REPORT

FORMULATION AND EVALUATION OF *FICUS GLOMERATA* MUCILAGE SUSTAINED RELEASE MATRIX TABLETS OF GLICLAZIDE

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ABSTRACT

The main aim of present investigation was to develop sustained release matrix tablets of Gliclazide using fruit mucilage from the plant *Ficus glomerata.* Varying ratios of drug and polymer viz. 1:0.25, 1:0.5, 1:0.75, 1:1.0 and 1:1.25 were selected for the study. The flow properties of powdered mucilage and physical properties of matrix tablets were performed. The swelling behavior and release rate characteristics were studied. The *in vitro* drug release data was analyzed by zero order, first order, Higuchi plot, Peppas plot and Hixon-Crowell Models. It was observed that as the proportion of mucilage increased the release of drug from the matrix tablets was retarded. Stability studies were conducted at 40±2ºC and RH 75±5% for 3 months indicates that Gliclazide was stable in the matrix tablets. The Differential Scanning Calorimetric (DSC) and Fourier Transform Infrared (FTIR) study revealed that there was no negative chemical interaction between drug and the mucilage used. From the dissolution study, it was concluded that dried *Ficus glomerata* mucilage can be used as an excipient for making sustained release matrix tablets.

Keywords: Gliclazide, *Ficus glomerata,* matrix tablets, sustained release.

INTRODUCTION

Gliclazide is a second-generation sulphonylurea oral hypoglycemic drug, used in the treatment of patients with non-insulin dependent diabetes mellitus. It stimulates insulin secretion by pancreatic β-cells. In the long-term, it reduces hepatic gluconeogenesis and increases insulin effects by acting at receptor or post-receptor sites (Dollery, 1991). The mechanism of action of Gliclazide is produced by blocking potassium channels in β-cells of Islets of Langerhans. The increase in calcium will initiate more insulin release from each beta cell. It increases the concentration of insulin in the pancreatic vein. By this, it decreases glucose concentration (Theodore *et al.,* 1991). Gliclazide is a weak acid (pKa = 5.9) practically insoluble in water and acidic environment but highly permeable (class 2) according to the Biopharmaceutical classification System (BCS) and soluble in alkali hydroxides. The oral absorption is uniform, rapid and complete with a bioavailability (Tripathi, 1999) of nearly 100%. Daily dose of Gliclazide is ranged from 80 to 320 mg per day. The pharmacokinetics and dosage schedule supports sustained release formulations for Gliclazide for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance. So, Gliclazide is selected as a model drug in this study.

In recent days natural mucilages and gums are gaining importance in formulating sustained release matrix tablets (Desai *et al.,* 2005; Kulkarni *et al.,* 2002). In the present study *Ficus glomerata* (*Fabaceae* family) fruit mucilage is used as release retardant in present study. *Ficus glomerata* is a tree, which grows all over the world. The tree grows to a height up to 12 m and has a trunk with a diameter of up to 1.2 m (Braby and Michael, 2005). The edible fruits of this plant were used in this study.

MATERIALS AND METHODS

Materials

Gliclazide was obtained as a gift sample from Dr. Reddy's Laboratories (Hyderabad, India). *Ficus glomerata* mucilage 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.

Methods

Extraction of mucilage

The *Ficus glomerata* mucilage 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 mucilage into the water. The mucilage was filtered using a multi-layer muslin cloth bag to remove the dirt and foreign matter from the solution. Acetone (in the quantities of three

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times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 35°C, collected, grounded, passed through a # 80 sieve and stored in desiccator at 30°C and 45% relative humidity till use (Baveja *et al.,* 1988). This mucilage was tested for flow properties (Carr, 1965; Lachman *et al.,* 1986; Martin, 2001; Mark *et al.,* 1977).

Preparation of matrix tablets

Sustained release matrix tablets of Gliclazide with *Ficus glomerata* fruit mucilage were prepared by using different drug: mucilage ratios viz. 1:0.25, 1:0.5, 1:0.75, 1:1.0 and 1:1.25. All the powdered materials were passed through mesh #80. Talc and magnesium stearate were finally added as a glidant and lubricants. The ingredients were directly compressed (10 mm diameter, biconvex punches) (Carter, 1986; Bhardwaj *et al.,* 2000; Stephen *et al.,* 2006; Timko and Lordi 1978) using a single-punch tablet compression machine (Cadmach, Ahmedabad, India) and named as FGG-1, FGG-2, FGG-3, FGG-4 and FGG-5 respectively, which were represented in table 1.

