

## Original Research Article

# Ispaghula Husk-Based Extended Release Tablets of Diclofenac Sodium: Formulation, Evaluation and *In vitro* Release Studies

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### Abstract

**Purpose:** To formulate extended-release tablets of diclofenac sodium based on ispaghula husk

**Methods:** Tablets with varying proportions of diclofenac sodium and ispaghula husk were formulated by wet granulation technique at a fixed compression force of 10 kN. The formulated tablets were evaluated for physicochemical parameters as well as by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and x-ray diffraction (XRD).

**Results:** Content uniformity, weight variation, thickness and friability of the formulated tablets were within acceptable limits. The hardness of the tablet decreased from 5.4 to 4.2 kg/cm<sup>2</sup> with increasing quantity of ispaghula husk in the formulation. In contrast, disintegration time increased from 12 to 70 min with increasing amount of husk. Tablets formulated with 1:0.25 and 1:0.5 drug/husk ratio failed to extend drug release whereas tablets prepared with 1:0.75 and 1:1 ratio extended release up to 5 and 6 h, respectively. FTIR, DSC and XRD analysis of tablets revealed the absence of diclofenac–ispaghula interaction and crystalline nature of diclofenac sodium. Drug release data fitted well with Korsmeyer-Peppas and the *n* value of 0.98 indicate non-Fickian diffusion. The tablets were stable on storage and retained its physicochemical properties within acceptable limits.

**Conclusion:** The results indicate the possibility of formulating extended-release tablets based on ispaghula husk. The tablets were stable during storage and free from drug-excipient interactions. However further studies are required to ascertain the safety of the husk and to optimize the release properties of the tablets.

**Keywords:** Ispaghula husk, Extended release tablet, Diclofenac sodium, Release kinetics.

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## INTRODUCTION

Ispaghula husk is obtained from dried ripe seeds of *Plantago ovata* Forkal which belongs to the family, Plantaginaceae. Psyllium consists of the seeds of *Plantago psyllium* and *Plantago arenaria*. Ispaghula and Psyllium are invariably named as psyllium [1] in the literature. The US National Formulary [2] includes all three species under the name "Plantago seed." The BP/EP

classifies the husk of *Plantago ovata* as ispaghula and other two as psyllium [3]. All these seeds contain mucilage, and its hydrolysis [1, 4] yields D-xylose, L-arabinose, D-galactose and D-galacturonic acid.

Ispaghula (also called as ispaggol) husk and psyllium regulate bowel function and are available as over the counter drugs to treat constipation. Both recently received attention in

tablet technology as disintegrating agent [5] release retardant [6] and floatation agent [7]. The intended application was achieved with the ispaghula/Psyllium alone [6, 8] or in combination with other polymers [9]. The unique nature of ispaghula husk is higher swelling factor (40 - 90), as it swells 4 - 5 times more than psyllium. In general, more swelling allows the drug to diffuse along a lengthier path length and thus produces extended release from the swollen matrix.

Extended release of drug from swellable matrix tablets [10] mainly depends on the nature of the polymer, drug solubility, drug-polymer ratio, particle size, moisture content of the granule and the force applied to produce tablets. No information is available in the literature about the compression force and the moisture content of granules employed in ispaghula-based extended release tablets. Hence, an attempt is made to formulate ispaghula husk based extended release tablets at various polymer-drug ratios.

## EXPERIMENTAL

### Materials

Diclofenac sodium was received as a gift from Cassel Research Lab., Chennai, India. Ispaghula (*Plantago ovata*) was purchased from Sidhpur Sat-Isapgol factory, Sidhpur, Gujarat, India. Magnesium stearate IP was procured from Sinai Pharma Pvt Ltd, India. Lactose IP was purchased from Lactose India Ltd. All other chemicals used were of analytical grade.

