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## Research Article

## COMPARING DIFFERENT COMPRESSION TECHNIQUES FOR OKRA GUM AS A COAT OVER DICLOFENAC SODIUM CORE TABLETS FOR COLON TARGETING

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## ABSTRACT

Context: Colon-specific tablet formulations for chronotherapeutic delivery of Diclofenac sodium have been proposed in this study. The objective of the present work was to employ Okra gum as compression coat over fast disintegrating core tablets of Diclofenac sodium. Materials and methods: Core tablets were prepared by direct compression method and further coated by okra gum by wet granulation and direct compression methods. Formulations were evaluated for physicochemical properties including in vitro drug release in presence or absence of rat caecal contents. *In vivo* pharmacokinetic study of optimized batch was performed in rabbits. Results and discussion: The compression coated tablets of Diclofenac sodium (CC8) prepared by direct compression method containing 500mg okra gum showed 3.11% drug release in 5h in upper GIT. The prepared formulations when studied in presence of rat caecal content in dissolution medium, as increase in the amount of drug released was observed by action of bacterial enzymes present in rat caecal content. *In vivo* pharmacokinetic study for above said formulation (CC8) showed minimum drug absorption in upper GIT with abrupt drug absorption as tablet formulation reaches lower part of GIT (colon). The insignificant changes in the physicochemical properties of tablet formulations (CC28) after storage at 40°C/75% RH for 6 months indicate that the formulation could have a minimum shelf life of 2years. Conclusion: The prepared tablet formulations of Diclofenac sodium can be considered suitable dosage form for chronotherapeutic treatment of rheumatoid arthritis.

**Keywords:** *In vivo* study, similarity factor, okra gum, compression coat, stability study

## INTRODUCTION

Many approaches have been attempted for the development of colon-specific delivery systems that rely on gastro-intestinal pH, transit times, enterobacteria and luminal pressure for site-specific delivery<sup>1</sup>. Each of these technologies represent a unique system in terms of design but has certain shortcomings, which are often related to degree of site-specificity, toxicity, cost and ease of scale up manufacturing. Recent research into the utilization of the metabolic activity and the colonic microenvironment in the lower gastrointestinal tract has attained great value in the design of novel colon-targeted delivery systems based on natural biodegradable polysaccharides. It appears that microbially-controlled systems based on natural polysaccharides have the greatest potential for colonic delivery, particularly in terms of site-specificity and safety because of the presence of the biodegradable enzymes only in the colon<sup>2</sup>. Advantageously colonic drug delivery system would be

valuable when a delay in absorption is therapeutically desirable in treatment of chronic medical conditions like rheumatoid arthritis had apparent circadian rhythm and peak symptoms in the early morning<sup>3</sup>. Rheumatoid Arthritis (RA) is a chronic autoimmune disease of unknown etiology and a major cause of disability. It is characterized by joint synovial inflammation and progressive cartilage and bone destruction resulting in gradual immobility<sup>4</sup>. The aim of rheumatoid arthritis treatment is to reduce inflammation in the joints, relieve pain, prevent or slow joint damage, reduce disability and provide support to help you live as active a life as possible<sup>5-9</sup>.

Diclofenac sodium belongs to a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs) is considered to be first line agent which generally used for the treatment of RA. The primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX) and it appears to inhibit DNA synthesis<sup>10</sup>. Since the therapy involves frequent administration of drug, chances of

patient noncompliance increase drastically. Additionally, patients suffering from rheumatoid arthritis feel more pain in the morning hours. In this case taking medication at night is an obvious solution and hence drug need to be administered 4 to 6 hours before achieving their maximum benefits, as a result peak will occur at patients waking and the effect will be decline as patient start to wake up. With orally administering conventional Diclofenac sodium formulation, it is difficult to achieve the desired clinical effect, because it elicits patients' noncompliance of administration in the early morning to coordinate the rhythm of these diseases, due to rapid absorption of the conventional formulation.

It is imperative to design a drug delivery system that administered at bedtime but releasing drug during morning hours would be ideal in this case. However, in comparison to the conventional formulation, colon specific drug delivery is very effective and more convenient for administration. Thus in present investigation orally-administered tablets of natural polysaccharide okra gum were prepared that would ensure chronotherapeutic delivery of drugs in colon for the treatment of diseases like asthma and rheumatoid arthritis.

## MATERIALS AND METHODS

Fresh Okra pods were purchased from local market. Diclofenac sodium was obtained as gift sample from Torrent Pharmaceuticals Ltd. Ahmadabad. Naproxen (Internal standard) was obtained from Sigma Aldrich, Mumbai. MCC and Sodium hydroxide were obtained from Chiti Chem Corporation, Vadodara. Other chemicals were purchased from Allied Chemical Corporation, Vadodara.