Evaluation for pre compression parameters

The dried powdered mucilage was evaluated for following pre compression parameters which were represented in table 2.

Angle of repose

The angle of repose of powdered mucilage was determined by the funnel method. The accurately weighed mucilage was 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 powdered mucilage. The powdered mucilage 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 Eq.1 (Martin, 2001).

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

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

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powdered mucilage, 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 Eq. 2 and 3 (IP, 2007).

LBD= Weight of the Powder/
Volume of the packing (2)

TBD= Weight of the powder/
Tapped volume of the packing (3)

Table 2: Flow properties of dried powdered mucilage and Gliclazide blend

Parameters	Value
Bulk density (g/ml)	0.578±0.08
Tapped density (g/ml)	0.788±0.03
Carr's index (%)	26.64±0.21
Hausner's ratio	1.24±0.04
Angle of repose (^{0})	29.45±1.68

All values were mentioned in mean ±S.D Number of trials (n)=3

Compressibility Index

The compressibility index of the powdered mucilage was determined by Eq. 4.

$$\text{Carr's Index (\%)} = (\text{TBD}–\text{LBD})/\text{TBD} \times 100 \quad (4)$$

Evaluation for post compression parameters

The formulated sustained release matrix tablets were evaluated for following post compression parameters which were represented in table 3.

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

Table 1: Formulae of matrix tablets

Ingredients (mg)	Formulations				
	FGG-1	FGG-2	FGG-3	FGG-4	FGG-5
Gliclazide	60	60	60	60	60
Ficus glomerata mucilage (dried)	15	30	45	60	75
Micro crystalline cellulose (Avicel)	120	105	90	75	60
Magnesium stearate	5	5	5	5	5
Total weight of tablet	200	200	200	200	200

were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed according to the official method.

Hardness and Friability

For each formulation, the hardness and friability of 10 tablets were determined (Lachman *et al.,* 1986) using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively.

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 226 nm after suitable dilution.

Estimation of Gliclazide

An ultraviolet spectrophotometric method based on measurement of absorbance at 226 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

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulations FGG-1, FGG-2, FGG-3, FGG-4 and FGG-5 were studied. One tablet from each formulation was kept in a Petri dish containing pH 7.4 phosphate buffer. At the end of 1 h, the tablet was withdrawn, kept on tissue paper and weighed. This procedure was repeated till 12 h (Killedar *et al.,* 2008). The swelling index was represented in fig. 1. The % weight gain by the tablet was calculated by Eq. 5.

$$S.I = \{(M_t - M_0) / M_0\} \times 100 \quad (5)$$

Where, S.I = swelling index, M_t = weight of tablet at time't' and M_o = weight of tablet at time t = 0.

In vitro Release Studies

The *in vitro* dissolution studies were carried out using USP apparatus type II (USP, 24), (Tab-Machines, Mumbai, India) at 100 rpm. The dissolution medium consisted phosphate buffer pH 6.8 for 12 h (900 ml), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophoto-meter (Systronics UV spectrophoto-meter-117, Mumbai, India) at wavelength of 226 nm after diluting suitably. 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 standard deviations less than 3, indicating the reproducibility of the results. The kinetic data of formulated matrix tablets were shown in table 4 and 5. The *in vitro* drug dissolution profile from optimized formulation (FGG-5) was compared with marketed formulation.

Accelerated stability studies

Optimized formulation FGG-5 were packed in blister and stored in ICH certified stability chambers maintained at 40±2°C and 75±5% RH for three months (Moffat, 1986). The matrix tablets were withdrawn periodically and evaluated for drug content and release studies.

RESULTS

The powdered blend (Gliclazide and mucilage) before compression was evaluated for angle of repose, LBD, TBD, compressibility index, Hausner's ratio and drug content. The results of angle of repose (^{0}) and compressibility index (%) were 29.45±1.68, 26.64±0.21 respectively. The results of LBD and TBD were 0.578±0.08, 0.788±0.03 respectively. The result of Hausner's ratio was 1.24±0.04. All these values were shown in table 2.

