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Formulation and *In-vitro* Evaluation of Once-Daily Sustained-Release Matrix Tablets of Glipizide

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Abstract

The main aim of the present investigation was to develop matrix tablets of Glipizide with *Prosophis juliflora* gum and to study its functionality as a matrix forming agent for once daily sustained release tablet formulations. Physicochemical properties of dried powdered *Prosophis juliflora* gum were studied. Various formulations of Glipizide *Prosophis juliflora* gum were prepared. They formulated tablets found to have better uniformity of weight and the drug content with low SD values. The swelling behavior and release rate characteristics were studied. The dissolution study proved that the dried *Prosophis juliflora* gum can be used as a matrix forming material for making once daily Sustained release matrix tablets.

Key words: Glipizide, *Prosophis juliflora*, matrix tablets, once daily sustained release.

Introduction

Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus [1]. Glipizide is a weak acid (pKa = 5.9) which is practically insoluble in water and acidic solutions but as per the Biopharmaceutical Classification System (BCS) it is highly permeable (class 2). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life [2] of 2–4 h. Glipizide is reported to have a short biological half-life (3.4 ± 0.7 h) requiring it to be administered in 2 to 3 doses of 2.5 to 10 mg per day. Hence we have selected Glipizide for the development of once daily sustained release matrix tablets. The pharmacokinetics and dosage schedule supports once daily sustained release formulations for Glipizide for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance.

Prosophis juliflora (*Fabaceae* family) is a shrub or small weed plant grows all over the world [3]. The tree grows to a height of up to 12 m and has a trunk with a diameter of up to 1.2 m. The plant is characteristic thorns and yellow flowers. The bark exudates a good amount of gum round the year. The objective of present investigation is to design and evaluate once daily sustained release tablets of Glipizide using *Prosophis juliflora* gum as release retardant the release of drug.

Materials and Methods

Glipizide was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. *Prosophis juliflora* gum was collected from plants growing in local areas of Anantapur, India. The plant was authenticated at the Botany Department of Sri Krishnadevaraya University, Anantapur, India. Micro crystalline cellulose (Avicel) and Magnesium stearate were procured from SD Fine chemicals (Mumbai, India). All other chemicals used were of analytical reagent grade and double distilled water was used throughout the experiments.

Extraction of gum

The *Prosophis juliflora* gum was collected and soaked in water for 5–6 h, boiled for 30 minutes and left to stand for 1 h to allow complete extraction of the gum into the water. The gum was filtered using a multi-layer muslin cloth bag to remove the dirt and foreign matter from the solution. Acetone (three times the volume of filtrate) was added to precipitate the gum [4]. The gum was separated, dried in an oven at 35°C, collected, ground, passed through a # 80 sieve and stored in desiccator at 30 °C & 45% relative humidity till use. This gum was tested for flow properties [5] and the values were represented in table 1. All values were found to be satisfactory.

Table1: Flow properties of dried powdered *Prosophis juliflora* gum

Parameters	Value
Bulk density (g/ml)	0.578±0.08
Tapped density (g/ml)	0.788±0.03
Carr's index (%)	26.59±0.21
Hausner's ratio	1.24±0.04
Angle of repose (^{0})	29.45±1.68

Number of experiments (n)= 3

Preparation of Matrix Tablets

Once daily sustained release matrix tablets of Glipizide with *Prosophis juliflora* gum were prepared by using different drug: gum ratios viz. 1:0.5, 1:1.0, 1:1.5, 1:2.0 and 1:2.5. Different tablet formulations were prepared by direct compression technique and the formulations were named as GP-1, GP-2, GP-3, GP-4 and GP-5 respectively (table-2). All the powders were passed through mesh #80. Talc and magnesium stearate were finally added as glidant and lubricants. The drug and powdered gum were compressed (10 mm diameter, biconvex punches) using a single-punch tablet compression machine (Cadmach, Ahmedabad, India). Prior to the compression, the powdered gum was evaluated for several tests.

Evaluation of Powdered Gum

Angle of Repose

The angle of repose of powdered gum was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way

that the tip of the funnel just touched the apex of the heap of the granules. The granules were 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]

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

Where h and r are the height and radius of the powder pile respectively

Table 2: Formulae of *Prosophis juliflora* gum -Glipizide matrix tablets

Ingredients (mg)	Formulations				
	GP-1	GP-2	GP-3	GP-4	GP-5
Glipizide	10	10	10	10	10
Prosophis juliflora gum (dried)	5	10	15	20	25
Micro crystalline cellulose (Avicel)	180	175	170	165	160
Magnesium stearate	5	5	5	5	5
Total weight of tablet	200	200	200	200	200

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas [7].

