

FORMULATION AND EVALUATION OF ONCE-DAILY SUSTAINED RELEASE ACECLOFENAC *PROSOPHIS JULIFLORA* GUM MATRIX TABLETS

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Abstract

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

Key words: Aceclofenac, *Prosopis juliflora*, matrix tablets, once daily sustained release.

INTRODUCTION

Aceclofenac is a potent non-steroidal anti-inflammatory drug, which is a commonly prescribed drug for the treatment of patients suffering with pain, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis [1]. It is a weak acid (pKa = 4.7) practically insoluble in water and acidic environment but highly permeable (class 2) according to the Biopharmaceutical classification System (BCS). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life [2] of 2–4 h. Aceclofenac is reported to have a short biological half-life (3.4 ± 0.7 h) requiring it to be administered in 100mg twice daily. Hence we have selected Aceclofenac for the development of once daily sustained release matrix tablets. The pharmacokinetics and dosage schedule supports once daily sustained release formulations for Aceclofenac for better control of pain, enhance clinical efficacy and patient compliance. *Prosopis 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 has 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 Aceclofenac using *Prosopis juliflora* gum as release retardant.

MATERIALS AND METHODS

Materials:

Aceclofenac was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. *Prosopis 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. Microcrystalline 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 gum: [4]

The *Prosopis 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. 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 *Prosopis 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 (°)	29.45±1.68
Number of experiments (n)= 3	

Preparation of Matrix Tablets

Once daily sustained release matrix tablets of Aceclofenac with *Prosopis juliflora* gum were prepared by using different drug: gum ratios viz. 1:0.250, 1:0.375, 1:0.500, 1:0.675 and 1:0.750. Different tablet formulations were prepared by direct compression technique and the formulations were named as AP-1, AP-2, AP-3, AP-4 and AP-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.

Table 2: Formulae of *Prosopis juliflora* gum - Aceclofenac matrix tablets

Ingredients (mg)	Formulations				
	AP-1	AP-2	AP-3	AP-4	AP-5
Aceclofenac	200	200	200	200	200
<i>Prosopis juliflora</i> gum (dried)	50	75	100	125	150
Microcrystalline cellulose (Avicel)	245	220	195	170	145
Magnesium stearate	5	5	5	5	5
Total weight of tablet	500	500	500	500	500

EVALUATION

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

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.

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

Drug Content

An accurately weighed amount of powdered matrix tablets (500 mg) was extracted with water and the solution was filtered through 0.45 μ membrane (Nunc, New Delhi, India). The absorbance was measured at 275 nm after suitable dilution.

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

Table 3: Physical properties of *Prosopis juliflora* gum Aceclofenac matrix tablets

Formulation	Thickness (mm)	Hardness (Kg/cm ²)	Friability (%)	Drug content (%)
AP-1	6.9 \pm 0.56	7.50 \pm 1.15	0.40 \pm 0.05	100.9 \pm 5.08
AP-2	5.9 \pm 0.15	6.10 \pm 1.40	0.85 \pm 0.08	100.6 \pm 6.24
AP-3	5.3 \pm 0.41	6.80 \pm 1.58	0.44 \pm 0.07	100.8 \pm 4.80
AP-4	6.4 \pm 0.39	7.50 \pm 1.45	0.52 \pm 0.06	99.6 \pm 5.50
AP-5	6.5 \pm 0.58	7.40 \pm 1.30	0.73 \pm 0.07	100.8 \pm 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

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 tablets equivalent to 6.5g were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the

Roche friabilator (Campbell Electronics, Mumbai, India), respectively.

Estimation of Aceclofenac: An ultraviolet spectrophotometric method based on measurement of absorbance at 245 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]

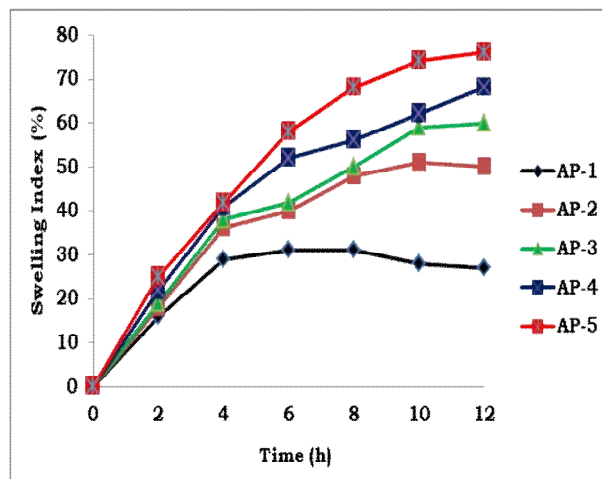
The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulations AP-1, AP-2, AP-3, AP-4 and AP-5 were studied. One tablet from each formulation was kept in a Petri dish containing pH 7.4 phosphate buffer. At the end of 1 hour, the tablet was withdrawn, kept on tissue paper and weighed then. This procedure was repeated till 12 h. 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_0 = weight of tablet at time t = 0. Swelling behavior of sustained release matrix tablets were represented in figure 1.

