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Research Article

EVALUATION OF *MORINGA OLEIFERA* GUM AS A SUSTAINED RELEASE POLYMER IN DICLOFENAC SODIUM TABLET FORMULATION

JN. Ravi Varma[1*], Ch. Pavan Kumar[2], A. Koushik Reddy[2] and P. Prudhvi Raju[1]

[1]Department of Pharmaceutical Technology, A.U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam - 530003, Andhra Pradesh, India.
[2]Aditya Institute of Pharmaceutical Sciences and Research, Surampalem - 533 437, Andhra Pradesh, India.

ABSTRACT

Diclofenac sodium is commonly used as anti-inflammatory and anti-pyretic agent. Frequent administration and undesired side effects, fluctuations of plasma concentrations of the drug may lead to patient incompliance, and hence, improper therapy. Therefore, the present work will be devoted to formulate the drug using *Moringa Oleifera* gum to explore its use as sustained release (SR) polymer. The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended and specified period of time. This is generally accomplished by attempting to obtain "zero-order" release from the dosage form. Moringa gum (MG) was separated and isolated from raw gum of *Moringa Oleifera* Linn and employed in formulating tablets of Diclofenac sodium at concentrations of 5, 10, 15, 20, 30, 40 % $^{w}/_{w}$. The tablets were prepared by wet granulation technique and were subjected to hardness, friability, weight variation, drug content uniformity and dissolution studies. The physical properties were found to be satisfactory for all the formulae. Dissolution data was used for calculation of zero order, first order, higuchi, korsmeyer, peppas plots. The drug release involved diffusion mechanisms. The *in vitro* study revealed that the optimized formulation has shown 96 % drug release following zero order compared to the marketed formulation (voltren) which followed first order release and has shown 95.6 % drug release. The developed sustained release tablet can perform therapeutically better than a conventional tablet.

Keywords: Diclofenac sodium, *Moringa Oleifera* Gum, Sustained release, Tablets, Zero order.

INTRODUCTION

Oral drug delivery is one of the widely employed routes for administration of the drugs that have been explored for the systemic of drugs via various pharmaceutical products in different dosage forms. These dosage forms are developed within the intrinsic characters of the GIT physiology, irrespective of their mode of delivery viz., IR, SR, CR. Hence it essential in understanding the pharmacokinetics, pharmacodynamics and formulation design to achieve a systemic approach for the successful development of an oral pharmaceutical dosage form. A number of variables such as drug properties, route of delivery, target sites, duration of therapy, the disease state and patient variables must be considered.

Over the few decades sustained release technology (SR) has emerged as a new interdisciplinary science that offers a novel approach to the delivery of bioactive agents into systemic circulation at a programmed rate. By developing a predictable and reproducible drug release rate for an extended period of time, SR formulations can succeed in attaining optimum therapeutic responses, prolonged efficiency and reduced toxicity[1].

The present research was aimed in using the economical, naturally available moringa gum as the sustained release polymer to design and evaluate SR tablets of Diclofenac sodium. SR formulations have become more popular in comparison to conventional dosage forms because, these release the drug slowly for a prolonged period of time, while reducing the frequency of administration, and improve the patient compliance.

Diclofenac sodium was selected as drug of choice as it is an ideal candidate for developing sustained release dosage forms because of its short biological half-life of 1-2 hrs and has to be administered in a dose of 100-150 mg 2-3 times a day. Diclofenac Sodium is a NSAIDS used as anti-inflammatory and Anti pyretic agent[2]. Many synthetic polymers are available for the preparations of sustained release tablets, but the use of plant polymers has more added advantages like natural in origin, biocompatible, biodegradable, low cost, free from side effects, etc. so in the present study moringa gum was used as a polymer in preparation of SR tablets of Diclofenac Sodium. Moringa gum is a natural polymer derived from bark of Moringa oleifera (Family: Moringaceae). Moringa gum is easily collected without any complicated procedure and it is also available in huge amount. The bark of this plant contains a white crystalline alkaloid, two resins, an organic acid, mucilage and ash. The moringa gum contains about galactose 41.5%, arabinose 26.9%, xylose 25.9%, rhamnose 5.6% and trace amount of uronic acid. Studies have shown that Moringa gum finds its use as both medicinal and additive properties. The swelling property of polymer was helpful for sustained release of the drug[3].