### Isolation of okra gum (OG)

Isolation of okra gum from fresh okra pods were performed as per method reported by Nipaporn et al. (2009).<sup>11</sup> A 3kg weight of fresh Okra pods, from which the stalk and apex of the pods had been removed, was weighed. The okra was sliced with a hand knife, homogenized with two times its weight of 70% (vol/vol) aqueous ethanol at room temperature. The resultant paste was then filtered to get insoluble residue. The residue was washed with double volumes of chloroform/methanol (1/1, vol/vol) with gentle stirring for 30min to remove low molecular weight (colored) compounds followed by filtration using muslin cloth to get pure residue of OG. The residue was finally washed with acetone and product was dried in an oven for 24h. Dried product (OG) was preserved for further study.

**Preformulation study by differential scanning calorimetry**  
Drug, polymer and excipients compatibility study was carried out by DSC Perkin Elmer pyris-1. Test was carried out in the heating range of 500<sup>o</sup>C to 4000<sup>o</sup>C at a heating rate of 10<sup>o</sup>C/min. DSC study was carried out individually for drug and for the combination of drug, polymer and excipients.

### Preparation of Diclofenac sodium compression coated tablets

#### Preparation of fast disintegrating core tablets

Core tablets containing 50mg of Diclofenac sodium were prepared using starch (50mg), microcrystalline cellulose (50mg) and magnesium stearate (5mg). Drug along with additives were weighed separately and thoroughly mixed by passing through a mesh (100#) to ensure uniform mixing. The

mixture was compressed into tablet using 8mm round, flat-faced, plain punches using a 10 station tablet punching machine by direct compression. The prepared core tablets were evaluated for properties like thickness, hardness, weight variation, friability, content uniformity and disintegration. Disintegration test was performed as per Indian Pharmacopoeia 2007<sup>12</sup> in pH 6.8 PBS to check the fast disintegrating property of the prepared tablets (Table 1).

### Compression Coating of Core Tablets

Compression Coating of Core Tablets was done by two methods:

1. Wet granulation method
2. Direct compression method

#### 1. Wet granulation method

To prepare compression coated tablets, coating was observed on core tablets. Granules were prepared to apply the coat on core tablets. To prepare granules, okra gum at various concentrations was blended and granulated using PVPK30 as binder. The wet mass was passed through 16# sieve and the obtained granules were dried in hot air oven at 50<sup>o</sup>C for 30min and dried granules were sieved through 22/44# sieves. About one third of the granules were placed in 12mm die cavity and the core tablets of Diclofenac sodium (8mm) were carefully positioned in the centre of the die cavity and remaining portion of die cavity was filled with the granules (2/3<sup>rd</sup>). It was then compressed around the core tablets at a maximum force on 10 station tablet punching machine (Table).

#### 2. Direct compression method

To prepare compression coated tablets, coating was observed on core tablets. The direct compression method was employed to apply the coat on core tablets. Okra gum at various concentrations was sieved through 100# sieve and blended. About one third of uniformly blended coating mixture was placed in 12mm die cavity and the core tablets of Diclofenac sodium (8mm) was carefully positioned in the centre of the die cavity and remaining portion of die cavity was filled with the coating mixture. It was then directly compressed around the core tablets at a maximum compression force on 10 station tablet punching machine using 12mm round flat faced punches that had been surface lubricated as and when necessary with magnesium stearate and talc mixture (Table).

### Evaluation of Diclofenac Sodium Compression Coated Tablets

Various evaluation tests like hardness, weight variation, friability, swelling and erosion were performed. *In vitro* drug release study was carried out in absence or presence of rat caecal contents as per the procedure described below.

#### Hardness test

Tablet hardness (tablet crushing strength) is defined as the force required to break the tablet in a diametric compression test. Tablets required an enough hardness or strength to withstand mechanical shocks during packaging and shipping. Hardness of the tablets (five tablets) was measured using Monsanto hardness tester.

#### Friability test

The friability of the tablets (weight of tablets equivalent to 6g) was measured in a Roche friabilator (DBK friability test apparatus, India). Tablets of a known weight ( $W_0$ ) or a sample

of tablets were dedusted in a drum for a fixed time (100 revolutions) and weighed ( $W_t$ ) again. Percentage friability was calculated from the loss in weight as per the given equation as below. The weight loss should not be more than 1% wt/wt.

$$\% \text{ Friability} = [(W_0 - W_t) / W_0] \times 10$$

#### Weight Variation Test

Weight variation test was performed as per the Indian Pharmacopoeia 2007. Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation.