Figure.1. Swelling Index of *Prosopis juliflora* gum Aceclofenac matrix tablets



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.

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

Formulations	Zero Order Plot			First Order Plot		
	Slope (n)	Rate Constant Ko= -Slope	Regression Co-efficient (r)	Slope (n)	Rate Constant K= -Slope X 2.303	Regression Co-efficient (r)
AP-1	0.003559	0.003559	0.99039	-0.00075	0.001727	-0.97846
AP-2	0.002955	0.002955	0.992511	-0.00049	0.001128	-0.99684
AP-3	0.005966	0.004966	0.996615	-0.00156	0.003593	-0.97261
AP-4	0.006498	0.006498	0.988149	-0.00153	0.003524	-0.99259
AP-5	0.006705	0.006705	0.995252	-0.00176	0.004053	-0.98238

Table 5: Kinetic Values Obtained from *In-Vitro* Release Profile for Matrix Tablets of Aceclofenac (Higuchi, Korsmeyer Peppas and Hixon-Crowell's models)

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

RESULTS AND DISCUSSION

Matrix tablets, each containing 200 mg of Aceclofenac, were prepared using dried gum of *Prosopis juliflora* in various drug: mucilage ratios (1:0.250, 1:0.375, 1:0.500, 1:0.675 and 1:0.750). Among these formulations, the release rate was increased in the following order: AP-1 > AP-2 > AP-3 > AP-4 > AP-5. To know the mechanism of drug release from these formulations, the data were treated using zero order, first order, Higuchi plot, Korsmeyer Peppas's plot and Hixon-Crowell Model were shown in figure 2, 3, 4, 5 and 6 respectively. The kinetic plots were perfectly fitting to the formulated *Prosopis juliflora* gum-Aceclofenac matrix tablets. Infrared Spectrum of Aceclofenac Pure drug, Infrared Spectrum of *Prosopis juliflora*, Infrared Spectrum of Aceclofenac with *Prosopis juliflora* were shown in fig. 7, 8 and 9. The graphs indicate there are no negative interactions between drug and matrix material used. This result has shown that as the proportion of *Prosopis 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.

Figure 2. Zero order release Plot of *Prosopis juliflora* gum Aceclofenac matrix tablets

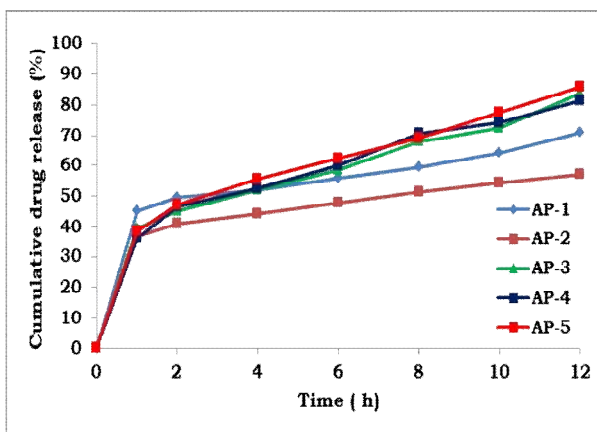


Figure 3. First order release Plot of *Prosopis juliflora* gum Aceclofenac matrix tablets

