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Preparation and In vitro Investigation of Chitosan Compressed Tablets for Colon Targeting

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ABSTRACT

Purpose: The aim of the present study was minimizing the drug release in upper gastro intestinal tract and targeting to colon by using the principles of compression coat. ***Methods:*** Compression coated tablets of Ibuprofen were prepared by direct compression method using chitosan (300, 250, 200 & 175 mg). Tablets were evaluated for their physicochemical properties and in vitro drug release studies. In vitro drug release studies were performed with and without rat caecal contents. ***Results:*** In the rat caecal contents tablets showed enhanced drug release due to degradation of chitosan coat by colonic colonic enzymes. The *in vitro release* studies in pH-6.8 phosphate buffer containing 2% w/v of rat caecal contents showed the cumulative percentage release of Ibuprofen after 26h as 31.94% ±0.59, 67.89% ± 0.45 and 55.87 % ± 0.45 and 82.52 % ± 0.92 respectively. Coat thickness and amount of chitosan controls the release rate. Formulations are best fitted with Korsmeyer-Peppas kinetics and mechanism of drug release was non-Fickian. FTIR studies reveals there is no drug-polysaccharide interaction. F_1 formulation was a promising system for drug targeting to colon. ***Conclusion:*** Based on the obtained results chitosan as a press coat could target ibuprofen to the colon.

Introduction

Among all the routes of drug administration that have been explored for the development of controlled release systems the oral route has by far achieved the most attention and success. This is due, in part to the ease of administration as well as to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. On the other hand the most direct route for delivery of drugs into the colon is by rectal administration. Since there are problems in both patient acceptability and accessing the proximal colon using rectally administered dosage forms, orally administered colon specific delivery systems have been developed. There are three practical mechanisms by which a delivery system can be targeted into the colon following oral administration[1]: Coating with pH dependent polymers, Time release dosage forms, and Delivery systems based on the metabolic activity of colonic bacteria. Colonic bacteria degraded the prodrugs and polysaccharides enzymatically and then the drug releases into the colon. Previously several polysaccharides have been reported as carriers to colon-specific drug delivery.[2-5]For example amylase, cross linked guar gum, chondrotinsulphate, chitosan for peptides, pectin and its salts. Oral compression coated tablets (CCT) compose of an inner solid core that contains an active pharmaceutical ingredient and any other pharmaceutically acceptable carriers or excipients which is substantially covered with an outer layer that dissolves or disintegrates slowly to produce the pre-determined lag time.[6] The advantage of this manufacturing technique is that it is simple, inexpensive and it is not hazardous to the environment since it doesnot require the use of high amounts of organic solvents. Ibuprofen was used as model drug because it is absorbed at different sites in the human gastrointestinal tract and also well absorbed throughout the colon.[1] It is a non-steroidal anti-inflammatory agent, which is widely used in treatment of mild to moderated

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pain and fever. This study selected ibuprofen as a drug for formulating colonic drug delivery system to avoid gastrointestinal discomfort associated with ibuprofen therapy.In the present study, chitosan in the form of compression coat was evaluated as a suitable carrier for colonic targeting of ibuprofen. Chitosan is a non-acetylated or partially acetylated chitin derivative which is tough, bio-degradable and non-toxic.[7] In vitro drug release studies were carried out on ibuprofen core tablets compression coated with different amounts of chitosan in simulated gastro intestinal fluids in the presence and absence of rat caecal contents.

Material and methods

Materials

Ibupeofen was obtained from Strides Acro Labs, Bangalore, India. Chitosan was purchased from Alembic Pharma, Baroda, India. Microcrystalline cellulose, Sodium starch glycholate, Potassium dihydrogen Phosphate and Magnesium stearate were obtained from Spectrochem Pvt. Ltd. Mumbai. Sodium hydroxide pellets were received from Sd fine chem. Ltd., Mumbai, India. Talk was obtained from Leo chem. Bangalore, India. Potassium chloride and Potassium bromide (IR grade) were from Thomas Baker , Mumbai, India and Merck specialities Pvt. Ltd., Germany respectively. Hydrochloride (HCl) was provided from Swastik Pharmaceuticals, Mumbai, India. The instruments used were as follows: Dissolution test apparatus (Lab India, India), Disintegration test apparatus (Serweal Instrument Inc., Bangalore, India), FT-IR Spectrometer (Shimadzu, Japan), UV- Visible Spectrophotometer (Shimadzu, Japan), Hot Air Oven (Serwell Instrument Inc., Bangalore, India), Digital weighing balance (Acculab Sartorius Group, Bangalore, India), Tablet compression machine (I.P/B.P/U.S.P. standard) 12 Station (Karnavati Engineering, Ahmedabad, India), Hardness tester (Scientific Engineering Corp., Delhi, India), Friability tester (Dutta Scientific Works., Madras, I*ndia*), Humidity cabinet (Remi Laboratories Ltd., India), Hydraulic pellet press (S.V.Scientific), pH meter (Serwell Instrument Inc., Bangalore, India).

