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Design and characterization of Diclofenac sodium tablets containing *Mangifera indica* resin as release retardant

Vipul Kumar Shingala, Anoop Kumar Singh, Sudhir Kumar Yadav,

T Sivakumar*

Department of Pharmaceutics, Bharathi College of Pharmacy
Bharathinagara, Mandya district, Karnataka, India

Corres. author: tsivakumaar@yahoo.com
Mobile: +91 9791141155

Abstract: The aim of the present study is to investigate the resin of *mangifera indica* (mango) as a tablet retardant polymer in the formulation development of sustained release of drugs, employing diclofenac sodium as a model drug. The resin was isolated from *mangifera indica* plant exudates. Various concentrations of resin ranging from 4 to 6% w/w were employed for the formulation of sustained release matrix tablets of diclofenac sodium. Wet granulation technique was adopted for the preparation of diclofenac sodium granules which shows good flow properties and compressibility. The fabricated tablets were evaluated for various physicochemical characteristics and *in vitro* release studies. Hardness of the tablets was found to be in the range of 6 to 7 kg/cm^2. The swelling index decreased with the increase in concentration of mango resin. Friability test was found to be less than 0.1% in all the cases. The release mechanisms and the release rate kinetics of the tablets were examined using *in vitro* dissolution testing model. The resin of *mangifera indica* exhibited excellent retarding effect on drug release even at its low concentrations (4% w/w). Among the formulation studied, formulation F2 and F3 showed release of drug more than 12 h. The kinetics of drug release from the resin matrix predominantly follows Higuchi patterns followed by first order, Peppas and then zero order. According to Peppas model, the mechanism of diffusion was found to be non-Fickian. The FT-IR spectral analysis shows drug is compatible with the polymer.

Keywords: Polymer matrix tablets, Mango resin, Diclofenac Sodium.

1. Introduction

Mangifera indica resin is a type of gum resins contains small amount of essential oil and so called as oleo-gum resins. Small quantities of resins exude on the surface of the trunk of mango tree due to injury by wind, fire, lightening or wound caused by animals and it is collected, isolated and purified. There is a possibility of using this resins as retardant polymers in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of modified release drug delivery systems[1]. The use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible[2]. Of increasing importance is the fact that plant resources are renewable and if cultivated or harvested in a sustainable manner, they can provide a constant supply of raw material. However, substances from plant origin also pose several potential challenges such as being synthesized in small quantities and in mixtures that are structurally complex, which may differ according to the location of the plants as well as other variables such as the season. This may result in a slow and expensive isolation and purification process. Another issue that has become increasingly important is that of intellectual property rights.

Diclofenac sodium is a well-known representative of non-steroidal anti-inflammatory drugs, widely used to control pain and inflammation of rheumatic and non-rheumatic origin[3]. The

conventional tablets make the drug immediately available for absorption in upper GI tract resulting local GI toxicity varying from minor gastric discomfort to ulceration and bleeding of the mucosa[4]. It is well documented that the GI toxicity is not only caused by the inhibition of the prostaglandin synthesis, but is probably also due to direct contact of the drug with the mucosa [5]. In addition, due to the rapid systemic clearance of this drug, repeated daily dosing of 3 to 4 times a day is required in maintenance therapy that influences patient compliance. Sustained release formulations of diclofenac sodium are thus warranted to promote patient compliance and to reduce upper GI toxicity to some extent. Diclofenac sodium is well adsorbed in the colon[6] and thus colon-specific release of this drug can be used for the treatment of wide spread inflammatory bowel diseases.

The aim of the present study is to investigate the resin of *mangifera indica* as a retardant polymer in the formulation development of sustained release of drugs, employing diclofenac sodium as a model drug.

2. Experimental

2.1 Materials

Crude *mangifera indica* plant exudates collected manually from Gujarat and Uttar Pradesh district from different verity of mango trees. The extraction of resin from crude *mangifera indica* plant exudates was carried out in our laboratory. Diclofenac sodium was generously gifted by Unique Pharmaceuticals Ltd. Gujarat, India. Lactose monohydrate, talc, magnesium stearate and absolute ethanol were purchased from S.D. Fine Chemicals Pvt. Ltd., Mumbai, India. All the chemicals used were of A.R grade.

2.2 Pre formulation studies

The parameters like drug excipients compatibility studies, angle of repose, bulk density, tapped density and Carr's index was investigated under pre formulation studies.