### Preparation of ispaghula husk-based extended release tablets

The husk was powdered and passed through the sieve #30. Other ingredients were passed through the sieve # 40. The tablet ingredients listed in Table 1 mixed in a rapid mixer-granulator (Rotamix HSMG-10, Kevin Engineers, India) for 5 min. A sufficient quantity of starch paste (10 %) was added in divided portions to the mixed powder and granulated in a rapid mixer granulator. The wet granules were passed through a sieve of 1000  $\mu\text{m}$  size and dried at 40 °C for 30 min in a tray drier (Bombay Engineering Works, India). The moisture content was determined by Karl Fischer method (Karl - Fischer titrator, Precision V/M MD, India) and drying continued until the moisture content fell to between 5.0 and 5.5 % w/w. The dried granules were passed through the sieve of 1410  $\mu\text{m}$  size, lubricated with magnesium stearate (1 % w/w) and talc (1 %w/w) and then compressed with a force of 10 kN using 11 mm flat punches in a

tablet compression machine (Clit, CJD3 20 stations) to obtain tablets of approximately 400 mg weight.

### Drug content

Twenty tablets were weighed and powdered. The quantity equivalent to 50 mg of diclofenac sodium was weighed accurately and taken in a 200 ml volumetric flask. Phosphate buffer (60 ml, pH 7.4) was added to the flask and sonicated (Sonicator- Branson, SmithKline) for 5 min. The volume was made up to 200 ml with phosphate buffer. After filtration (Whatman filter paper, no. 1) and appropriate dilution, diclofenac sodium content was determined at 276 nm [11] using a UV-visible spectrophotometer (UV-1601, Shimadzu, Japan).

### Physical parameters

The formulated tablets were tested [12] for weight variation, thickness, friability, hardness and disintegration. The weight of 20 tablets from each batch was taken using an electronic balance (Mettler Toledo, PL 303) and the mean weight calculated. The tablets were weighed individually to determine the variation from average weight. The individual thickness of 10 tablets from each batch was measured using a Vernier caliper. Preweighed tablets ( $n = 20$ ) tablets were placed and rotated in friability test apparatus (Hicon, India). The tablets were weighed once again after 100 revolutions to find out the weight loss. The hardness of 6 tablets was measured using a hardness tester (Dr Schleuniger Pharmatron, India) and the mean calculated. Disintegration test was carried out on 6 tablets using a tablet disintegration apparatus (Sakti Scientific, India) and water as medium. Each tablet was dropped in the moving (30 cycles per min) glass tube ( $n = 6$ ) immersed in 1000 ml of medium maintained at  $37 \pm 2^\circ\text{C}$ . The time required to disintegrate each tablet was noted visually.

### Fourier transform infrared spectroscopy (FTIR)

The infrared spectra of the powdered tablet and diclofenac sodium were recorded on a Nicolet 20 DXB FTIR spectrophotometer using KBr pellet technique. The tablets were powdered in a mortar and pestle, mixed with KBr and compressed to produce pellets using a hydraulic press. Diclofenac sodium and husk were used as such to make KBr pellets.

## Differential scanning calorimetry

Differential scanning calorimetry (DSC) analysis of diclofenac sodium and powdered tablets were done using Perkin-Elmer DSC-7 model. The instrument was calibrated with indium. All the samples ( $\approx 5$  mg) were heated in sealed aluminum pans with perforated lid using dry nitrogen as the effluent gas. The analysis was performed over the heating range of 50 – 300 °C at a rate of 20 °C min<sup>-1</sup>.

## X-ray diffraction

Diclofenac sodium and powdered tablets were analyzed using an x-ray diffractometer (XD-D1, Shimadzu, Japan) in the 2 $\theta$  range 5 - 80°. Operating conditions include CuK $\alpha$  radiation, 30 kV, 20 mA and a slit of 1-1-0.3 mm.

## In vitro release studies

The *in vitro* release study of diclofenac sodium from the formulated tablets was carried out in 900 ml of phosphate buffer (pH 7.4) using a USP dissolution apparatus 1 (model TDT 067, Electrolab, India) at 37  $\pm$  2°C and 100 rpm. Samples were taken at regular intervals and diclofenac content measured spectrophotometrically at 276 nm [11].

## Drug release kinetics

The data obtained from *in vitro* release studies were fitted to various kinetic equations [11] to determine the mechanism of drug release from the tablets. The kinetic models used were zero order equation, first order equation and Higuchi release, i.e.,  $Q_t$  vs  $t$ ,  $\log(Q_0 - Q_t)$  vs  $t$  and  $Q_t$  vs square root of  $t$ , respectively; where  $Q_t$  is the amount of drug released at time  $t$  and  $Q_0$  is the initial amount of drug present in the tablets. To further ascertain the mechanism of drug release,

the first 60 % of drug release was fitted to Korsmeyer-Peppas model (Eq 1).

$$M_t/M_\infty = kt^n \dots\dots\dots (1)$$

where  $M_t/M_\infty$  is the fraction of drug released at time,  $t$ ,  $k$  is the rate constant and  $n$  is the release exponent. The  $n$  value is used to characterize different release mechanisms.

