.7, 1627.8, 1427.2, 1342.4 and 1072.3 were observed both in pure Glimepiride and Glimepiride *Aloe barbadensis miller* leaves mucilage and Povidone mixture. The formulated tablets were shown uniformity of swelling in controlled manner. The swelling indexes of formulated tablets were shown in Figure 6. The formulated tablets pass uniformity in weight (less than ±7.5%) which was within the limits as per Indian Pharmacopoeia. The thickness of formulated tablets was ranged from 4.3±0.21 to 4.9±0.15 mm indicating the uniformity in weight. The hardness of the tablets was ranged from 5.10±0.14 to 6.50±0.14 kg/cm^2, which were more than 5 kg/cm^2 and passes hardness test. The loss on friability was not more than 1% which was within the limits. The amount of Glimepiride in formulated tablets was ranged from 99.84±2.56 to 100.62±5.25%. All these physical properties of formulated matrix tablets were shown in Table 5. The formulated tablets released more than 30% of the drug in first 1 h and further release was in controlled manner in zero order. Since these plots did not yield a straight line, the dissolution data was subjected to linear regression analysis (r) in zero order kinetics was 0.006705 (for F-5) and the 'r' values obtained for first order kinetics was found to be 0.004053(for F-5). Since greater degree of association best fitted with zero order kinetic models. It can be concluded that, all the matrix tablets followed zero order kinetics as the release pattern of the drug. The 'r' values for remaining formulations were represented in Table 6 and 7 respectively and these values were shown in Figure 7 and 8. The *in Vitro* drug dissolution data when treated according to Higuchi's diffusion equation ($Q=Kt^{½}$) indicated that the formulations released the drug by diffusion which was shown in Figure 9 and represented in Table 8. Further to know the release pattern of Glimepiride from the matrix tablets, the results were analyzed according to Korsmeyer Peppas exponential equation ($q = K_t^n$). The slope 'n' was computed to know whether the release was Fickian or non-Fickian. For non-Fickian release ('n' values = 0.5to 1.0), while for Fickian diffusion ('n' value = ≤0.5). The slope value for optimized Glimepiride matrix tablets (F-5) was 3.308515. The values of 'n' were more than 0.5. So, the F-5 matrix tablets follow the non-Fickian release. These values were tabulated in Table 9 and shown in Figure 10. The *in-vitro* drug release data was further plotted as $(1-m_t/m_\infty)^{1/3}$ verses time proposed by Hixson Crowell's to verify whether the drug release is by erosion mechanism. Figure 11 shows the plots of $(1-m_t/m_\infty)^{1/3}$ vs. Time and shown in Table 10. The 'r' value was found to be -0.99214 for the formulation F-5. This observation showed that the drug release from the formulated matrix tablets was fitted well to the erosion mechanism. The slope of line indicated that the rate of disappearance of the tablets by erosion. The slope was calculated and it was found to be -0.00092 for matrix tablets. The surface morphology of optimized matrix tablets (F-5) at time intervals of 0, 1st, 2nd and 3rd h of dissolution were shown in Figure 12. The mean percentage reduced blood glucose levels with Glimepiride matrix tablets (F-5) was represented in Table 11 and shown in Figure 13. And the F-5 shown very highly significant values (P***<0.001) compared with orally given Glimepiride pure drug. The promising formulation was tested for a period of 3 months at accelerated storage conditions of temperatures 40^{0}C and the relative humidity of 75% RH. The parameters viz., Thickness, diameter, weight of the tablet, hardness, friability and drug contents were observed before and after stability studies and they found unchanged.

DISCUSSION

The extracted mucilage of *Aloe barbadensis miller* was in brownish yellow in colour with a characteristic odour.