#### Drug Content

The drug content in each formulation was determined by triturating 5 tablets and powder equivalent to average weight was added in water, followed by stirring for 30min. The solution was filtered, diluted suitably and the absorbance of resultant solution was measured by double beam UV spectrophotometer at respective  $\lambda_{\text{max}}$ .

#### In Vitro Drug Release Studies

Drug release studies were carried out using USP Dissolution Test Apparatus Type I (100rpm,  $37^\circ\text{C} \pm 0.5^\circ\text{C}$ ). The tablets were tested for drug release upto 2h in pH 1.2, 0.1N HCl (900mL) as the average gastric emptying time is about 2h. Then the dissolution medium was replaced with Phosphate buffer saline pH 7.4 (900mL) and tested for drug release upto 3h as the average small intestine transit time is about 3h. At the end of the time periods, two samples each of 1mL were taken, suitably diluted and analyzed for drug content at respective  $\lambda_{\text{max}}$  using UV visible spectrophotometer.

#### In Vitro Drug Release Studies in presence of rat caecal content

The susceptibility of OG to the enzymatic action of colonic bacteria was assessed by method reported by Rama Prasad et al., 1999.<sup>13</sup> Where by drug release study was continuing in 100mL of PBS pH 6.8 containing 4% wt/vol of rat caecal contents as per the guideline of CPCSEA (Committee for the purpose of control and supervision of Experiments on animal, Ministry of Culture, Government of India) and all the study protocols were approved by the Local Institutional Animal Ethical Committee. The caecal contents were obtained from male albino rats (weighing 150–200g). Rats were sacrificed and abdomen was opened. Caecal contents was collected and immediately transferred in PBS pH 6.8 to get a final caecal dilution of 4% wt/vol. The drug release studies were carried out in USP dissolution rate test apparatus (Type II, 100rpm,  $37^\circ \pm 0.5^\circ\text{C}$ ) with slight modification of apparatus design. A beaker (capacity 150mL) containing 100mL of dissolution medium was immersed and fixed by rubber packing in the 1000mL vessel of dissolution test apparatus. The 1000mL vessel was filled with 200mL of water to maintain  $37^\circ\text{C}$  temperature of 100mL dissolution medium. The tablets were placed in the baskets and immersed in 100mL dissolution medium containing rat caecal contents. The experiment was carried out with continuous  $\text{N}_2$  gas supply into 100mL dissolution medium to simulate anaerobic environment of the Caecum. The drug release studies were carried out upto 3h and 1mL samples were taken at different time intervals. Collected samples were not filtered. Media was replaced with 1mL of fresh PBS pH 6.8. To the withdrawn samples, 1mL of

methanol was added to solubilize the released drug from tablet formulations due to break down of OG by the caecal enzymes. 1mL withdrawn sample was diluted upto 10mL with PBS pH 6.8, then it was centrifuged and the supernatant was collected. The collected supernatant was filtered through a bacteria-proof filter (45 $\mu\text{m}$ ) and the filtrate was analyzed for drug content at the respective  $\lambda_{\text{max}}$  as procedure described in methodology section. The above study was carried out for all the formulations with rat caecal contents and also without caecal contents in PBS pH 6.8 (control).

#### Scanning electron microscopy of selected formulation

A scanning electron microscope (Philips FE1, TGA-7DSC-PYRIS-IDTA-7, Gaseous secondary electron detector, acceleration voltage of 20kV, chamber pressure of 0.6mm Hg) was employed to study the morphology and topography of tablets (CC8) before and after dissolution study. After predetermined time intervals tablets were removed from the dissolution apparatus and undisturbed tablets were subjected to scanning electron microscopy to study the morphological and topographical changes after dissolution in various dissolution medium.

#### In vivo pharmacokinetic study of selected formulations

##### Sample Preparation

1mL rabbit plasma was taken in a 10mL capacity test tube. In this test tube 100 $\mu\text{l}$  of internal standard solution, 1mL of 1M orthophosphoric acid, and 5mL of a mixture of hexane:isopropyl alcohol (90:10) were added. Final sample concentrations were calculated by determination of the peak area ratio of Diclofenac sodium related to internal standard and comparing the ratio with the standard curve, obtained after analysis of calibration samples.