## Stability studies

The tablets (batch 4) were kept for a short term accelerated stability study in a high-density polyethylene bags with a sealed cover at 40  $\pm$  2°C/75  $\pm$  5 %RH as per International Convention on Harmonization (ICH) guidelines. Samples were withdrawn after 1, 2 and 3 months of storage and evaluated [12] for appearance, hardness, drug content, and dissolution.

## Statistical analysis

Drug loading, entrapment and encapsulation efficiency data were analyzed using independent sample t-test while drug release data were analyzed using ANOVA. PASW 18 statistics software (IBM, USA) was used for statistical analysis and the confidence level was set at  $p < 0.05$ .

## RESULTS

### Physicochemical characteristics of ispaghula tablets

The physical and chemical parameters of the formulated tablets are presented in Table 1. Physicochemical parameters such as uniformity in drug content, thickness, friability and weight variation of the tablets were within the acceptable limits stipulated in British Pharmacopoeia. Drug content, thickness and weight of all formulated tablets were within 5 % variation ( $p > 0.05$ ) and the % of loss during friability test was less than 1

**Table 1:** Composition and characteristics of formulated tablets

	Batch 1	Batch 2	Batch 3	Batch 4
<b>Composition per tablet</b>				
Drug: Isapgol	1:0.25	1:0.5	1: 0.75	1:1
Diclofenac sodium (mg)	100	100	100	100
Isapgol husk (mg)	25	50	75	100
Starch (mg)	100	100	100	100
Lactose (mg)	175	150	125	100
<b>Physicochemical properties</b>				
Disintegration time (min)	12.0 $\pm$ 1.7	16.0 $\pm$ 2.2	30.0 $\pm$ 3.2	70.0 $\pm$ 3.2
Hardness ( kg/cm <sup>2</sup> )	5.40 $\pm$ 0.18	5.20 $\pm$ 0.26	4.80 $\pm$ 0.34	4.20 $\pm$ 0.23
Thickness (mm)	3.14 $\pm$ 0.04	3.18 $\pm$ 0.08	3.20 $\pm$ 0.05	3.22 $\pm$ 0.08
Friability (%)	0.92	0.89	0.91	0.89
Average weight (mg)	401.0 $\pm$ 1.7	398.0 $\pm$ 2.1	405 $\pm$ 1.1	409.0 $\pm$ 1.63
Drug content (% w/w)	99.6 $\pm$ 0.7	100.4 $\pm$ 1.1	99.2 $\pm$ 1.8	102.1 $\pm$ 1.5

Results are expressed as mean  $\pm$  SD.

% w/w ( $p > 0.05$ ). Each batch of tablets was found consistent with respect to measured hardness (5.4 to 4.2 kg/cm<sup>2</sup>,  $p > 0.05$ ). The tablet hardness was decreased as husk proportion increased in the formulation. Batch 4 tablets showed longer disintegration time (70 min,  $p < 0.05$ ) than tablets of other batches in spite of their lower hardness.

#### Fourier transform infrared spectroscopy

The FTIR spectrum of ispaghula (Figure 1A) showed identical peaks similar to those already reported in literature [13, 14]. The FTIR spectrum of diclofenac sodium (Figure 1B) showed characteristic peaks at 1167 and 682 cm<sup>-1</sup> for aromatic -C-Cl. The stretches between 800 and 600 cm<sup>-1</sup> also support the presence of -C-Cl group. The strong peaks in the region of 1600 - 1700 - 1800 cm<sup>-1</sup> indicate the presence of -C=O. Furthermore, the presence of peaks in the region of 1200, 1283 and 1044 cm<sup>-1</sup> confirms -C-O-group. The peaks at 1603, 1507 and 869-716 cm<sup>-1</sup> indicate the presence of the aromatic ring. Similar peaks also appeared in the spectrum of drug-containing tablets (Figure 1C). We previously reported similar findings for diclofenac sodium loaded microspheres [11].