LBD = Weight of the Powder/Volume of the packing

TBD = Weight of the powder /Tapped volume of the packing

Compressibility Index

The compressibility index of the gum powder was determined by Carr's compressibility index.

Carr's Index (%) = (TBD – LBD)/TBD x 100

Drug Content

An accurately weighed amount of powdered matrix tablets (250 mg) was extracted with water and the solution was filtered through 0.45µ membrane (Nunc, New Delhi, India). The absorbance was measured at 223 nm after suitable dilution.

The above physical properties of formulated matrix tablets were shown in table 3.

Table 3: Physical properties of *Prosophis juliflora* gum Glipizide matrix tablets

Sl. No	Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
1	GP-1	6.5±0.21	7.50±1.25	0.50±0.02	101.2±7.08
2	GP-2	5.9±0.15	8.10±1.40	0.85±0.05	100.6±6.24
3	GP-3	5.4±0.41	6.80±1.35	0.44±0.03	99.8±1.80
4	GP-4	6.4±0.39	6.50±1.45	0.62±0.06	99.6±2.50
5	GP-5	6.5±0.58	7.40±1.30	0.73±0.07	100.8±4.25

Number of trials (n) = 5

Evaluation of Tablets

Thickness

The thickness of the tablets was determined using a thickness screw gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used and average values were calculated.

Uniformity of Weight Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed according to the official method [8].

Hardness and Friability [9]

For each formulation, the hardness and friability of 10 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively

Estimation of Glipizide:

An ultraviolet spectrophotometric method based on measurement of absorbance at 223 nm in alkaline borate buffer of pH 7.4. The method obeyed Beer-Lambert's law in the concentration range of 1-20 µg/ml. When a standard drug solution was assayed for 6 times, the accuracy and Precision were found to be 0.96% and 1.17% respectively. No interference was observed from the excipients used.

Swelling behavior of Sustained release matrix tablets [10]

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulations GP-1, GP-2, GP-3, GP-4 and GP-5 were studied. One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 7.4. At the end of 1 hour, the tablet was withdrawn, kept on tissue paper and weighed then. This procedure was repeated till 12 hours. The % weight gain by the tablet was calculated by the following formula.

$$S.I = \{(M_t - M_0) / M_0\} \times 100$$

Where, S.I = swelling index, M_t = weight of tablet at time (t) and
M_o = weight of tablet at time t = 0. Swelling behavior of sustained release matrix tablets were represented in fig.1.

Fig.1. Swelling Index of *Prosophis juliflora* gum Glipizide matrix tablets

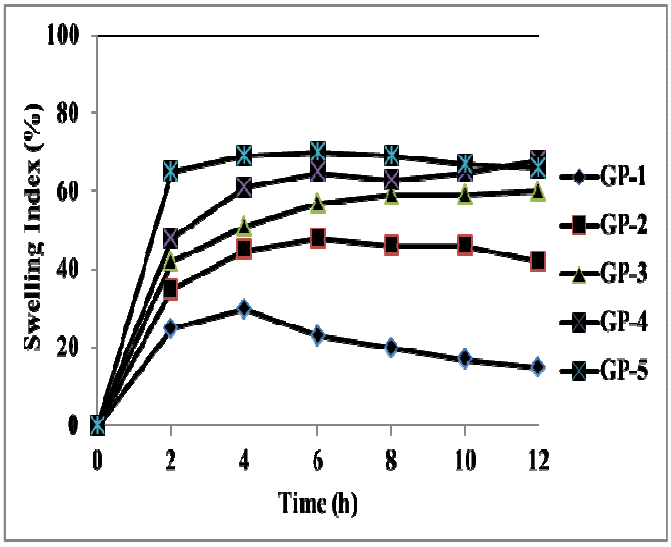


Table 4: Kinetic Values Obtained from *in-Vitro* Release Profile for Matrix Tablets of Glipizide (Zero order and First order)

Formulations	First Order Plot			Zero Order Plot		
	Slope (n)	Rate Constant K= -Slope X 2.303	Regression Co-efficient (r)	Slope (n)	Rate Constant Ko=-Slope	Regression Co-efficient (r)
GP-1	-0.00075	0.001727	-0.97846	0.003559	0.003559	0.99039
GP-2	-0.00049	0.001128	-0.99684	0.002955	0.002955	0.992511
GP-3	-0.00156	0.003593	-0.97261	0.005966	0.004966	0.996615
GP-4	-0.00153	0.003524	-0.99259	0.006498	0.006498	0.988149
GP-5	-0.00176	0.004053	-0.9823	0.006705	0.006705	0.995252

