PREPARATION AND CHARACTERIZATION OF CHITOSAN TABLETS OF ACECLOFENAC FOR COLON TARGETED DRUG DELIVERY

S. K. UMA DEVI, R. THIRUGANESH, S.SURESH

For author affiliations, see end of text

ABSTRACT:

The present study objective was to develop novel colon specific drug delivery systems for aceclofenac using chitosan as a microbially degradable polymeric carrier and to coat the optimized batches with a pH dependent polymeric coating solution containing Eudragit L 100 and S 100 (1:4). Tablets containing four proportions of chitosan were prepared. The tablets were evaluated for physicochemical properties, drug content, dissolution, water uptake & erosion characteristics, in vitro drug release studies. The amount of aceclofenac released from the chitosan tablets at different time intervals was estimated by UV spectrophotometric method at 275nm. Eudragit coated Chitosan tablets prevented release of the aceclofenac in the physiological environment of stomach and small intestine depending on the proportion of chitosan used in the formulation. The dissolution profile and *in vitro* release kinetics showed that chitosan tablets were promising for controlled delivery of the drug. The findings of the present study conclusively state that chitosan tablets are promising for colon targeting of aceclofenac to synchronize the chronobiological symptoms for effective treatment of rheumatoid arthritis.

KEYWORDS:

Aceclofenac, chitosan, eudragit coating, targeted delivery, colon targeting, *In vitro* dissolution.

INTRODUCTION

Colon targeted drug delivery has the potential to deliver bioactive agents for the treatment of a variety of colonic diseases including inflammatory bowel disease (IBD) and rheumatoid arthritis and can be effectively treated by the local delivery of drugs to the large intestine. The treatment of colonic disease is particularly improved by their local delivery to the bowel. By this technique, absorption of the drug from the stomach and small intestine can be minimized until the drug reaches the large intestine. Various drug delivery systems have been designed that delivers the drugs quantitatively to the large bowel and subsequently to trigger the release of active drug.[1] Colon as a site offers distinct advantages on account of a near neutral pH, a much longer transit time, reduced digestive enzymatic activity and a much greater responsiveness to absorption enhancers. The colon is a site where both local and systemic drug delivery can take place. A local means of drug delivery could allow topical treatment of inflammatory bowel disease, irritable bowel syndrome. It is also preferred as an absorption site for oral administration of peptides drugs, because of the comparatively less hostile environment and low proteolytic enzyme activities in the colon. [2] ,[3] ,[4]

Colon specific drug delivery has been the focus of importance now a days because, the large intestine is targeted not only for local diseases but also for systemic absorption. Various colon specific drug delivery systems are being developed, by taking advantage of the luminal pH in the ileum and microbial enzymes in the colon. It is extremely useful when a delay in drug absorption is required from a therapeutic point of view. eg. Angina pectoris, rheumatoid arthritis, and nocturnal asthma[5]. Four basic approaches have been exploited for colon specific drug delivery, namely prodrugs[6], pH dependent systems[7],[8], Time dependent systems[9] and Microbial degradable systems[10].

The microflora-activated systems formulated with non-starch polysaccharides are having potential because they remain as undegraded in the stomach and small intestine and degraded by the vast microflora of the colon where the release of the drug is required.Aceclofenac, a non steroidal anti-inflammatory drug used for the treatment of rheumatoid arthritis is selected as a model drug. The aim of the study was to design a novel colon specific drug delivery systems containing chitosan tablets coated with pH dependent polymers (Eudragit L 100 and S 100 in the ratio of 1:4). The goal in drug delivery research is to develop formulations to meet therapeutic needs related to particular pathological conditions. Variation of physiological and pathophysiological functions at a particular time of a day has brought a new approach to the development of drug delivery systems [11]. Rheumatoid arthritis (RA) is traditionally considered a chronic, inflammatory autoimmune disorder that causes the immune system to attack the joints. It is a disabling and painful inflammatory condition, which can lead to substantial loss of mobility due to pain and joint destruction [12]. Multiparticulate approaches tried for colonic delivery include formulations in the form of pellets, granules, microparticles and nanoparticles. The multiparticulate drug delivery systems are used in preference to single unit dosage forms for colon targeting. The multiparticulate systems enabled the drug to reach the colon quickly .The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulations. [13]

MATERIALS AND METHODS

Materials

Materials used included aceclofenac, which was kindly provided as a gift sample by Restek Pharma, Pondicherry. Chitosan 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 chitosan tablets

Step-I

Matrix tablets, each containing 100 mg of aceclofenac and weighing 230 to 390 mg were prepared by wet granulation and direct compression techniques using chitosan as a polymer. Formulations (F1–F4) were blended and granulated with different percentage of starch mucilage. The wet mass was passed through a mesh (1000 μm) sieve and the granules were dried at 50°C for 2–3 h. The dried granules were sieved (650 μm), lubricated with magnesium stearate: talc (1:2) mixture and compressed on a single-punch tablet machine, using 12 mm round slightly concave punches[14], [15]. The preparation of chitosan tablets were given in table 1.

