IJPSR (2013), Vol. 4, Issue 8 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 March, 2013; received in revised form, 02 May, 2013; accepted, 27 July, 2013; published, 01 August, 2013

DEVELOPMENT OF CHITOSAN CAPSULE FOR COLON SPECIFIC DELIVERY OF BUDESONIDE

B.S. Wakure*[1], A.V. Yadav [2], N.M. Bhatia [3] and M.A. Salunke [1]

Vilasrao Deshmukh Foundation, Group of Institutions, VDF School of Pharmacy [1], Latur- 413 531, Maharashtra, India
Gourishankar Education Society's Institute of Pharmaceutical Sciences & Research [2], Limb, Satara- 415 004, Maharashtra, India
Bharati Vidyapeeth's, College of Pharmacy [3], Kolhapur- 416 004, Maharashtra, India

Keywords:

Crohn's disease, Chitosan capsule, Budesonide, Colon specific Drug Delivery

Correspondence to Author:

B.S. Wakure

Asst. Professor (Pharmaceutics), Vilasrao Deshmukh Foundation, Group of Institutions, VDF School of Pharmacy, Educity, New MIDC, Airport road, Latur-413 531, Maharashtra, India

E-mail: balaji.wakure@vdf.in

ABSTRACT: The principal derivative of chitin is Chitosan, produced by alkaline deacetylation of chitin, is a non-toxic, biodegradable and biocompatible, cationic polymer. Chitosan has been widely used in the formulation of particulate drug delivery systems to achieve controlled drug delivery. The main objective of the study was to develop enteric coated Chitosan capsule containing budesonide for targeting the ileum and ascending colon sites which were mainly affected in Crohn's disease. This work describes a new colonic drug delivery system utilizing capsule shells prepared from Chitosan. Coating of drug filled Chitosan capsule with pH dependent enteric polymer like Eudragit S100 / L100 (1:1) provides it a special feature of releasing drug at colonic pH. The *in-vivo* study involves the Gamma scintigraphic evaluation of enteric coated Chitosan capsule. The enteric coated Chitosan capsule proved to be efficient to deliver the drug at ileum and ascending colon in Crohn's disease.

INTRODUCTION: Chitin is one of the most abundant organic materials, beings second only to cellulose in the amount produced annually by biosynthesis. It occurs in animals, particularly in crustacean, molluscs and insects, where it is a major constituent of the exoskeleton, and in certain fungi, where it is the principal fibrillar polymer in the cell wall. Chitin has a crystalline structure and it constitutes a network of organized fibers, this structure confers rigidity and resistance to organisms that contain it (Roberts 1992).

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(8).3239-49

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.4(8).3239-49

The principal derivative of chitin is Chitosan, produced by alkaline deacetylation of chitin. Chitosan also occurs naturally in some fungi but its occurrence is much less widespread than that of chitin. Chitosan is poly ß-(1, 4)-2-amino-2-deoxy-D glucopyranose [1].

Chitosan a deacetylation product of chitin is biodegradable and nontoxic. Chitosan forms acetate when dissolved in acetic acid. The acetate can be cast into a film, which is clear, flexible, tough and soluble in water.

Hence considering the filmogenic property of Chitosan; the objective was to prepare capsules of Chitosan and examine their suitability as an alternative to gelatin capsule shell [1-6].

In the present work, we have attempted to utilize Chitosan in the form of capsule shells; which were filled with budesonide coated sugar spheres and then the capsule is coated with enteric polymers, Eudragit L-100 and Eudragit S-100 in the 1:1 ratio. With this system we aimed to deliver drug at colonic site in a sustained release fashion. It was with the intention that the Carboxylic groups of Eudragit S/L 100 and amino groups of Chitosan could interact to form a complex through which drug would release slowly; the anionic enteric polymer combination was selected.

Ulcerative colitis and Crohn's disease are recurrent, idiopathic inflammatory disorders involving the mucosa and sub-mucosa of the colon. Budesonide is a new type of corticosteroid for treating Crohn's disease. Like other corticosteroids, budesonide is a potent anti-inflammatory medication. Unlike other corticosteroids, however, budesonide acts only via direct contact with the inflamed tissues (topically) and not systemically [7].

As soon as budesonide is absorbed into the body, the liver converts it into inactive chemicals. Therefore, for effective treatment of Crohn's disease, budesonide, like topical 5-ASA, must be brought into direct contact with the inflamed intestinal tissue. Hence, colon specific delivery of budesonide by using Chitosan capsule was proved to be beneficial in the treatment of Crohn's disease.