FT-Infrared spectroscopy

To find out the compatibility between the ibuprofen and the chitosan, 10 mg of the sample and 400 mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and was compressed at 10 kg/cm^2 using a hydraulic press. The pellet was kept onto the sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1} in Shimadzu FT-IR spectrophotometer. Samples were prepared for drug ibuprofen, polymer chitosan, and physical mixture of drug and polymer. The spectra obtained were compared and interpreted for the functional group peaks.

Preparation of ibuprofen core tablets

Each core tablet (average weight 150 mg) for invitro drug release studies consisted of ibuprofen(100 mg), microcrystalline cellulose (MCC, 46 mg) , dried starch (4mg). The materials were weighed, mixed and passed through a mesh(250 µm) to ensure complete mixing. The tablets were prepared by compressing the thoroughly mixed materials using 7 mm round, flat and plain punches on a single station tablet machine (Cadmach, India). The thickness of the core tablet was 0.2 mm and their crushing strength was checked. It was about 3 Kg/cm^2.

Compression coating of ibuprofen core tablets

The Ibuprofen core tablets were compression coated with different concentrations of chitosan. Since the coating material alone gave very soft coats. Microcrystalline cellulose was included in the coat formulations to impart enough hardness. Half the quantity of the coating material was placed in the die cavity, the core was carefully positioned in the center of the die cavity and was filled with other half of the coating material. The coating material was compressed around the core at an applied force of 5,000 kg using 10 mm round, flat and plain punches. The strength of the compression coat tablet was 5 kg/cm^2 (Table 1).

Table 1. Composition of chitosan coats used to cover ibuprofen core tablets

Batch code	Coat Weight (mg)	Composition (mg)			
		Chitosan	MCC	MgStearate	Talc
F_1	300	270	25	2	3
F_2	250	220	25	2	3
F_3	200	170	25	2	3
F_4	175	145	25	2	3
F_5	150	120	25	2	3

Characterization of ibuprofen compression coated tablets

Hardness test

The prepared tablets were subjected to hardness test. It was carried out using hardness tester and expressed in Kg/cm^2.

Friability test

The friability was determined using Roche friabilator and expressed in percentage (%). 10 tablets from each batch were weighed separately and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed and the percentage friability was calculated for each batch using the following formula:

$$F(\%) = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \text{ X } 100$$

Weight variation test

Twenty tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than 10%.

Uniformity of drug content

The prepared ibuprofen tablets were tested for their drug content. Five tablets of each formulation were weighed and finely powdered. About 0.1 g equivalent of ibuprofen was accurately weighed and completely dissolved in pH 6.8 phosphate buffer and the solution was filtered. One ml of the filterate was further diluted to 100 ml with pH 6.8 buffer. Absorbance of the resulting solution was measured by UV- visible spectrophotometer at 223 nm and the amount of drug in the solution were calculated using the standard curve (r^2=0.999).

In vitro drug release studies

USP dissolution apparatus type I was employed to study the in vitro drug release from various formulations prepared. The dissolution medium used was 900 ml of acidic buffer of pH 1.2 for 2 h and phosphate buffer of pH 7.4 for 3 h. Temperature was maintained at 37°C ± 0.5°C and the stirring rate was 100 rpm. Two samples each of 1 ml were taken, suitably diluted and analyzed spectrometrically.