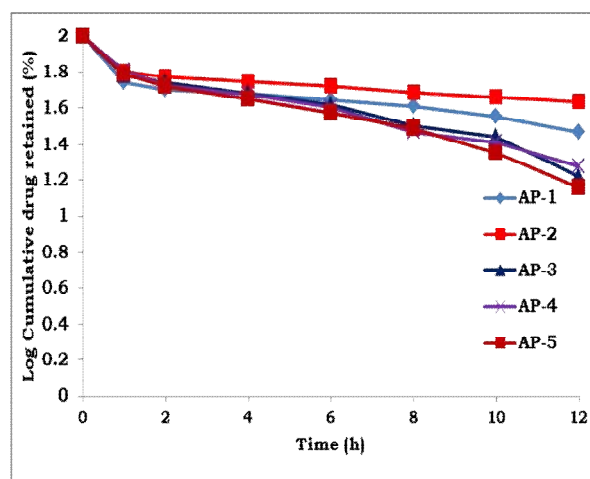


Fig.4. Higuchi Plot of *Prosopis juliflora* gum Aceclofenac matrix tablets

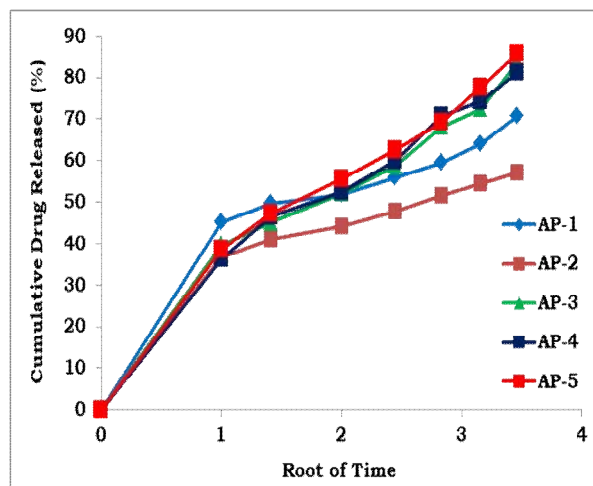


Figure 5. Korsmeyer Peppas's Plot of *Prosopis juliflora* gum Aceclofenac matrix tablets

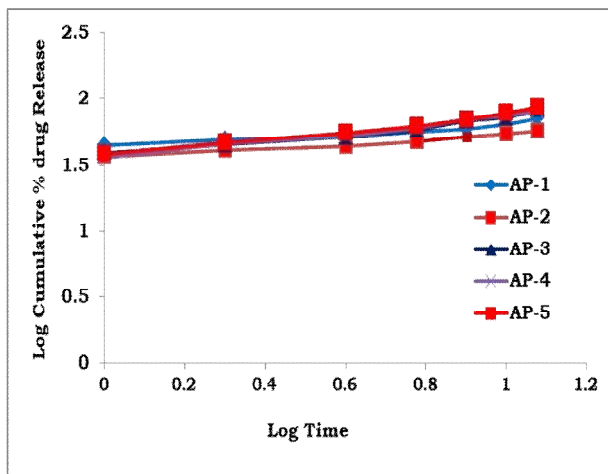


Figure 6. Hixon-Crowell Plot of *Prosopis juliflora* gum Aceclofenac matrix tablets