MATERIALS AND METHOD

Materials

Diclofenac Sodium and starch were purchased from Lobachemie Pvt. Ltd. Magnesium stearate, Talc, Sodium hydroxide and Potassium dihydrogen phosphate were purchased from Merck Pvt. Ltd., Mumbai. Lactose was purchased from Global pharma, Mumbai.

Isolation of Moringa Oleifera gum

The gummy extracts from the injured sites of moringa trees was collected, dried, pulverized and passed through sieve #80. The dried gum was stirred in distilled water (10 gm. in 250ml) for around 6-8 hours at room temperature using magnetic stirrers. The Supernatant was obtained by centrifugation and kept separately; the residue was washed with water and this water was added to the separated supernatant. This process was repeated for 4-5 times. The finally obtained supernatant was made up to 500 ml with water and then treated with acetone by continuous stirring. The precipitated material was washed with distilled water and further dried at 50-60° C under vacuum[4].

Preparation of Tablets by wet granulation method

Six batches of DS SR tablets were prepared as per the composition shown in Table 1 corresponding to different concentrations of 5%, 10%, 15%, 20%, 30%, and 40% of MG coded as, F-1, 2, 3, 4, 5 and 6 respectively. Drug with and without the diluents was deagglomerated using the Sieve #80. Then the mixture was transferred to a mortar and solution of starch paste was added drop wise to get wet dough mass. The wet mass was passed manually through Sieve # 60. The granulations were dried at 60 ºC for 2 hours until the loss on drying of the granules was between 1% and2% w/w. The dried granules were passed through Sieve # 20 and evaluated for flow properties and compressibility index[5]. The granules were blended with magnesium stearate and talc. The blends were compressed using 12 mm flat punches on a rotary tablet press.

Tablet evaluation

The thickness of the tablets was determined using a screw gauge (Mitutoyo, New Delhi, India). Weight variation was recorded using an electronic balance (AXIS-*AGN200C*). The hardness and friability were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Electrolab, Mumbai, India), respectively. Drug content of the tablets was also determined.

In vitro drug release studies

The *in vitro* dissolution studies of the developed SR tablets were carried out in USP dissolution

apparatus type-II (LabIndia DS-8000) using 900 ml of pH 6.8 phosphate buffer solution as dissolution medium, maintained at 37 ± 0.5 °C with 50 rpm. An accurately weighed tablet of each of the prepared formulations and the marketed product (Voltren) were added to each basket. Samples were withdrawn at regular time intervals to measure the drug release. Sink conditions were maintained. For each formula, release runs were performed in triplicate and absorbance was measured in UV spectroscopy at 276 nm. The cumulative percentage of drug released was determined as a function of time.

Kinetics and mechanism of drug release

The *in vitro* drug release profiles were fitted to Peppas, Higuchi and zero-order equations (Eqs. (1)– (3), respectively) by employing the method of least squares, the mechanism of *in vitro* drug release was analyzed and compared with the release profile differences among the formulations.

$$M_t/M_\infty = Kt^n \quad (1)$$

$$M_t/M_\infty = b + k_2 t^{1/2} \quad (2)$$

$$M_t/M_\infty = a + k_3 t \quad (3)$$

In Peppas equation, Mt/M_∞ is the fraction of drug released up to time t, K is the kinetic constant and n is the release exponent indicative of the release mechanism[6]. In Higuchi (1963) and zero-order release equations, k_1, k_2 and k_3 are constants[7]. On the other hand, Higuchi equation expresses a diffuse release mechanism. The results were analyzed by one way analysis of variance.

