

Formulation and evaluation of xanthan gum based aceclofenac tablets for colon targeted drug delivery

Thiruganesh Ramasamy^{1,4}, Uma Devi Subbaih Kandhasami^{2,3,*}, Himabindhu Ruttala⁴,
Suresh Shanmugam²

¹Research Associate, Department of Bioengineering and Regenerative medicine, Utah-Inha DDS & Advanced Therapeutics Research Center, South Korea, ²Department of Pharmaceutics, School of Pharmaceutical Sciences, Vel's University, Chennai, India, ³Department of Pharmaceutics, Rao's College of Pharmacy, Nellore, India, ⁴Department of Pharmaceutics, Pydah College of Pharmacy, Kakinada, India

The objective of the present study is to develop a colon targeted drug delivery systems for Aceclofenac using xanthan gum as a carrier. In this study, multilayer coated system that is resistant to gastric and small intestinal conditions but can be easily degraded by colonic bacterial enzymes was designed to achieve effective colon delivery of Aceclofenac. The xanthan gum, the drug and the physical mixture were characterized by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). All the formulations were evaluated for hardness, drug content uniformity and other physical properties. Release aspects of Aceclofenac in simulated gastrointestinal fluid and colonic fluid with enzymes were investigated. From these results, Eudragit coated system exhibited gastric and small intestinal resistance to the release of Aceclofenac. The rapid increase in release of Aceclofenac in SCF was revealed as due to the degradation of the xanthan gum membrane by bacterial enzymes. The designed system could be used potentially as a carrier for colon delivery of Aceclofenac by regulating drug release in stomach and the small intestine.

Uniterms: Drugs/release colon targeted. Aceclofenac/release colon targeted. Xanthan gum. Colon targeting. Eudragit coating. *In vitro* dissolution. Targeted delivery.

O presente estudo teve como objetivo o desenvolvimento de sistema de liberação cólon-alvo de aceclofenaco empregando goma xantana. Nesse trabalho, o revestimento de múltiplas camadas com característica de resistência às condições do intestino delgado além de gastrorresistência oferece como vantagem a rápida degradação desse sistema por enzimas bacterianas colônicas. Dessa forma, o planejamento de tal sistema possibilitou a liberação específica do aceclofenaco no cólon. A goma xantana e o fármaco, além da mistura física desses dois componentes, foram caracterizados por espectroscopia no infravermelho com transformada de Fourier (FTIR) e calorimetria diferencial exploratória (DSC). Todas as formulações foram avaliadas no que se refere à dureza, à uniformidade de conteúdo do fármaco além de outras propriedades físicas. Os perfis de liberação do aceclofenaco no fluido gástrico simulado e fluido colônico simulado contendo enzimas foram investigados. Os resultados revelaram que o sistema revestido com Eudragit® exibiu resistência gástrica e intestinal à liberação de aceclofenaco. O rápido aumento na liberação de aceclofenaco no fluido colônico simulado foi atribuído à degradação da goma xantana por enzimas bacterianas. O sistema apresenta aplicação potencial no desenvolvimento de produtos para a liberação cólon-alvo de aceclofenaco.

Unitermos: Fármacos/liberação cólon-alvo Aceclofenaco/perfil de liberação. Goma xantana. Direcionamento ao cólon. Cobertura de Eudragit. Dissolução *in vitro*. Liberação dirigida.

*Correspondence: S. K. Uma Devi. Department of Pharmaceutics, School of pharmaceutical sciences, Vel's University, Chennai, Tamil Nadu, India- 600117.
E-mail: umadeviphd@gmail.com

INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the gastrointestinal tract (GIT) (Paharia *et al.*, 2007). Dosage forms that deliver drugs into the colon rather than upper GIT offers number of advantages (Sarasija, Hota, 2000; Vaidya *et al.*, 2009).

Many attempts have been made to achieve colon targeting that is advantageous in the treatment of colonic disease and as well as in the treatment of rheumatoid arthritis. A novel oral colon-specific drug delivery system (CDDS) has been developed as one of the site-specific drug delivery systems (Dhawale *et al.*, 2010). This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GIT) tract, but rapidly releases drug in the colon following oral administration. CDDS is convenient for treating localized colonic diseases, i.e. ulcerative colitis, Crohn's disease and constipation etc., CDDS, also selectively deliver drug to the colon, but not to the upper GI tract (Kinet *et al.*, 1998; Watts, Illum 1997; Yang *et al.*, 2002; Ravikumar *et al.*, 2009). CDDS would be advantageous when a delay in absorption is desirable from a therapeutically point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthma, angina and rheumatoid arthritis (Halsas *et al.*, 1999b, 2001a).

Natural polysaccharides such as xanthan gum, xylan and guar gum are not digested in the human stomach or small intestine, but are degraded in the colon by resident bacteria (Salyers *et al.*, 1977). A suspension of natural polygalactomannans in polymethacrylate solution applied as a degradable coating around the drug core delayed the drug release in the small intestine, but was degraded by colonic bacterial enzymes thereby releasing the drug (Lehmann, Dreher, 1991). Xanthan gum is a high molecular weight extracellular polysaccharide. The molecule consists of a backbone identical to that of cellulose, with side chains attached to alternate glucose residues. It is a hydrophilic polymer, which until recently had been limited for use in thickening, suspending and emulsifying water based systems (Dhopeswarkar *et al.*, 1994; Yeole *et al.*, 2006). It appears to be gaining appreciation for fabrication of matrices, as it not only retards drug release, but also provides time- independent release kinetics with added advantages of biocompatibility and inertness. Release of soluble drugs was mainly through diffusion, whereas spa-

ringly soluble or insoluble drugs were released via erosion. Xanthan gum has been evaluated as a hydrophilic matrix for controlled release preparations, using different model drugs including theophylline (Parfitt, 1999; Raja Sekharan *et al.*, 2009), cephalexin (Kay, Alldred, 2003).

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line drugs in the symptomatic treatment of rheumatoid arthritis (Moskowitz, 2001), osteoarthritis (Nisha *et al.*, 2000) and ankylosing spondylitis (Medical online). Sustained release dosage forms deliver the drug at a slow rate over an extended period of time and achieve this object. Aceclofenac, (2-[2-[2-(2,6-dichlorophenyl) amino phenyl] acetyl] oxy acetic acid, a non steroidal anti-inflammatory drug (NSAID) is one of the emerging NSAID molecules for arthritis treatment (Rheumatoid arthritis guide; Drug details). Short biological half life (about 4 hour) and dosing frequency more than one per day make Aceclofenac an ideal candidate for sustained release. It is a newer derivative of diclofenac and has less gastrointestinal complications. The successful treatment of arthritis depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired (Munira Momin, Pundarikakshudu, 2004; Liu, *et al.*, 2003). In this study, multilayer coated system that is resistant to gastric and small intestinal conditions but can be easily degraded by colonic bacterial enzymes was designed to achieve effective colon delivery of aceclofenac.

MATERIALS AND METHODS

Materials

Materials used included Aceclofenac, which was kindly provided as a gift sample by Restek Pharma, Pondicherry. Xanthan gum was purchased from Indian Research Products, Chennai. Eudragit S 100 and Eudragit L 100 were purchased from Loba chemicals, Mumbai. All other chemicals were of analytical grade.