Step -II

The optimized batch of chitosan tablets were coated with a combination of Eudragit L-100 and S-100 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 SGF fluid. Coating was continued until complete polymer weight gain was achieved. 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 as described in the SGF, SIF and SCF separately. [16]

Preformulation studies

Differential scanning calorimetry

In this technique the difference in energy inputs into a substance and reference material is measured as a function of temperature as the specimens are subjected to controlled temperature program.

Fourier transforms Infrared spectroscopy

The Fourier transform infra-red analysis was conducted for the structural characterization. FTIR of pure drug, polymers, and their physical mixtures were recorded. Samples were taken in a KBr pellet using BOMEN MB SERIES FTIR instrument.

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[17]

Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (Vo) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 tabs and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the formulae

Bulk density $= W / V_0$

Tapped density $= W / V_f$

Where,

W= Weight of the powder

V_0 = Final volume

Compressibility index (Cars indices)

Compressibility index was calculated by using the formula

$$Ci = \frac{(V_0 - V_f)}{V_0} \times 100$$

Ci < 15 % shows good flow property

Ci > 25 % shows poor flow property

Ci >50 % shows great potential problems.

Ci 20 % - 40 % shows reasonable flow property.

Hausner's Ratio

Hausner's ratio was measured by the ratio of tapped density to bulk density.

Hausner's ratio = Tapped density/ Bulk density

Evaluation of Tablets[18-20]

Tablet hardness was measured with a monsanto tester. The hardness of 10 tablets was measured, and the mean hardness was calculated and reported. The tablet friability was determined on a Coel HX-4 friabilator. The weight of 20 tablets was measured on an analytical balance (Mettler H15) and then loaded into the friabilator. After 100 revolutions, the tablets were removed, dedusted, and reweighed. The difference of the weight was calculated as a percent loss.

Diameter and thickness were measured using Paquimetre Mitutoyo for 10 tablets. To study weight variation, 20 tablets were weighed individually using an electronic balance (Mettler H15), and the test was performed according to the official method.

The drug content was determined by crushing and powdering five tablets. The amount of powder equivalent to the mean of these five tablets was weighed in 100 mL of water and the volume adjusted to 200 mL. After 20 minutes of centrifugation, aliquots of 1 mL were taken from this

solution and diluted to 100 mL with water. Absorbance of resulting solutions was measured in a spectrophotometer at 257 nm. Simultaneously, a 10 μg/mL of aceclofenac standard solution prepared in the same medium was recorded. Content of aceclofenac was calculated.

In Vitro Drug Release Studies in Simulated Fluids[21]

Tablets were evaluated for the in vitro drug release in simulated GI fluids (SGF). The drug dissolution test of tablets was performed by the paddle method specified in USP XXIII. Tablets were dissolved over the surface of 500 mL of dissolution medium (SGF). The content was rotated at 100 rpm at 37°C ± 0.5°C. Perfect sink conditions prevailed during the drug dissolution study period. The simulation of GI transit condition was achieved by altering the pH of dissolution medium at different time intervals. The pH of the dissolution medium was kept 1.2 for 2 hours then, the pH of the dissolution medium was adjusted to 7.4 and maintained up to 24 hours. The samples were withdrawn from the dissolution medium at various time intervals using a pipette fitted with a microfilter. The receptor volume was maintained constant by replacing equivalent amount of SGF and SIF. The concentration of aceclofenac in the samples was calculated based on average calibration curves (n = 6). All dissolution studies were performed in triplicate.

In Vitro Drug Release Study in the Presence of Rat Cecal Content[21]

Rat cecal content was prepared by the method reported by Van den Mooter et al. Four albino rats of uniform body weight (150-200 g) with no prior drug treatment were used for all the present *in vivo* studies. They were weighed, maintained on normal diet, and administered 1 mL of 2% dispersion of chitosan 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 CO_2. 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 CO_2 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 spectrophotometer method. All the experiments were performed in triplicate.

Quantification of the Water Uptake and Erosion Determination[22]

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°C ± 0.5°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°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 Equation1

$$Q = 100 \, (W_w - W_i) / W_w \qquad (1)$$

Where Q is the percentage of the liquid uptake, and Ww and Wi 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 2

$$E = 100 \, (W_i - W_f) \, W_i \qquad (2)$$

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.

Stability studies

The selected formulation of tablets were stored in amber-colored glass bottles at 45°C+75% RH for a period of 3 months and observed for any change in colour, odour, and percentage drug content and entrapment efficiency.

