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DEVELOPMENT AND EVALUATION OF DICLOFENAC SODIUM SUSTAINED RELEASE MATRIX TABLETS EMPLOYING NATURAL POLYMERS

G. Sravan Kumar*[1], M. Srinivasa Rao[2], B. Kishore Kumar Reddy[3], K. Suresh Kumar[4], S.V.N. Gangadhar[5].

[1]Department of Pharmaceutics, Vagdevi College of Pharmacy, Gurajala, Guntur Dist, A.P, India.

[2]Department of Quality Assurance, Beloorbayirbiotec Ltd., Tumkur, Karnataka, India.

[3]Department of Pharmaceutics, A.K.R.G College of Pharmacy, Nallagerla, W.G.Dist, A.P, India.

[4]Department of Pharmaceutics, University College of Pharmacy, JNTU Kakinada, E.G. Dist, A.P, India.

[5]Department of Pharmaceutics, Adarsha College of Pharmacy, Kottapalli, E.G.Dist, A.P, India.

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***Correspondence for Author:**

G. Sravan Kumar
Department of Pharmaceutics,
Vagdevi College of Pharmacy,
Gurajala, Guntur Dist, A.P,
India.
sriintegrity@gmail.com

ABSTRACT

Oral route of administration is the most widely accepted route of delivery due to the ease of administration, avoidance of pain and other risks of parenteral administration and has a good patient compliance. The aim of current research work is to design and characterize sustained release matrix tablets of Diclofenac sodium employing natural polymers like Tamarind seed polysaccharide (TSP) and Guar gum in view to improve therapeutic action and patient compliance by reducing dosage frequency. TSP and Guar gum are individually checked for sustaining the drug release at different concentrations ranging 10%-35% of tablet weight. A drug excipient compatibility study performed by FTIR spectroscopy. Total 12 formulations were developed, which were evaluated for parameters like thickness, hardness, frialbility, swelling index, uniformity of weight, assay and in vitro drug release. The two optimized formulations F5 containing 30% of TSP and F12 containing 35% of Guar gum were successful in sustaining the release of Diclofenac sodium for 12hrs. The results suggest that the developed sustained release matrix tablets prepared employing TSP and Guar gum of Diclofenac sodium could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance.

Key words: Diclofenac sodium, matrix tablets, Tamarind seed polysaccharide, Guar gum, sustained release.

INTRODUCTION

The drug may be administered by a variety of routes but oral administration is adopted wherever possible. It is safest, easiest and most economical route of drug administration[1]. Sustained release technology is a relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. New and more sophisticated sustained release drug delivery system constantly being developed and tested[2].

Diclofenac sodium is an acetic acid nonsteroidal antiinflammatory drug (NSAID) with analgesic and antipyretic properties. Diclofenac sodium is used to treat pain, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and actinic keratosis[3]. Diclofenac sodium is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3hr after an oral dose (C_{max})[4]. The plasma elimination half-life of Diclofenac sodium is approximately 3-4 hour and the frequency of dosing is high. So by formulating it into a sustained release formulation we can reduce dosing frequency to improve the patient compliance and to reduce the systemic side effects.

The aim of current research work is to design and characterize sustained release matrix tablets of Diclofenac sodium employing natural polymers like Tamarind seed polysaccharide (TSP) and Guar gum in view to improve therapeutic action and patient compliance by reducing dosage frequency.

MATERIALS AND METHODS

Materials

Diclofenac sodium was a gift sample from M/s Supra Chemicals, Mumbai, Tamarind seed polysaccharide was self extracted, Guar gum was supplied by BASF Pvt. Ltd., Mumbai, PVP K 30, Avicel PH102 and Magnesium stearate were procured from commercial sources. All the other materials used were laboratory grade.

METHODS

Drug-Excipient compatibility study by FTIR

Fourier Transform Infrared Spectroscopic studies (FTIR) spectra of the Diclofenac sodium and its 1:1 mixture with TSP and Guar gum were obtained with a FTIR spectrophotometer

(Bruker ATR Alpha-e, Germany) in KBr disc.