Preparation of rat caecal content medium

To induce bacterial enzymes postulated to be in the caecum, five Wister rats, weighing 200-300 g were intubated with Teflon tubing for 7 days before the release experiments were initiated.Each day 1 ml of 2% w/v of chitosan dispersion was directly administered to the rat stomach through the Teflon tubing. This process provides the best conditions for in vitro evaluation 30min before the commencement of drug release studies, rats were killed by spinal traction. The abdomen was opened, the caecum was isolated, ligated at both ends, dissected and immediately transferred into pH 6.8 phosphate buffer previously bubbled with CO_2.[7,8] The caecal bags were opened, their contents were individually weighed, pooled and then suspended in PBS, to give a final caecal dilution of 2% w/v. As the caecum is naturally anaerobic, all these operations were carried out under CO_2. The studies simulating the drug release in colon were carried out using USP dissolution rate test apparatus (apparatus I, 100 rpm. 37°C) with slight modification.[7] A beaker containing 200 ml of dissolution medium immersed in water containing 1000 ml vessel, which was placed in the water bath of the apparatus. The tablets were placed in the baskets of the apparatus and immersed in the dissolution medium containing rat caecal contents. The drug release studies were carried out for 21 h. (asuming colonic transit time of 20-30 h) and 1 ml samples were taken at different time intervals and replaced with 1 ml of fresh 6.8 pH PBS to maintain a constant volume and pH. The samples were diluted and analyzed spectrometrically. This part of the study was approved by Institutional Animal Ethics Committee.

Release kinetics

Data obtained from the in vitro release studies of compression coated tablet of ibuprofen formulations were fitted to various kinetic equations such as zero order, first order, Higuchi model and Korsmeyer-Pappas model using following equations: $Q = Q_0 - K_0t$ (For Zero order model), $\ln Q = \ln Q_0 - K_1t$ (for First order model), $Q = K_2t_{1/2}$ (for Higuchi model), and $Q/Q_0 = K\ t_n$ (for Korsmeyer - Pappas model). Where, K_0 to K_2 were release rate constants, Q/Q_0 was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism.[9] For Fickian (diffusion controlled), $n \leq 0.5$; for non- Fickian (anomalous/ zero order) release, 'n' value is in between 0.5 to 1.0; for zero order release, n=1.0; for super case transport II, $n > 1.0$.

Results and Discussion

Drug-polymer interaction study by FTIR spectrophotometer

The spectra obtained from FTIR studies at wavelength from 4000 cm^{-1} to 400 cm^{-1} are shown in Figure 1. Comparing the IR spectrum of ibuprofen, chitosan and their mixtures confirm that the drug and polymer in the formulation are compatible with each other. From the figures, it is clear that, there is no appreciable change in the positions of the characteristic bands of the drug along with the IR spectrum of the drug/polymer physical mixture during the present investigation. Since there is no change in the nature and position of the bands in the physical mixture, it can be concluded that the drug maintains it's identity without going any chemical interaction with the chitosan.

Characterization of Ibuprofen core tablets

The results of physicochemical evaluation of prepared core tablets are shown in Table 2. The tablets were evaluated for weight variation, drug content, hardness and friability and disintegration. The drug content was found to be 97.84 ± 0.15%. The hardness was found to be 4.58 ± 0.42 (kg/cm^2) and in all cases the friability was less than 1%.

The results of physicochemical evaluation of compression coated tablet of ibuprofen are shown in Table 3. The tablets were evaluated for weight variation, hardness and friability. The hardness was found to be from 4.58 ± 0.42 to 5.06±0.18 (kg/cm^2) and in all the cases the friability was less than 1%.