The mucilage was slowly soluble in water produces hage viscous solution. The percentage yield was satisfactory and the powdered mucilage has an uniform particle size. The weight loss on drying was minimal with minimal microbial count. The mucilage gave all positive reactions as all mucilages gives and the heavy metals present in the mucilage were within the limits. The angle of repose of extracted mucilage was found to be less than 30^0 indicate the powdered mucilage has excellent flow properties. The compressibility Index and Hausner ratio were fair flow properties which were improved by the addition of magnesium stearate. The DSC scan of Glimepiride showed a short endothermic peak at 215.50^0C. The thermo gram of formulated matrix tablets with *Aloe barbadensis miller* leaves mucilage and Povidone showed an endothermic peak of drug at 215.68^0C indicating a slight change in terms of shifting towards the lower temperature. It has been reported that the quantity of material used effects the peak shape and enthalpy. Thus these minor changes in the melting endotherm in the drug could be due to the mixing of the drug and excipients which lower the purity of each component in the mixture and may not necessarily indicate potential incompatibility. The characteristic peaks of FTIR spectrum of Glimepiride were observed both in pure Glimepiride and Glimepiride *Aloe barbadensis miller* leaves mucilage and Povidone mixture. This indicates that there is no chemical incompatibility between Glimepiride and the polymers (*Aloe barbadensis miller* leaves mucilage and Povidone) used. The formulated tablets were shown uniformity of swelling in controlled manner. The formulated tablets pass uniformity in weight as per Indian Pharmacopoeia. The thickness of formulated tablets was found to be uniform. The hardness of the tablets was more than 5 kg/cm^2 and the loss on friability was less than 1%, indicates that the formulated tablets have good mechanical strengths and can withstand the mechanical shocks during handling and transport. The amount of Glimepiride in formulated tablets was found to be within the limits. The formulated tablets released more than 30% of the drug in first 1 h and further release was in controlled manner in zero order. Since these plots did not yield a straight line, the dissolution data was subjected to linear regression analysis (r) in zero order kinetics was 0.006705 (for F-5) and the 'r' values obtained for first order kinetics was found to be 0.004053(for F-5). Since greater degree of association best fitted with zero order kinetic models. It can be concluded that, all the matrix tablets followed zero order kinetics as the release pattern of the drug. Higuchi's diffusion equation indicated that the formulations released the drug by diffusion mechanism. The F-5 matrix tablets follow the non-Fickian release. Hixson Crowell's treatment to the *in vitro* drug release data indicates the drug release from the formulation was by erosion mechanism. The surface morphology of optimized matrix tablets (F-5) at time intervals of 0, 1^{st}, 2^{nd} and 3^{rd} h of dissolution showed that the release of drug form the dosage form was by diffusion controlled. The mean percentage reduced blood glucose levels with Glimepiride matrix tablets (F-5) was very highly significant values (P***<0.001) compared with orally given Glimepiride pure drug. The optimized formulation (F-5) retains the parameters viz., Thickness, diameter, weight of the tablet, hardness, friability and drug content even after the accelerated stability studies.

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Table 1: Physical characterization of *Aloe barbadensis miller* leaves mucilage

Physical Properties	**Observation**
Appearance	Brownish yellow powder
Odour	Characteristic
Solubility	Slowly soluble in water produces hage viscous solution
Percent yield (g /kg)	23 ±2.173
Average particle size (µm)	165.15±10.265
Weight loss on drying (mg)	4.20±2.573
Swelling Index (%)	45±3.841
pH	7.0±0.56
Charring (^{0}C)	220±4.52
Density of liquid (0.5% w/v)	0.997±0.055
Microbial count (cfu/g)	Bacteria:5 ; Fungi: 2
Cfu = Colony forming units	

Table 2: Chemical characterization of *Aloe barbadensis miller* leaves fruit mucilage

Chemical properties	**Observation**
Mounted in 96% ethanol	Transparent angular masses
Mounted in ruthenium red	Particles stained red
Mounted in Iodine solution	Particles stained blue
Test for Carbohydrate (Mollish test)	+ve
Test for Tannins (Ferric chloride test)	-ve
Test for chloride (Silver-nitrate test)	-ve
Test for Sulphate (Barium chloride test)	-ve
Test for Uronic acid	+ve
Test for foreign matter (%)	NMT 0.1
Test for heavy metal (lead)	23 ppm
Test for Arsenic	<1 ppm
Ppm = Parts per million; NMT = Not more than; +ve = Positive; -ve= Negative	