Preparation of Xanthan gum tablets

Step-1

Aceclofenac tablets, each containing 100 mg of aceclofenac and weighing 232 to 262 mg were prepared by wet granulation and direct compression techniques using xanthan gum as a polymer. Formulations (F1-F4) were blended and granulated with starch mucilage. The wet mass was passed through a mesh (1000 μm) sieve and the granules were dried at 50 $^{\circ}\text{C}$ for 2-3 h. The dried granules were sieved (650 μm), lubricated with magnesium stearate

TABLE I - Composition of aceclofenac tablet

Ingredients (mg)	Quantity (mg) present in each tablet			
	AXT ₁	AXT ₂	AXT ₃	AXT ₄
Aceclofenac	100	100	100	100
Xanthan gum	10	20	30	40
Microcrystalline cellulose	90	90	90	90
Mucilage of starch 7.5 %	20	20	20	20
Magnesium stearate 3 %	7	7	7	7
Talc (2%)	5	5	5	5
Total	232	242	252	262

and talc mixture and compressed on a single-punch tablet machine, using 12 mm round slightly concave punches (Gang Cheng *et al.*, 2004; Lachman *et al.*, 2004). The preparation of xanthan gum tablets were given in Table I.

Step -II

The optimized batches of xanthan gum tablets were given a coating of Eudragit L-100 and S-100 mixture in a fluidized bed coating apparatus. In-process samples at various coating levels 5, 10% w/w (% polymeric weight gain) were taken to check the morphology of coating to do dissolution studies in simulated fluids of stomach and small intestine. After the coating, the tablets were gently fluidized for about 5 min after which they were air dried in an oven for 24 h at 40 °C. A 10% w/w increase in the coating level was selected as an optimum coating percentage level for all the tablets. Then the pH dependent polymeric coated tablets were tested for drug release studies in the simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and simulated colonic fluid (SCF) separately (Train 1958).

Preformulation studies

Differential scanning calorimetry

The DSC curves of Aceclofenac, xanthan gum and mixture of Aceclofenac/xanthan gum (10:4) were generated by a differential scanning calorimeter (DSC 220C, SEIKO, Japan) at heating rate of 10 °C/min from 60 to 200 °C. Accurately 12 mg of sample was taken in a standard pan and placed at sample stage. Nitrogen flow was set at 50 cm³/min and the nitrogen flow rate to the chamber was 80 cm³/min.

Fourier transforms Infrared spectroscopy

FT-IR spectra of Aceclofenac, xanthan gum and mixture of Aceclofenac/xanthan gum were recorded at room temperature in KBr pellets by applying 6000 kg/cm²

pressure by using a Shimadzu FT-IR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) in the wavelength region between 400 to 4000cm⁻¹.

Standard plot of aceclofenac in pH 7.0 phosphate buffer saline

100 mg of aceclofenac (standard drug) was accurately weighed and dissolved using pH 7.0 phosphate buffer saline (PBS) solution in 100 ml standard flask and 5, 10, 15, 20 and 25 µg/mL were prepared by suitably diluting the stock solutions with pH 7.0 PBS, each sample was then analysed spectrophotometrically at 275 nm using ELICO SL -159 double beam UV Visible spectrophotometer.

Evaluation of granules

The granules were evaluated for their flow properties, the Carr index (compressibility index) and Hausner ratio. The flow rate (g/s) was calculated from the time needed for the entire sample (40 g) to empty from the funnel. Bulk density was calculated from the amount of granules poured into a 100 mL graduated cylinder up to a total volume of 50 mL while for the tap density determination; the cylinder was tapped until no measurable change in the volume was observed. The bulk density (BD) and tapped density (TD) were calculated from equation 1 and 2.

$$\text{Bulk density} = \text{Weight of the powder} / \text{Bulk volume} \quad \text{Eq. 1}$$

$$\text{Tapped density} = \text{Weight of thr powder} / \text{Tapped volume} \quad \text{Eq. 2}$$

Based on bulk density and tap density, both the Carr Index (%) and Hausner's ratio were calculated.

The Carr's index was calculated by the equation 3:

$$\text{Carr's index (\%)} = [(TD-BD)*100] / TD \quad \text{Eq. 3}$$

The Hausner's ratio was calculated by the equation 4:

$$\text{Hausner's Ratio} = \text{TD} / \text{BD} \quad \text{Eq. 4}$$

Angle of repose was determined by fixed funnel method. Funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip at a given height (H) above a graph paper placed on a flat horizontal surface. The material was carefully poured through the funnel until the apex of the conical pile so formed just touches the tip of the funnel. The mean diameter of the base of powder cone was determined and the tangent of the angle of repose was calculated by equation 5: (Carr, 1965; Hausner, 1967; US Pharmacopeia, 2004; Bi *et al.*, 1996).

$$\tan\alpha = H/R \quad \text{Eq. 5}$$

where α is the angle of repose.

Evaluation of tablets

Prepared matrix tablets were evaluated for thickness by using digital micrometer (Mityato, Japan). Hardness of the tablet was determined by using a Monsanto hardness tester, which is expressed in kg/cm². Friability of the tablet was determined using Roche Friabilator, which is expressed in percentage. Twenty tablets were initially weighed (W_{initial}) and transferred into the friabilator. The friabilator was operated at 25 rpm per min for four minutes (per 100 revolutions). The tablets were weighed again (W_{final}) and the percentage of friability was then calculated by using the following formula, ($F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$). For Weight Variation, USP 2004 procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance (Shimadzu, Japan). The average weight of one tablet was determined from the collective weight (Gohel *et al.*, 2005; Chourasia, Jain, 2003; James Swarbrick, 2003).

Drug content

The drug content was determined by Absorbance of aliquots solutions and was measured in a spectrophotometer at 275 nm. Simultaneously, a 10 µg/mL of aceclofenac standard solution prepared in the same medium was recorded and content of Aceclofenac was calculated (United States Pharmacopoeial Convention 1999; Sinha *et al.*, 2004).

In vitro drug release studies in simulated fluids

The ability of xanthan gum tablets of Aceclofenac to remain intact in the physiological environment of stomach and small intestine was assessed by mimicking mouth to

colon transit. Drug release studies were carried out using USP XXIII dissolution apparatus (100 rpm, 37± 0.5 °C) in 900 mL of simulated gastric fluid (SGF) pH 1.2 (USP 2008) for 2 h as the average gastric emptying time is ~2 h. The dissolution medium was replaced with 900 mL of simulated intestinal medium (SIF) pH 7.4 (USP 2008) and the dissolution was continued for 24 h. 1 mL of the sample was taken at the end of the specified time period and analyzed for Aceclofenac spectrophotometrically at 275 nm. A 10 mL volume of filtered, fresh dissolution medium was added to make the volume after each sample withdrawal (Paharia *et al.*, 2007). The susceptibility of the matrix tablets to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in simulated colonic fluids prepared using rat cecal content as described by Sinha *et al.* (2004).

In vitro drug release study in the presence of rat cecal content

Rat cecal content was prepared by taking four albino rats of uniform body weight (150–200 g) with no prior drug treatment. They were weighed, maintained on normal diet, and administered 1 mL of 2% dispersion of xanthan gum in water, and this treatment was continued for 7 days for polymer induction to animals. Thirty minutes before starting the study, each rat was humanely killed and the abdomen was opened. The cecal were traced, legated at both ends, dissected, and immediately transferred into phosphate buffered saline (PBS) pH 6.8, which was previously bubbled with CO₂. The cecal bag was opened; the contents were weighed, homogenized and then suspended in PBS (pH 7.4) to give the desired concentration (2%) of cecal content, which was used as simulated colonic fluid. The suspension was filtered through cotton wool and ultrasonicated for 10 minutes in an ice bath at 40% voltage frequency using a probe sonicator (Soniweld, Imeco Ultrasonics, Mumbai, India) at 4 °C to disrupt the bacterial cells. After sonication, the mixture was centrifuged (Remi) at 2000 rpm for 20 minutes.

