



Preparation and Evaluation of Glipizide *Azadirachta indica* Fruit Mucilage Poly Vinyl Pyrrolidone Sustained Release Matrix Tablets

Siva Prasad Reddy S¹, Hindustan Abdul Ahad², Sreenivasulu R², Kishore Kumar Reddy B², Krishna Mahesh CH², Kranthi G², Chandrasekhar A²

¹Balaji College of Pharmacy, Anantapur, Andhra Pradesh, INDIA.

²College of pharmacy, Sri Krishnadevaraya University, Anantapur, Andhra Pradesh, INDIA.

ABSTRACT

The purpose of the present investigation was to prepare matrix type sustained release tablets of Glipizide with Azadirachta indica fruit mucilage and Poly Vinyl Pyrrolidone. The polymers were studied for its functionality as a matrix forming property to sustain the Glipizide release from the dosage form. Physicochemical properties of dried powdered mucilage of Azadirachta indica fruit mucilage and Poly Vinyl Pyrrolidone blend were studied. Various formulations of Glipizide Azadirachta indica fruit mucilage and Poly Vinyl Pyrrolidone were prepared. The prepared tablets were found to have better pharmacopoeial parameters with low standard deviation values. The swelling behavior and release rate characteristics were studied. The in-vitro dissolution study proved that the dried Azadirachta indica fruit mucilage and Poly Vinyl Pyrrolidone combination can be used as a matrix forming polymers for making sustained release matrix tablets.

Key words: Glipizide, *Azadirachta indica*, Poly Vinyl Pyrrolidone, matrix tablets, sustained release.

INTRODUCTION

The mucilage of *Azadirachta indica* fruits clinically and experimentally proved anti-diabetic activity [1] and release retardant property in the present investigation.

Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus [2]. Glipizide is a weak acid ($pK_a = 5.9$) 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 of 2–4 h [3]. 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. The objective of present investigation is to prepare and evaluate sustained release tablets of Glipizide using *Azadirachta indica* fruits mucilage and Poly Vinyl Pyrrolidone combination as release retardant for making sustained release matrix tablets.

MATERIALS AND METHODS

Glipizide was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. *Azadirachta indica* fruits 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. Poly Vinyl Pyrrolidone, 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 mucilage

The fresh *Azadirachta indica* fruits were collected and washed with water. The outer shells were removed and the seeds with mucilage were placed in water for 5–6 h, boiled for 30 minutes and left to stand for 1 h 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 (in the quantities of three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40°C, collected, powdered, passed through a # 80 sieve and stored in desiccator at 30°C & 45% relative humidity till use [4]. The collected mucilage was tested for flow properties which were shown in Table 1. All values were found to be satisfactory.

Drug-Excipient compatibility studies

Differential Scanning Calorimetry (DSC)

DSC analysis was performed using Shimadzu DSC-60, Shimadzu Limited Japan. A 1:1 ratio of drug and excipient was weighed into aluminum crucible. The sample was analyzed by heating at a scanning rate of 20°C over a temperature range 20⁰-300⁰C under nitrogen environment.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The samples were scanned at wavelength 500 to 4000 cm⁻¹.

Preparation of matrix tablets

Sustained release matrix tablets of Glipizide with *Azadirachta indica* fruit mucilage and Poly Vinyl Pyrrolidone were prepared by using different drug: mucilage ratios as shown in Table 2, *Azadirachta indica* fruits mucilage and Poly Vinyl Pyrrolidone were used as matrix forming materials while microcrystalline cellulose as a diluent and Magnesium stearate as a lubricant [5]. All ingredients used were passed through a # 100 sieve, weighed and blended. The granules were prepared by wet granulation technique and compressed by using 10 mm flat faced punches. The compositions of formulations were showed in Table 2. These matrix tablets were evaluated for their physical properties as per I.P methods [6-8] which were shown in Table 3.

Swelling behavior of matrix tablets

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation GPA-1, GPA-2, GPA-3, GPA-4 and GPA-5 were studied. 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. The % weight gain by the tablet was calculated by formula [9].

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

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

M_0 = Weight of tablet at time 0. Swelling behavior of Sustained release matrix tablets were represented in Fig. 7.