RESULTS AND DISCUSSION

Physical evaluation of the granules and tablets

The granules properties of the different DS SR batches are shown in Table 2. The data reveal that all the batches were having moderate to good flow capacity, loose bulk density (LBD) and tapped bulk density (TBD). These properties assisted uniform fill weight and avoided problems during tablet compression. Each batch showed limited moisture content and good Carr's index. Hence, all batches contained uniform drug content and hardness. Characteristics of different batches of tablets are shown in Table 3. It was observed that the friability values decreased with the increase in polymer concentration. All batches showed uniform thickness with respect to hardness. Optimum tablet hardness has been maintained by compression force and thickness, hence, the tablets had enough strength for shipping. All the physical parameters of tablets were thus found to be practically within controls. The concentration of the polymer does not exhibit any effect on the drug content of different batches.

The granules property showed that MG envelops DS uniformly and blending was done properly, hence, uniform drug content of each batch. All the granules' parameters are under acceptable limits. The prepared tablets were in uniform thickness and hardness. This may be due to physicochemical characters of MG and the uniform mixing of tablet blend.

In vitro drug release profiles of DS SR tablets

In vitro drug release results for six different batches F-1 to F-6 are shown in Fig. 1. The data reveal that the concentration of polymer had a significant impact on the drug release. The drug release of DS was retarded when MG concentrations have increased. Drug release from the tablets with 20% and 40% polymer content was comparatively slower than tablets with 5–15% polymer content (F1 to F4). The dissolution profile of F6 batch for the first 12 hours was steady till the polymer relaxation becomes predominant (Fig. 1).

Kinetic assessment of the in vitro release of DS from the prepared tablets

The release data obtained were fitted into zero order, first order and hugushi models to determine the best pattern of drug release from the formulation[8]. These conclusions on release model were based on the correlation coefficient (r) for the parameters studied, the formulation was assumed to follow the mechanism of release showing the highest value of correlation coefficient.

Successive evidence of the relative validity of diffusion and first order models obtained by analyzing the data using the following equation of Korsmeyer and Peppas (1983).

$$M_t/M_\infty = Kt^n$$

Where $M_t/M\infty$ is the fraction released by the drug at time t, K is a constant incorporating structural and geometric characteristic and n is the release exponent characteristic for the drug transport mechanism. When n= 0.5 Fickian diffusion is observed and the release rate in dependent on t, while 0.5< n <1.0 indicate anomalous (non-Fickian) transport and when n = 1, the release is zero order.

In swellable systems, the release kinetics will be affected by factors like diffusion rate of liquid and the length of polymeric side chain. The diffusion is Fickian when the rate of diffusion of liquid is slower than the relaxation of polymeric side chains. Case II transport is observed when the relaxation process is very slow in comparison with the diffusion rate. When the polymer relaxation rate and the liquid diffusion are of same order then anomalus or non-fickian diffusion is observed.

The regression values and release rate constant values were considered for fitting. The value of n are estimated by linear regression of log Mt/ M_∞ v/s log t of different formulations are tabulated in Table 4, the obtained values of n ranges between 0.59 and 0.77 for the release of DS for all the prepared tablets indicating that the release mechanism includes both diffuion and chain relaxation mechanisms[9]. Hence the release of DS from the prepared tablets was controlled by the swelling of the polymer followed by the drug diffusion through the swelled polymer and slow erosion of the tablet. This was in accordance with a previously published data[10].

Kinetic data expose the results that drug release from DS MG tablets follow diffusion mechanism because r^2 values of the formulations (0.992-0.998). At the end of 12 hours dissolution, the tablet formulated with 40% polymer content (F6) showed a better release profile than the other formulations (Fig:1). F6 was therefore is selected for evaluation with marketed formulation. The results fitted to Zero order, Higuchi, Peppas and plots are shown in Fig 3, 4 and 5 respectively. Further the plots indicate that F6 followed diffusion controlled release mechanisms according to the simplified Higuchi model[8].