#### Thermal properties

The thermogram of ispaghula husk (Figure 2) did not show any peak and indicated its amorphous nature. The thermogram of diclofenac sodium showed a crystalline peak at 296 °C, same as for the physical mixture of diclofenac sodium: husk as well as the tablet formulation. The extent of the peak increased as the degree of crystallinity

of the drug in the formulation increased.

#### X-ray diffraction (XRD)

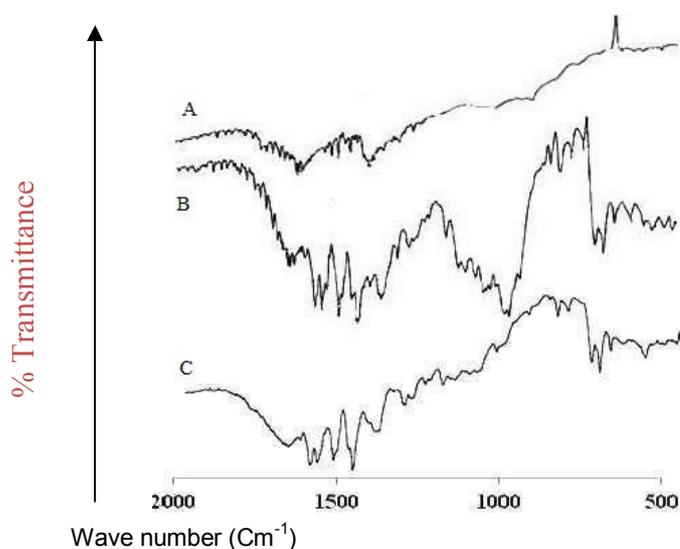
The XRD of ispaghula husk did not produce any sharp peak (Figure 3) and confirmed its amorphous nature. The XRD of diclofenac sodium showed sharp peaks in the region 10 - 20°, indicating the crystalline nature of the drug. These peaks also appeared in the diffractogram of the tablet formulations.

#### In vitro drug release

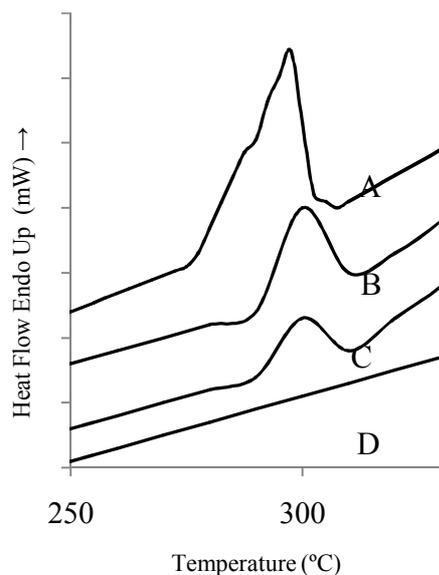
In vitro release profiles of diclofenac sodium from the tablets are shown in Figure 4. Batches 1 and 2 did not show extended release of the drug whereas batches 3 and 4 extended drug release up to 5 and 6 h, respectively. There was no significant difference ( $p > 0.05$ ) between the release profiles of diclofenac sodium from batch 1 and 2 tablets but release was significant ( $p < 0.05$ ) between batches 3 and 4.

#### Drug release kinetics and release mechanism

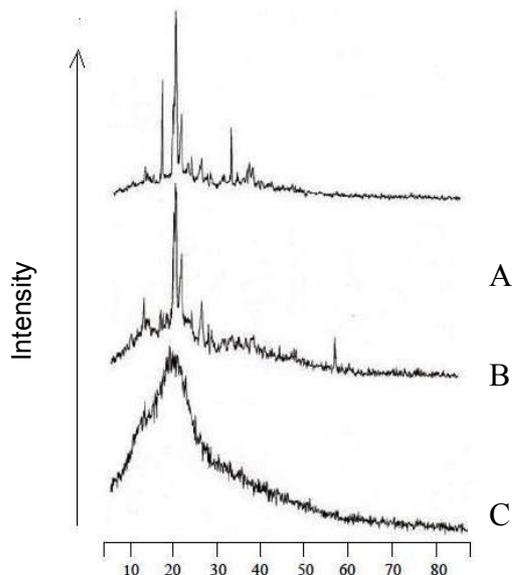
The first 90 % release data of batches 3 and 4 tablets were fitted to various kinetic models. The best fit (highest correlation coefficient) was first order model ( $r^2 = 0.9720$  and  $0.9852$  for batches 3 and 4, respectively.) followed by Higuchi (diffusion controlled,  $r^2 = 0.9662$  and  $0.9678$  for batches 3 and 4, respectively); zero order ( $r^2 < 0.9517$ ); and Hixson-Crowell or modified cube root (dissolution controlled, showed poor correlation ( $r^2 < 0.7328$ )). When the first 60 % drug release data were fitted to Korsmeyer-Peppas model for batch 4 tablets, it yielded a value of  $r^2 = 0.9829$  and  $n$  value of 0.98.