2.3 Isolation of mango resin

Crude plant exudate was collected in session of March to June. Mango gum resins obtained from the incised trunk of *Mangifera indica*. The mango gum resin was extracted by ethanol with intermittent stirring, extraneous materials were removed by straining through a muslin clothe. The resin was filtered and evaporated at room temperature.

2.4 Preparation of matrix tablets

Wet granulation method was used to prepare granules of drug. The formulation was developed by using diclofenac sodium as model drug. The resin concentrations were used 4.0, 5.0 & 6.0 % w/w (Table 2). All the formulations, ingredients were passed through sieve No.80. Then the ingredients were accurately weighed and granulated using isopropyl alcohol. Granules were allowed to dry at room temperature (37±2°C). Dried granules were compresed by round flat-faced punches on a hand operated single punch tablet machine.

2.5 Evaluation Parameters:

a) Weight variation test[7]

Randomly twenty tablets were selected after compression, weighed individually and average weight was determined.

b) Drug content[8]

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 276 nm after suitable dilution using a Systronics UV- Vis double beam spectrophotometer 2201.

c) Hardness[9]

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

d) Thickness

The thickness of the tablets was determined by using vernier calipers. Five tablets were used and average values were calculated.

e) Friability Test[8]

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by,

$\%F = 100\ (1-W_0/W)$

% Friability of tablets less than 1% are considered acceptable.

f) Swelling index[9]

The swelling index of tablets was determined in pH 6.8 phosphate buffer at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$SI\% = \frac{(weight\ of\ swollen\ tablet - initial\ weight\ of\ tablet)}{(initial\ weight\ of\ tablet)} \times 100$$

g) Invitro drug release study [9]

Drug release study was carried out in USP paddle-type dissolution test apparatus. Dissolution medium was 0.1 N HCL buffer (pH 1.2) for initial 2 h and phosphate buffer pH 6.8 for remaining 8 h. Volume of dissolution medium was 900 ml, and bath temperature was maintained at 37±1° C throughout the study. Paddle speed was adjusted to 100 rpm. After each hour, 5 ml of sample was withdrawn and analysed for diclofenac sodium content by UV-spectrophotometer at 276 nm.

h) Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t], Higuchi's square root of time (Q v/s t1/2) and Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t.

In short, the results obtained from in vitro release studies were plotted in four kinetics models of data treatment as follows:

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

3. Result and Discussion

The formulated matrix tablets have hardness 6 - 7 kg/cm^2, thickness 3.82 to 3.86 mm. Percent weight loss in the friability test was found to be less than 0.1% in all the cases. All the matrix tablets contain diclofenac sodium within 100±5% of the labeled amount Percentage friability and weight variation passes the test as per standard pharmacopoeial limit.

The *in-vitro* drug release profile of diclofenac sodium from all the formulations and the marketed product isshown in Fig.1. The results indicated retardant release ofdrug from all the formulations with increase in the polymer concentration. The cumulative percentage of drug release from the various formulations after 12 hours were 88.19%, 62.15%, 48.81% for F1, F2 and F3 respectively. The maximum cumulative percentage of drug released from different formulations is given in the following order:

F1 > F2 > F3

The cumulative percentage drug release data obtained were fitted to zero order, first order, Higuchi's and Peppas equations to understand the mechanism of drug release from the matrix tablet. The slopes and the regression co-efficient of determinations R^2 were listed in Table 4.

The drug release kinetics of all of the fabricated formulations, F1, F2 and F3 predominantly follows Higuchi pattern of drug release followed by first order, Peppas and then zero order. According to Peppas model, the 'n'value for F1, F2 and F3 was found to be 0.8556, 0.7882 and 0.9755 respectively, which are more than 0.5, indicates that the release approximates non-Fickian diffusion mechanism.

The drug release profiles of the fabricated formulations were compared with the release profiles of standard marketed product Voveran-SR-100 (Fig.1). The drug release profiles of F1 and F2 were closely approximates the release profiles of the standard Voveran-SR-100. The drug release from the Voveran-SR-100 tablets at the end of 12th hour is 87.93%, which is comparable to F1 resulting 88.19 % of the drug release at the same hour.

From IR spectroscopic study, it was found that there was no evidence of interaction between drug and polymer.