***In vitro* release kinetics[23]**

The *in vitro* drug release data were fitted to various release kinetic models. viz. first order, zero order model, Higuchi and Korsemeyer - Peppas equation. The goodness of fit was found out from the above mathematic models.

RESULTS AND DISCUSION

DSC studies

DSC provides information about the physical properties of the sample as crystalline or amorphous nature and demonstrates a possible interaction between drug and polymers in formulations. According to the thermo grams, aceclofenac presented a sharp endothermic peak at 158.3ºC corresponding to the melting point of the drug in the crystalline form. While the thermogram of physical mixture of aceclofenac and chitosan was 158.7ºC.

However a broad endothermic peak observed for chitosan at 92.0ºC. Thus the thermograms of physical mixture showed that drug was in its crystalline form and also there is no interaction between the aceclofenac and the polymer .The DSC graphs are given in fig. 1-3.

IR studies

The FTIR of aceclofenac showed intense bands 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 respectively. The peaks observed in FTIR of physical mixture of aceclofenac and chitosan were 1771.69 cm^{-1}, 1716.89 cm^{-1}, 1589.72 cm^{-1}, 1056.13 cm^{-1} respectively for the above mentioned functional group. From the above interpretation it was understood that there was no major shifting in the frequencies of aceclofenac which indicated that there is no chemical interaction between aceclofenac and polymer which were used in the formulations. The FTIR spectra were given in fig. 4-6 respectively.

Micromeritic properties

When micromeritic properties of all the formulations were compared and it was found that $ACHT_1$ batch was optimal due to Hausner's ratio (1.15), carr's index (14.96) and angle of repose (17°06') were within the specified limit and were good. The results for micromeritic properties of all the formulations were given in table 2

Physical properties

The hardness varied from 4.12 ± 1.06 to 6.21 ± 0.82 kg/cm^2 for $ACHT_1$ to $ACHT_4$ tablets made with 22 % w/w to 51.2 % w/w of guar gum to tablet weight

respectively. The other test such as weight variation, thickness and friability and percentage drug content were within the pharmacopoeial limits. The results for physical properties of all the formulations were given in table 3.

Percentage swelling

The swelling was 9.9% for $ACHT_1$ and it increased to 24.8% for $ACHT_4$ in 30 min with the increase in the polymer concentrations as due to more of the polymer caused more water uptake and thus swelling increased. The swelling increased for first 3 hours upto 33.1% for $ACHT_1$ and thereafter shown a declining trend, while in case of other formulation it increased upto 5 hours due to increased polymer concentrations and after that the swelling decreased gradually. The results for percentage swelling of ACHT were shown in fig. 7.

Percentage erosion

The percentage erosion decreased from 16.4 % ($ACHT_1$) to 1.2 % ($ACHT_4$) at 30th min of the study. At the end of 8th hour the values were 98.6 and 26.0% for $ACHT_1$ and $ACHT_4$ respectively. As time of study increased, the erosion increased. The erosion in SCF revealed that the colonic enzymes present in the caecal contents in the buffer solution helped in degrading the polysaccharide and thereby erosion started. It took almost 8 to 12 hour for the complete degradation of the polymer (chitosan) in the colonic fluid. The $ACHT_1$ released maximum amount of drug at the end of 8th hour in SCF, thus it was considered to be the optimized batch, because it released about 101.16 % in colonic fluid at the 8th hour of the study selected for the pH dependent polymeric coating. The results for percentage erosion of ACHT were given in fig.8

In vitro **drug release studies in SGF, SIF and SCF.**

In SGF (pH 1.2 buffer)

In the simulated gastric fluid, the $ACHT_1$ batch started release at 15 min and a maximum release of 21.12 ± 1.2 % of the drug found at the end of 120 min of the study. This highest percentage of drug release is due to the solubility of chitosan in acid which is its inherent property. The batch $ACHT_2$ released about 16.28 ± 0.82 % and $ACHT_3$ and $ACHT_4$ released about 13.62 ± 0.12 and 8.12 ± 0.82 % of drug for the same time period respectively. The decrease in the percentage was due to more complex structure which is in turn due to increased concentration of chitosan from $ACHT_1$ to $ACHT_4$. It reveals that the time taken for the solubility of chitosan increases as the chitosan concentration increased.

Percentage drug release in SIF (pH 7.4 buffer)

There was no release for the first two formulations $ACHT_1$, $ACHT_2$ at 30 min while there found a minimal release for the next two formulations namely $ACHT_3$, $ACHT_4$. However the release was 1.10 ± 1.2% for $ACHT_1$ and it increased gradually with the increase in polymer concentration and it was 6.92 ± 0.82% for $ACHT_4$ at 1h. The release rate increased with the prolongation of time and it was 22.01 ± 0.54 % for $ACHT_1$ at the end of 6th hour and 36.21 ± 0.23 % for $ACHT_4$ for the same period of time. The results for *in vitro* drug release in SIF were shown in fig.9.