Objectives: The objective of this study was to achieve the colon-specific delivery of budesonide using Chitosan capsules and to assess suitability of Chitosan capsule to deliver the drug at colonic site. The approach is based on enteric coating of Chitosan capsule with Eudragit S-100/L-100 polymers, thereby taking drug filled Chitosan capsule to the colon followed by mucoadhesion, biodegradation of Chitosan by colonic bacteria and pH dependant slow release of drug from Chitosan – Eudragit complex [8].

The biodegradation of Chitosan by colonic bacteria and pH dependant release of drug from Chitosan capsule coated with Eudragit to achieve pH dependent dissolution and slow release of budesonide in time controlled manner may improve the site specificity of drug delivery system to the colon.

The integration of all release function into single drug delivery system will be better alternative to all other approaches which were used to deliver drug to the colon [9].

MATERIALS AND METHODS:

Materials: Budesonide was obtained from Cipla Ltd. Mumbai, India. Chitosan capsules and gelatin capsules were obtained from Aicello Chemical Company Ltd. (Toyohashi, Japan), and the mean diameters and weight of these capsules were 15.6 mm × 5.8 mm and about 60.0 mg, respectively. Eudragit S-100 and Eudragit L-100 was obtained from Evonik Degussa India Pvt. Ltd. Mumbai, while Ethyl cellulose, Polyvinyl Pyrrolidone (K-25), PEG 6000 & talcum powder were purchased from SD-Fine Chemicals Limited and Burgoyne India Ltd., respectively. The Nonpareils Seeds were of pharmaceutical grade and all other chemicals were of analytical grade.

Instruments: The Shimadzu UV double beam spectrophotometer, FTIR (Varian-IR), Gamma Scintigraphy from Siemens (E.cam single sign), Instacoater was used in this study. The pH measuring instrument was from Equiptronics. The tensile strength testing apparatus was from Ubique Ltd. Electrolab Dissolution Tester was used to test the dissolution rate of drug dosage forms.

Preparation of Chitosan Capsule: The Chitosan capsules were obtained from Aicello Chemical Company Ltd. (Toyohashi, Japan) [10]. The scheme of Chitosan capsule used in this study is shown in **Fig. 1**. The mean dimensions and weight of these capsules were 15.6 mm×5.8 mm and about 60 mg respectively. Each Chitosan capsule or gelatin capsule contains 3 mg budesonide adsorbed on nonpareil sugar spheres. The surface of these capsules was coated with Eudragit S100 and L100 (1:1) as an enteric coating material [11, 39].

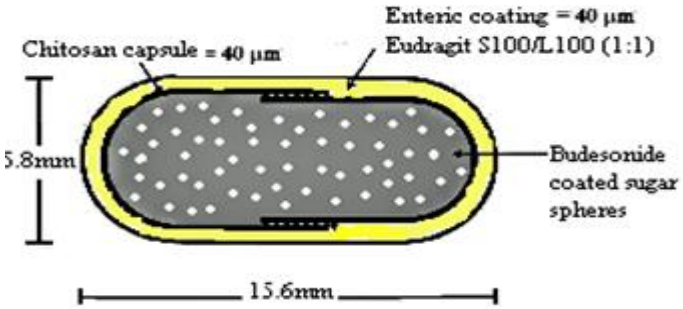

FIGURE 1: SCHEME OF CHITOSAN CAPSULE

Preparation of Budesonide Coated Sugar Pellets: The budesonide coated sugar pellets were prepared by using Instacoat coating instruments. The budesonide pellets are normally produced by stirring the active substance with a binder in an alcoholic liquid and spraying this suspension or solution onto so called starter pellets [12]. These starter pellets can be any desired pharmaceutically utilizable neutral pellets such as sugar pellets. The nonpareil seeds of diameter 1.0 mm were used as core material.

Firstly, PVP K25 was dissolved in (9:1) water: ethanol mixture and components ethyl cellulose, micronized budesonide and talc were suspended in above mixture by using Ultra Turrax. The suspension was sprayed on to the rotating sugar pellets in a pan by using Instacoat coating machine. The inlet and outlet temperature, spray rate were controlled during coating. The budesonide coated sugar spheres are dried at room temperature [13]. The core compositions for one capsule are reported [23-30] in **Table 1**.