Melting Point

The melting point of the drug was determined by using melting point apparatus.

Preparation of Matrix tablets of Diclofenac sodium

The Matrix tablets of Diclofenac sodium with matrix forming agents TSP and Guar gum were prepared as per formulae given in Table: 1 by direct compression method employing Avicel PH102 as a directly compressible vehicle. Magnesium stearate was used as a lubricant. Required quantities of all the ingredients except magnesium stearate (pre sifted through sieve # 60) were passed through sieve # 80 and blended to uniformity. Then the lubricated blend was compressed into tablets of 500mg by using 12mm round and flat punches on a Cadmach 16 station rotary tabletting machine (M/s Cadmach Engineering Co. Ltd., Mumbai.) to a hardness of 5 Kg/cm^2.

Table 1: Formulae for preparation of Diclofenac sodium Matrix tablets

Ingredients (mg/tablet)	FORMULATIONS											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Diclofenac sodium	200	200	200	200	200	200	200	200	200	200	200	200
TSP	50	75	100	125	150	175	-	-	-	-	-	-
Guar Gum	-	-	-	-	-	-	50	75	100	125	150	175
Avicel PH 102	222	197	172	147	122	97	222	197	172	147	122	97
PVP K30	25	25	25	25	25	25	25	25	25	25	25	25
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3

Evaluation of prepared Matrix tablets

1. Tablet weight variation

The tablet weight variation test was performed as per procedure specified in Indian Pharmacopoeia (IP).

2. Tablet thickness

A vernier caliper (For-bro Engineers, Mumbai, India) was used to determine thickness of 10

randomly selected tablets.

3. Uniformity of the Drug content

Ten tablets from each formulation were powdered. The powdered sample equivalent to 100 mg of Diclofenac sodium was transferred to a 100ml volumetric flask. The required quantity of Phosphate buffer of pH 7.4 was added, mixed and filtered, the filtrate was suitably diluted with buffer and analysed for Diclofenac sodium content against blank UV spectrophotometrically at 274nm (n=3).

4. Tablet hardness

Hardness of five randomly selected tablets from each formulation was determined using the Monsanto Hardness Tester.

5. Tablet friability

Ten tablets were randomly selected and friability was checked using Roche friabilator for 100 revolutions at 25rpm, (n=2).

6. Tablet swelling ability

The tablet swelling ability was determined by the method described by Dorozynski et al. [5] Briefly, a tablet from each formulation was weighed (W1) and placed in a glass beaker, containing 200 ml of Phosphate buffer of pH 7.4, maintained in a water bath at 37 ± 0.5°C. At regular time intervals, the tablet was removed and the excess surface liquid was carefully wiped off with a filter paper. The swollen tablet was then reweighed (W2). The swelling index (SI) was calculated using the formula

$$SI = \frac{W2 - W1}{W1} \times 100$$

7. In-vitro Drug release rate study

The release of Diclofenac sodium from the prepared Matrix tablets was studied up to 12 hours in 900 ml of Phosphate buffer of pH 7.4 employing dissolution rate test apparatus (M/s LABINDIA, Disso 8000) at the paddle rotation speed of 50rpm. A temperature of 37 ± 0.5°C was maintained throughout the study. One tablet from each formulation was placed in the basket containing buffer and samples of 5ml were withdrawn at specified time intervals, the same quantity of fresh buffer was replaced after every sampling. The samples withdrawn were suitably diluted with Phosphate buffer of pH 7.4 and assayed for Diclofenac sodium

content UV-spectrophotometrically at 274nm. All the release rate experiments were conducted in triplicate (n=3).

8. Kinetic modelling of drug release profiles

The dissolution profiles of all formulations in Phosphate buffer of pH 7.4 were plotted by zero-order, first-order, Higuchi[6] and Korsmeyer–Peppas[7] kinetic models. The model with the highest correlation coefficient was considered to be the best fitting one.