Tablets were placed in 200 mL of dissolution media (PBS, pH 7.4) containing 2% w/v rat cecal content. The experiment was performed with continuous CO₂ supply into the dissolution medium. At different time intervals, the samples were withdrawn and replaced with fresh PBS. The experiment was continued up to 24 hours. The withdrawn samples were pipetted into a series of 10 mL volumetric flasks, and volumes were made up to the mark with PBS and centrifuged. The supernatant was filtered through 0.45-µm membrane filter and the filtrate analyzed for Aceclofenac content at 275 nm using UV spectrophoto-

tometer method. All the experiments were performed in triplicate (Avachat *et al.*, 2007). The interference of rat caecal content on the aceclofenac determination was not significant (P-value>0.001) and hence not taken into consideration.

Quantification of the water uptake and erosion determination

For conducting water uptake studies, the dissolution jars were marked with the time points of 0.5, 1, 2, up to 9 hours. One tablet was placed in each dissolution jar containing 900 mL of phosphate buffer pH 7.4 buffers at $37 \pm 0.5 \text{ }^\circ\text{C}$, and the apparatus was run at 100 rpm using paddle. The tablets were taken out after completion of the respective stipulated time span as mentioned above and weighed, after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at $40 \text{ }^\circ\text{C}$ up to constant weight. The increase of the weight on the tablet reflects the weight of the liquid uptake. It was estimated according to Equation 6.

$$Q = 100 (W_w - W_i) / W_w \quad \text{Eq. 6}$$

Where Q is the percentage of the liquid uptake, and W_w and W_i are the masses of the hydrated samples before drying and the initial starting dry weight, respectively.

The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using Equation 7.

$$E = 100 (W_i - W_f) / W_i \quad \text{Eq. 7}$$

Where W_f is the final mass of the same dried and partially eroded sample.

The entire process was repeated to get 3 values for each time point, and the average was calculated.

In vitro release kinetics

In order to investigate the mode of release from tablets, the release data of F1 was analyzed with the following mathematical models: $Q = K_0 t$ (Zero order kinetic), $\ln(100-Q) = \ln Q_0 - K_1 t$ (First order kinetic) and $Q = K_p t^n$ (Korsmeyer and Peppas equation), where, Q is the percent of drug released at time t and K_0 and K_1 are the coefficients of the equations. K_p is constant incorporating structural and geometric characteristics of the release device, and n is the release exponent indicative of mechanism of release (Hadi, Seyed 2005).

Statistical analysis

The cumulative percent release of aceclofenac from tablets in different medium was compared and the statistical significance was tested using student's t-test. A P-value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

DSC studies

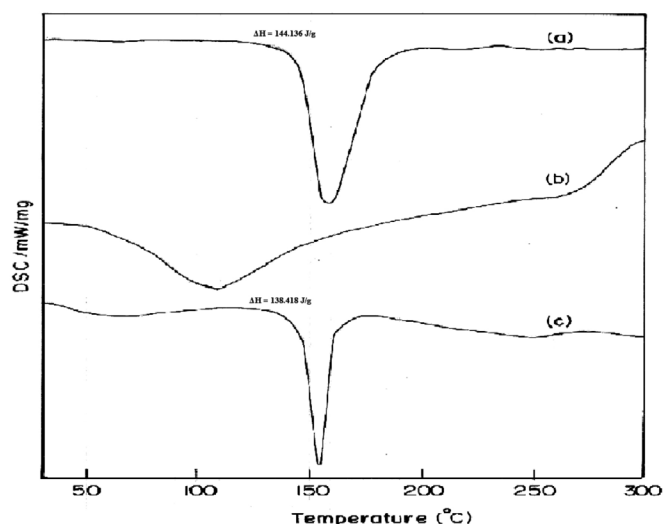


FIGURE 1 - DSC graphs of (a) Aceclofenac, (b) Xanthan gum, (c) Physical mixture of aceclofenac and xanthan gum.

DSC provides useful information about the physical properties of the sample as crystalline or amorphous nature and demonstrates a possible interaction between drug and polymers in formulations. The thermal curves of pure Aceclofenac, xanthan gum and Aceclofenac/xanthan gum mixture were reported in Figure 1. The thermal curve of Aceclofenac exhibited a profile typical of a pure, crystalline, anhydrous drug, with a sharp endothermic peak ($T_{\text{peak}} = 158.3 \text{ }^\circ\text{C}$) due to its melting process. The thermal profile of xanthan gum revealed a melting phenomenon at around $90\text{--}120 \text{ }^\circ\text{C}$, that is endothermic peak observed for xanthan gum at $108.9 \text{ }^\circ\text{C}$. While the drug melting peak is still well visible in physical mixture (Aceclofenac/xanthan gum) thermogram at $160 \text{ }^\circ\text{C}$, Thus the thermograms of physical mixture showed that no interactions between Aceclofenac and xanthan gum. With regard to crystallinity, there was no noticeable reduction in heat of fusion (ΔH), in physical mixtures (138.418 J/g) as compared to pure Aceclofenac (144.316 J/g). These suggest that the physical mixture could able to maintain the crystalline form of Aceclofenac. However it has been known that

transforming the physical state of the drug to amorphous or partially amorphous state leads to a high energy state and high disorder, resulting in enhanced solubility and faster dissolution.

IR STUDIES

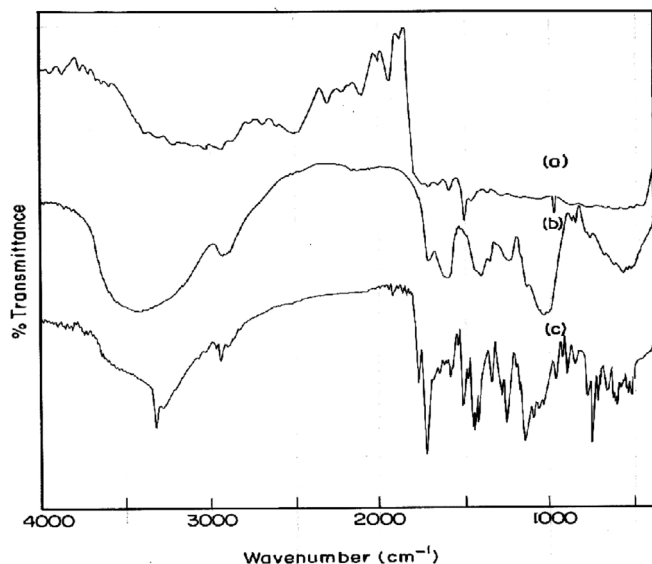


FIGURE 2 - FT-IR graphs of (a) Aceclofenac, (b) Xanthan gum, (c) Physical mixture of aceclofenac and xanthan gum.

FT-IR spectral data were used to ensure no chemical interaction and to confirm the chemical stability of Aceclofenac in the physical mixture. The FTIR of Aceclofenac showed intense band at 1771.47 cm^{-1} , 1716.89 cm^{-1} , 1589.53 cm^{-1} and 1055.9 cm^{-1} corresponding to the functional groups C=O, COOH, NH and OH bending. The peaks observed in FTIR of physical mixture of aceclofenac and

xanthan gum was almost unchanged and was found to be at 1771.56 cm^{-1} , 1716.94 cm^{-1} , 1586.5 cm^{-1} , 1054.5 cm^{-1} respectively. Hence, all the peaks observed in plain aceclofenac were also observed in the physical mixture too, indicating no interaction of aceclofenac with the polymer. The IR graphs were given in Figure 2.