The thickness of the tablets was ranged from 5.4±0.41 to 6.5±0.58 mm. The average percentage deviation of 20 tablets of each formula was less than ±7.5%. Drug content was found to be uniform among different batches of the tablets and ranged from 99.6±2.50 to 101.2±7.08. The hardness of formulated tablets were ranged from

Table 3: Physical properties of *Ficus glomerata* fruit mucilage Gliclazide matrix tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
FGG-1	6.3±0.21	7.50±1.25	0.50±0.02	101.2±7.08
FGG-2	5.9±0.15	8.10±1.40	0.85±0.05	100.6±6.24
FGG-3	5.4±0.41	6.80±1.35	0.44±0.03	99.8±1.80
FGG-4	6.4±0.39	6.50±1.45	0.62±0.06	99.6±2.50
FGG-5	6.5±0.58	7.40±1.30	0.73±0.07	100.8±4.25

All values were mentioned in mean ±S.D. Number of trials (n)=3

Table 4: Kinetic Values for dissolution profile of formulated Gliclazide matrix tablets-I

Formulation	First order plot			Zero order plot		
	Slope (n)	Rate constant K= -Slope × 2.303	Regression co-efficient (r)	Slope (n)	Rate constant Ko=-Slope	Regression co-efficient (r)
FGG-1	-0.00075	0.001727	-0.97846	0.003559	0.003559	0.990391
FGG-2	-0.00049	0.001128	-0.99684	0.002955	0.002955	0.992511
FGG-3	-0.00156	0.003593	-0.97261	0.005966	0.004966	0.996615
FGG-4	-0.00153	0.003524	-0.99259	0.006498	0.006498	0.988149
FGG-5	-0.00176	0.004053	-0.98238	0.006705	0.006705	0.995252

Table 5: Kinetic values for dissolution Profile of formulated Gliclazide matrix tablets-II

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

6.50±1.45 to 8.10±1.40 kg/cm^2 and percentage friability of the tablets of all formulations were ranged from 0.44±0.03 to 0.85±0.05 (<1%), (table 3). The results of *in vitro* dissolution studies and its pharmacokinetic models of formulations FGG-1, FGG-2, FGG-3, FGG-4 and FGG-5 with *Ficus glomerata* fruit mucilage in 1:0.25, 1:0.5, 1:0.75, 1:1.0 and 1:1.25 ratios respectively were represented in fig. 2-6. The result of dissolution rate of matrix tablets was decreased with increase in mucilage concentration. Among the formulations, FGG-5 showed the least deviation from the theoretical release pattern.

Table 6: Comparison of dissolution profiles of optimized formulation (FGG-5) with marketed tablet

Time (h)	% of drug Release	
	FGG-5	Marketed tablet
2	41.02±2.58	35.6±6.65
4	58.06±3.35	48.5±3.78
6	69.59±1.72	64.2±6.58
8	80.26±5.42	70.2±4.59
10	90.35±5.87	82.1±3.56
12	99.98±2.56	98.7±1.59

All values were mentioned in mean ±S.D. Number of trials (n)=3.

Table 7: *In vitro* drug release (%) at 12th h of optimized formulation (FGG-5) before and after stability studies

Time (months)	*In vitro* drug release at 12th h (%)
0	99.98±2.56
1	99.91±3.65
2	99.62±4.15
3	99.23±2.23

All values were mentioned in mean ±S.D. Number of trials (n)=3

Table 8: Table of abbreviations used

Abreviation	Meaning
DSC	Differential Scanning Calorimetry
FTIR	Fourier Transform Infrared
BCS	Biopharmaceutical classification System
FGG-1, FGG-2, FGG-3, FGG-4 and FGG-5	*Ficus glomerata* and Glipizide formulations 1 to 5
LBD	Loose bulk density
TBD	Tapped bulk density
IP	Indian Pharmacopoeia
USP	United States Pharmacopoeia
ICH	International Conference on Harmonization
RH	Relative humidity

The hardness test of formulated tablets was ranged from 6.50±1.45 to8.10±1.40 kg/cm^2. The weight loss on friability was ranged from 0.44±0.03 to 0.85±0.05 %. To know the mechanism of drug release from these formulations, the data was plotted for zero order (fig. 2), first order (fig. 3), Higuchi plot (fig. 4), Peppas plot (fig. 5) and Hixson-Crowell (fig. 6). The *in vitro* drug dissolution profile from optimized formulation (FGG-5) was identical with marketed formulation, which was represented in table 6 and shown in fig. 7.