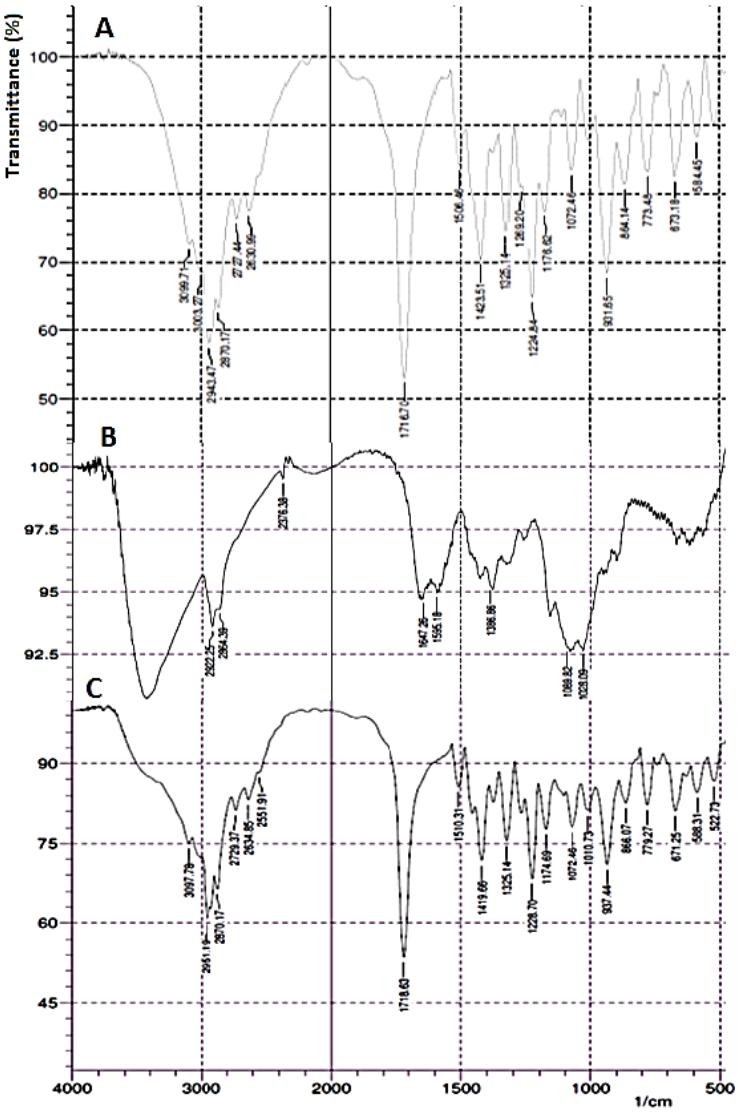

Figure 1. IR Spectrum of (A), Chitosan (B), and their physical mixture (C)

Table 2. Physicochemical evaluations of Ibuprofen core tablets.

Hardness(kg/cm^2)(±S.D)	Friability(%)(±S.D)	Weight variation(%)(±S.D)	Drug content (%)(±S.D)	Disintegration(sec)
4.58±0.42	0.20±0.021	1.403±0.012	97±0.15	60

Table 3. Physicochemical evaluations of Compression Coated Tablet of Ibuprofen

Batch Code	Parameter		
	Hardness (kg/cm^2)(± S.D)	Friability (%) (± S.D)	Weight variation (%)(± S.D)
F_1	5.06±0.18	0.065±0.014	0.51±0.016
F_2	4.8±0.09	0.14±0.034	0.67±0.038
F_3	4.7±0.12	0.11±0.017	0.96±0.052
F_4	4.6±0.35	0.13±0.015	0.57±0.034
F_5	4.82±0.12	0.062±0.029	0.73±0.056

In vitro drug release studies

Drug release studies from compression coated tablets with different coat weight, are presented in figure 2. For colon targeting, it is desirable that the system remains intact and shows minimal drug release in the stomach and the small intestine and starts drug release in the tracts of the colon. Therefore in this investigation an attempt was made to formulate a dosage form, which showed minimal drug release in conditions mimicking mouth-to-colon transit and ensured maximum drug release in the environments of the colon. The compression coat was designed to undergo bacterial degradation in the colon, exposing the rapidly disintegrating drug containing core in the colon.

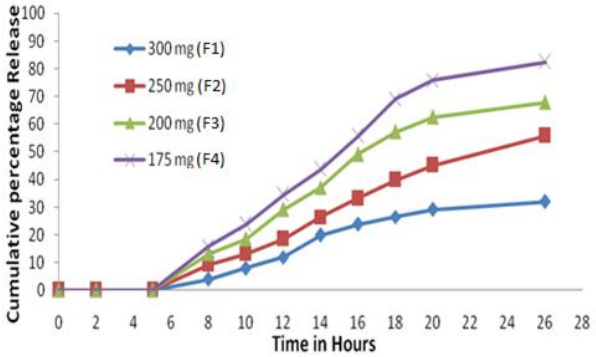

Figure 2. Cumulative percentage release profile of ibuprofen in formulations F_1 to F_4 with rat caecal content.