Cumulative percentage drug release in SCF (pH 7.4 buffer with enzyme)

Due to the abundance of colonic enzymes in the colonic fluid, the release started immediately so that percent release was 12 ± 0.26% ($ACHT_1$) at 30 min and it decreased as the polymer concentration increased as release

was 6.25 ± 0.17 % for $ACHT_3$ and no release for $ACHT_4$. The drug release increased proportionately with time and reached to 101.16 ± 1.0 % at the end of 8th hour for the $ACHT_1$ and while the release rate decreased according to the increase in polymer concentration to 33.38 ± 0.26 % for $ACHT_4$ for the same time period. The same results were observed by orient et al.[28] The results for *in vitro* drug release in SCF were shown in fig.10. Based on the above in vitro results the batch $ACHT_1$ was selected as the optimized batch as it released maximum amount of drug at 8th hour and also possessed good micromeritic and physicochemical properties.

Step II

Thus the batch $ACHT_1$ was given pH dependent polymeric coating as explained under the general methodology until to get a weight increase of 10 % w/w. There was absolutely no release in SGF, where as in SIF, it released upto 9.2 ± 0.62% which was less than the uncoated tablets. This was due to the pH dependent solubility of the coating layer. In SCF, the percentage drug release was 102.24 ± 1.2 which was comparable with the uncoated tablets. Though the polymeric coating dissolved at SIF itself the internal fluid causes swelling. But when it was brought in contact with the SCF which contains microbial enzymes, it swelled upto 3 hours and then enzymes penetrated into the gel layer of the tablet and caused the erosion of the gelled layer which made the high percentage drug release. So, it was evident from the results that the $ACHT_1$ batch is a promising formula to target the colon. The results for Cumulative drug release in SIF and SCF of E-$ACHT_1$ were given in fig.11.

In vitro release kinetics

When the data were plotted according to the first order equation, all the formulation showed a fair linearity, with R^2 value between (0.8001- 0.8026), when the same data was plotted according to the zero order equation, it shown a good linearity with R^2 value between (0.9623 - 0.9883). In our experiment, the *in vitro* release profiles of aceclofenac could be best expressed by Higuchi's equation, as the plots showed good linearity ,thus confirmed that the mode of release was diffusion while to further confirm the diffusion mechanism, the data were fit into Korsmeyer et al equation, which showed high linearity with a comparatively high slope value. This n-value, however appear to indicate a coupling of diffusion and erosion mechanism – so called anomalous diffusion. Presence of swelling polymers within the matrix structure might be responsible for the drug release controlled by more than one process. It showed a non fickian mode of release.

Stability studies

The stability studies revealed that $ACHT_1$ formulae did not show any changes in its appearance and drug content after 3 months at an accelerated temperature and humidity condition.

Table: 1 Preparation of the chitosan tablets

Ingredients (mg)	Quantity (mg) present in each tablet			
	$ACHT_1$	$ACHT_2$	$ACHT_3$	$ACHT_4$
Aceclofenac	100	100	100	100
Chitosan	50	100	150	200
Microcrystalline cellulose	25	25	25	25
Mucilage of starch 7.5 %	18	20	20	21
Magnesium stearate 3%	7	8	10	11
Talc 2%	5	6	7	8
Starch powder	25	25	25	25
Total	230	284	337	390

Table:2 Micromeritic properties of aceclofenac and chitosan granules

Test	ACHT$_1$	ACHT$_2$	ACHT$_3$	ACHT$_4$
Bulk density	0.588	0.611	0.638	0.698
Tapped density	0.676	0.714	0.759	0.844
Carr's index	14.96	16.85	18.96	20.91
Hausner's ratio	1.15	1.17	1.19	1.21
Angle of repose	17°06'	17°01'	18°26'	19°42'