Results of Drug-polymer interaction studies

The characteristic peaks in FTIR spectrum of Gliclazide were also found in Gliclazide-*Ficus glomerata* fruit mucilage spectrum, which indicates that, there are no negative interactions between drug and polymers used.

Results of Accelerated stability studies

The tablets under stability studies were tested for *in-vitro* drug release every month for the period of three months. The *in-vitro* drug release was 99.98±2.56% (initial), 99.91±3.65% (after 1 month) 99.62±4.15% (after 2 month) and 99.23±2.23% (after 3 month). The results were tabulated in table 7.

The meanings of abbreviations used were showed in table 8.

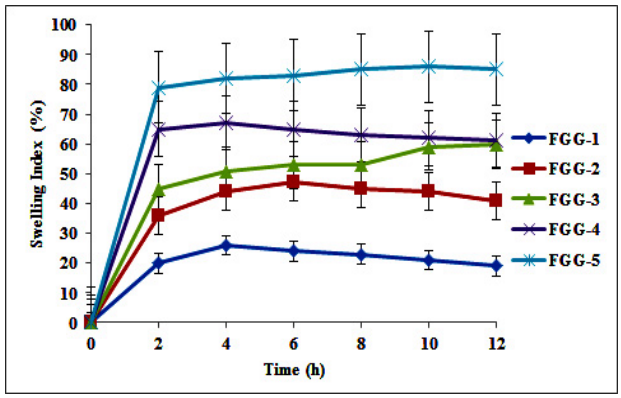

Fig. 1: Swelling Index of matrix tablets.

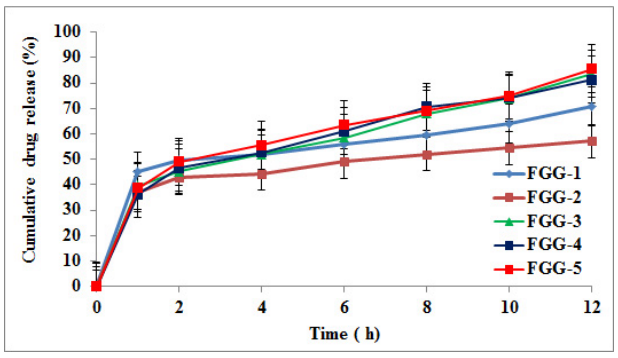

Fig. 2: Zero order release Plot of matrix tablets.

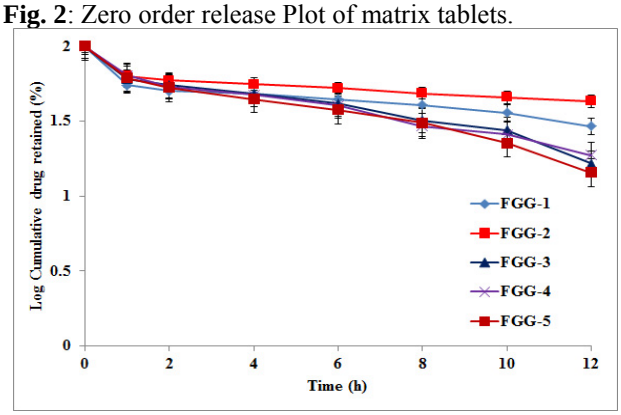

Fig. 3: First order release Plot of matrix tablets.