Estimation of Glipizide

An ultraviolet spectrophotometric method based on measurement of absorbance at 223 nm in Phosphate buffer of pH 7.4. The method obeyed Beer-Lambert's law in the concentration range of 1-20 µg/ml. No interference was observed from the excipients used.

In vitro drug release studies

Release of Glipizide from the matrix tablets was studied in phosphate buffer of pH 7.4 (900 ml) using United States Pharmacopoeia (USP) 8-station Dissolution Rate Test Apparatus (Model Electro lab, TDT- 06T, Mumbai, India) with a rotating paddle stirrer at 50 rpm and $37^\circ \pm 0.5^\circ\text{C}$. A sample of Glipizide matrix tablets equivalent to 10 mg of Glipizide was used in each test. Samples of dissolution fluid were withdrawn through a filter (0.45 µm) at different time intervals and were assayed at 223 nm for Glipizide content [10] using a UV/ visible single-beam spectrophotometer-117 (Systronics Corporation, Mumbai, India). The drug release experiments were conducted in triplicate ($n = 3$). The *in vitro* release rates were showed in Fig. 8.

RESULTS AND DISCUSSION

The DSC of Glipizide Pure drug, *Azadirachta indica* fruits mucilage with Poly Vinyl Pyrrolidone and physical mixture were shown in Fig 1, 2 and 3 respectively. Infrared Spectrum of Glipizide Pure drug, Infrared Spectrum of *Azadirachta indica* fruits mucilage with Poly Vinyl Pyrrolidone, Infrared Spectrum of formulation was obtained. The FTIR spectra revealed that the formulation spectrum retains the peaks of drug used and these spectra were represented in Fig. 4, 5 and 6 respectively.

Matrix tablets, each containing 10 mg of Glipizide, were prepared using dried fruit mucilage of *Azadirachta indica* and Poly Vinyl Pyrrolidone in various drug: mucilage ratios. The Angle of repose of formulated blend was $29.45^\circ \pm 1.68$ indicating good flow, The Loose Bulk Density was found to be 0.578 ± 0.08 g/ml, Tapped Bulk Density was found to be 0.788 ± 0.03 g/ml, Compressibility index was ranged from $26.59 \pm 0.21\%$ and Hausner's ratio was found to be 1.24 ± 0.04 . All these values were shown in Table 1. The formulated tablets showed uniformity in swelling and the values plotted and shown in Fig.7. The thickness of formulated tablets were ranged from 5.7 ± 0.23 to 6.2 ± 0.19 mm, hardness was ranged from 5.85 ± 1.55 to 7.56 ± 0.52 kg/cm², the loss on friability was ranged from 0.19 ± 0.04 to 0.80 ± 0.01 % and drug content was ranged from 99.1 ± 3.66 to 100.8 ± 6.37 %. All these values were shown in Table 3. *In-vitro* drug release profile of Glipizide from formulated matrix tablets were studied using zero order, first order, Higuchi, Korsmeyer Peppas's and Hixson-Crowell's Models which were shown in Fig. 8, 9, 10, 11 and 12 respectively. The rate of release was faster in GPA-1 and slower in GPA-5. The kinetic plots were perfectly fitting to the formulated *Azadirachta indica* fruits mucilage,

Poly Vinyl Pyrrolidone - Glipizide matrix tablets. This result shown that as the proportion of *Azadirachta indica* fruits mucilage and Poly Vinyl Pyrrolidone 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 *Azadirachta indica* fruits mucilage and Poly Vinyl Pyrrolidone combination appears to be suitable for use as a release retardant in the manufacture of 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 *Azadirachta indica* fruits mucilage can be used as an excipient for making sustained release matrix tablets.

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Table 1: Flow properties of dried polymers blend fruit mucilage