4. Conclusions

The result of the present study demonstrated the isolated *mangifera indica* resin can be used as a drug release retardant in the formulation of sustained release dosage forms. The drug release was extended over a period of more then 12 h employing the resin even at low concentrations of 4% w/w. The drug release kinetics of all formulations follows Higuchi pattern and the mechanism of diffusion was observed to be Non-Fickian. Thus *mangifera indica* resin could serve as an effective retardant polymer in formulation development of sustained release dosage forms offering better patient compliance.

Table 1. Preformulation parameters of diclofenac sodium granules prepared from *magnifera indica* resin

Formulations	Angle of Repose (□)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index (%)
F1	29° 30'±0.28	0.35±0.05	0.41±0.03	6.11±0.28
F2	32° 41'±0.41	0.48±0.02	0.52±0.09	7.69±0.19
F3	34° 13'±0.27	0.54±0.07	0.61±0.01	10.00±0.13

All values are expressed in mean ± standard deviation (n=3).

Table 2. Formulation of diclofenac sodium matrix tablets with average weight of 250 mg

Ingredients (mg/tablet)	Formulations		
	F1(4% resin)	F2(5% resin)	F3(6% resin)
Diclofenac sodium	100	100	100
Mango Resin	10	12.5	15
Lactose	132.5	130.0	127.5
Mg. Stearate	5	5	5
Talc	2.5	2.5	2.5

Table 3. Evaluation data for physical parameters of matrix tablets

Formulations	Weight variation (%)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Drug Content (%)
F1	±2.55	0.92	6.1 ±0.47	3.82 ± 0.18	97.42
F2	±3.53	0.72	6.9±0.63	3.91 ±0.080	95.09
F3	±2.88	0.91	6.4 ±1.27	3.86 ±0.019	98.51

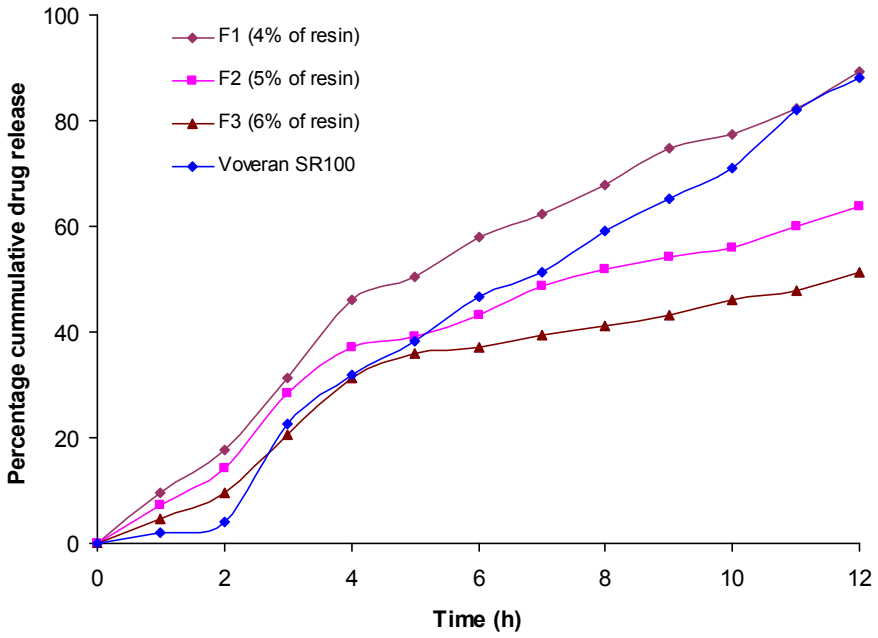
All values are expressed in mean ± standard deviation (n=3).

Table 4. In Vitro release kinetics of matrix tablets of diclofenac sodium

Formulations	Higuchi Model (R^2)	First Order (R^2)	Zero Order (R^2)	Peppas Equation	
				(R^2)	n
F1	0.9942±0.001	0.9727±0.008	0.9630±0.002	0.9780±0.004	0.8556±0.027
F2	0.9708±0.011	0.9682±0.011	0.9185±0.015	0.9443±0.009	0.7882±0.050
F3	0.9346±0.026	0.9045±0.036	0.8769±0.045	0.8875±0.049	0.9755±0.052

All values are expressed in mean ± standard deviation (n=3).

Figure 1. *In-vitro* release profile of fabricated diclofenac sodium matrix tablet (F1 to F3) compared with a marketed formulation (Voveran SR100)



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