RESULTS AND DISCUSSION

Drug-Excipient compatibility study by FTIR

The FTIR spectra of Diclofenac sodium and its combination with TSP and Guar gum were shown in Fig: 1. The FTIR spectra of Diclofenac sodium as well as its physical mixtures with TSP and Guar gum were shown characteristic peaks at 3273 cm^{-1} due to N-H stretching, 3319 cm^{-1} due to COOH stretching, 2937 cm^{-1} due to C-H stretching, 1056 cm^{-1} due to O-H stretching, 1589 cm^{-1}, 1508 cm^{-1}, 1452 cm^{-1} due to C=C ring stretching, 1438 cm^{-1} due to C-H bending, 1288 cm^{-1} due to C-N stretching, 1281 cm^{-1} due to C-O cm^{-1} bending and 749 cm^{-1} aromatic deformation indicating no interaction between Diclofenac sodium and matrix forming polymers.

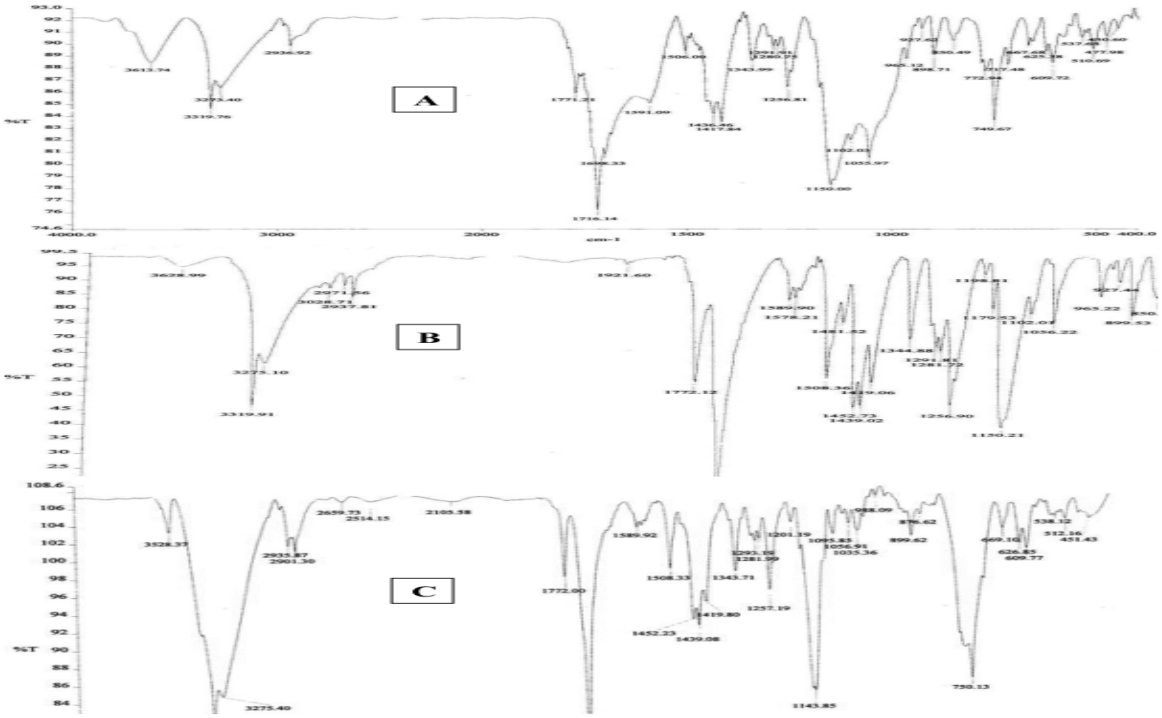

Fig 1: FTIR Spectra of Diclofenac sodium (A) and its physical mixture with TSP (B) and Guar gum (C)

Melting point

Melting point was found to be 149-153 ^{o}C and it is within the range specified in the official limits, which indicates the purity of drug.