TABLE 1: COMPOSITION OF BUDESONIDE COATED SUGAR PELLET [23-30]

Name of the Ingredients	Qty. /capsule	Functions
Sugar sphere	100 mg	Starter pellets
Ethyl cellulose	12 mg	Filler (for Extended release)
Budesonide, micronized	03 mg	Active substance
PVP K25 (MW 25000)	01 mg	Binder
Talc	04 mg	Releasing agent
*Water: Ethanol solution	(9:1)	Solvents * volatile constituents
Total capsule content		**120 mg**

Filling and enteric coating of Chitosan Capsule: The budesonide coated sugar sphere was filled in Chitosan capsules containing Budesonide 3 mg/capsule using volumetric method for powder filling capsules in a manual encapsulator (MultilaborTM) (Allen, 1999).

The surface of filled Chitosan capsule was coated by using anionic enteric polymer coating. The Eudragit S100 and L100 in ratio of 1:1 was optimized and used for the enteric coating of Chitosan capsule [14]. Eudragit S/L 100 as dry polymer substance PEG 6000 (plasticizer) 10% and Talc (glidant) 50% of dry polymer substance was dissolved in ethanol-water mixture. The Titanium dioxide was added as pigment in coating solution.

The preheated Chitosan capsule was coated by continuously spraying the above mentioned coating solution of 50^{o}C. The total solid content for organic coating solution was 10 % and the coating should be done 4-6 mg/cm^2 of capsule surface. All the parameters, inlet and outlet temperature, spray rate were controlled during coating. The coating operation was performed by using Instacoat [15].

The coated Chitosan capsules were checked for individual weights according to US/NF. The enteric coating compositions for Chitosan capsule are reported [23-30] in **Table 2**.

TABLE 2: COMPOSITION OF ENTERIC COATING FOR CHITOSAN CAPSULE [23-30]

Name of the Ingredients	Qty. used	Qty.
Eudragit S 100 – L 100 (Anionic polymer-enteric coating)	7 parts by wt.	7.0 gm
Ethanol	70 parts by wt	80 ml
Water	18.8 parts by wt	18.8 ml
Talc (Glidant)	3.5 parts by wt	3.5 gm
PEG 6000 (plasticizer)	0.7 parts by wt	0.7 gm
Titanium dioxide (pigment)	q.s.	q.s.

Characterization of Drug:

1. **Melting Point Determination:** Melting point of drug was determined using programmable melting point apparatus (Veego Scientific, Model: VMP-PM). Precaution was taken to maintain the uniform heating of silicon bath, in which the capacity containing drug was placed.

2. **IR Spectroscopy** [16]: The dry sample of Budesonide was mixed and triturated with dry KBr. This mixture was analyzed by using Varian IR. The infrared absorption spectrum was recorded and the spectrum was compared with the reference spectrum of budesonide.

3. **UV Spectroscopy** [16, 17]: 10 mg of Budesonide was accurately weighed and was first dissolved in 0.1N HCl (pH 1.2), pH 6.8 Phosphate buffer and pH 3.5 Acetate buffer solutions to plot

spectrum and calibration curve in respected solutions. UV spectrum was recorded in the wavelength range 200-400 nm to get spectrum, λ_{max} and calibration curve of Budesonide in 0.1N HCl, pH 6.8 Phosphate buffer and pH 3.5 Acetate buffer solutions respectively.

4. **Capsule weight variation, locking length and thickness:** The individual weight variation according to USP/NF was performed by weighing 20 capsules individually, calculating the average weight, and comparing the individual capsule weight to the average. The capsule locking length and thickness of both uncoated and coated Chitosan capsule were measured by digital micrometer.

5. ***In-vitro* Drug Release Study:** *In vitro* release testing Release testing was carried out by the Japanese Pharmacopoeia (JP XIV) basket method (100 rpm) or USP XXIV Apparatus-I for evaluation of drug release [18, 19].

   The drug release study from Chitosan capsules was carried out using USP-Basket dissolution apparatus. The release of drug was studied sequentially in three dissolution media of different pH. Three kinds of fluids, i.e. JP 1st fluid simulating a gastric juice (pH 1.2), JP 2nd fluid simulating an intestinal fluid (pH 6.8) and pH 3.5 acetate buffer solution simulating the colon fluid were used as the dissolution medium.

   In the beginning the release of drug in Hydrochloric acid buffer pH 1.2 was studied for two hours (mean gastric emptying time). The dissolution medium was then replaced by Phosphate buffer pH 6.8 and drug release was studied for 2 hours.

   Finally the dissolution medium was replaced by Acetate buffer pH 3.5 (Colonic environment) and release rate was studied until the end of experiment. The temperature of the medium is 37±0.5°C and the speed of the rotation of basket was 100 RPM. The 5 ml of aliquots were taken every 30 minute for first four hours & then after every 60 minutes up to the end of experiment.