CONCLUSION

SR matrix tablets of Diclofenac sodium were prepared using different concentrations of moringa gum by employing wet granulation technique. The comparitive release studies of SR matrix tablets of diclofenac revealed that the rate of release was dependent on polymer concentration. The tablets formulated were found to satisfy the official compendial requirements of hardness and friability. The drug release was found to be diffusion mechanism in all the formulations. Polymer extracted from the injured parts of moringa trees had shown good physicochemical properties. *In vitro* drug release studies of optimized batch F6 when compared with marketed product revealed that the drug release takes place slowly up to 12 hours period and was fitted into Higuchi kinetic mechanism. Hence the polymer MG isolated from moringa gum can therfore be used as a sustained release polymer in the development of SR dosage forms.

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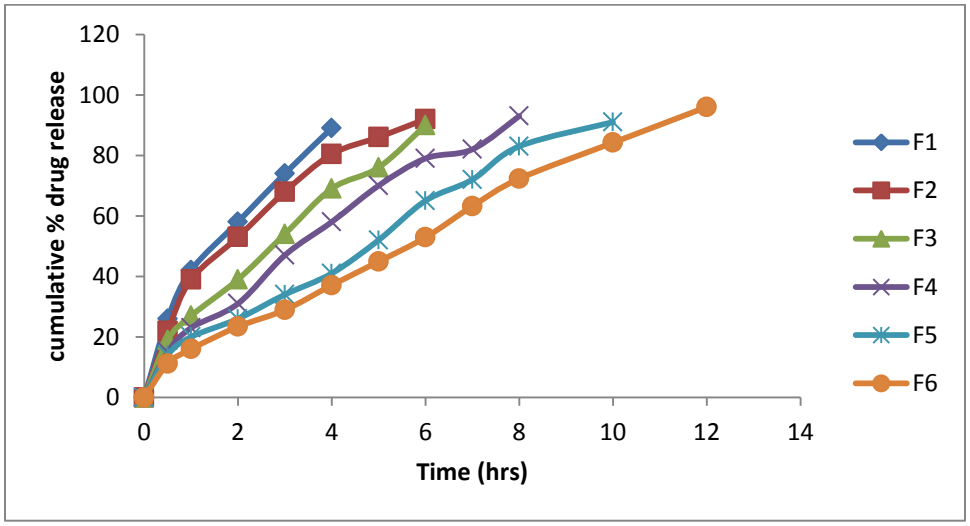