Physical characteristics of prepared Matrix tablets

The physical characteristics of the tablets were summarized in the Table 2. All the tablet formulations showed acceptable physical properties and complied with the pharmacopoeial specifications (IP) for weight variation, drug content and friability. The weight of the tablet ranged from 498-503 mg. The percentage of drug content was found to be in the range of 98.4%-100.5%. The percentage friability for all the formulations was less than 1 %, indicating a good mechanical resistance.

Table 2: Physical Characteristics of the Prepared Diclofenac sodium Matrix Tablets

Formulation	Thickness (mm) Mean±SD	Weight variation (mg) Mean±SD	Hardness Kg/cm^2 Mean±SD	Friability (%)Mean±SD	Drug Content (%)Mean±SD
F1	3.88± 0.16	503±3.56	5.8±0.10	0.163± 0.13	100.5±0.5
F2	3.89± 0.18	503.5±4.32	6.0±0.24	0.220± 0.41	98.4±1.26
F3	3.85± 0.32	500.5±3.65	5.7±0.14	0.320± 0.21	99.7±0.98
F4	3.90± 0.03	498±4.13	5.9±0.12	0.262± 0.12	99.8±0.74
F5	3.93± 0.16	501.5±2.75	6.3±0.35	0.420± 0.35	100.9±1.23
F6	3.96± 0.14	503±3.47	6.2±0.13	0.490± 0.21	99.9±1.45
F7	3.91± 0.16	500±4.23	6.2±0.25	0.341± 0.013	99.9±0.89
F8	3.75± 1.31	499±3.34	6.0±0.34	0.549± 0.11	100.1±0.76
F9	3.77± 0.58	498±4.56	5.9±0.15	0.269± 0.014	100.5±0.76
F10	3.87± 1.42	500±3.62	6.3±0.44	0.420± 0.012	101.5±0.56
F11	3.76± 1.57	501±3.56	5.6±0.13	0.368± 0.016	99.4±1.23
F12	3.74± 1.22	499±2.64	6.4±0.34	0.450± 0.010	99.7±1.68

Swelling indices

The hydration ability of formula is important because it influences 1. Adhesion ability of swellable polymers in contact with test fluid 2. Drug release kinetics[8].