Micromeritic properties

The micromeritic properties of all the formulations were compared and presented in Table II.

The Hausner ratio is used widely in pharmaceutical industry as an indication of the flowability of a powder. A Hausner ratio less than 1.25 is considered to be an indication of good flowability and anything below 1.20 is regarded as excellent flow. The Hausner's ratio varied from 1.19 to 1.25 for AXT 1 to AXT4 indicating its excellent flowability. The Carr's index is also used in pharmaceuticals as an indication of the flowability of a powder and the values ranging from 15-25 is regarded as the good value for flowability perhaps our observation of the result was good for all the formulations. Similarly angle of repose of all the formulations were also good, showing good flowability.

However from all the observations, we learned that, AXT₁ batch was optimal due to good Hausner's ratio (1.19), good carr's index (16.66) and good angle of repose ($16^{\circ}16'$), which indicates the batch AXT₁ granules have good flow property and easily compressed into tablets. The results of micromeritic properties of AXT were given in Table II.

Physical properties

The hardness of tablet increased with the increase

TABLE II - Physical and micromeritic properties of aceclofenac and xanthan gum granules

Test	AXT ₁	AXT ₂	AXT ₃	AXT ₄
Bulk density	0.507±0.92	0.557±1.12	0.612±0.18	0.672±0.15
Tapped density	0.603±1.23	0.668±0.08	0.746±1.94	0.833±1.17
Carr's index	18.93±1.18	19.92±0.54	21.89±1.08	23.95±1.76
Hausner's ratio	1.19±1.67	1.22±0.65	1.23±0.87	1.25±0.67
Angle of repose	16°16'±0.35	16°78'±0.56	17°78'±1.42	19°21'±1.42
Weight (mg)	232 ± 1.02	242 ± 1.05	252 ± 0.12	263 ± 0.26
Drug content (%)	99.20± 0.20	101.2± 0.86	99.53 ± 0.12	99.16 ± 0.26
Hardness kg/cm ²	5.3 ± 1.0	5.5 ± 0.15	5.6 ± 0.80	6.2 ± 1.12
Thickness (mm)	3.01 ± 0.66	3.2 ± 1.04	3.5± 1.08	3.9 ± 0.12
Friability (%)	0.17 ± 0.84	0.20 ± 0.62	0.34 ± 0.56	0.32 ± 0.48

n=3, the values are mean ± S.D

in the polymer concentrations as evident from the following data i.e. the hardness was 5.3 kg/cm^2 (AXT₁) and it increased to 6.2 kg/cm^2 (AXT₄) for the rise in polymer concentration. Similarly the thickness also increased with the raised polymer concentrations. It varied from 3.01 mm to 4.0 mm for AXT₁-AXT₄ batches. The total drug content also varies between 99-101% for all the formulations and was lying within the pharmacopoeial limits. The results of physical properties of AXT were given in Table II.

Percentage swelling and erosion

The quantity of water uptake increased from 15.12 ± 0.83 to $43.15 \pm 0.45\%$ w/v for AXT₁ to AXT₄ tablets respectively. The water uptake for each batch of tablets had increased upto 3rd hour and then started to decrease. This indicates that the xanthan gum tablets require minimum 3 hours for reaching the maximum swelling. The results of swelling ratio were given in Figure 3. Where as the percent erosion decreased with the increase in the polymer concentration as the percent erosion was $25.1 \pm 0.22\%$ w/v

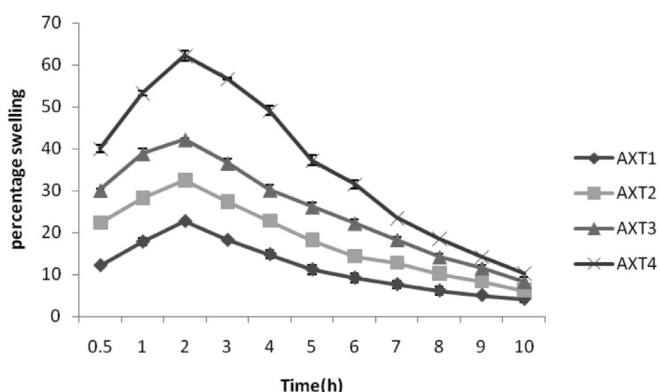


FIGURE 3 - Percentage swelling of aceclofenac-xanthan gum tablets (AXM 1 to AXM 4).

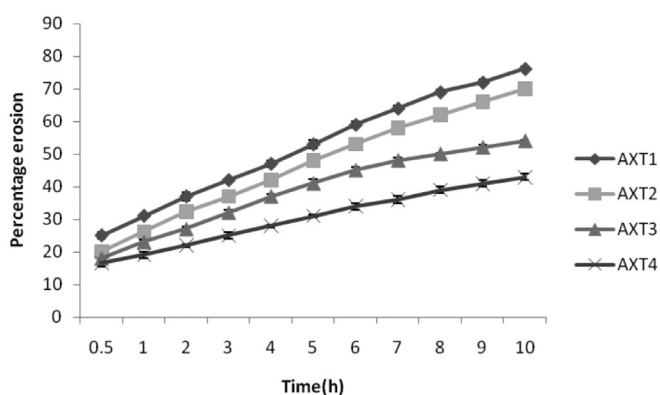


FIGURE 4 - Percentage erosion of aceclofenac-xanthan gum tablets (AXM 1 to AXM 4).

for AXT₁ and $16.5 \pm 0.15\%$ w/v for AXT₄ at 30 min. While erosion increases with the increase in the time period so that erosion percentage was $76.2 \pm 0.28\%$ w/v for AXT₁ batch and $42.2 \pm 0.08\%$ w/v for AXT₄ batch at 10th hour. The results of percentage erosion are given in Figure 4.

In vitro drug release studies

The matrix tablets were subjected to *in vitro* drug release study in SGF, SIF and SCF.

In simulated gastric fluid (SGF)

The percent drug release decreased with the increase in the xanthan gum concentration and virtually there is no release at the 30th min. At the 120th min the release was $8.1 \pm 0.26\%$ w/v for AXT₁ and it decreased towards the final formulation as it was found to be $1.15 \pm 0.08\%$ w/v for AXT₄. This is due to the time lag for swelling of the tablets. It requires at least 30 min for swelling and then it started releasing the drug, in a very controlled manner. All formulation showed very low drug release in pH 1.2 buffer. This may be due to the less solubility of Aceclofenac in pH 1.2.

In simulated intestinal medium (SIF) and in simulated colonic fluid (SCF)

The cumulative drug release decreased in pH 7.4 buffer also with the increase in the polymer concentration as evident from the Figure 5. In SIF, AXT₁ batch showed a release of $4.64 \pm 0.06\%$ w/v and it reduced to $3.12 \pm 0.08\%$ w/v for AXT₂ while there is a no release for the next two formulations at 30 mins. The same trend persisted at 6th hour i.e. drug release was $43.17 \pm 0.04\%$ w/v for AXT₁ and it decreased towards AXT₄ with a drug release of $15.13 \pm 0.12\%$. However the release percentage for AXT₁

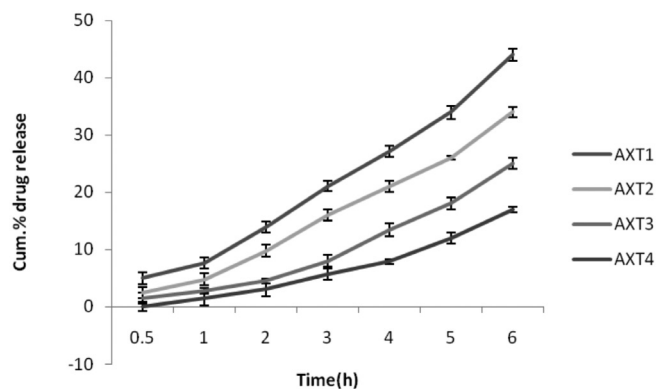


FIGURE 5 - Cumulative percentage drug release of formulations (AXT 1 to AXT 4) in SIF.

was up to 101.14 ± 0.89 % w/v at the end of 12th hour in the dissolution medium containing pH 7.4 buffer with rat caecal contents (4 % w/v) and it decreased towards the final formulation. From this it was proved that AXT₃ and AXT₄ batch were not releasing much amount of drug in the stomach and intestinal medium.