Table 5: Kinetic Values Obtained from *in-Vitro* Release Profile for Matrix Tablets of Glipizide (Higuchi, Korsmeyer Peppa's and Hixson-Crowell's models)

Formulation	Higuchi's		Korsmeyer Peppa's		Hixson Crowell's	
	Slope (n)	Regression Co-efficient (r)	Slope (n)	Regression Co-efficient (r)	Slope (n)	Regression Co-efficient (r)
GP-1	1.725046	0.971738	0.162456	0.930212	-0.00043	-0.98355
GP-2	1.865816	0.996448	0.171559	0.955678	-0.00032	-0.99574
GP-3	3.103433	0.985042	0.287578	0.947332	-0.00064	-0.99517
GP-4	3.227632	0.993489	0.313169	0.974429	-0.00083	-0.99441
GP-5	3.308515	0.993936	0.304558	0.968565	-0.00092	-0.99214

***In Vitro* Release Studies [11]**

The *in vitro* dissolution studies were carried out using USP apparatus type II (Tab-Machines, Mumbai, India) at 75 rpm. The dissolution medium consisted phosphate buffer pH 7.4 for 12 hours (900 ml), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer (Systronics UV spectrophotometer-117, Mumbai, India) at 223 nm using Chemstation software (Agilent Technologies, New Delhi, India). It

was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate (6 tablets in each set) and the mean values were plotted versus time with SDs of less than 3, indicating the reproducibility of the results. The kinetic data of formulated matrix tablets were shown in table 4 and 5.

Results and Discussion

Matrix tablets, each containing 10 mg of Glipizide, were prepared using dried gum of *Prosophis juliflora* in various drug: mucilage ratios (1:0.5, 1:1.0, 1:1.5, 1:2.0 and 1:2.5). Among these formulations, the release rate was increased in the following order: GP-1 > GP-2 > GP-3 > GP-4 > GP-5. To know the mechanism of drug release from these formulations, the data were treated using zero order, first order, Higuchi plot, Korsmeyer Peppa's plot and Hixson-Crowell's Model were shown in figure 2, 3, 4, 5 and 6respectively. The kinetic plots were perfectly fitting to the formulated *Prosophis juliflora* gum- Glipizide matrix tablets.

Fig.2. Zero order release Plot of *Prosophis juliflora* gum Glipizide matrix tablets

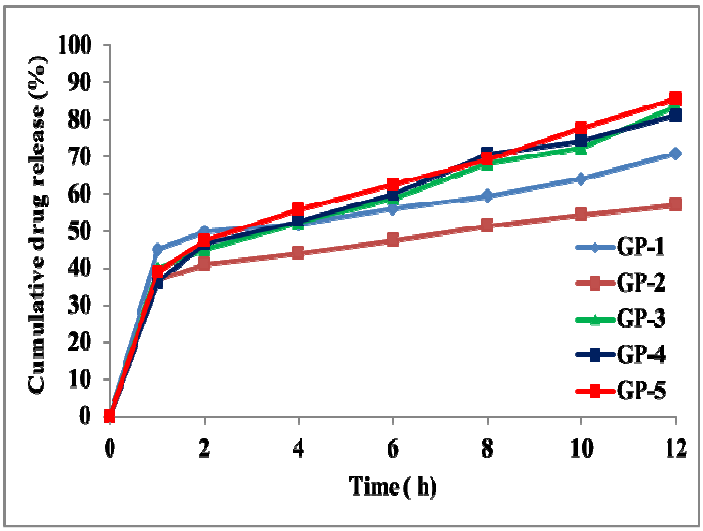


Fig.3. First order release Plot of *Prosophis juliflora* gum Glipizide matrix tablets