Table 3: Flow properties of *Aloe barbadensis miller* leaves mucilage

Flow properties	**Observation**
Angle of repose (θ°)	27.0±0.05
Loose Bulk density (g/cm3)	0.55±0.04
Tapped bulk density(g/cm3)	0.74±0.04
Carr's Index (%)	21.6±0.02
Hausner ratio	1.36±0.01
Number of trials (n)=5	

Table 4: Formulae of matrix tablets

Ingredients (mg)	Formulations				
	F-1	F-2	F-3	F-4	F-5
Glimepiride	2	2	2	2	2
Aloe barbadensis miller leaves dried mucilage	2.5	5	7.5	10	12.5
Povidone	2.5	5	7.5	10	12.5
Micro crystalline cellulose (Avicel)	188	183	178	173	168
Magnesium stearate	5	5	5	5	5
Total weight of tablet	200	200	200	200	200

Table 5: Physical properties of formulated matrix tablets

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F-1	4.3±0.21	6.50±0.12	0.80±0.02	99.85±3.95
F-2	4.9±0.15	5.10±0.14	0.55±0.05	100.62±5.25
F-3	4.4±0.41	5.80±0.13	0.64±0.03	99.84±2.56
F-4	4.4±0.39	6.50±0.14	0.69±0.06	99.96±5.68
F-5	4.5±0.58	6.40±0.13	0.84±0.07	99.97±3.94

Table 6: Zero order modeling of matrix tablets

Formulation	Zero Order		
	Slope	Regression coefficient(r)	k value
F-1	0.003559	0.003559	0.990392
F-2	0.002955	0.002955	0.992511
F-3	0.005966	0.004966	0.996615
F-4	0.006498	0.006498	0.988149
F-5	0.006705	0.006705	0.995252

Table 7: First order modeling of matrix tablets

Formulation	First Order		
	Slope	Regression coefficient (r)	k value
F-1	-0.00075	0.001727	-0.97846
F-2	-0.00049	0.001128	-0.99684
F-3	-0.00156	0.003593	-0.97261
F-4	-0.00153	0.003524	-0.99259
F-5	-0.00176	0.004053	-0.98231

Table 8: Higuchi modeling of matrix tablets

Formulation	Higuchi's values	
	Slope (n)	Regression co-efficient (r)
F-1	1.725046	0.971738
F-2	1.865816	0.996448
F-3	3.103433	0.985042
F-4	3.227632	0.993489
F-5	3.308515	0.993936

Table 9: Korsmeyer Peppas modeling of matrix tablets

Formulation	Korsmeyer Peppas values	
	Slope (n)	Regression co-efficient (r)
F-1	0.162456	0.930212
F-2	0.171559	0.955678
F-3	0.287578	0.947332
F-4	0.313169	0.974429
F-5	0.304558	0.968565

Table 10: Hixson-Crowell's modeling of matrix tablets

Formulation	Hixson-Crowell's values	
	Slope (n)	Regression co-efficient (r)
F-1	-0.00043	-0.98355
F-2	-0.00032	-0.99574
F-3	-0.00064	-0.99517
F-4	-0.00083	-0.99441
F-5	-0.00092	-0.99214

Table 11: Mean % Reduced blood glucose levels with F-5 matrix tablets

Time (h)	Mean Reduced blood glucose levels (%)	
	Group-I (Control) Glimepiride(p.0)	Group-II F-5
0 (basal BGL)	0.00±0.00	0.00±0.00
0.5	18.21±2.65**	25.41±2.10***
1	26.42±2.48**	27.89±1.49***
2	42.89±1.98**	33.01±2.15***
3	40.52±2.54**	36.38±3.01***
4	21.51±2.68**	40.69±2.78***
5	16.53±1.26**	39.81±0.91***
8	0.01±0.00**	38.89±1.54***
10	0.00±0.00**	33.88±2.54***
12	0.02±0.00**	36.39±0.36***