From the dissolution studies conducted for AXT₁, AXT₂, AXT₃ & AXT₄ in simulated intestinal medium it has been understood that AXT₁ & AXT₂ tablets which were containing gum in 1:10 and 2:10 ratio are not protecting the drugs release in the gastric media. Upto 38.17 ± 0.04 % w/v and 34.12 ± 0.12 % w/v of drug have been released from the AXT₁ and AXT₂ batches at the end of the studies where as AXT₃ & AXT₄ batch significantly (p -value<0.05) released lesser amount of drug at the end of 6th hour.

Since the batches AXT₁ & AXT₂ were released 80.15 ± 1.04 % w/v & 70.19 ± 0.14 % w/v of the drug in the colonic fluid at 8th and 10th hour, they were considered as suitable batches for colon targeting. To prevent the drug release from AXT₁ & AXT₂ batches in the stomach & intestinal media, a suitable enteric coating can be given. So that the drug release will be completely prevented in the SGF.

The present study was aimed to develop a targeted drug delivery system of Aceclofenac to treat the symptoms of rheumatoid arthritis. By observing the above results it was found that, though AXT₁ and AXT₂ batches released 10.28 ± 0.83 % w/v and 8.16 ± 0.48 % w/v of the drug in simulated gastric fluid and 38.17 ± 0.04 % w/v and 34.12 ± 0.12 % w/v in the simulated intestinal fluid. They release upto 101.14 ± 0.89 % w/v & 89.11 ± 0.17 % w/v at end of the 12th hour in the simulated colonic medium. If they were given an enteric coating, the drug release in the stomach and intestine can be completely prevented. The AXT₃ and AXT₄ batches, though they prevent drug release in the simulated stomach and intestinal fluid to a considerable extent, they are not showing good release in the simulated colonic medium. So they were not considered as suitable formulations.

So the AXT₁ batch, which released a maximum percent of drug i.e. 80.12% w/v at the 8th hour in colonic medium was selected to give Eudragit coating to prevent the drug release in acidic medium and to start release the drug at the ileocaecal junction at the threshold value of pH upon dissolution of Eudragit in 7 or above 7.0. The results for cumulative drug release of various formulations in SCF were given in Figure 6.

Step II

The optimized batch AXT₁ was given a pH dependent polymeric coating to get a weight of 15% w/w to the tablet weight. The percentage weight gain was checked

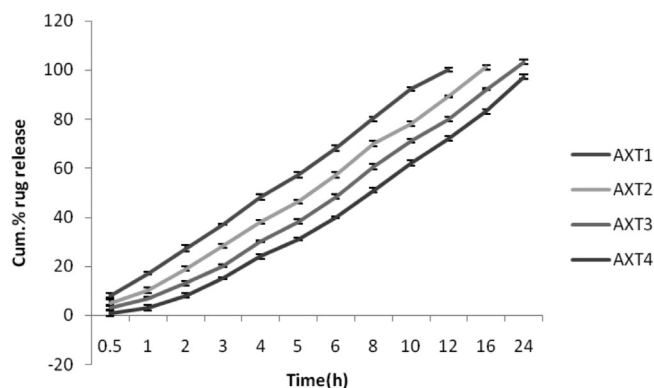


FIGURE 6 - Cumulative percentage drug release of formulations (AXT 1 to AXT 4) in SCF.

during the coating process to find the coating level necessary to retard the drug release in simulated gastric fluid for 2 hours. The coated tablets were subjected for dissolution studies in SIF and SCF.

In SGF

Upto 120 min, there was no drug release obtained in the simulated stomach fluid which reveals that a 15% w/w increase in coating level is enough to prevent the drug release in SGF upto 120 min.

In SIF and SCF

The percentage release was 4.88 ± 0.86 in SIF at the end of 6th hour and 103.12 ± 0.6 % in SCF at the end of 24th hour. These results revealed that concentration of 4.3% w/w of xanthan gum to tablet weight was the optimized one as it released 80.64 ± 0.65 % w/v in SCF at the end of 8th hour. The results for percentage drug release of E-AXT₁ tablets in SIF and SCF are given in Figure 7.

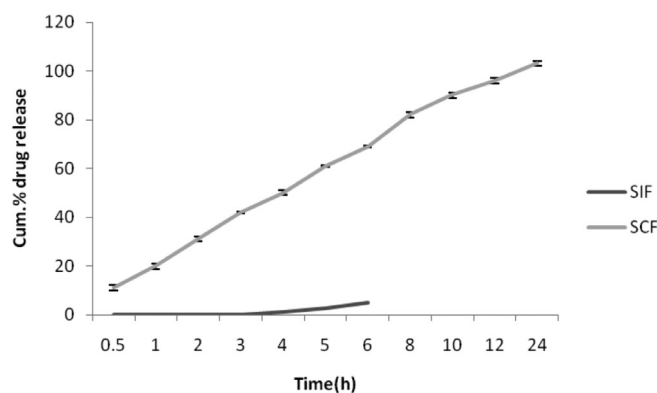


FIGURE 7 - Cumulative % drug release of E-AXT₁ in SIF and SCF.

TABLE III - In vitro release kinetics of AXT₁-AXT₄ tablets

Formulation	Zero order R ²	First order R ²	Higuchi R ²	Korsmeyer-Peppas	
				R ²	'n'
AXT1	0.9978	0.566	0.9985	0.998	0.81
AXT2	0.9888	0.716	0.9845	0.991	0.74
AXT3	0.9865	0.701	0.9802	0.982	0.70
AXT4	0.9848	0.668	0.9824	0.979	0.73

R²: Coefficient of determination

In vitro release kinetics

When the data were plotted according to the first order equation, all the formulation showed a fair linearity, with R² value between (0.566- 0.716), when the same data was plotted according to the zero order equation, it shown a good linearity with R² value between (0.9848 - 0.9978). The *in vitro* release kinetics of AXT₁ is given in Table III.

DISCUSSION

The objective of the present study was to develop a controlled release colon targeted drug delivery system of Aceclofenac to approximate the chronobiology of rheumatoid arthritis. A combination of pH sensitive polymer coating and embedment in biodegradable matrices has been followed for preparation of formulations. The Eudragit coated matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach the colon, they are acted upon by the bacterial polysaccharidase resulting in degradation and release of entrapped drug. Xanthan gum have been reported to possess ideal qualities for sustained release of the drug to the targeted site (Mundargi *et al.*, 2007; Sinha *et al.*, 2007).