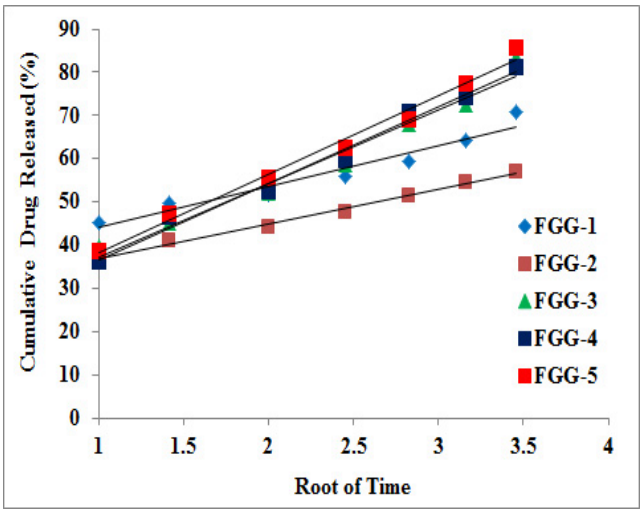

Fig. 4: Higuchi Plot of matrix tablets.

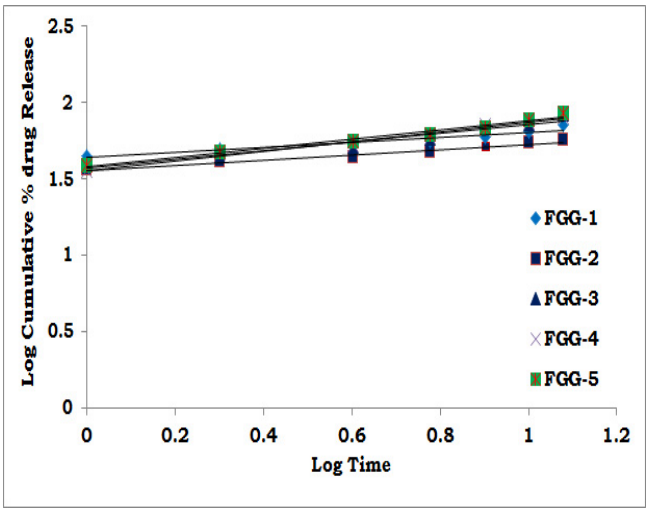

Fig. 5: Peppas Plot of matrix tablets.

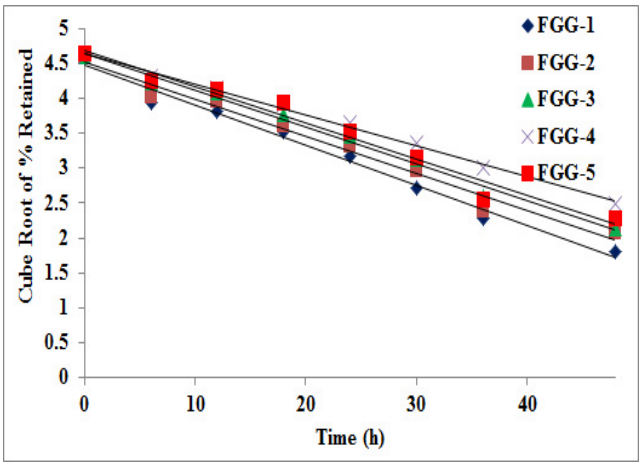

Fig. 6: Hixson-Crowell Plot of matrix tablets

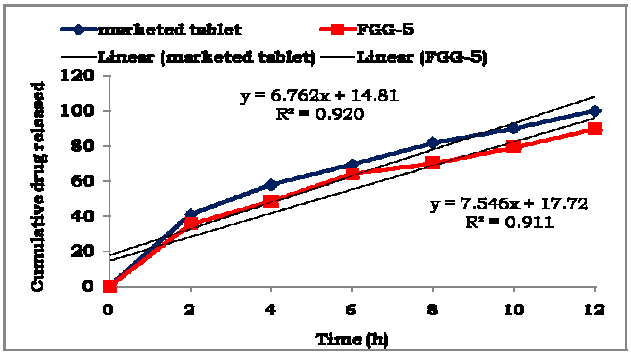

Fig.7: Plots of dissolution profile (FGG-5 with marketed)