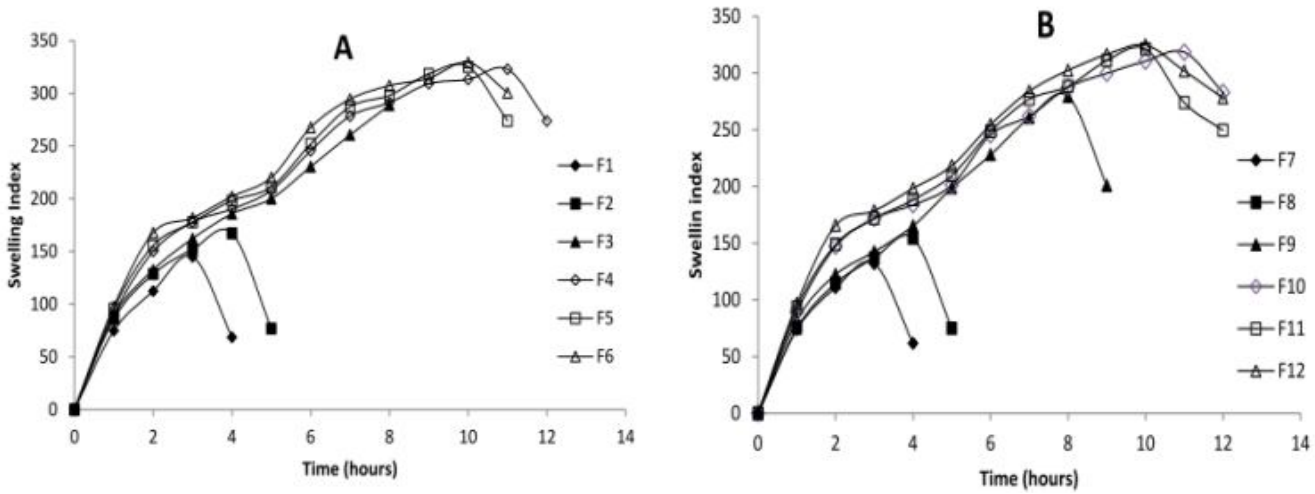

Fig 2: The influence of the Matrix is forming polymers TSP (A) and Guar gum (B) on the Diclofenac sodium Matrix tablet Swelling Index at different concentrations.

From Fig: 2 it could be concluded that medium uptake of prepared matrices depends on the concentration of polymer and also on the type of polymer. Guar gum having the better swelling ability compared to TSP and both the polymers showed better swelling ability at the concentration levels above 20%.

***In-vitro* Drug Release studies:**

In-vitro drug release studies were carried out up to 12 hours. The Diclofenac sodium release profiles from the prepared matrix tablets showed in Fig: 3 and Fig: 4.

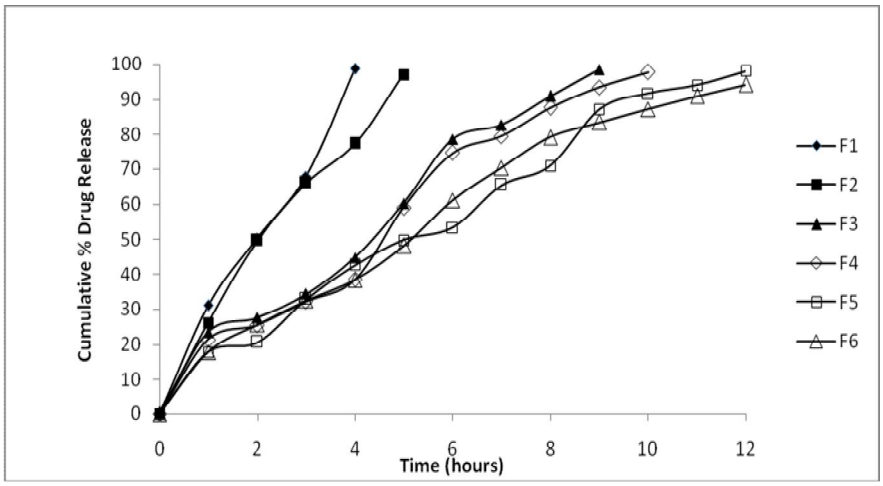

Fig 3: Diclofenac sodium release profiles from formulations F1 to F6 (TSP)

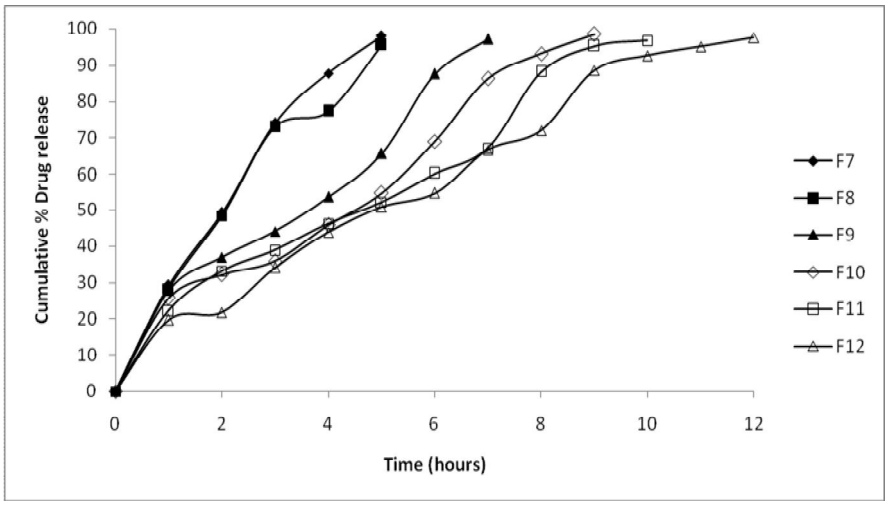

Fig 4: Diclofenac sodium release profiles from formulations F7 to F12 (Guar gum)