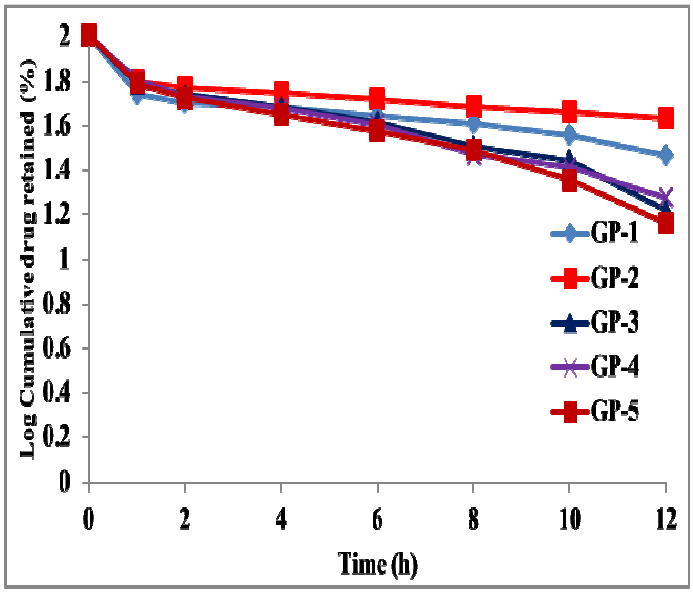


Fig.4. Higuchi Plot of *Prosophis juliflora* gum Glipizide matrix tablets

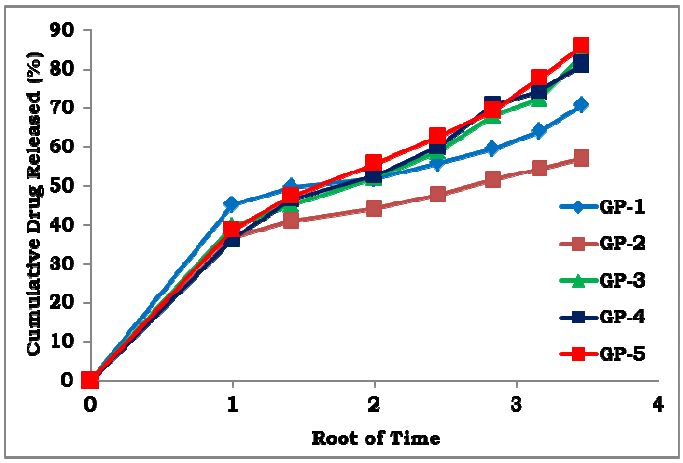


Fig.5. Korsmeyer Peppa's Plot of *Prosophis juliflora* gum Glipizide matrix tablets