Fig. 1: *In vitro* release of diclofenac sodium tablets

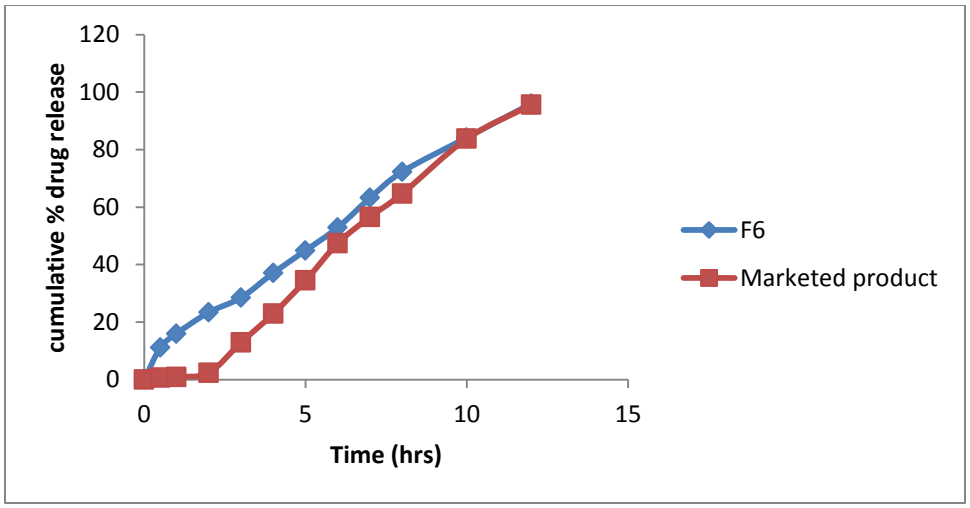

Fig. 2: *In vitro* release of F6 and Marketed product

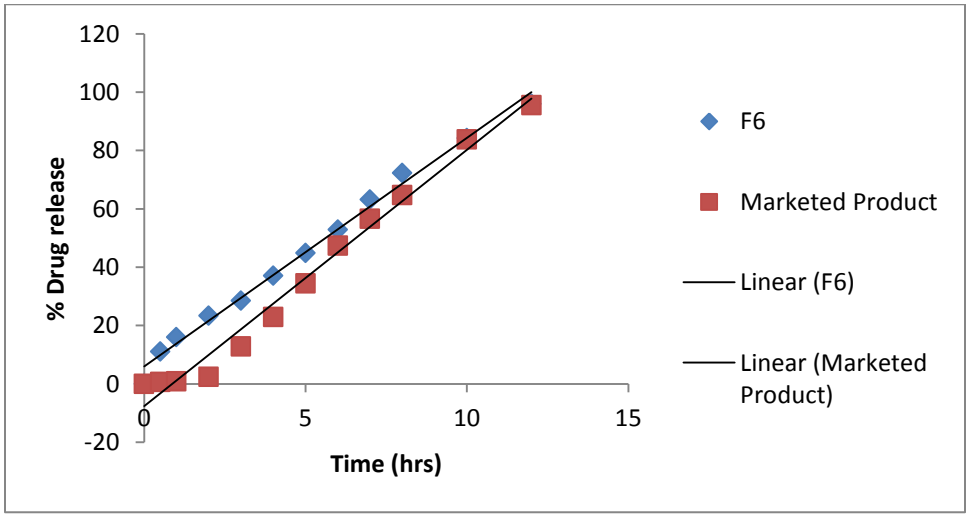

Fig. 3: Zero order plot for F6 and marketed product

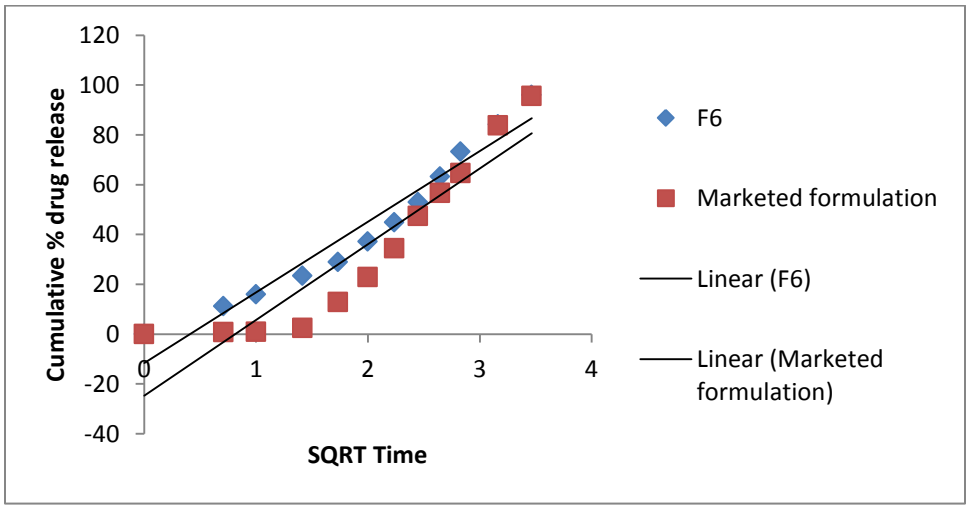

Fig. 4: Higuchi plots for F6 and marketed product

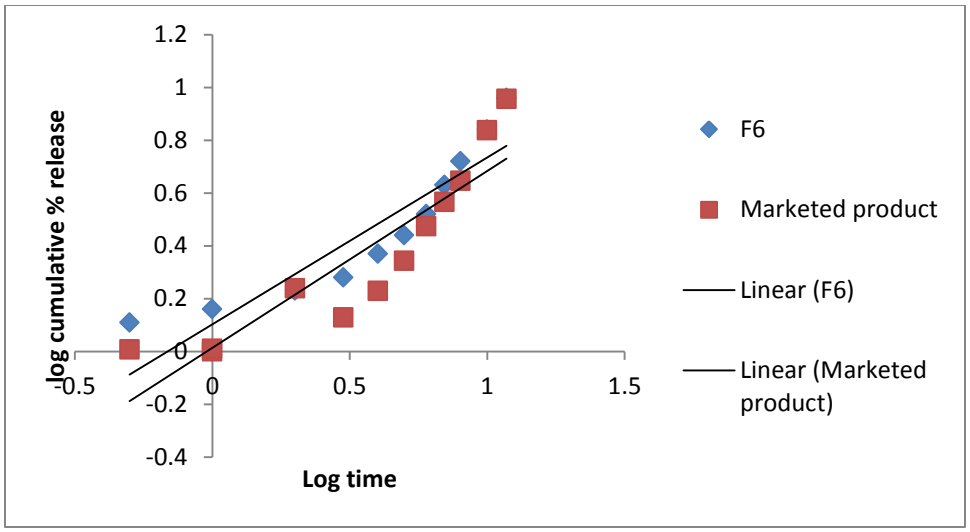

Fig. 5: Peppas plots for F6 and marketed product

Table 1: Formulae of Diclofenac Sodium SR tablets (the weight of each tablet is 500mg)

Ingredients (in mg)	F1	F2	F3	F4	F5	F6
Diclofenac Sodium	100	100	100	100	100	100
Moringa Gum (%)	05	10	15	20	30	40
Lactose	365	340	315	290	240	190
Starch paste	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium Stearate	05	05	05	05	05	05
Talc	05	05	05	05	05	05

Table 2: Granules[a] properties of different DS SR batches

Batch No.	Angle of repose (°)	LBD[b]	TBD[c]	Carr's index	Hausner ratio	Moisture content
F1	20.9	0.32± 0.00	0.41± 0.00	12.6	1.05	1.56
F2	21.2	0.33± 0.00	0.41± 0.00	11.5	1.12	1.49
F3	19.6	0.30± 0.00	0.42± 0.00	15	1.05	1.23