##### Study design

The pharmacokinetic study on rabbit for tablet dosage form containing drug was carried out to study the pharmacokinetic parameters of the formulations using HPLC technique of analysis. Rabbits (New Zealand, White) of either sex weighing 2.5-3.0kg were used to carry out the in vivo pharmacokinetic study with prior approval from the animal ethical committee of Indukaka Ipcowala College of Pharmacy, New Vallabh Vidyanagar (Protocol no. IICP/PH/12-201/03). The animals were divided into two groups, and each group of three rabbits received one of the tested formulations (compression coated tablets of Diclofenac sodium and commercial tablets). The animals fasted overnight before tablet administration and during the experiment but were given free access to water. The test formulations were given orally to the rabbits with sufficient flush of water in fasting conditions which was assisted by a local veterinary doctor. Food was withdrawn from the rabbits 12h before drug administration and until 12h post-dosing. All rabbits have free access to water throughout the study. Blood samples (1mL) were collected from marginal ear vein before dosing (zero time) and at different time intervals after dosing, namely 1h, 2h, 4h, 5h, 6h and 8h using heparinized tubes. The collected samples were immediately centrifuged at 5000rpm for 15min and plasma was separated. The collected plasma then stored at  $-20^\circ\text{C}$  until analysis.

**Analysis of plasma level of Diclofenac sodium**  
Waters HPLC system model 746 (USA), consisting of a model

515 intelligent solvent delivery pump, a 50 $\mu$ l injection loop, a computerized system controller, and a Waters 487 UV detector was used for analysis of plasma level of Diclofenac sodium. The plasma protein was precipitated with acetonitrile. Separation was performed on a  $\mu$ -bondapak C18 (150mm  $\times$  4.6mm) column. The mobile phase was acetonitrile, deionized water, orthophosphoric acid (45:54.5:0.5) with final pH of 3.5 and the flow rate was 1mL/min. A wavelength of 278nm was used to monitor the drug and the naproxen (Internal standard). The peak area ratio was selected as the basis for quantification.

#### Short term stability study

Stability studies on selected formulations of Diclofenac sodium were carried out as per ICH guidelines at 40 $\pm$ 2 $^{\circ}$ C/75 $\pm$ 5% RH and formulations were subjected to accelerated stability studies for 6months, as India falls under climatic Zone III.<sup>14</sup> The samples were withdrawn monthly and evaluated for physical attributes of tablets such as physical appearance, percentage drug content and dissolution characteristics as per the procedure described earlier.

## RESULTS AND DISCUSSION

#### Preformulation study by Differential Scanning Calorimetry

The DSC thermogram of the drug (Figure 1) depicts a sharp endothermic peak at 282.30 $^{\circ}$ C corresponding to the melting transition temperature of Diclofenac sodium followed by an exotherm. This result is indicative of melting of drug followed by decomposition. The melting point of the drug was 284 $^{\circ}$ C with an enthalpy variation ( $\Delta H$ ) of 19.446 Jg $^{-1}$  (within the 265–295 $^{\circ}$ C range). The DSC thermogram (Figure 2) of core tablet of drug showed similar peaks corresponding to pure drug indicated the absence of well defined chemical interaction between the drug and excipients.

#### Formulation of fast disintegrating core tablets

Fast disintegrating core tablets of Diclofenac sodium were prepared by using direct compression method that would allow the core tablets to disintegrate rapidly once the coat material is digested by the resident microflora of the colon. Average weight of the core tablets was fixed at the lowest possible level (155mg) to accommodate maximum amount of coat material over the core tablet and the average percentage deviation of core tablet was within the official limit (within 7.5%). and the core tablet formulation was disintegrated within 18sec showing required fast disintegration characteristics of core tablet. Diclofenac sodium core tablet formulation contains fast disintegrating additives like microcrystalline cellulose (50mg) and starch (50mg) which might have contributed for such a fast disintegration of core tablets (disintegration time=18sec) that would ensures abrupt and complete release of drug when the dosage form reaches colon.

#### Compression coating of fast disintegrating core tablets

##### Wet granulation method for the formulation of compression coat

The results of weight variation ( $\leq$ 1.42%), friability ( $\leq$ 0.89%) and hardness (3.1  $\pm$  0.09kg/cm $^2$  to 3.6  $\pm$  0.11kg/cm $^2$ ) for the