Formulation F_1 containing 300 mg of Chitosan released 31.94% of drug, Formulation F_2 containing 250mg of Chitosan released 67.89% of drug, Formulation F_4 containing 175 mg of Chitosan released 82.52% of drug, Formulation F_5 containing 150 mg of Chitosan was not able to cover the core tablet,From the above results, it was found that the rate of drug release, from the ibuprofen tablets decreased with increasing concentration of coating polymer. At the end of the 26 h of testing, ibuprofen tablet coated with coat formulation F_1 was found to be intact. Tablets with coat formulation F_3 found broken at one point indicating commencement of the disintegration of the coat, whereas the coat formulation F_4 was completely disintegrated.

Dissolution studies without rat caecal content

The percentage drug released at different time periods from ibuprofen tablets compression coated with coat formulations F1-F4 in 0.1N HCl (2 h), pH 7.4 phosphate buffer (3 h) and pH 6.8 phosphate buffer are shown in figure 3. At the end of the experiment, all these formulations were found to be intact retaining their coats and slight swelling of coats due to water sorption were observed. The results were found to be F_1:10.37%, F_2: 16.63%, F_3: 30.25%, F_4: 32%. From these results, it was found that the percent drug released from ibuprofen tablets were less in 6.8 phosphate buffer than the percent drug released in 6.8 phosphate buffer containing 2% w/v of rat caecal contents.

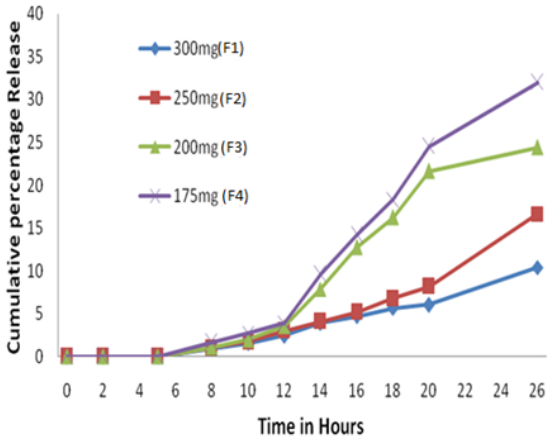

Figure 3. Cumulative percentage release profile of ibuprofen in formulations F_1 to F_4 without rat caecal content.

Successful delivery of drugs specifically to the colon requires the protection of drug from being released in stomach and small intestine. In this study polymer in the form of compression coat was applied over ibuprofen core tablets and drug release studies were carried out under conditions mimicking mouth to colon transit. The drug delivery systems targeted to the colon should not only protect the drug from being released on the physiological environment of stomach and small intestine, but also release the drug in colon after enzymatic degradation by colonic bacteria. Hence in vitro drug release studies were carried out in pH 6.8 phosphate buffer containing 2% w/v of rat caecal contents. At the end of 26 h of testing which includes testing simulated gastric and intestinal fluid, the percent drug released from ibuprofen tablets coated with coat formulation F_1 was found to be 39.91% and the coat remained intact. The presence of higher amount of polymer might not have allowed the disintegration of the coat during the time period of testing. This also indicates that the drug will not be released unless the coat is broken. The percent drug release from tablets coated with coat formulation F_3 were found to increase from 18 h on wards indicating the commencement of breaking of gum coats. The percent drug released after 26 h of testing was 67.89% and the tablet coat was found to be broken at one point making way for the release of the drug. In the case of tablet coated with coat formulation F_4 a significant increase in percent drug released was observed from 16 h on wards and at the end of the experiment and 94.46% of ibuprofen was released. The coat was completely degraded by the rat caecal thereby releasing the drug into the dissolution medium. Since the polymer content and thickness of coat formulation F4 was lesser compared to others, the coat might have been completely hydrated and subsequently degraded by the caecal enzymes at a faster rate resulting in the release of about 94.46%. On the other hand, drug release studies in the absence of rat caecal contents showed that at the end of 26 h of testing which includes testing simulated gastric and

intestinal fluid, the percent drug released from the coated tablets are lesser when compared to the results of study with rat caecal contents. Moreover at the end of 26 h of testing, the coat for all the tablets remained intact which proved that the drug release were found to be dependent on bacterially triggered delivery system. In a study by A.V. Bhosale et al., tablet systems coated with films composed of guar gum and HPMC offered potential as colonic drug delivery systems for ibuprofen.[1] In another study by Kalyani Chithaluru and co-workers combination of guargum/metalose 90 SH polymers were used to prepare compression coated ketorolac tablets.[10] As it was seen in the present study, in the rat caecal contents formulations showed enhanced ketorolac release due to degradation of guar gum coat by colonic galactomannanase enzyme. Stability study were carried out at room temperature and 40°C / 75% RH over a period of 1 month for tablets prepared using coat F_4. Samples were evaluated at 0, 10, 20 and 30 days for different parameters such as physical appearance, hardness, weight variation, drug content and dissolution. The results of the stability studies are given in Table 4.