The release of Diclofenac sodium from the prepared Matrix tablets sustained for 4 hours to 12 hours. Release of the Diclofenac sodium prolongs with the increase in the concentration of matrix forming agent in both cases. The formulations F1 to F4 and F7 to F10 could not sustain the drug release upto 12 hours. This might be attributed to the insufficiency of the polymer concentration in controlling the drug release. A slow and spread over the release of the drug for 12 hours was found with the other formulations. The formulations F5 and F12, which were fabricated using TSP (30%) and Guar gum (35%), found to be the best formulation among the other formulated tablets, with a 100 % drug release upto 12 hours.

When the release data were analysed as per zero and first order models the correlation coefficient (R^2) values were relatively higher in the zero order model with all Matrix tablets formulated indicating that the drug release from all these tablets followed zero order kinetics. Diclofenac sodium drug release data was also obeyed Higuchi and Peppas models with R^2 values greater than 0.9. When percentage drug released was plotted against √time, linear regressions with 'R^2' > 0.921 were observed with all Matrix tablets prepared indicating that the drug release from all these formulations was diffusion controlled.

Korsmeyer and Peppas equation superposes two apparently independent mechanisms of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer. For a matrix tablet, when 'n' takes the value of 0.45 it indicates diffusion-controlled drug release and for the value 0.89, it indicates swelling-controlled drug release. Values of n between 0.45 and 0.89 can be regarded as an indicator for both the phenomena

(anomalous transport). The values of the diffusion exponent (n) with the corresponding correlation coefficients for all the formulations were shown in Table 3. The 'n' values of various formulations were found to be between 0.45 and 0.89, indicating anomalous transport. The relative complexity of the prepared formulations may indicate that the drug release is controlled by more than one process; a coupling of diffusion and erosion[9].

Table 3: Mathematical Modelling and Release Kinetics of Diclofenac sodium Matrix Tablets

Formulation	Zero order correlation coefficient R^2	First order correlation coefficient R^2	Higuchi's plot correlation coefficient R^2	Korsmeyer-Peppas plots		
				Correlation coefficient R^2	Diffusional exponent (n)	Order of release
F1	0.988	0.735	0.952	0.982	0.807	Non-Fickian
F2	0.982	0.832	0.991	0.992	0.794	Non-Fickian
F3	0.979	0.821	0.947	0.936	0.729	Non-Fickian
F4	0.972	0.899	0.949	0.937	0.756	Non-Fickian
F5	0.984	0.870	0.971	0.974	0.761	Non-Fickian
F6	0.973	0.961	0.976	0.981	0.729	Non-Fickian
F7	0.972	0.898	0.967	0.991	0.774	Non-Fickian
F8	0.965	0.89	0.966	0.984	0.751	Non-Fickian
F9	0.953	0.831	0.921	0.951	0.797	Non-Fickian
F10	0.975	0.845	0.925	0.925	0.658	Non-Fickian
F11	0.973	0.819	0.937	0.964	0.651	Non-Fickian
F12	0.980	0.892	0.969	0.968	0.727	Non-Fickian

CONCLUSION

In this study matrix tablet of Diclofenac sodium was prepared by direct compression, using TSP and Guar gum Polymers used as release retardant. It was found that increase in the concentration of TSP and Guar gum in polymeric ratio decreases the drug release. The formulation F5 and F12 containing 30% and 35% of TSP and guar gum respectively showed good drug release with good matrix integrity. The results suggest that the developed sustained

release matrix tablets prepared employing TSP and Guar gum of Diclofenac sodium could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance

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