formulations (CC1-CC4) are depicted in Table 1. Values of Rel $_{5h}$  were found to be decreased with increasing concentration of OG in the formulations (16.24% to 5.14%). This may be due to increased thickness of coat with increase OG concentration that act as resistance and thus retarded the drug release. Cumulative percentage drug release from the formulations (CC1-CC4) is shown in Table 2. Comparison of dissolution profiles for the formulations (CC1-CC4) is shown in Figure 3. The drug delivery systems targeted to the colon should not only protect the drug from being released in the physiological environment of stomach and small intestine, but also release the drug in colon after enzymatic degradation by colonic bacteria. Hence, drug release study was carried out with PBS pH 6.8 in presence or absence of rat caecal content for the formulation (CC4) because it shows restricted drug release in upper GIT (5.14%). Comparison of dissolution profiles for the formulation (CC4) in presence or absence of rat caecal content is shown in Figure 4. The percent drug released from tablets coated with coat formulation CC4 (500mg OG) was found to increase from 5h onwards indicating the commencement of breaking of gum coats in presence of rat caecal content. During drug release study, the percentage drug released after 8h was 80.14% in presence of rat caecal content as compared to 30.24% in absence of rat caecal content. This significant increase in drug release was explained by similarity factor ( $f_2$ ). The  $f_2$  value for dissolution data of tablet formulation (CC4) in presence and absence of rat caecal content was found to be less than 50 indicating that drug release profiles of the formulation (CC4) in presence and absence of rat caecal content are dissimilar. It may be due to bacterial population present in the rat caecal content that uses OG coat as a substrate and carrying out its hydrolysis with subsequent release of drug. It was found that PVPK30 as binder restricted the drug release in upper GIT (5.14%) and thus further batches were prepared using PVPK30.

#### Direct compression method for the formulation of compression coat

A direct compression method was used to prepare coat which is to be given on core tablet with the aim of controlling further drug release in upper GIT. Tablet formulations (CC5-CC8) containing increasing concentration of OG were prepared where coat was given by direct compression method. These prepared tablets were evaluated for weight variation, friability, hardness and Rel $_{5h}$ . The results of weight variation ( $\leq$ 1.99%), friability ( $\leq$ 0.89%) and hardness (3.1  $\pm$  0.14kg/cm $^2$  to 3.7  $\pm$  0.09kg/cm $^2$ ) for the formulations (CC5-CC8) are depicted in Table 2. Values of Rel $_{5h}$  were found to be decreased with increasing concentration of OG in the formulations (11.14% to 3.11%). This was attributed to the increased thickness with increase OG concentration that act as resistance and thus retarded the drug release. The drug delivery systems targeted to the colon should not only protect the drug from being released in the physiological environment of stomach and small intestine, but also release the drug in colon after enzymatic degradation by colonic bacteria. Hence, drug release study was carried out with PBS pH 6.8 in presence or absence of rat caecal content. Drug release study in presence

or absence of rat caecal content was performed for the formulation (CC8) that restricted drug release in upper GIT. Comparison of dissolution profiles for the formulation (CC8) in presence or absence of rat caecal content is shown in Figure 5. The percent drug released from tablets coated with coat formulation CC8 (500mg OG) was found to increase from 5h onwards indicating the commencement of breaking of gum coats. The percent drug released after 8h was 78.24% in presence of rat caecal content as compared to 27.27% in absence of rat caecal content. Moreover, similarity factor ( $f_2$ ) was used to compare dissolution profiles for the formulation (CC8) in presence and absence of rat caecal content. The  $f_2$  value for comparison of dissolution data of tablet formulations was found to be less than 50 indicating that drug release profiles of the formulation in presence and absence of rat caecal content are dissimilar. So it was concluded that in presence of rat caecal contents the drug release from the formulation was increased significantly.

During dissolution study, formulation (CC8) shows controlled drug release in upper GIT with subsequent rapid drug release in colonic fluid was subjected to scanning electron microscopy (SEM) to check the surface integrity of tablet during different phases of dissolution. Images were taken before and after dissolution and shown in Figure 6. SEM image of fresh tablet formulation (CC8) showed smooth surface before dissolution. SEM image of same tablet after 5h of dissolution exhibited increased porosity with intactness. The higher porosity of tablet surface in PBS (pH 7.4) may be due to its solubility at near neutral pH (pH 6.5).<sup>15</sup>

Based on the above study it was found that directly compressed formulation (CC8) containing OG (500mg) as coat were able to control the drug release in upper GIT to a great extent. Thus, formulation (CC8) was evaluated and compared with marketed formulation (Voveran) for in vivo pharmacokinetic study in rabbit. The area under the curve ( $AUC_{0-t}$ ) was estimated by the linear trapezoidal rule and  $AUC_{0-\infty}$  was calculated by equation  $AUC_{0-t} + C_t / k_e$ , where  $C_t$  is the last measurable concentration and  $k_e$  the elimination rate constant which was determined from the slope of the linear portion of graph plotted between logarithm of plasma concentration and time. The peak plasma concentration ( $C_{max}$ ,  $\mu\text{g/mL}$ ) and corresponding time to peak ( $T_{max}$ , h) were determined by the inspection of the individual drug plasma concentration-time profiles.  $T_{1/2}$  was determined using the equation  $T_{1/2} = 0.693/K_e$ .