Table:3 Physical properties of aceclofenac and chitosan tablets

Test	ACHT$_1$	ACHT$_2$	ACHT$_3$	ACHT$_4$
Weight (mg)	232 ± 1.02	284 ± 0.87	337 ± 0.67	392 ± 0.65
Drug	100.40 ± 0.98	99.27 ± 0.78	99.97 ± 0.78	99.7 ± 0.8
Hardness kg/cm2	4.12 ± 1.06	4.8 ± 0.45	5.6 ± 0.34	6.21 ± 0.4
Thickness (mm)	3.0 ± 0.6	3.3 ± 0.76	4.24 ± 0.56	4.4 ± 1.0
Friability	0.34 ± 0.54	0.20 ± 0.78	0.54 ± 0.34	0.35 ± 0.1
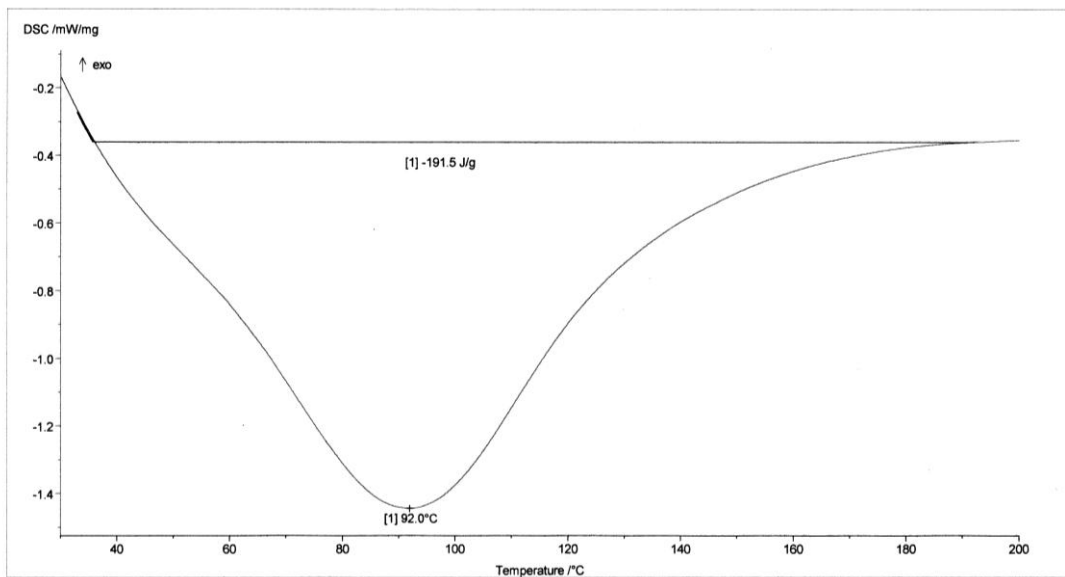
Instrument: DSC 200 PC   Project: IIT Madras   Sample: Aceclofenac

Fig: 1 DSC of Aceclofenac

Fig: 2 DSC of Chitosan

Fig: 3 DSC of aceclofenac and chitosan
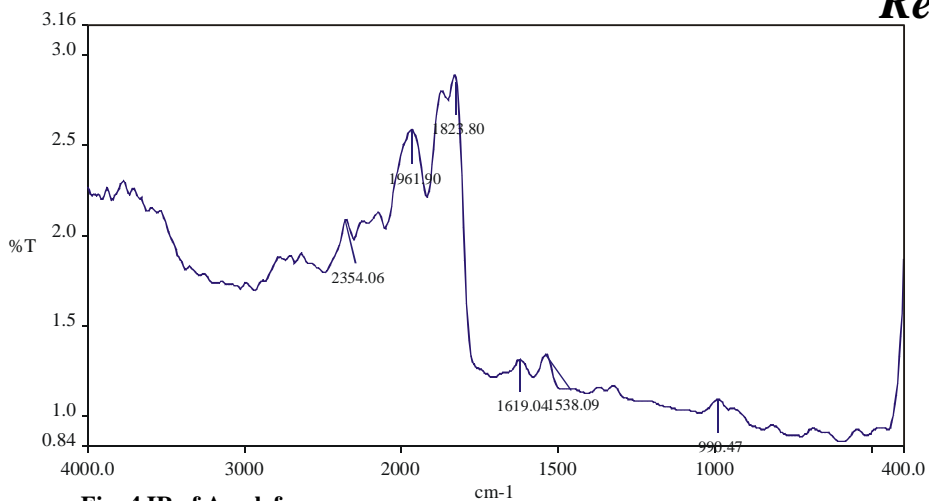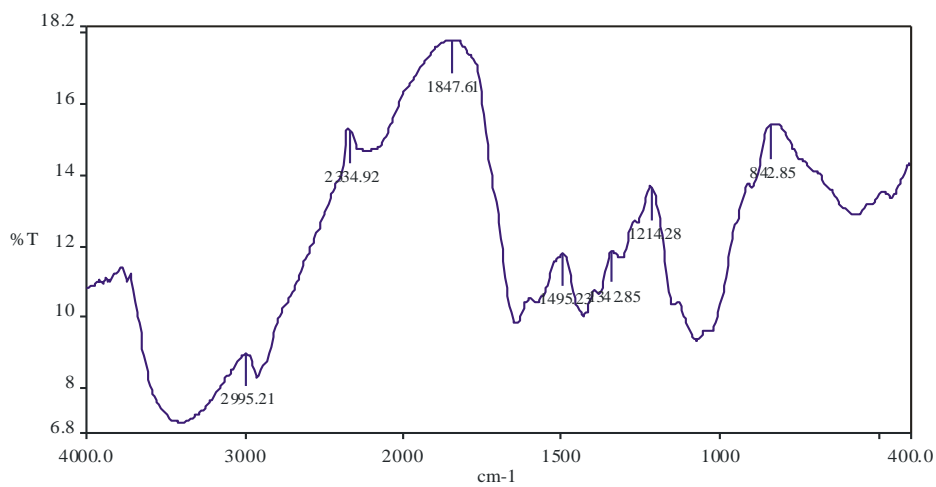
Fig: 4 IR of Aceclofenac
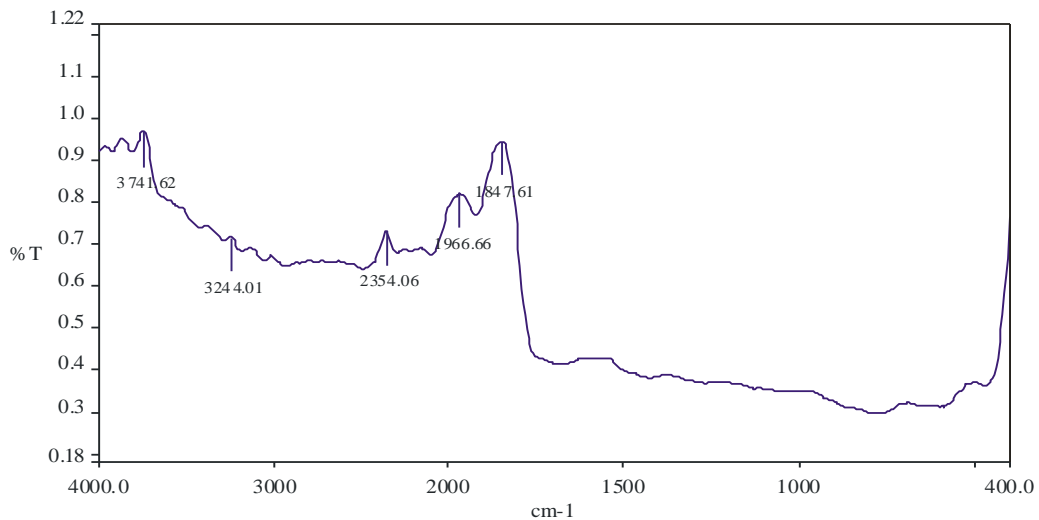