F4	19.5	0.32± 0.00	0.43± 0.01	12.2	0.99	1.64
F5	20.1	0.34± 0.01	0.42± 0.00	12	1.11	1.26
F6	19.3	0.31± 0.00	0.38± 0.01	12.4	1.13	1.84

[a] The values represent mean ±SD (n=6).
[b] Loose bulk density.
[c] Tapped bulk density.

Table 3: Physical evaluation of DS SR tablets

Formulations	Friability (%)	Hardness (kg/cm^2)	Drug content (%)	Weight variation(mg)
F1	0.39	4.0	98.7	497
F2	0.27	5	99.2	502
F3	0.29	6	100.2	501
F4	0.29	5	98.1	505
F5	0.25	5	94	496
F6	0.24	5	99.3	500

Table 4: Kinetic release rate of the different batches of developed DS sustained release tablets

Formulation	Zero Order		First Order		Higuchi Model		Peppas Model	
	K_0	R^2	K_1	R^2	K	R^2	n	R^2
F_1	17.3	0.993	0.050	0.980	47.41	0.998	0.67	0.986
F_2	12.3	0.972	0.39	0.996	40.25	0.995	0.65	0.993
F_3	12.8	0.997	0.34	0.965	40.74	0.992	0.64	0.959
F_4	10.4	0.991	0.27	0.967	37.4	0.993	0.65	0.959
F_5	8.6	0.994	0.22	0.963	33.0	0.978	0.59	0.921
F_6	7.5	0.997	0.21	0.950	31.4	0.981	0.77	0.942
Marketed Formulation	6.12	0.864	0.223	0.920	0.66	0.889	0.66	0.890

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