The comparative plasma concentrations at different time intervals of prepared formulation (CC8) with Voveran (marketed formulation) are depicted in Table 3. Plasma concentration profiles at different time intervals of prepared formulation (CC8) with Voveran (marketed formulation) are shown in Figure 7. The values of  $C_{max}$  were found to be  $23.64 \pm 2.11 \mu\text{g/mL}$  and  $21.21 \pm 2.24 \mu\text{g/mL}$  for the formulations Voveran (marketed formulation) and CC8, respectively. *In vivo* pharmacokinetic parameters for optimized formulation (CC8) and marketed formulation (Voveran) are summarized in Table 4. It was found that the absorption was relatively rapid with marketed formulation (Voveran) as indicated by low  $T_{max}$

value (1.9h); whereas the prepared colon targeted formulations exhibited delayed absorption as demonstrated by high  $T_{max}$  values (6.2h for CC8). This indicates that the absorption of Diclofenac sodium from the prepared formulations was most likely occurred in the lower GI tract of the rabbit. The delayed onset of Diclofenac sodium absorption can be attributed to the presence of the okra gum coating over the core tablet, which has prevented the drug release in the upper GIT. The half-life of marketed formulation (Voveran) was found to be 3.01h, which specifies the relatively rapid removal of drug from plasma and the rapid elimination of drug was further supported by relatively high elimination rate constant ( $0.23\text{h}^{-1}$ ). On the contrary, the prepared colon targeted formulation exhibited high half-life viz. 6.3h for CC8 and low elimination rate constant values viz.  $0.11\text{h}^{-1}$  for CC8 indicating that drug remains in the body for a longer period of time and exhibits the prolonged effect. Based on these results it can be predicted that prepared colon specific formulation (CC8) showed a lag time of 4h before finally showing maximum concentration ( $C_{max}$ ). This indicates the good control over drug release in upper GIT with abrupt drug release as the tablet formulations reaches the lower part of GIT.

#### Stability study

In view of the potential utility of the formulation CC8 for colonic release of Diclofenac sodium, stability studies were carried out by storing the formulation at  $40^\circ\text{C}/75\% \text{RH}$  for 6 months to access the long term stability.<sup>16</sup> There was no change in the physical properties of these formulations at the end of storage period. When the dissolution study was conducted in SGF, SIF and colonic fluid as described in methodology section. No significant differences ( $f_2$  values were ranged from 50 to 100 for all the formulations) were observed in the cumulative percentage of Diclofenac sodium released from the formulation CC8 (Table 4.72) stored at  $40^\circ\text{C}/75\% \text{RH}$  for 6 months when compared to that released from same formulation before storage. The insignificant changes were observed in the physical appearance, drug content and dissolution profile of these formulations after storage at  $40^\circ\text{C}/75\% \text{RH}$  for 6 months which indicate the formulation could have a minimum shelf life of 2 years.

### CONCLUSION

Colon-specific tablet formulations for chronotherapeutic delivery of Diclofenac sodium have been proposed in this study. The compression coated tablets of Diclofenac sodium (CC8) prepared by direct compression method containing 500mg okra gum showed 3.11% drug release in 5h in upper GIT. The prepared formulations when studied in presence of rat caecal content in dissolution medium, as increase in the amount of drug released was observed by action of bacterial enzymes present in rat caecal content. *In vivo* pharmacokinetic study for above said formulation (CC8) showed minimum drug absorption in upper GIT with abrupt drug absorption as tablet formulation reaches lower part of GIT (colon). The insignificant changes in the physicochemical properties of tablet formulation (CC8) after storage at  $40^\circ\text{C}/75\% \text{RH}$  for 6 months indicate that the formulation could have a minimum shelf life of 2years. Based on the encouraging results, the

prepared tablet formulations of Diclofenac sodium can be considered suitable dosage form for chronotherapeutic treatment of rheumatoid arthritis and thereby accompanying some of the benefits like reduction in total dose, frequency of administration, dose related side effects and better patient compliance.

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**Table 1: Composition of coats and physical properties of core coat tablets prepared with these coats**

Code	OG (mg)	Mg stearate (%)	Weight variation (mg)	Hardness (Kg/cm <sup>2</sup> )	Friability (%)
<b>Wet granulation method</b>					
CC1	200	1	355 ± 1.31	3.1 ± 0.09	0.89
CC2	300	1	455 ± 1.42	3.3 ± 0.16	0.84
CC3	400	1	555 ± 1.25	3.7 ± 0.14	0.79
CC4	500	1	655 ± 1.14	3.6 ± 0.11	0.66
<b>Direct compression method</b>					
CC5	200	1	355 ± 1.24	3.1 ± 0.14	0.79
CC6	300	1	455 ± 1.34	3.3 ± 0.11	0.75
CC7	400	1	555 ± 1.11	3.7 ± 0.09	0.82
CC8	500	1	655 ± 1.99	3.6 ± 0.08	0.77