Fig: 5 IR of Chitosan

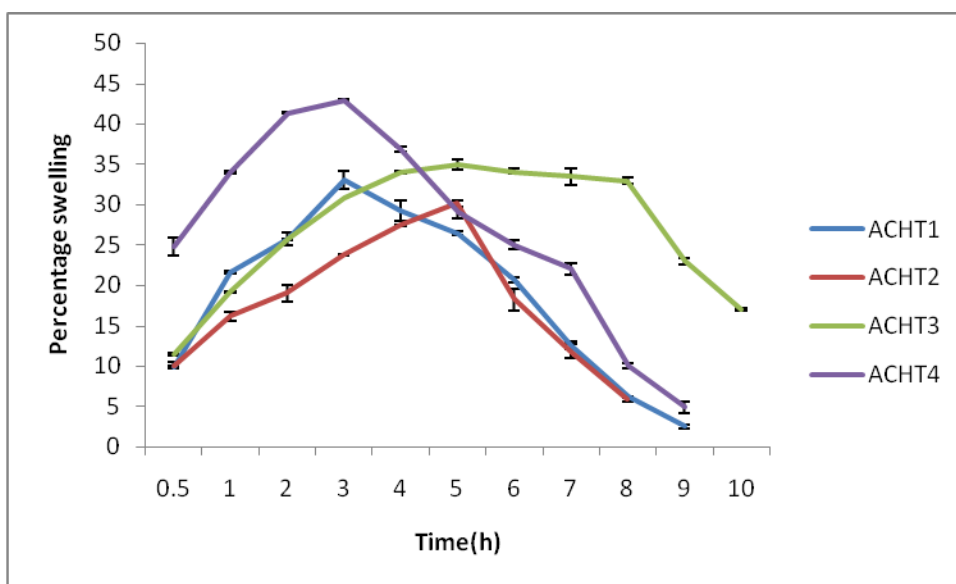Fig: 6 IR of Aceclofenac and Chitosan

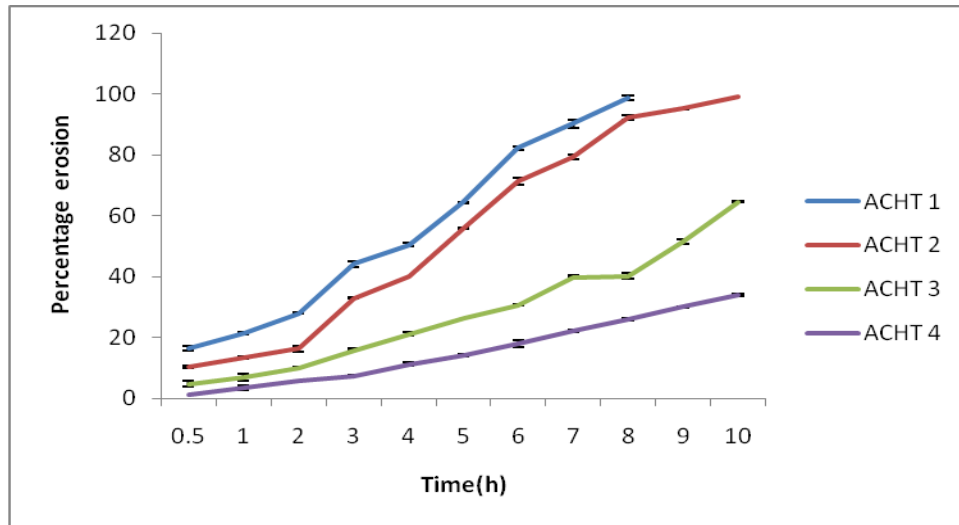Fig: 7 Percentage swelling of aceclofenac and Chitosan tablets

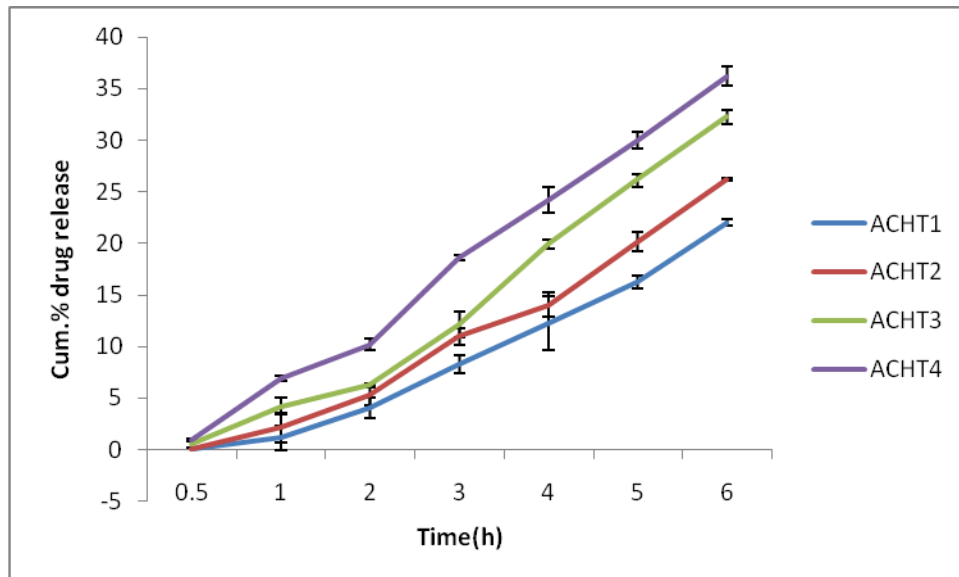**Fig:8 Percentage erosion of aceclofenac and Chitosan tablets in SCF**

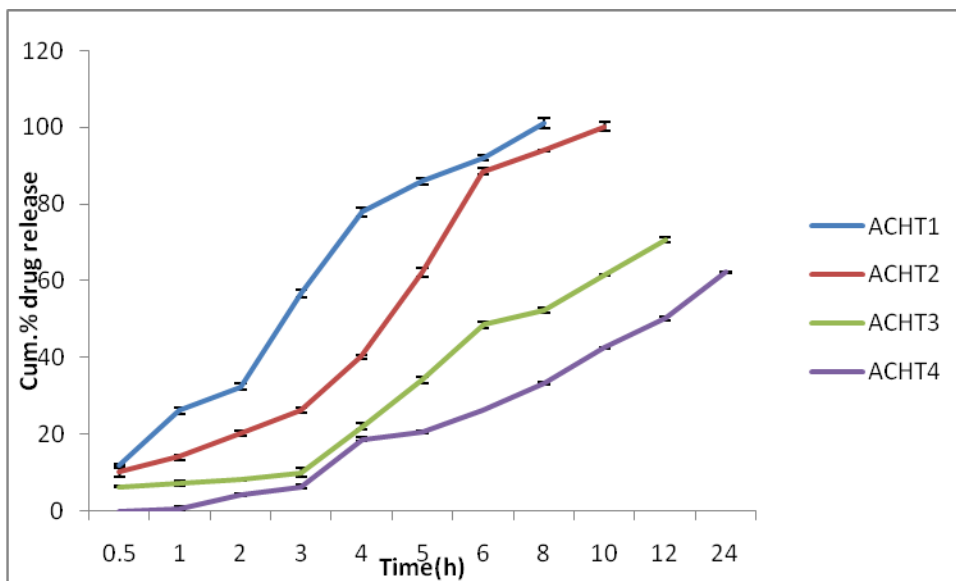**Fig:9 Cumulative percentage drug release of ACHT in SIF**

