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Fabrication and evaluation of Nimesulide Azadirachta indica fruit mucilage based sustained release matrix tablets

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Abstract: The main purpose of the present investigation was to develop sustained release matrix tablets of Nimesulide with the fruit mucilage of *Azadirachta indica* and to study its functionality as a matrix former for sustained release of Nimesulide from tablet formulations. Physicochemical properties of dried powdered mucilage of *Azadirachta indica* fruits were studied. Various formulations of Nimesulide with *Azadirachta indica* fruit mucilage were prepared by direct compression technique. The formulated matrix tablets were found to have better uniformity of weight and drug content with low statistical deviation. The swelling behavior and *in vitro* release rate characteristics were studied. The dissolution study and pharmacokinetic studies proved that the dried *Azadirachta indica* fruit mucilage can be used as a matrix forming material for making sustained release Nimesulide matrix tablets.
Key words: *Azadirachta indica*, Nimesulide, matrix tablets, sustained release.

Introduction

Nimesulide (*N*-4'-nitro-2'-phenoxyphenyl methane sulfonamide) is a weakly acidic Non-Steroidal Anti-inflammatory drug (NSAID). It differs from other NSAIDs in that its chemical structure contains a sulfonamide moiety as the acidic group rather than a carboxylic group. Nimesulide shows high anti-inflammatory, antipyretic and analgesic activities in addition to low toxicity, a moderate incidence of gastric side effects and a high therapeutic index[1]. Nimesulide has a biological half-life of 1.8-4.7h. The oral absorption is uniform, rapid and complete. The normal adult dose of Nimesulide is usually 100-200 mg[2].

Material and Methods

Materials

Nimesulide was obtained as a gift sample from the Dr. Reddy's Laboratories, Hyderabad, India. The *Azadirachta indica* fruits were collected from the plants growing in local areas of Anantapur, India. The plant was authenticated at the Department of Botany, Sri Krishnadevaraya University, Anantapur, India. Micro crystalline cellulose 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 fresh *Azadirachta indica* fruits were collected and separately washed with purified water to remove dirt and debris. The outer rind was removed and the inner pulp with seeds were soaked in water for 5–6 h, boiled for 30 min 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 and seeds 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 35°C, collected, grounded, passed through a # 80 sieve and stored in desiccators at 30 °C & 45% relative humidity till use [3]. This dried mucilage was tested for viscosity and flow properties (Table 1and 2). All values were found to be satisfactory.

Preparation of Sustained release matrix tablets

Sustained release matrix tablets of Nimesulide with *Azadirachta indica* fruit mucilage were prepared by using different drug: mucilage ratios viz. 1:0.2, 1:0.4, 1:0.6, 1:0.8 and 1:1.0. *Azadirachta indica* fruits mucilage was used as matrix forming material while microcrystalline cellulose as a diluent and magnesium stearate as a lubricant. All ingredients used were passed through a # 100 sieve, weighed and blended. The above formulations were compressed by a direct compression technique using 12 mm flat faced punches (Table 3). These matrix tablets were evaluated for their physical properties[4, 5, and 6] like general appearance, thickness, hardness, friability, uniformity of weight and uniformity of drug content, as per I.P. method (Table 4).

Swelling behavior of sustained release matrix tablets [7, 8, and 9]

The swelling behavior of formulations AIN-1, AIN-2, AIN-3, AIN-4 and AIN-5 were studied. One tablet from each formulation was kept in a Petri dish containing pH 8.4 alkaline borate buffer. At the end of 1 h, the tablet was withdrawn, kept on tissue paper and weighed. The tablets were weighed every 2 h till the end of 12 h. % weight gain by the tablet was calculated by 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 figure 1.

***In Vitro* drug release studies[10]**

Then release of Nimesulide from the formulated matrix tablets was studied in pH 8.4 alkaline borate buffer (900 ml) using a United States Pharmacopoeia (USP) 6-station Dissolution Rate Test Apparatus (Model Electro lab , TDT- 06T, Mumbai, India) with a rotating paddle stirrer at 50 rpm and 37° ± 0.5°C as prescribed for Nimesulide tablets in USP XXIV. A sample of Nimesulide matrix tablets equivalent to 100 mg of Nimesulide 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 397 nm for Nimesulide content using a UV/ visible single-beam spectrophotometer-117 (Sistronics Corporation, Mumbai, India). The drug release experiments were conducted in triplicate (n = 3). The *in vitro* release rate (zero order release) were showed in figure 2.