Table 2: *In vitro* dissolution study of prepared compression coated tablets with or without rat caecal content

Time (h)	Cumulative percentage release			
	CC4		CC8	
	Without RC	With RC	Without RC	With RC
0	0	0	0	0
1	0	0	0	0
2	0	0	0	0
3	2.1	2.14	0	0
4	3.14	3.2	2.22	2.31
5	5.14	5.18	3.11	3.16
6	12.26	34.21	10.34	30.14
7	18.24	58.24	16.34	55.51
8	30.24	80.14	27.27	78.24
$f_2$ values	23.53		23.65	

RC-Rat caecal

Table 3: *In vivo* Pharmacokinetic Study of orally administered compression coated tablet (CC8) and Voveran (Marketed formulation) to three rabbits under fasted conditions (n=3)

Time (h)	Plasma concentration ( $\mu\text{g/mL}$ )	
	CC8	Marketed formulation
0	0	0
1	0	16.22 $\pm$ 2.31
2	0	23.64 $\pm$ 2.11
3	0	12.32 $\pm$ 2.0
4	1.23 $\pm$ 0.12	7.45 $\pm$ 1.94
5	8.64 $\pm$ 1.46	4.31 $\pm$ 1.64
6	21.21 $\pm$ 2.24	2.64 $\pm$ 0.84
8	18.24 $\pm$ 1.14	1.24 $\pm$ 0.67

Table 4: *In vivo* pharmacokinetic parameters for optimized formulations

Parameters	CC8	Marketed formulation (Voveran)
$C_{\max}$ ( $\mu\text{g/mL}$ )	21.21 $\pm$ 2.24	23.64 $\pm$ 2.11
$T_{\max}$ (h)	6.2	1.9
$K_e$ ( $\text{h}^{-1}$ )	0.11	0.23
$T_{1/2}$ (h)	6.3	3.01
$AUC_{0 \rightarrow t}$ ( $\mu\text{g} \cdot \text{h/mL}$ )	59.87	69.11
$AUC_{0 \rightarrow \infty}$ ( $\mu\text{g} \cdot \text{h/mL}$ )	225.68	74.50

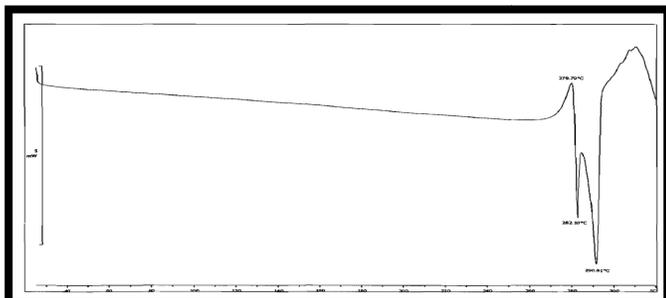


Figure 1: DSC thermogram of Diclofenac sodium

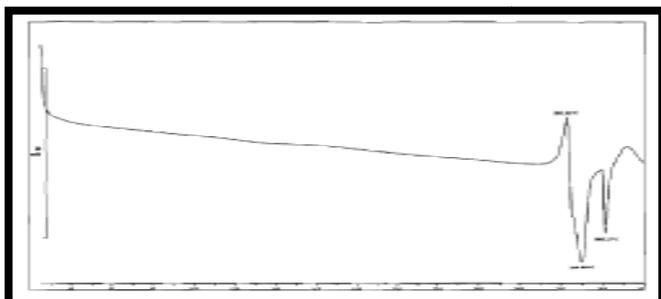


Figure 2: DSC thermogram of prepared core tablet

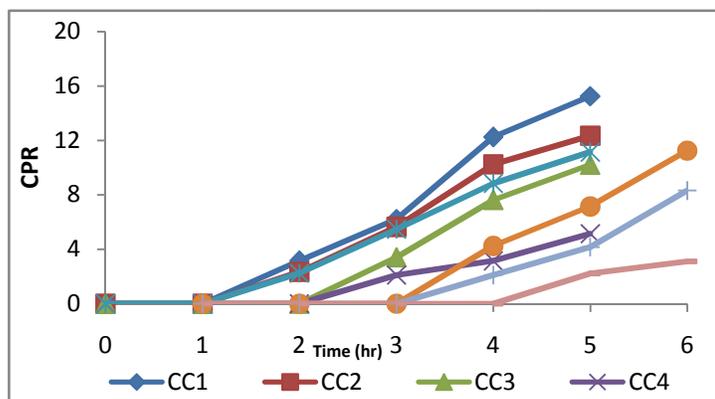


Figure 3: Comparative dissolution profiles of prepared compression coated tablets (CC1-CC8)