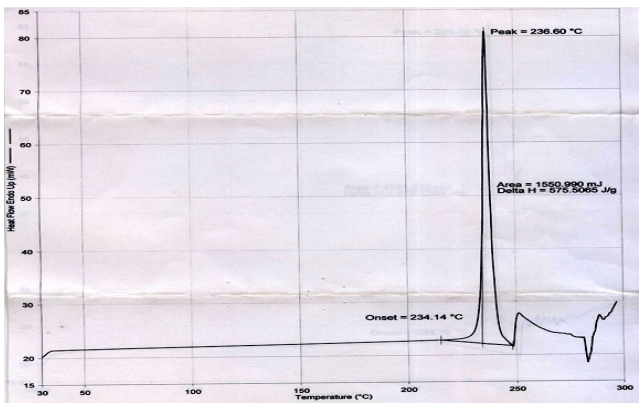

Fig. 1: The DSC thermo gram of Glimepiride

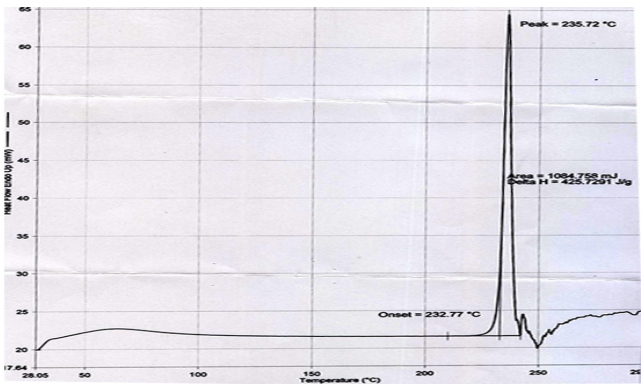

Fig. 2: The DSC thermo gram of matrix tablets

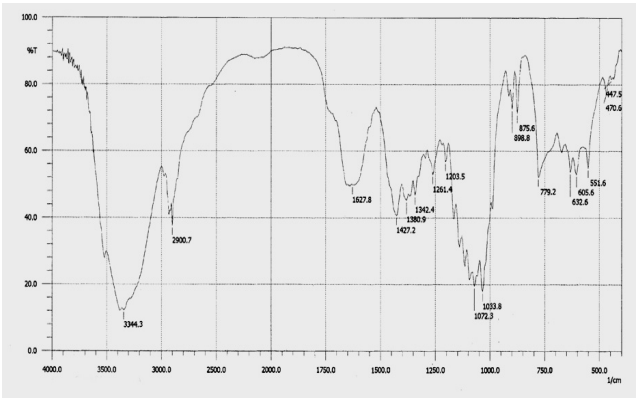

Fig. 3: FTIR Spectrum of Glimepiride Pure drug

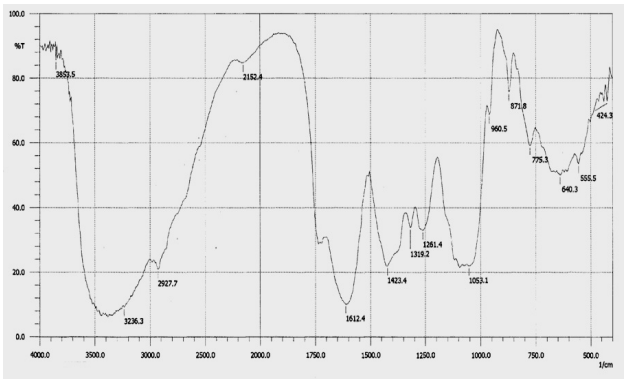

Fig. 4: FTIR Spectrum of Placebo tablets

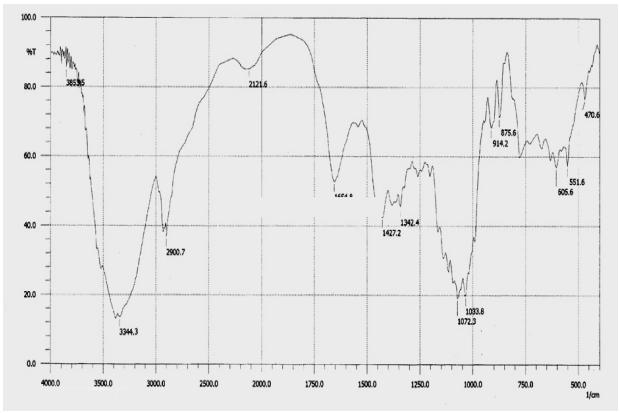