The amount of budesonide released from the capsule was determined by spectrophotometrically by measuring absorbance at 248 nm. Systronic 2203 Double beam UV-Visible spectrophotometer was used for the measurement.

Gamma Scintigraphic Evaluation:

1. **Study Design:** This study was of an open design. Controlled-release Chitosan capsules containing pellets of budesonide (3mg) mixed with 99mTc-labelled colloids were administered immediately after breakfast or in the fasting state 1 h before breakfast. Gastric emptying could be followed as the outline of the stomach was visualized by 99mTc colloid. The transit of the formulation through the gastrointestinal tract was recorded by a gamma camera [20, 21].

2. **Subjects and Drug administration plan:** Six male controls (three each on fed and fasted conditions), healthy as judged by physical examination, hematology and clinical chemistry tests, were included in the study. All had normal bowel and defecation habits (1–2 defecations⁄day). Concurrent medication, smoking and the regular use of snuff were not allowed [21].

3. **Study drugs:** Budesonide (3 mg) controlled-release pellets had a diameter of 1-1.4 mm are administered with 99mTc colloid formulation (1.00MBq, $t_{1/2}$ 6.02h). This labeled formulation was prepared as per standard hospital practice & filled in empty Chitosan capsule. These Chitosan capsules are coated with Eudragit S-100/L-100 (1:1 ratio) PH dependant polymers. The radioactivity of the capsules was measured immediately before administration.

4. **Ethics:** The study was performed in accordance with the principles stated in the Declaration and was approved by the Ethics Committee of Hospital. Before admission to this study the subject will be informed of the nature of the clinical study and its purpose, possible risks and discomfort, and the duration of study, the selection criteria, the experiment procedure and all the examinations to be performed [21].

Subjects are also going to be informed that they are taking part in a research project and their clinical records may be seen by the regularity authority. The investigator will explain the participation to the study is entirely voluntary, and that the subject will retain the right to withdraw at any time without prejudice by simply informing the investigator.

5. **Nuclear imaging and Radioactivity measurements:** The nuclear imaging and radioactivity measurements were performed at Spect Lab, Nuclear Medicine services, KEM Hospital, Pune, India. Scintigraphic imaging was performed with the subject standing (anterior and posterior, each with a duration of 2 min) using a gamma camera (Siemens E-Cam) with a collimator (diameter of field of view, 40.0cm) [22]. The scintigraphic data were collected in a computer for subsequent analysis. Five minutes after administration of the pellets, the first scintigraphic images were recorded. Subsequent images were recorded every 30 min during the first 4 h, every hour between 4 and 9 h.
6. **Gastrointestinal Transit Measurement:** Gastric emptying, ascending colon arrival and transverse colon arrival time were measured for fasted and fed state. The gastrointestinal transit of radiolabelled formulation was computed from nuclear imaging and radioactivity measurements [22].

RESULTS AND DISCUSSION:

Melting Point Determination: The melting point of Budesonide was determined by using programmable melting point apparatus (Veego Scientific, Model: VMP-PM) and it was found to be 226.5^{o}C.

IR Spectrum Interpretation: The IR spectrum of Budesonide is shown in **Fig. 2**. The interpretation of IR frequencies is done and shown in **Table 3**. From the IR Spectral data, functional group analysis, it can be concluded that given sample was the drug Budesonide [38].