**Figure 1:** FTIR spectra of ispaggol husk (A), diclofenac sodium (B) and formulated tablet (C)



**Figure 2:** DSC thermograms of diclofenac sodium (A), physical mixture of diclofenac sodium and husk (1:1) (B), batch 4 tablet (C) and ispaggol husk (D).



**Figure 3:** X-ray diffraction of diclofenac sodium (A), tablet formulation (batch 4, B) and ispaggol husk (C)

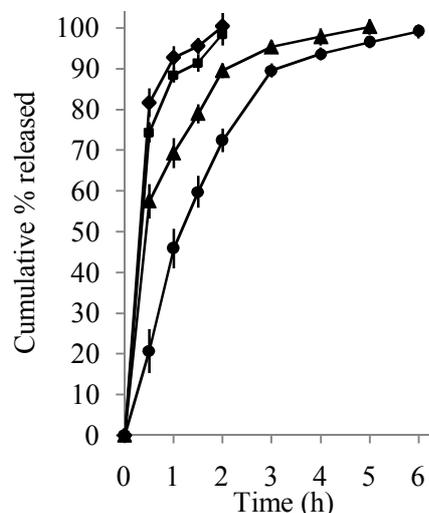
### Storage stability

The tablets largely retained their physicochemical properties under accelerated storage conditions, showing less than 5 % variation in their original values as shown in Table 1. Almost same release profile ( $p > 0.05$ ) was observed after 3 months storage.

### DISCUSSION

Tablets formulated with 1:1 ratio of ispaghula/diclofenac sodium showed lower hardness than other batches. Increase in husk content resulted in weaker tablets. This could be

due to the soft nature and poor compressibility of ispaghula husk. A higher proportion of ispaghula in the formulated tablets also prolonged disintegration time.



**Figure 4:** *In vitro* release of diclofenac sodium from batch 1 (♦), 2 (■), 3 (▲) and 4 (●) tablets

FTIR is capable of indicating a potential chemical interaction in a formulation. The spectra indicate that there was no chemical interaction. This was confirmed by both DSC and XRD results. DSC and XRD also confirmed that the crystalline nature of drug was retained in the formulated tablets.

More than 90 % of the drug in batches 1 and 2 tablets was released within 1 h due to the rapid disintegration of these tablets. Batch 3 and 4 tablets disintegrated in 30 and 70 min, respectively. Batch 3 formulation extended release in a bi-phasic manner. An initial burst release was observed for batches 3 and 4 probably due to the free drug present on the surface of the tablets as well as faster swelling of husk matrix which is beneficial as it could serve as prompt dose for immediate pharmacological activity.

Drug release from batches 3 and 4 tablets followed first order kinetics more closely than the other release models. The release exponent,  $n$ , value of 0.98 obtained from Korsmeyer-Peppas analysis indicates non-Fickian diffusion [15]. Thus, drug release from the tablets is swelling-controlled rather than diffusion-controlled. A similar release mechanism has previously been observed for arabinoxylans-based diclofenac sodium sustained release tablets [6]. The high  $n$  value of 0.98 (close to 1) also indicates that the initial 60 % release of loaded drug followed zero order kinetics [15]. It is also evidenced by the linear relationship between time (initial 2 h) and

% release. Later the release was slowed down and eventually followed first order kinetics.

## CONCLUSION

The present study reveals the possibility of formulating extended release tablets using ispaghula husk as a sole release retarding polymer without interaction with diclofenac sodium. However, further studies are required to optimize both the physical and release properties of the tablets.

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