The xanthan gum tablets were prepared by wet granulation method. All the formulations showed a good micromeritic property. The values for Carr's index (%) and Hausner's ratio, angle of repose(°) were within specified range indicating good flowability, which is inturn required for the good tableting. Plain Aceclofenac exhibited poor flowability as evident by the angle of repose value of 38.42±0.52. It was further supported by high Carr's index value of 29.69±0.27 and Hausner's ratio of 1.44±0.08 (Mutalik *et al.*, 2008). Where as all the prepared granules possessed good flow properties as indicated by low values of Angle of repose (16°16'±0.35–19°21'±1.42), Carr's index (18.93±1.18–23.95±1.76) and Hausner's ratio (1.19±1.67–1.25±0.67). Among all the preparation, AXT₁ was found to be good due its low Hausner's ratio,

compressibility index and angle of repose values. The hardness of the tablets was increased with the increase in xanthan gum concentration. Thus various concentrations of polymers had influence on physical characteristics of the tablets.

Evaluation of polymer swelling and erosion is a valuable exercise to better understand the mechanisms of release and the relative importance of participating parameters. The tablets prepared with high concentrations of xanthan gum showed a lower rate of erosion and a faster rate of swelling, as compared with the tablets containing lower concentrations of xanthan gum. This effect may be attributed to an increase of water uptake in the presence of a larger amount of the polymer and viscoelastic mass formation (Talukdar *et al.*, 1995). Perhaps the viscoelastic mass formation also attributed to interaction of xanthan gum with the starch mucilage due to intermolecular interaction (Ntawukulilyayo *et al.*, 1996) 1, 2 After 4th h, the linear mechanism of water uptake is altered due to the high erosion percentage of the formulations and probable change in gel structure. The swelling behavior indicated a rate at which this formulation absorbed water from dissolution media and swelled. The change in weight, characteristic of water uptake and swelling, started from the beginning and continued until 120 min of experiment and after that it started decreasing. The erosion measured the weight loss from matrix tablets immersed in dissolution media as a function of time. Weight loss from the tablets increased progressively with the erosion time. Polymer swelling and erosion was distinguishable among four formulations.

The evaluation of release profiles is recommended as an valuable exercise in the development and optimization of drug formulations. The release rate of aceclofenac in first two hours in acid media was so negligible (less than 10%) for all the formulation that the result was not shown in the release curve. At this pH, Aceclofenac exists in its acidic form which is well known to be practically insoluble in the stomach (Sheu *et al.*, 1962; Kincl *et al.*, 2004). When the dissolution was changed to pH 6.8 phosphate buffer media, the drug release rate was slightly increased,

possibly because the aceclofenac was partially converted to aceclofenac salt which is soluble and also because of swelling and erosion phenomenon. The release of drug in SCF is very high due to the presence of enzymes and a significant differences (P -value $\ll 0.05$) was observed between different formulations formulated with varying proportions of xanthan gum. The drug release from AXT₁ ($101.14 \pm 0.89\%$) was high, while it was low for AXT₄ ($89.11 \pm 0.17\%$) at the end of the 12th hour. The reason for this may be low concentration of polymer in AXT₁ and high concentration in AXT₄ which caused hydration of xanthan gum particles in neutral medium resulted in extensive swelling. Hence it may be suggested that, the well Separated particles comes in contact with the dissolution media and thereby swollen and coalesced. This resulted in formation of continuous viscoelastic matrix which fills the interstices, maintaining the integrity of the tablet and retarding further liquid penetration (Dhopeswarkar *et al.*, 1993). As a result of a high swelling, Xanthan gum matrix tablets can sustain drug release in SCF. Xanthan gum has a substantial ability to swell and form a hydrogel in neutral medium hence the initial drug release takes place in SIF (Yeole *et al.*, 2006) where as the enteric polymers remain insoluble in the gastric pH and intestinal pH and thus controlling the release of drug within the desired range (Sinha *et al.*, 2007) It has been reported that polymer concentration is found to influence the release characters of the drug from the dosage form (Akanksha, Raj Kumar, 2009). 3 In our study, Xanthan gums in varying proportions (4, 8, 12 and 15 % w/w to tablet weight) release the drug in the following order. AXT₁ > AXT₂ > AXT₃ > AXT₄ over a period of 8 hr in SCF.

The second part of the formulation focused on the polymer coating of the xanthan gum tablets. The tablets were coated in a fluidized bed coating apparatus. Owing to the ability of Eudragit S-100 and Eudragit L-100, to dissolve above pH 7.0 and to protect the drug in the upper gastrointestinal tract, they are employed in the pH sensitive coating. Hence when the enteric coating comes in contact with the colonic pH, it dissolves, and there after it is expected that drug release would be controlled by xanthan gum. Taking into account the dissolution profiles of all the xanthan gum-aceclofenac tablets, the AXT₁ was selected as optimized formulation as its dissolution profile was akin to the expected requirements of the study. Further the Eudragit coating of the optimized formulation E-AXT₁ has reduced the drug release to a great extent in the stomach, however maintain the same dissolution profile in SCF.

The drug release kinetics was evaluated by fitting various mathematical models, viz, zero-order, first-order, Higuchi, or Korsmeyer-Peppas equation. The reason why

drug release rate from the tablet is reduced in the presence of increasing concentration of xanthan gum, was may due to the formation of a gel through which the drug must diffuse. The drug release kinetics of all the formulations were presented in table.3. Interestingly, release data of all the tablet formulations fitted well with zero-order release model with a coefficient of determination (r^2) greater than 0.99. Where as matrix tablets did not show a good fit with first order model with a coefficient of determination (r^2) between 0.566-0.75. From the coefficient of determination values (shown in Table III), it appears that the Higuchi model seems the best-fitting model, which suggests a diffusion-controlled release mechanism by pore formation. The release mechanism is also influenced by porosity and tortuosity of the matrix (Florence, Attwood, 1988). Thus gradually reducing the diffusion path length, which in turn attenuates the decrease of the release rate in the Higuchi model, making the pattern to resemble zero-order model. The drug release data were fitted to the power law or the Korsmeyer-Peppas equation as shown in Table III. In this study, xanthan gum tablets showed a good fit into the Korsmeyer-Peppas equation, exhibited a c coefficient of determination (r^2) greater than 0.98 for all the formulation. For the case of matrix tablets, $0.45 < n$ corresponds to a Fickian diffusion mechanism and $n = 0.89$ indicates a purely relaxed controlled delivery which is referred to as Case II transport. Intermediate values $0.45 < n < 0.89$ indicate an anomalous behavior (non-Fickian kinetics corresponding to coupled diffusion / polymer relaxation). Occasionally, values of $n > 0.89$ have been observed, which has been regarded as Super Case II kinetics. The calculated exponents (n) were in the range from 0.70 to 0.81, indicating a non-Fickian diffusion mechanism. Our results clearly advocate the non-Fickian diffusion owing to the coupling of diffusion process with the mechanical response of the polymer. The value of n is 0.5 for Fickian transport and > 0.5 and < 1.0 for non-Fickian transport and 1 for zero-order (Case-II transport). When the value of n approaches 1.0, phenomenologically one may conclude that the release is approaching zero-order. Figs. 5-6 reveal that the rate of release decreased with time and this may be due to an increase in diffusional path length for the drug which in turn may be due to slower erosion rate of the rubbery layer and faster advancement of swelling front into the glassy polymer. The release pattern swiftly deviated from AXT₁ to AXT₄. This may also be attributed to the synergistic increase in gel viscosity at the tablet periphery. This will decrease the rate of advancement of swelling front into the glassy matrix resulting in a slow diffusion of the drug. As the swelling front advances into the glassy polymer, the rubbery state, polymer (gel at the tablet periphery) which

is devoid of the drug, undergoes attrition. When these two rates are equal, the diffusional path length for the drug remains constant and zero-order release will be seen. The value of r^2 was also found to be higher for the Higuchi model. Hence the release pattern also follows the Higuchi model. The solvent molecule diffuses into the polymer creates an osmotic pressure. The initial swelling at the surface then creates additional surface for the additional penetrant and thus leads to the formation of viscoelastic mass which gives its glassy state. Moreover the accumulation of solvent around the periphery of tablet creates a solvent shock which also causes the drug release. At the end of the release process, all the polymer materials are completely dissolved in case if it follows the zero order and Higuchi mechanisms. The drug release slows down with the increase in the viscosity of the gel forming polymer. The exponent 'n' decreases with the increase