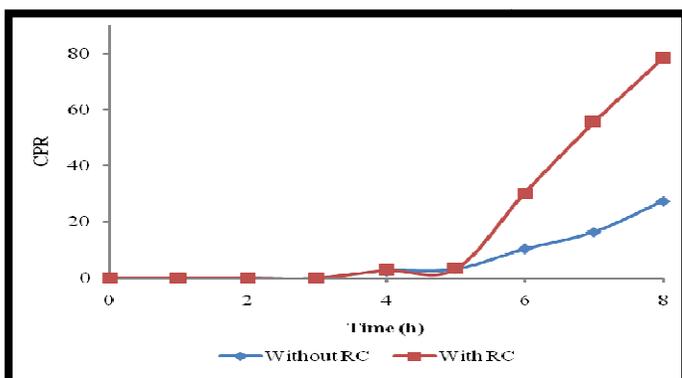


Figure 4: Comparative dissolution profile of prepared compression coated tablet with and without rat caecal content (CC4)

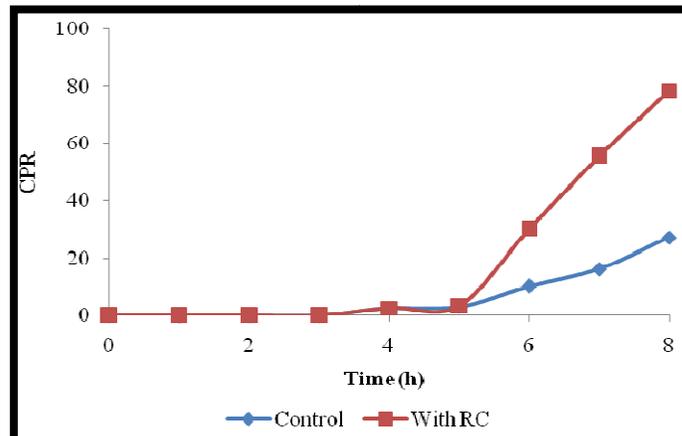


Figure 5: Comparative dissolution profiles of prepared compression coated tablet with and without rat caecal content (CC8)

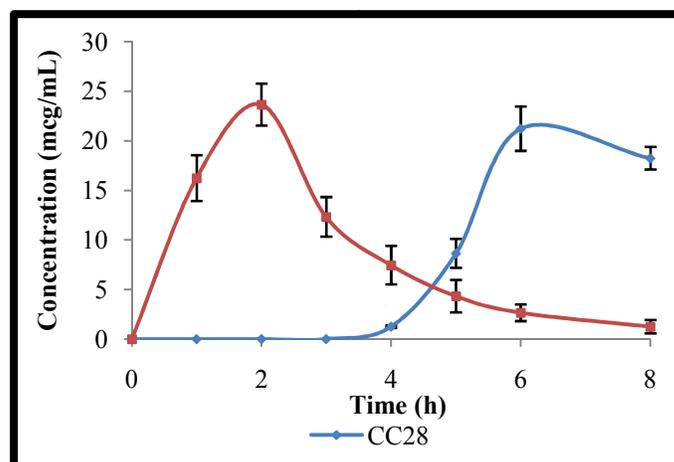


Figure 6: Plasma concentration profiles of orally administered compression coated tablet (CC8) and Voveran (Marketed formulation) to three rabbits under fasted conditions. Each value represents mean  $\pm$  S.D. (n=3)

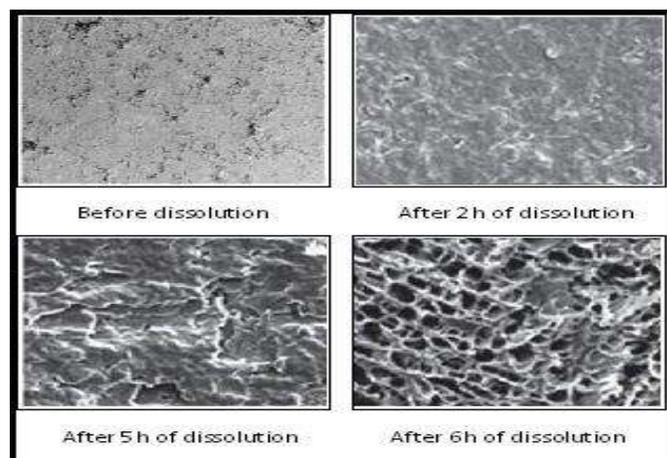


Figure 7: SEM images of formulation (CC8) before (a) and after dissolution (b) Figure legends

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