Fig. 5:FTIR Spectrum of formulated matrix tablets

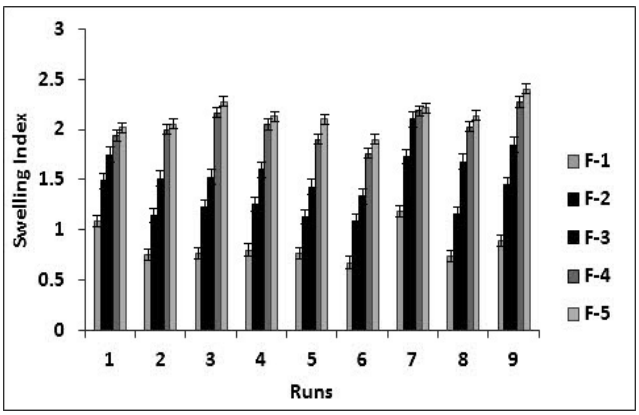

Fig. 6: Swelling Index of matrix tablets

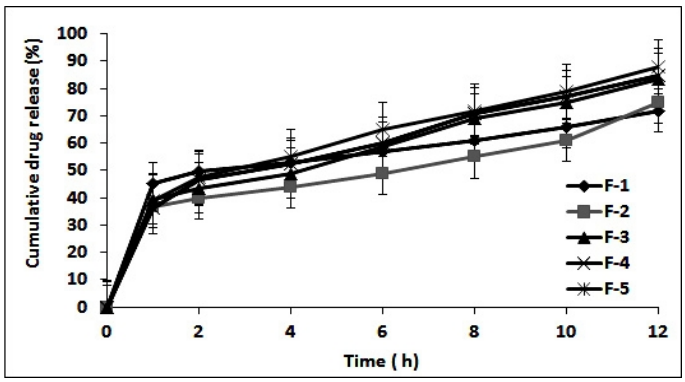

Fig. 7: Zero order release Plots

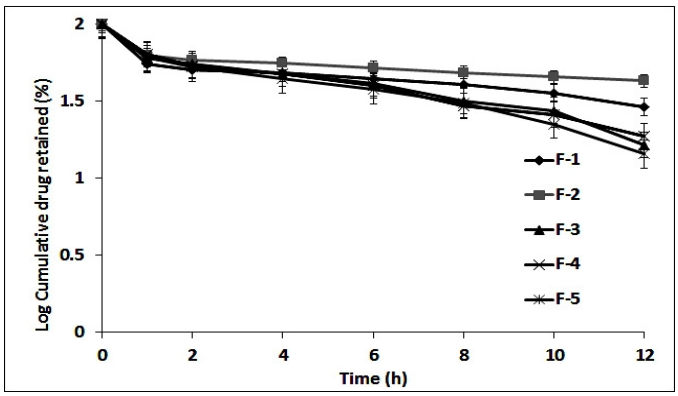

Fig. 8: First order release Plots

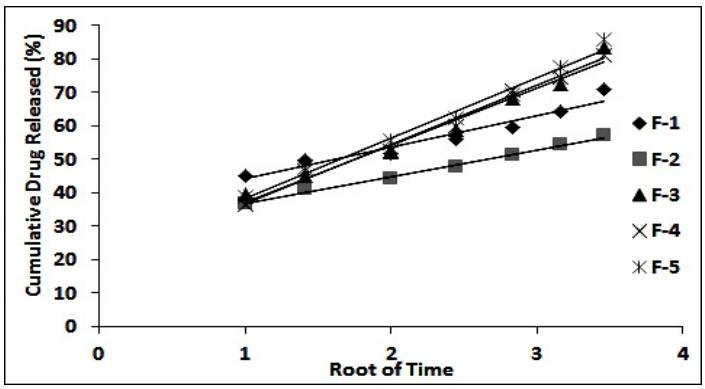

Fig. 9: Higuchi Plots

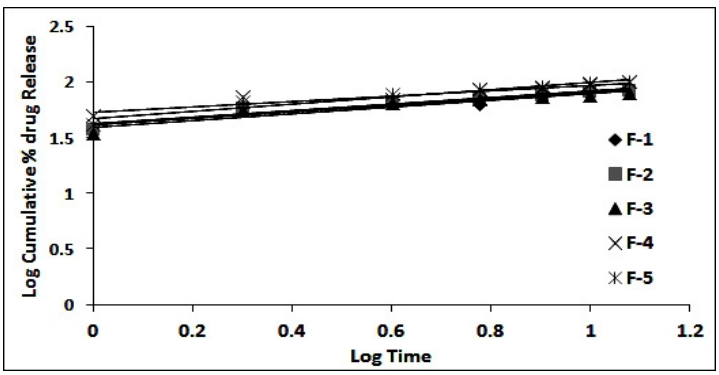

Fig. 10: Korsmeyer Peppas Plots