Results and Discussion

The viscosity of *Azadirachta indica* fruit mucilage for 1, 2, 3, 4 and 5% w/v solution was ranged from 3.51±0.08 to 9.33±0.16 mPas (Table 1). The results of angle of repose and compressibility index (%) were found to be satisfactory. The results of LBD and TBD were found to be good. The thickness of the tablets ranged from 5.5±0.21 to 5.8±0.11mm. The average weight of 20 tablets of each formula was ±7.5%. Drug content was found to be uniform among different batches of the tablets and ranged from 99.8±1.80 to 101.2±7.08. The hardness of formulated matrix tablets were more than 5 kg/cm^{2}and percentage friability of the tablets of all batches was less than 1%(Table4). The results of dissolution studies of formulations AIN-1, AIN-2, AIN-3, AIN-4 and AIN-5 with *Azadirachta indica* fruit mucilage in 1:0.2, 1:0.4, 1:0.6, 1:0.8 and 1:1.0 ratios respectively were shown in figure 2. The result of dissolution rate of matrix tablets was decreased as increase in mucilage concentration. Among the formulations, AIN-5 showed the least deviation from the theoretical release pattern.

In vitro drug release profile of Nimesulide from formulated matrix tablets were studied using zero order, shown in figure 2, first order, shown in figure 3, Higuchi plot shown in figure 4, Peppa's plot shown in figure 5 and Hixon-Crowell Model shown in figure 6. The rate of release was faster in AIN-1 and slower in AIN-5. The kinetic plots were perfectly fitting to the formulated *Azadirachta indica* fruit mucilage-Nimesulide matrix tablets. This result shown that as the proportion of *Azadirachta indica* fruit mucilage 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

By performing the above study, the mucilage of *Azadirachta indica* fruits appears suitable for use as a pharmaceutical excipient in the formulation and manufacture of sustained release matrix tablets because of its good swelling, good flow and suitability for direct compression formulations. From the dissolution study, it was concluded that dried *Azadirachta indica* fruit mucilage can be used as an excipient for making sustained release tablets.

Table 1: Rheological data of *Azadirachta indica* mucilage

Concentration (%w/v)	Viscosity of *Azadirachta indica* Mucilage (mPas)
1	3.51±0.08
2	4.29±0.19
3	6.22±0.21
4	7.42±0.25
5	9.33±0.16
Number of experiments (n) =3	

Table 2: Flow properties of dried *Azadirachta indica* fruit mucilage powder

Parameters	*Azadirachta indica* mucilage
Bulk density (g/ml)	0.63±0.15
Tapped density(g/ml)	0.89±0.23
Carr's index (%)	29.21±0.09
Hausner's ratio	1.41±0.11
Angle of repose(^{0})	39.55±0.24
Number of experiments =3	

Table 3: Formulations of matrix tablets

Formulation	Nimesulide	AI	MCC	MS	TWT
AIN-1	100	20	127	3	250
AIN-2	100	40	107	3	250
AIN-3	100	60	87	3	250
AIN-4	100	80	67	3	250
AIN-5	100	100	47	3	250