DISCUSSION

The angle of repose, bulk densities and compressibility index values indicate that the *Ficus glomerata* fruit mucilage (dried) possessed satisfactory flow properties and compressibility index. The matrix tablets of different formulations showed uniform thickness. The percentage deviation in weights of all tablets was within the limits (±7.5%) as prescribed in Indian Pharmacopoeia and hence all matrix tablets passed the test for uniformity of weight as per Indian Pharmacopoeia. The hardness of for formulated tablets was which was more than 4 kg/cm^2 and passed the test for hardness. The weight loss in friability was less than 1% as per Indian Pharmacopoeia and passes the friability test. The formulated tablets showed uniformity in drug content. The rate of release was faster in FGG-1 and slower in FGG-5. The mathematical models for the *in vitro* dissolution data were perfectly fitting to the release pattern of formulated matrix tablets. The kinetic data revealed that the drug release from the formulation was by dissolution, diffusion or a combination of both. The formulated tablets showed elegant and uniform swelling pattern.

Results of accelerated stability studies showed that there was no remarkable change in the release profile of the Gliclazide from the formulated matrix tablets after the stability studies.

CONCLUSION

The present study revealed that *Ficus glomerata* fruit mucilage 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 *Ficus glomerata* fruit mucilage can be used as an excipient for making sustained release matrix tablets.

REFERENCES

Baveja SK, Rao KV and Arora J (1988). Examination of natural mucilages as sustaining agents in tablet dosage forms. *Indian J. Pharm. Sci.* **50**(2): 89-92.

Bhardwaj TR, Kanwar M and Lal R (2000). Natural gums and modified natural gums as sustained release carriers. *Drug Dev. Ind. Pharm.*, **26**: 1025-1038.

Braby, Michael F (2005). The complete field guide to butterflies of Australia. Collingwood, Victoria: CSIRO Publishing, p.194.

Carr RL (1965). Evaluating flow properties of solids, *Chem. Eng*. **72**: 163-168.

Carter SJ (1986). Tutorial Pharmacy, CBS Publishers and Distributors, New Delhi, India, pp.211-233.

Desai A, Shidhaye S and Malke S (2005). Use of natural release retardant in drug delivery system. *Indian Drugs*, **42**: 565-575.

Dollery SC (1991). Therapeutic Drugs. Churchill Livingstone, London, p.A21.

Indian Pharmacopoeia (2007). Controller of Publications, Ministry of Health and Family Welfare, Government of India, New Delhi.

Killedar SG, Bhagwat DA, Adnaik RS, More HN and D'souza JI (2008). optimization of method for determination of swelling factor of Ispaghula seeds. *Indian Drugs,* **45**(4): 310-313.

Kulkarni GT, Gowthamarajan K, Rao BG and Suresh B (2002). Evaluation of binding properties of selected natural graecum mucilages. *Indian Drugs*, **39**: 422-425.

Lachman L, Lieberman HA and Kanig JL (1986). The Theory and Practice of Industrial Pharmacy. 3rd ed., Lea & Febiger, Philadelphia, PA, pp.293-45.

Mark Woolfe L, Martin Chapli F and Gifty Otchere (1917). Studies on the Mucilages Extracted from Okra Fruits (*Hibiscus esculentus* L.) and Baobab Leaves (*Adansonia digitata* L.), *J. Sci. Fd Agric*. **28**:519-529.

Martin A (2001). Physical Pharmacy: Lippincott Williams & Wilkins, Baltimore, MD, pp.423-454.

Moffat AC (1986). Clarke's Isolation and Identification of Drugs, 2nd ed. The Pharmaceutical Press, London.

Stephen M and Churms SC (2006). Introduction. *In*: Food Polysaccharides and their Application. Edi., AM Stephen, GO Phillips PA Williams. Taylor and Francies, CRC Press, New York, pp.1-24.

Theodore WR, Alan SN, Taylor P, Gilman AG, (eds) (1991). Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed, McGraw-Hill, New York, p.1484.

Timko, RJ and Lordi NG (1978). *In vitro* evaluation of three commercial sustained release papaverine hydrochloride products, *J. Pharm. Sci.*, **67**: 496.

Tripathi KD (1999). Essentials of Medical Pharmacology. 4th ed. Medical Publishers (Pvt.) Ltd, New Delhi, pp.142-44.

United States Pharmacopoeia 24, NF 19 (2000). United States Pharmacopoeial Convention, Rockville, M.D. Asian Edi., 1462-5, pp.1913-1914.