The insoluble polymeric matrix of the table core of the present invention is sufficiently strong to retard the rate of release of the active ingredient or drug from the core. In addition, the tablet core provides a backbone for the outer rate controlling membrane. The polymeric matrix core prevents shrinkage and rupture of the membrane coating on exposure to gastrointestinal fluid. It also provides a tortuous path for penetrating gastrointestinal fluid, thereby keep a drug reservoir in the membrane coated polymeric matrix for a longer period of time.

From the comparative analysis of different concentrations of the polymers on the dissolution profile of the drug in the colon, we learned that the xanthan gum-Aceclofenac formulation E-AXT₁ appears promising for colon targeting as it inhibited drug release in upper GIT and exhibited maximum release in SCF in a sustained manner. From the over all results, it can be understood that the drug release takes place through the formation of pores and channels initially, followed by swelling of the polymer around the drug matrix that sustain the release of the drug. From the dissolution profile, it was evident that with the increase in polymer concentration, thickness of the swelling around the drug matrix increases which further slows down the release characteristics of the drug. Hence drug release could be a result of the combination of fine dependent hydration of xanthan gum and enzymatic degradation by colonic bacteria.

CONCLUSION

The present study focussed on viability of tablets of Aceclofenac prepared with xanthan gum for controlled and colon specific delivery in chronotherapy of rheumatoid arthritis. Xanthan gum and Eudragit coated tablets

offer a greater degree of protection from premature drug release in the upper GI tract than xanthan gum alone. The xanthan gum is still available for enzymatic degradation, which allows greater drug release under conditions that may be expected to pertain in the colon. By changing the variables such as the xanthan gum to aceclofenac ratio, it may be possible to produce a system with a release profile, which is tailored to meet the particular requirements of any individual drug. The *in vitro* studies suggest that xanthan gum tablets of aceclofenac are promising for the therapy of rheumatoid arthritis. A further detailed study in human subjects will through more light on their efficacy and compliance.

ACKNOWLEDGEMENT

We are extremely thankful to Dr. Ramakrishnan, for helping us in the technical aspect of the project and also for useful scientific discussions, which produced ground breaking results. We also would like to extend our gratitude to Prof. Indhrani Ramasamy and Prof. Karthika Ramakrishnan for sharing their passion for chemistry and bio-engineering and thus helping us in the chemistry basis of polymers, which lead to better understanding of polymers and materials.

REFERENCES

- AKANKSHA, T.; RAJ KUMAR, S. Natural polymer in colon targeting. *Int. J. Pharm. Clin. Res.*, v.1, n.2, p. 43-46, 2009.
- AULTON, M.E.; WELLS, J.I. *Pharmaceutics*. The science of dosage form design. London: Churchill Livingstone, 1988. p.247-249.
- AVACHAT, A.; KOTWAL, V. Design and evaluation of matrix-based controlled release tablets of diclofenac sodium and chondroitin sulphate. *AAPS PharmSciTech.*, v.8, n.4, p.88-96, 2007.
- BI, Y.; SUNADA, H.; YONEZAWA, Y.; DANJO, K.; OTSUKA, A.; LIDA, K. Preparation and evaluation of a compressed tablet rapidly disintegrating in oral cavity. *Chem. Pharm. Bull.*, v.44, n.11, p.2121-2127, 1996.
- CARR, R.L. Evaluating flow properties of solids. *Chem. Eng.*, v.72, n.3, p.163-168, 1965.
- CHOURASIA, M.K.; JAIN, S.K. Pharmaceutical approaches to colon targeted drug delivery systems. *J. Pharm. Sci.*, v.6, n.1, p.33-36, 2003.

- DHAWALE, S.C.; BANKAR, A.S.; PATRO, M.N. Formulation and Evaluation Porous Microspheres of 5- Fluorouracil for Colon Targeting. *Int. J. Pharm. Tech. Res.*, v.2, n.2, p.1112-1118, 2010.
- MEDICINE ONLINE. Diclofenac Sodium Delayed-release Tablets, USP. Available at: <<http://www.medicineonline.com/drugs/d/2288/Diclofenac-Sodium-Delayed-release-Tablets-USP.html>>. Accessed on: 14. jun. 2010
- DRUG DETAILS. EPG Mobile beta. Available at: <http://www.epgonline.org/mobile/drug-details.cfm/id/DR004273/page/atoz/letter/a/language/LG0001/startrow_drug/1/drugName/Aceclofenac-100-mg-Tablets>. Accessed on: 13 may 2010.
- DHOPESHWARKAR, V.; O'KEEFFE, J.C.; HORTON, M. Development of an oral sustained release antibiotic matrix tablet using invitro/invivo correlations. *Drug Develop. Ind. Pharm.*, v.20, n.11, p.1851-1867, 1994.
- FLORENCE, A.T.; ATTWOOD, D. *Physicochemical principles of pharmacy*. 3.ed. London: Macmillan Press Ltd., 1998. H 48. p.5-85.
- GANG CHENG; FENG AN; MEI-JUAN ZOU; JIN SUN; XIU-HUA HAO; YUN-XIA HE. Time- and pH- dependent colon-specific drug delivery for orally administered diclofenac sodium and 5- aminosalicic acid. *World J. Gastroenterol.*, v.10, n.12, p.1769-1774, 2004.
- GOHEL, M.C.; BANSAL, G.; BHATT, N. Formulation and evaluation of orodispersible taste masked tablets of famotidine. *Pharm. Biol. World*, v.3, n.6, p.75-80, 2005.
- MEHRGAN, H.; MORTAZAVI, S.A. The release behavior and kinetic evaluation of diltiazem HCL from various hydrophilic and plastic based matrices. *Iran J. Pharm. Res.*, v.3, n.3, p.137-146, 2005.
- HALSAS, M.; HIETALA, J.; VESKI, P.; JURJENSON, H.; MARVOLA, M. Morning versus evening dosing of ibuprofen using conventional and time controlled release formulations. *Int. J. Pharm.*, v.189, n.2, p.179-185, 1999.
- HALSAS, M.; PENTTINEN, T.; VESKI, P.; JURJENSON, H.; MARVOLA, M. Time controlled release pseudoephedrine tablets: bioavailability and in vitro/in vivo correlations. *Pharmazie*, v.56, n.114, p.718-723, 2001.
- HAUSNER, H.H. Friction conditions in a mass of metal powder. *Int. J. Metall.*, v.3, n.9, p.7-13, 1967.
- KAY, A.E.; ALLDRED, A. Rheumatoid arthritis and osteoarthritis. In: WALKER, R., EDWARDS, C. (Eds.). *Clinical pharmacy and therapeutics*. 3.ed. London: Churchill Livingstone, 2003. p.791-807.
- KINCL, M.; VREVER, F.; VEBER, M. Characterization of factors affecting the release of low-solubility drug from prolonged release tablets. *Anal. Chim. Acta.*, v.502, n.7, p.107-113, 2004.
- KINGET, R.; KALALA, W.; VERVOORT, L.; VAN DEN MOOTER, G. Co- ionic drug targeting. *J. Drug Target.*, v.6, n.2, p.129-149, 1998.
- LACHMAN, L.; LIEBERMAN, H.A.; KANIG, J.L. *The theory and practice of industrial pharmacy*. 3.ed. Mumbai: Varghese Publishing House, 1987. p.182-184, 296-303, 311-312.
- LEHMANN, K.O.R.; DREHER, K.D. Methacrylate-galactomannan coating for colon-specific drug delivery. *Proc. Int. Symp. Control. Rel. Bioact. Mater.*, v.18, n.194, p.331-332, 1991.
- LIU, L.; FISHMAN, M.L.; KOST, J.; HICK, K.B. Chondroitin sulphate based systems for colon – specific drug delivery via oral route. *Biomaterials*, v.246, n.3, p.3333-3343, 2003.
- MANEK, N. J.; LANE, N.E. Osteoarthritis: Current Concepts in Diagnosis and Management. *Am. Fam. Physician*, v.61, n.12, p.1795-804, 2000.
- MOMIN, M.; PUNDARIKAKSHUDU, K. In vitro studies on guar gum based formulations for the colon targeted delivery of sennosides. *J. Pharm. Pharmaceut.*, v.7, n.3, p.325-331, 2004.
- MOSKOWITZ, R.W. The role of anti-inflammatory drugs in the treatment of osteoarthritis: a United States viewpoint. *Clin. Exp. Rheumatol.*, v.19, n.6, p.S3-8, 2001.
- MUNDARGI, R.C.; PATIL, S.A.; AGNIHOTRI, S.A.; AMINABHAVI, T.M. Development of polysaccharide-based colon targeted drug delivery systems for the treatment of amoebiasis. *Drug Dev. Ind. Pharm.*, v.33, n.3, p.255-264, 2007.