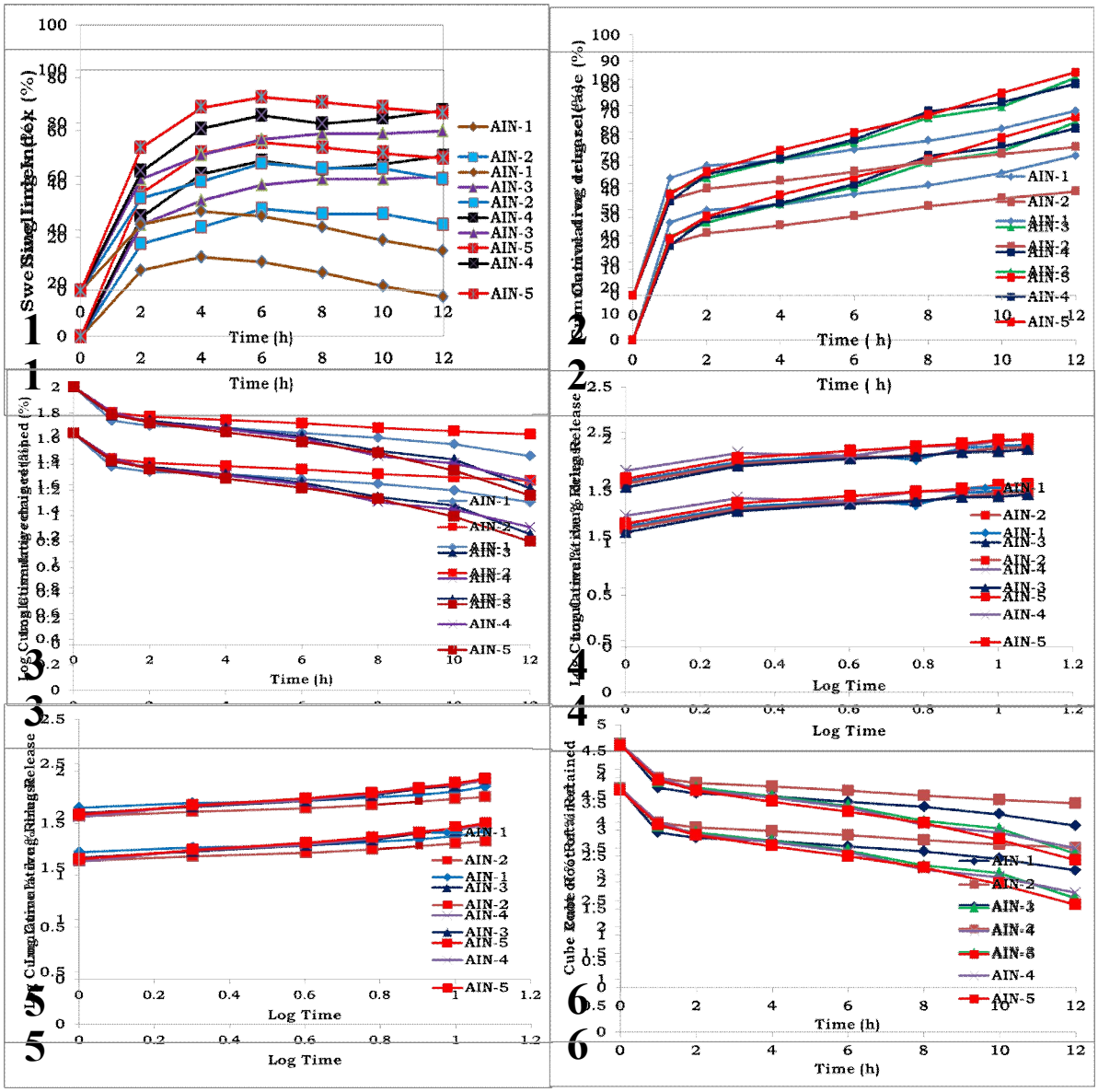
AI- *Azadirachta indica* fruit mucilage, MCC-Microcrystalline Cellulose
MS- Magnesium stearate, TWT-Total weight of tablet

Table 4: Physical properties of matrix tablets

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
AIN-1	5.5±0.21	6.50±1.35	0.51±0.01	99.7±0.41
AIN-2	5.6±0.18	6.70±1.87	0.45±0.11	99.2±0.23
AIN-3	5.8±0.11	8.70±1.45	0.21±0.017	100.8±0.09
AIN-4	5.7±0.15	7.80±1.24	0.36±0.19	99.4±0.41
AIN-5	5.6±0.11	8.40±1.15	0.38±0.12	99.1±0.27

AIG - *Azadirachta indica* & Nimesulide

Figure 1: Swelling Index of matrix tablets, Figure 2: Zero order plot of matrix tablets, Figure 3: First order plot of matrix tablets, Figure 4: Higuchi plot of matrix tablets, Figure 5: Peppa's plot of matrix tablets and Figure 6: Hixon-Crowell's plot of matrix tablets.



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