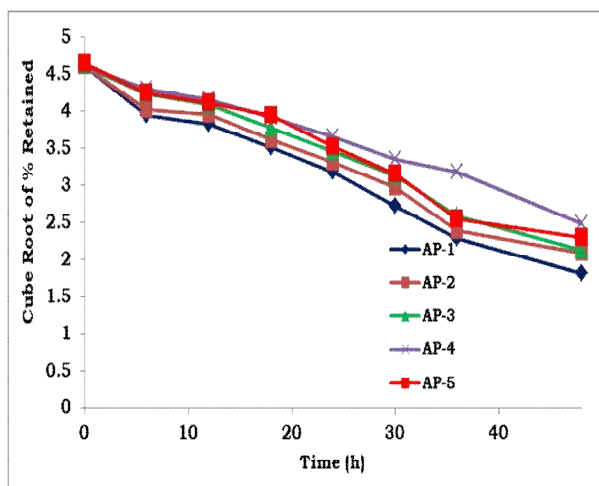


Figure 7. Infrared Spectrum of Aceclofenac Pure drug

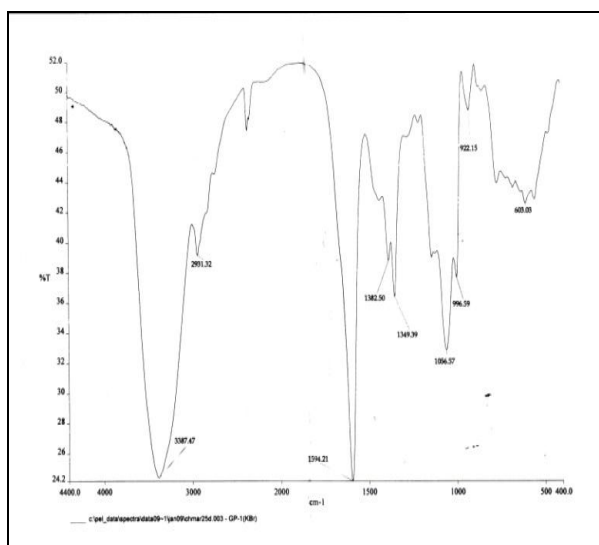


Figure 8. Infrared Spectrum of *Prosopis juliflora* gum

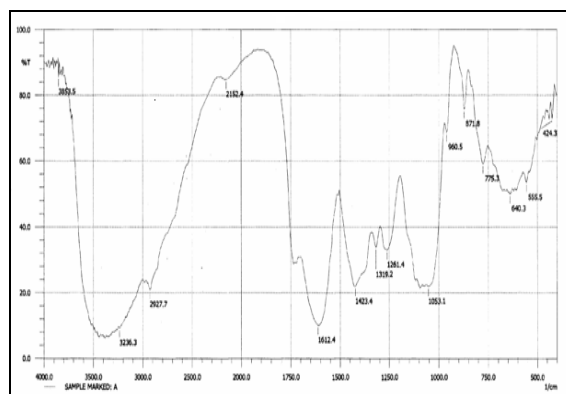
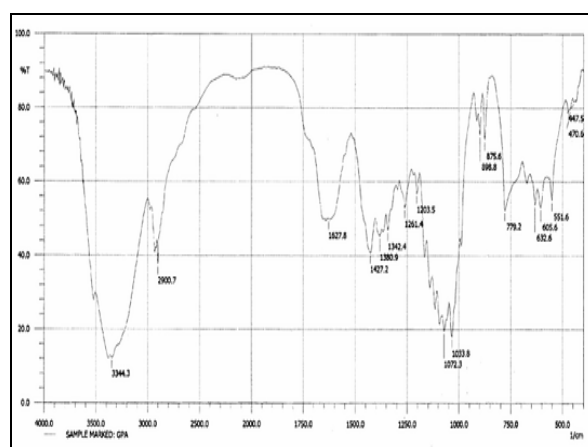


Figure 9. Infrared Spectrum of Aceclofenac with *Prosopis juliflora* gum



CONCLUSION

The present study revealed that *Prosopis 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 *Prosopis juliflora* gum can be used as an excipient for making once daily sustained release matrix tablets.

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REFERENCES

- [1] Theodore WR, Alan SN, Taylor P, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed, New York, NY: McGraw-Hill; 1991; 1484
- [2] Kahn CR, Shechter Y. In: Theodore WR, Alan SN, Taylor P, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, NY: McGraw-Hill; 1991; 712.

- [3] Duke, James A. (1983): *Prosopis juliflora* DC; Handbook of Energy Crops. Purdue University Center for New Crops & Plant Products, Version of 1998
- [4] S.K. Baveja, K.V. Rao, and J. Arora, "Examination of Natural Gums and Mucilages as Sustaining Agents in Tablet Dosage Forms," *Indian J. Pharm. Sci.* 50 (2), 1988; 89–92
- [5] R.L. Carr, Evaluating flow properties of solids, *Chem. Eng.* 72 1965; 163–168.
- [6] Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, eds. *Tutorial Pharmacy*. New Delhi, India: CBS Publishers and Distributors; 1986; 211-233.
- [7] Martin A. Micromeritics. In: Martin A, ed. *Physical Pharmacy*. Baltimore, MD: Lippincott Williams & Wilkins; 2001; 423-454.
- [8] Pharmacopoeia of India. New Delhi: Ministry of Health and Family Welfare, Government of India, Controller of Publications; 2007
- [9] Lachman L, Lieberman HA, Kanig JL. *The Theory and Practice of Industrial Pharmacy*; Philadelphia, PA: Lea and Febiger; 1987; 317-318.
- [10] Killedar S.G, Bhagwat D.A, Adnaik R.S, More H.N. and D'souza J.I. "optimization of method for determination of swelling factor of Ispaghula seeds," *Indian Drugs* 45 (4) April 2008; 310–313
- [11] The United State Pharmacopoeia 24, NF 19, United State pharmacopoeial convention, Rockville, M.D. Asian Edi., 2000; 1462-5, 1913-4