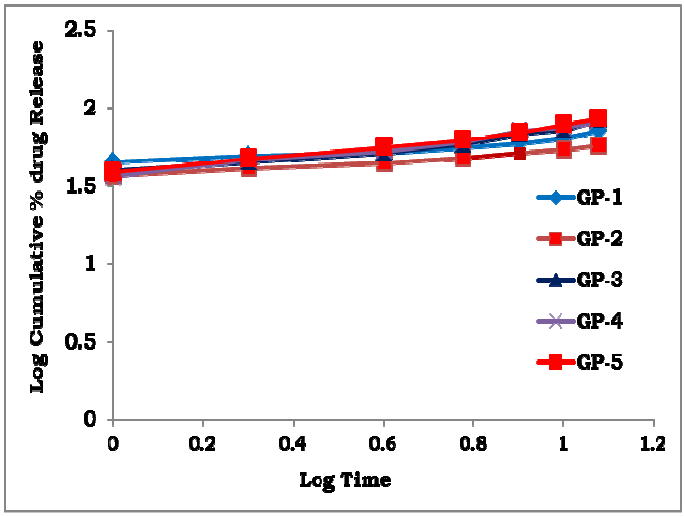


Fig.6. Hixson-Crowell Plot of *Prosophis juliflora* gum Glipizide matrix tablets

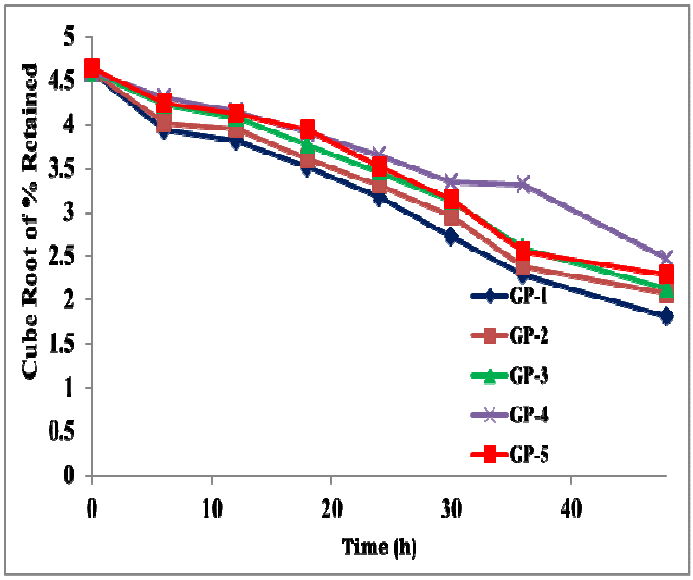


Fig.7. Infrared Spectrum of Glipizide Pure drug

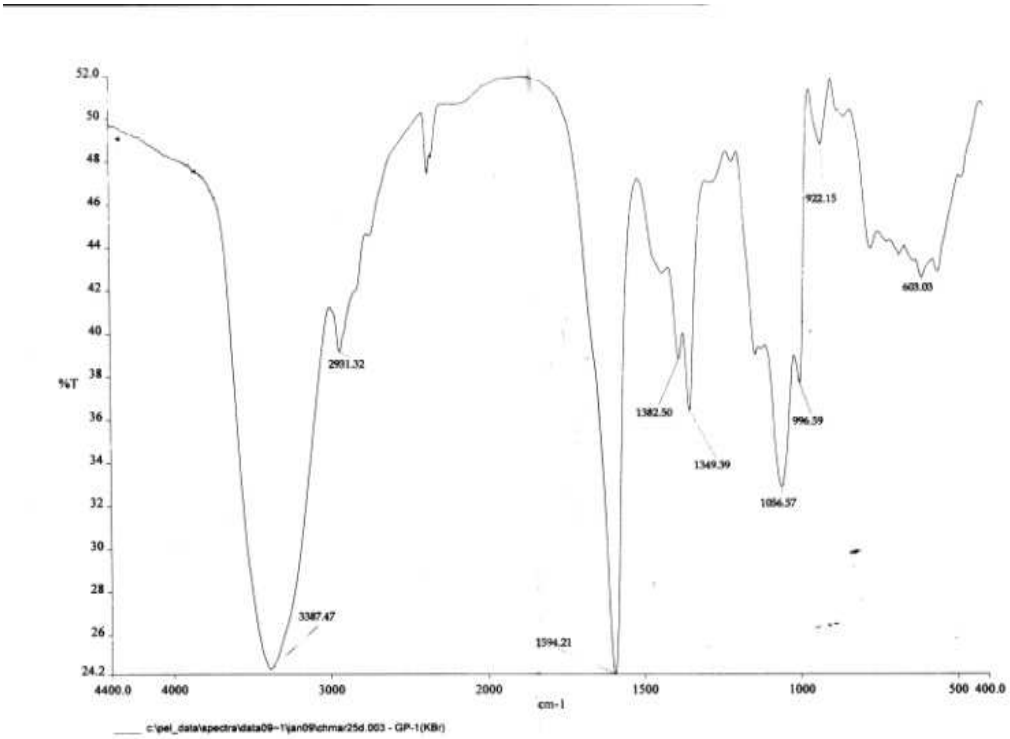


Fig.8. Infrared Spectrum of *Prosophis juliflora* gum

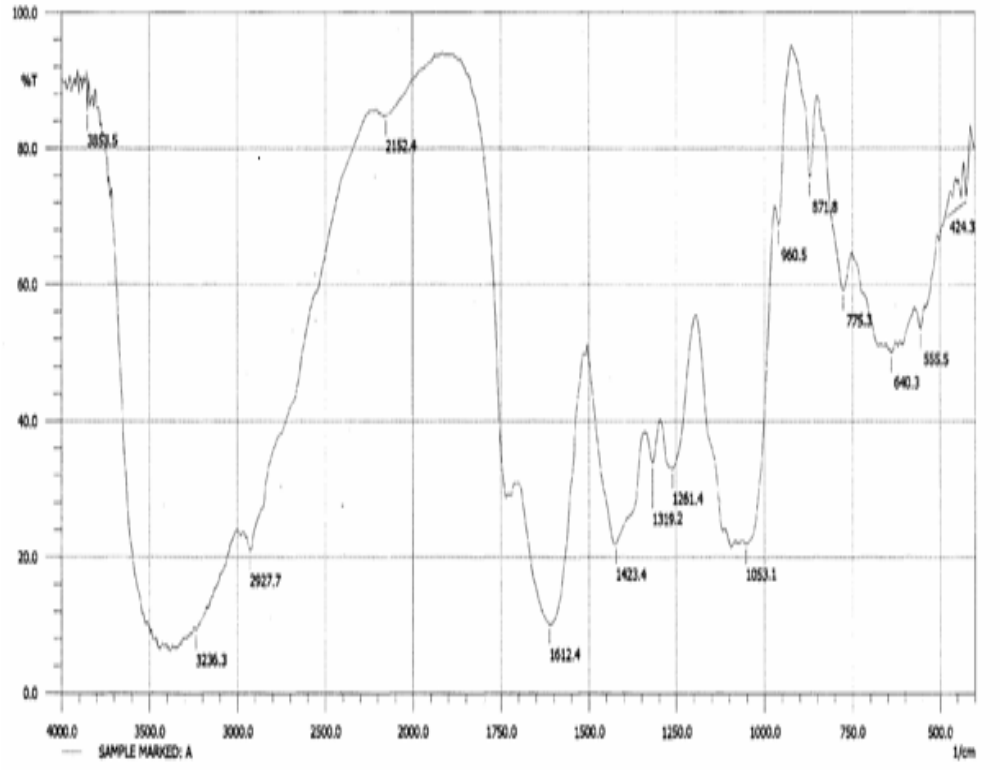
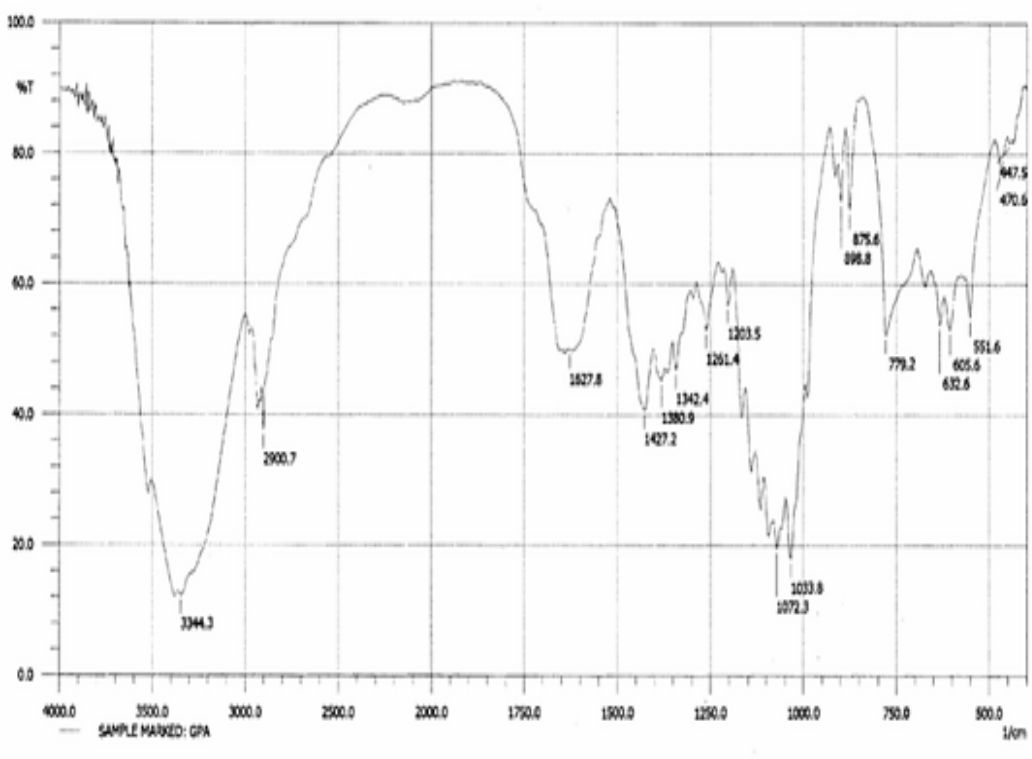


Fig.9. Infrared Spectrum of Glipizide with *Prosophis juliflora* gum



Infrared Spectrum of Glipizide Pure drug, Infrared Spectrum of *Prosophis juliflora*, Infrared Spectrum of Glipizide with *Prosophis juliflora* were shown in figure 7, 8 and 9. The graphs indicate there are no negative interactions between drug and matrix material used. This result shown that as the proportion of *Prosophis juliflora* gum increased, the overall time of release of the drug from the matrix tablet was also increased. Drug releases from matrix tablets were by drug dissolution, drug diffusion or a combination of both.

Conclusion

The present study revealed that *Prosophis juliflora* gum appears to be suitable for use as a release retardant in the manufacture of once daily sustained release matrix tablets because of its good swelling, good flow and suitability for matrix formulations. From the dissolution study, it was concluded that dried *Prosophis juliflora* gum can be used as an excipient for making once daily sustained release matrix tablets.

Acknowledgement

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