- MUTALIK, S.; MANOJ, K.; SREENIVASA REDDY, M.; KUSHTAGI, P.; NAYAK USHA, A.; ANJU, P.; KUMAR RANJITH, A.; UDUPA, N. Chitosan and enteric polymer based once daily sustained release tablets of Aceclofenac: *in vitro* and *in vivo* studies. *AAPS PharmSciTech.*, v.9, n.2, p.651-659, 2007.
- NSAIDs for Rheumatoid Arthritis. Rheumatoid arthritis guide. Available at: <<http://www.webmd.com/rheumatoid-arthritis/guide/nsaids-rheumatoid-arthritis>>. Accessed on: 12. april 2009.
- NTAWUKULILYAYO, J.D.; VERVAET, C.; REMON, J.P.; GÖRTZ, J.P.; BERLO, J.A. In vitro and in vivo evaluation of a xanthan gum-n-octenylsuccinate starch matrix tablet containing ibuprofen as a model containing ibuprofen as a model drug. *Int. J. Pharm.*, v.139, n.2, p.79-85, 1996.
- PAHARIA, A.; YADAV, A.K.; RAI, G.; JAIN, S.K.; PANCHOLI, S.S.; AGRAWAL, G.P. Eudragit-coated chondroitin sulphate microspheres of 5-fluorouracil for colon targeting. *AAPS PharmSciTech.*, v.8, n.1, p.135-146, 2007.
- PARFITT, K. Analgesics, anti-inflammatory and antipyretics. In: REYNOLDS, J.E.F. (Ed.). *MARTINDALE: The complete drug reference*. 32.ed. Massachusetts, London: Pharmaceutical press, 1999. p.1-12.
- RAVI KUMAR; PATIL, M.B.; PATIL, S.R.; MAHESH S.P. Polysaccharides based colon specific drug delivery: A Review. *Int. J. Pharm. Tech. Res.*, v.1, n.2, p.334-346, 2009.
- RAJA SEKHARAN, T.; PALANICHAMY, S.; SHANMUGANATHAN, S.; KARTHIKEYAN, A.; SENTHILKUMAR, S.R.; THIRUPATHI, T. Formulation and Evaluation of Theophylline Controlled Release Matrix Tablets using Xanthan gum. *Der Pharm. Let.*, v.1, n.2, p.93-101, 2009.
- SALYERS, A.A.; VERCELLOTTI, J.R.; WEST, S.H.E.; WILKINS, T.D. Fermentation of mucin and plant polysaccharides by strains of bacteroides from the human colon. *Appl. Environ. Microbiol.*, v.33, n.2, p.319-322, 1977.
- SARASIJA, S.; HOTA, A. Colon-specific drug delivery systems. *Ind. J. Pharm. Sci.*, v.62, n.1, p.1-8, 2000.
- SHEU, M.; CHOU, H.; KAO, C.; LIU, C.; SOKOLOSKI, T.D. Dissolution of diclofenac sodium from matrix tablets. *Int. J. Pharm.*, v.85, n.1-3, p.57-63, 1992.
- SINHA, V.R.; MITTAL, B.R.; BHUTANI, K.K.; RACHNA KUMARI. Colonic drug delivery of 5 fluorouracil: an *in vitro* evaluation. *Int. J. Pharm.*, v.269, n.1, p.101-108, 2004.
- SINHA, V.R.; ASMITA SINGH.; SANJAY SINGH.; BHINGE, J.R. Compression coated systems for colonic delivery of 5-fluorouracil. *J. Pharm. Pharmacol.*, v.59, n.3, p.359-365, 2007.
- SWARBRICK, J. *Encyclopedia of pharmaceutical technology*. 3.ed. New York: Informa healthcare, 2007. v.6, p.2614-2629.
- TALUKDAR, M.M.; KINGE, R. Swelling and drug release behaviour of xanthan gum matrix tablets. *Int. J. Pharm.*, v.120, n.1, p.63-72, 1995.
- TRAIN, D. Some aspects of the property angle of repose of powders. *J. Pharm. Pharmacol.*, v.10, n.11, p.127-135, 1958.
- UNITED STATES PHARMACOPOEIA. 24-NF-19. Rockville: US Pharmacopeial Convention, 1999. p.587-598.
- UNITED STATES PHARMACOPOEIA. XXVII. Rockville: US Pharmacopeial Convention, 2004. p.2300-2304.
- UNITED STATES PHARMACOPOEIA, 19th ed., 2008. Available at: <<http://www.usp.org>>. Accessed on: 9th Sep 2009.
- VAIDYA, A.; JAIN, A.; KHARE, P.; AGRAWAL, R.K.; JAIN, S.K.; Metronidazole loaded pectin microspheres for colon targeting. *J. Pharm. Sci.*, v.98, n.11, p.4229-4236, 2009.
- YANG, L.; CHU, J.S.; FIX, J.A. Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation. *Int. J. Pharm.*, v.235, n.1, p.1-15, 2002.
- YEOLE, P.G.; GALGATTE, U.C.; BABLA, I.B.; NAKHAT.P.D. Design and evaluation of Xanthan gum-based sustained release Matrix tablets of Diclofenac sodium. *Ind. J. Pharm. Sci.*, v.68, n.2, p.185-189, 2006.
- WATTS, P.J.; ILLUM, L. Colonic drug delivery. *Drug Dev. Ind. Pharm.*, v.23, n.9, p.893-913, 1997.

Received for publication on 24th May 2010.

Accepted for publication on 04th December 2010.