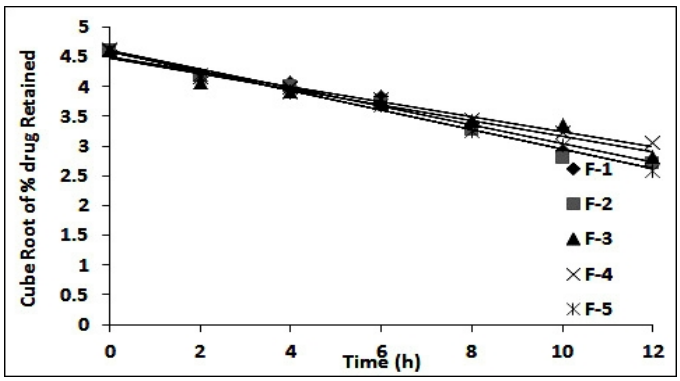

Fig. 11: Hixson-Crowell's Plots

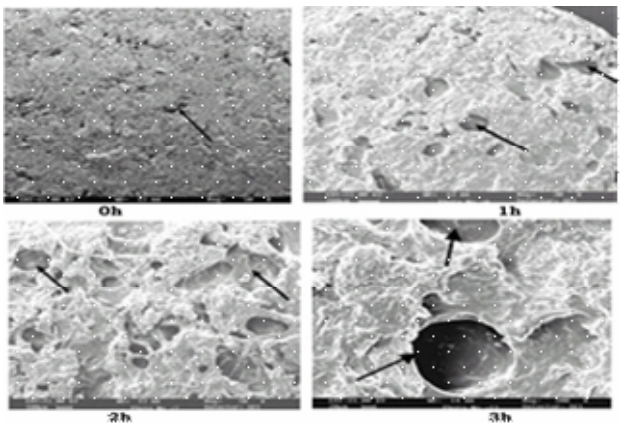

Fig. 12: SEM photographs of F-5 at time intervals of 0, 1st, 2nd and 3rd h of dissolution

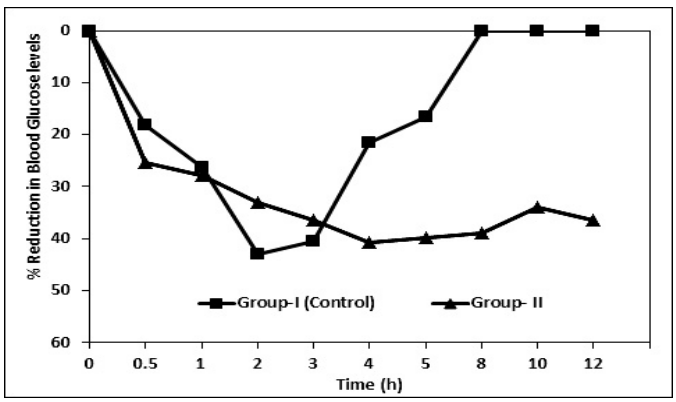

Fig. 13: Reduced blood glucose levels (%) of F-5 tablets vs. Glimepiride oral control

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