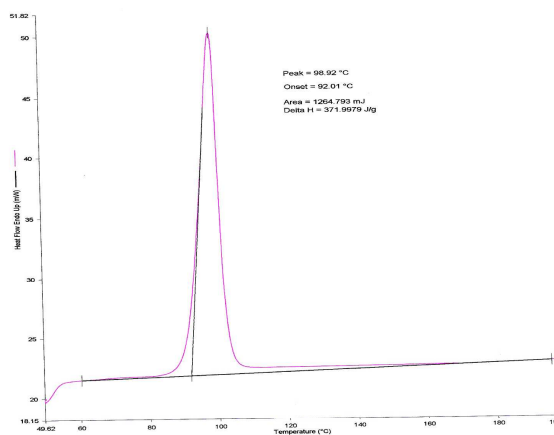
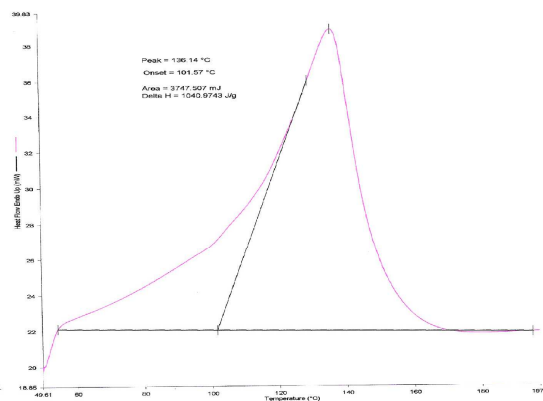
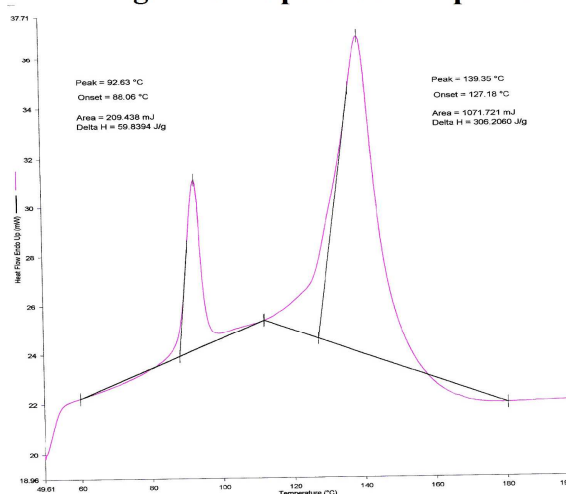
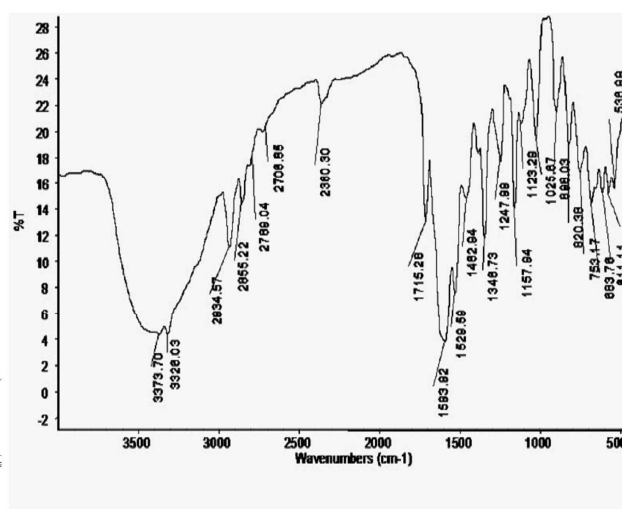
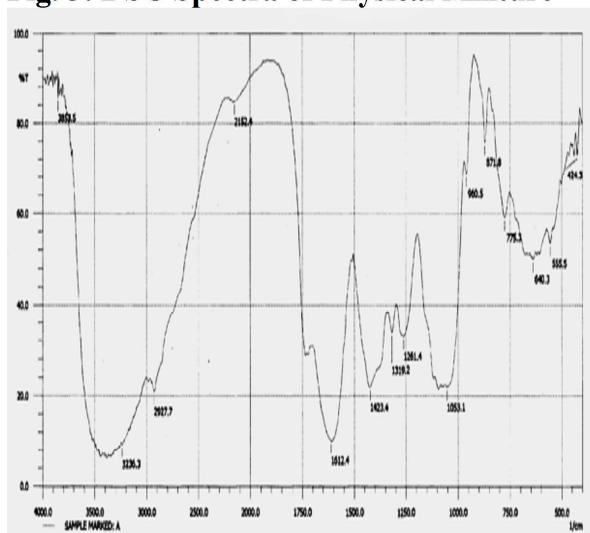
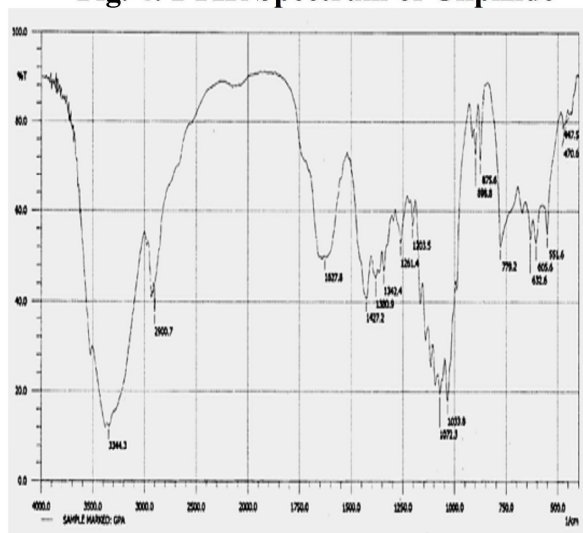
Parameters	Value
Loose Bulk Density (g/ml)	0.578±0.08
Tapped Bulk Density (g/ml)	0.788±0.03
Compressibility index (%)	26.59±0.21
Hausner's ratio	1.24±0.04
Angle of repose (°)	29.45±1.68
Number of experiments (n)= 3	