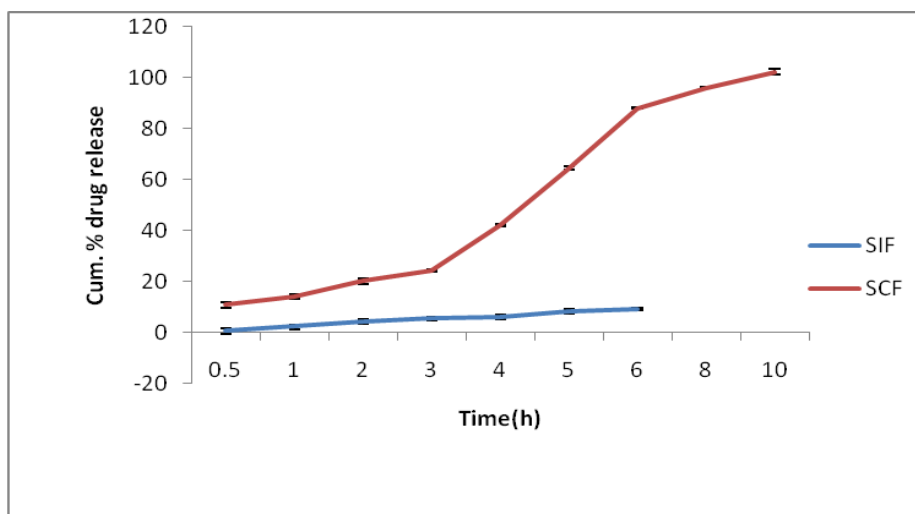**Fig: 10 Cumulative percentage drug release of ACHT in SCF**

Fig 11 Cumulative drug release in SCF and SIF of E-ACHT$_1$

SUMMARY

The objective of the present study was to develop a controlled release colon targeted drug delivery system of aceclofenac, the non steroidal anti-inflammatory drug to approximate the chronobiology of rheumatoid arthritis. The system as a potential value when a delay in absorbtion is desired from a therapeutic point of view in the treatment of disease such as rheumatoid arthritis which have peak symptoms in early morning. Research in this so called chronopharmacological field has assumed significance in developing drug delivery systems that demonstrate the importance of biological rhythms in drug therapy.

Of the several approaches of colon specific delivery of drugs, a combination of coating with pH sensitive polymers and embedding in biodegradable matrices has been followed for preparation of formulations. The combination of these two polymers in a various ratios makes it possible to manipulate drug release within pH range of 6.0 to 7.0. The 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 the bacterial polysaccharidases and results in the degradation of the matrices.

Chitosan have been reported to possess ideal qualities for sustained release of the drug to the targeted site (colon). Colon-specific delivery of the investigational drug (aceclofenac) was aimed through tablets in order to ascertain the efficacy of these formulations for delivery of drug to the colon. It has been reported that polymer concentration is found to influence the release characters of the drug from the dosage form. Chitosan in varying concentrations (22, 35, 45 and 51% w/w total tablet weight)

did not influence the physical characteristics of the tablets, however the swelling index and the percentage erosion appears to be dependent on polymeric concentration. Taking into account the dissolution profile of chitosan-aceclofenac tablets, the $ACHT_1$ was an optimized formulation as its dissolution profile was akin to the expected requirements of the study. The eudragit coating of the optimized formulation $E\text{-}ACHT_1$ has reduced the drug release to the extent of about 9.2 ± 0.02 %, however maintain the same dissolution profile in SCF thus suggesting that chitosan seems to be superior to other polymer in influencing the drug release characteristics.From the overall results on the behavior of chitosan-aceclofenac tablets, it appears promising, since the drug release could be a result of the combination of fine dependent hydration of chitosan and enzymatic degradation by colonic bacteria.

CONCLUSION

The present study focussed on viability of tablets of aceclofenac with polymer chitosan for controlled and colon specific delivery in chronotherapy of rheumatoid arthritis. The *in vitro* studies suggest that a chitosan tablet of aceclofenac is promising for therapy of rheumatoid arthritis. A further detailed study in human subjects will through more light on their efficacy and compliance.

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AUTHOR AFFILIATIONS:

School of pharmaceutical sciences

Vels university, chennai- 117

India

ADDRESS FOR COMMUNICATION:

R. Thiruganesh

Assistant Professor, Dept. of Pharmaceutics

School of Pharmaceutical Sciences

Vels University, Chennai- 117

India

Cell: +91-9618144271

E-Mail: gracewell.nic@gmail.com