Table 4. Stability studies of compression coated tablet of ibuprofen using chitosan polymer coat 175 mg (F_4)

Evaluationparameter	Initial	Observation in Day					
		Room temperature			45± 1°C / 75% RH		
		10	20	30	10	20	30
Physicalappearance	Coated tablets	No change	No change	No change	No change	No change	No change
Averageweight (mg)	176	178	179	177	179	180	184
Hardness (kg/cm^2)	4.6	4.6	4.8	4.8	4.7	4.7	4.9
Drug content* (%w/w)	100	98.87±0.23	98.65±0.11	98.73±0.05	98.89±0.32	98.54±0.14	98.23±0.21
% CDR*	82.52±0.92	82.31±0.21	82.62±0.19	81.07±0.43	85.64±0.35	82.44±0.29	82.23±0.35

*(n=3 ± SD), Initial Drug content as 100% w/w

Invitro release of Ibuprofen from formulation F_4 as a sample was best explained by Korsmeyer-Peppas equation indicated a good linearity (r^2=0.997). The respected values for first-order, zero-order and Higuchian release models were 0.609, 0.934 and 0.838 respectively. The release exponent n was between 0.5 and 1, which indicates a coupling of the diffusion and erosion mechanism so called anomalous diffusion and may indicate that the drug release is controlled by more than one process.[10]

Conclusion

The result from this study clearly shows chitosan in the form of compression coat, is a potential carrier for drug targeting to the colon. This polymer is capable of retarding the release of core materials until they reach the colon, an environment rich in bacterial enzymes, which degrade the chitosan allowing the drug release.

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Conflict of interest

The authors report no conflicts of interest in this work.

References

1. Bhosale AV, Hardikar SR, Patil N, Patel U, Sumbe Y, Jagtap R. Formulation and in-vitro evaluation of microbially triggered ibuprofen delivery for colon targetting. *Int J Pharm Tech Res* 2009;1:328-333.
2. Chithaluru K, Tadikonda RR. Formulation and evaluation of microbially triggered compression coated tablets of ketorolac tromethiamine. *Der Pharmacia Lettre* 2011;3:485-495.
3. Hovgaard L, Brøndsted H. Current applications of polysaccharides in colon targeting. *Crit Rev Ther Drug Carrier Syst* 1996;13:185-223.
4. Esseku F, Adeyeye MC. Bacteria and pH-sensitive polysaccharide-polymer films for colon targeted delivery. *Crit Rev Ther Drug Carrier Syst* 2011;28:395-445.
5. Krishnaiah YS, Muzib YI, Rao GS, Bhaskar P, Satyanarayana V. Studies on the development of colon targeted oral drug delivery systems for ornidazole in the treatment of amoebiasis. *Drug Deliv* 2003;10:111-117.
6. Shah R, Patel S, Patel H, Pandey S, Shah S, Shah D. Formulation development of Carvedilol compression coated tablet. *Pharm dev Technol* 2011 Jul 28. [Epub ahead of print]
7. Raghavan CV, Muthulingam C, Jenita JA, Ravi TK. An in vitro and in vivo investigation into the suitability of bacterially triggered delivery system for colon targeting. *Chem Pharm Bull* 2002;50:892-895.
8. Sinha VR, Mittal BR, Bhutani KK, Kumria R. Colonic drug delivery of 5-fluorouracil: an in vitro evaluation. *Int J Pharm* 2004;269:101-108.
9. Dash V, Mishra SK, Singh M, Goyal AK, Rath G. Release kinetic studies of aspirin microcapsules from ethyl cellulose, cellulose acetate phthalate and their mixtures by emulsion solvent evaporation method. *Sci Pharm* 2010; 78; 93–101.
10. Chithaluru K, Tadikonda RR. Formulation and evaluation of microbially triggered compression coated tablets of ketorolac tromethiamine. *Der Pharmacia Lettre* 2011;3:29-39.