Table 2: Formulae of matrix tablets

Ingredients (mg)	Formulations				
	GPA-1	GPA-2	GPA-3	GPA-4	GPA-5
Glipizide	10	10	10	10	10
<i>Azadirachta indica</i> fruits mucilage	2	4	6	8	10
Poly Vinyl Pyrrolidone	2	4	6	8	10
Micro crystalline cellulose (Avicel)	181	177	173	169	165
Magnesium stearate	5	5	5	5	5
Total weight of tablet	200	200	200	200	200

Table 3: Physical properties of formulated matrix tablets

Sl. No	Formulation code	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
1	GPA-1	5.9±0.19	6.52±1.04	0.70±0.08	99.8±7.51
2	GPA-2	5.8±0.48	7.52±1.18	0.80±0.01	100.8±6.37
3	GPA-3	5.7±0.23	5.85±1.55	0.19±0.04	99.9±5.81
4	GPA-4	6.1±0.16	7.56±0.52	0.53±0.04	99.1±3.66
5	GPA-5	6.2±0.19	6.92±0.29	0.64±0.01	100.4±2.55
Number of trials (n) = 5					

**Fig.1: DSC Spectra of Glipizide****Fig. 2: DSC Spectra of polymer blend****Fig. 3: DSC Spectra of Physical Mixture****Fig. 4: FTIR Spectrum of Glipizide****Fig. 5: Infrared Spectrum of polymer blend****Fig. 6: FTIR Spectrum of the F5**

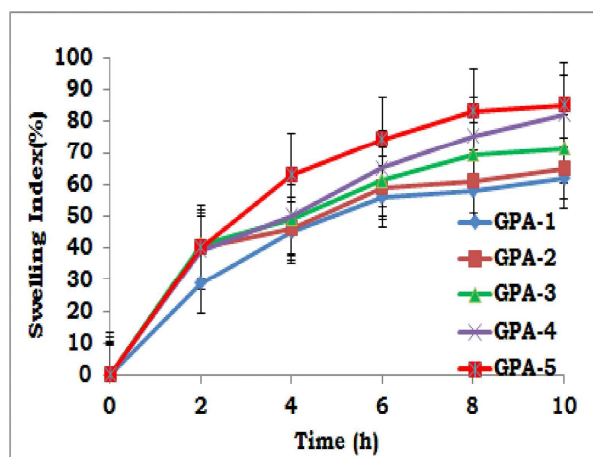


Fig. 7: Swelling Index of formulated tablets

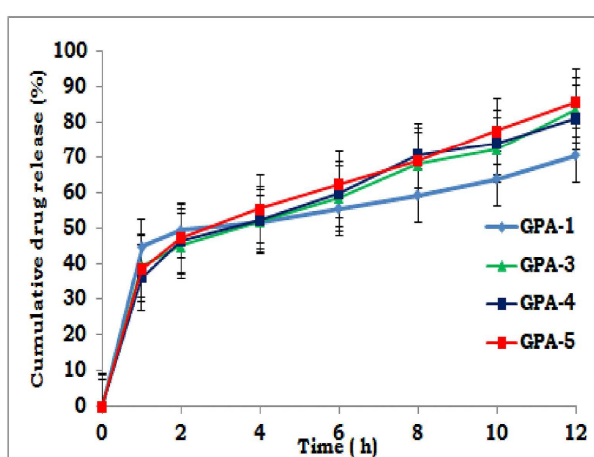


Fig. 8: Zero order release Plots

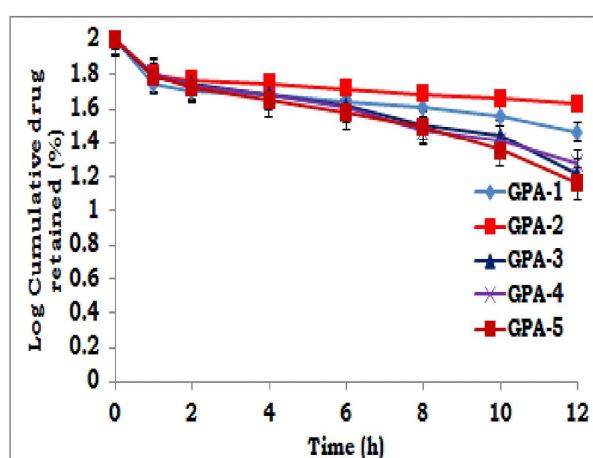


Fig. 9: First order release Plots

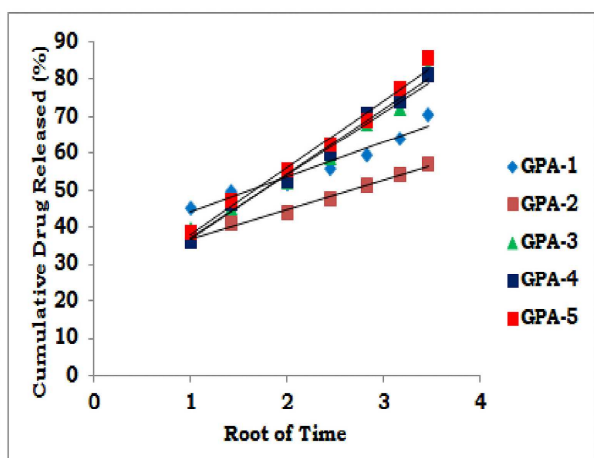


Fig. 10: Higuchi Plots

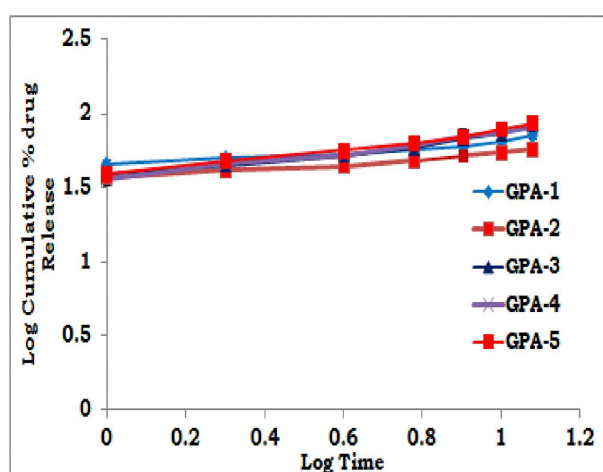


Fig. 11: Korsmeyer Peppas's Plots

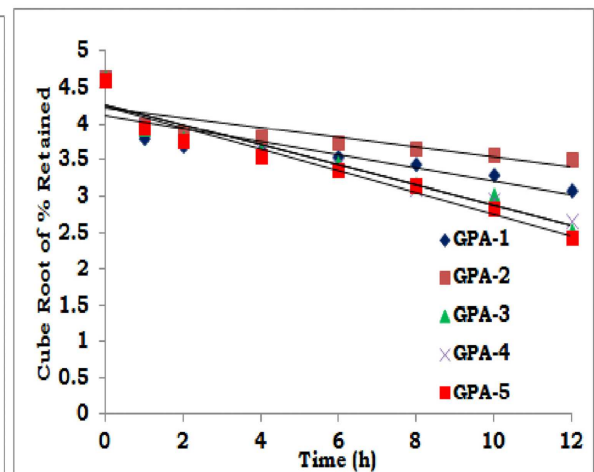


Fig. 12: Hixson-Crowell's Plots

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