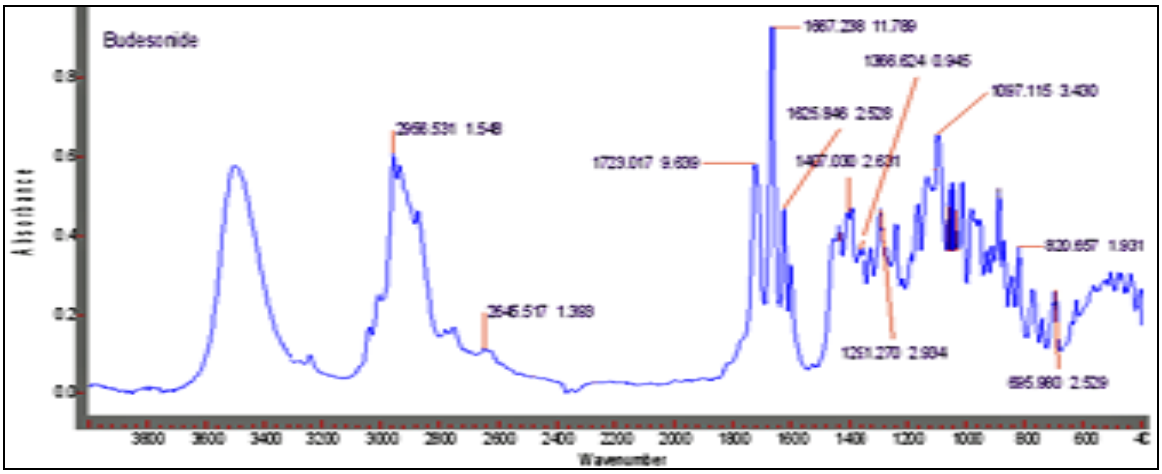

FIGURE 2: IR SPECTRUM OF BUDESONIDE

Physical Evaluation of Chitosan Capsules: The uncoated empty Chitosan capsule and drug filled enteric coated Chitosan capsules were evaluated for weight variation, thickness and capsule locking length. The data of these entire tests are given in **Table 4**. All the formulations showed acceptable pharmacopoeial limits for weight variation and locking length [31, 40, 42].

TABLE 4: EVALUATION OF CHITOSAN CAPSULE

Formulation	Weight* (mg)	Thickness* (mm)	Locking Length*(mm)
Empty Chitosan Capsule	60±1.37	5.7±0.08	15.6±0.28
Uncoated filled Capsule	180.05±1.21	5.7±0.04	15.6±0.28
Enteric Coated Capsule	191.13±0.87	5.8±0.02	15.7±0.26

* Each sample was analyzed in triplicate (n=3)

***In-vitro* Drug Release Study:** In the experiments comparing the in vitro release of drug from gelatin and Chitosan capsules, the release rate from Chitosan capsules was found slow and extended when the dissolution medium of colonic pH was used. *In-vitro* drug release from enteric coated Chitosan capsule was studied in three media of different pH, such as pH 1.2 HCl buffer, pH 6.8 phosphate buffers and pH 3.5 Acetate buffer. From the results, which clearly indicate that below the solubility pH of enteric polymer, no drug release occurred.

After this lag time of 4 hrs, the drug release occurred continuously for a period of more than 9 hours. The release of drug from uncoated Chitosan capsule in acetate buffer was studied. **Fig. 3** shows the drug release pattern from enteric coated and uncoated Chitosan capsules. The slow and hence extended release of drug from Eudragit coated Chitosan capsule was observed. This is suggestive of the fact that the superficial layer of Eudragit started dissolving in the medium of acetate buffer pH 3.5. Beneath this layer of Eudragit S100 / L100, there seems to be a layer of Eudragit – Chitosan complex from which the drug diffuses very slowly [32-33, 41].

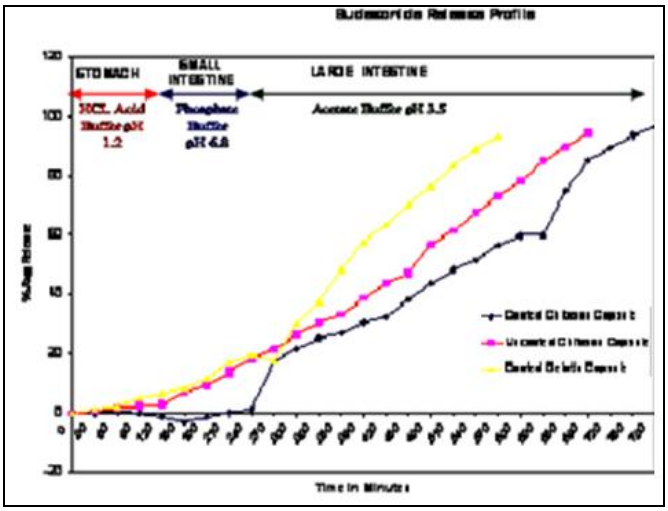

FIGURE 3: COMPARATIVE STUDY OF BUDESONIDE RELEASE FROM UNCOATED, COATED CHITOSAN CAPSULE AND COATED GELATIN CAPSULE

Moreover after several hours of dissolution study the enteric coated capsule does not dissolve completely but rather a fluffy complex of Eudragit and Chitosan was still observed. This observation justifies the slow release of drug from Eudragit coated capsule. As intended, to confirm whether a complex resulting from the interaction between amino group of Chitosan and carboxylic groups of Eudragit has been formed or not, the samples of Chitosan, Eudragit S100 / L100 (1:1) and Eudragit coated Chitosan capsule were analyzed by Infra-red spectroscopy.

Based on these observations, the possible mechanisms involved in the site specific delivery of the drug could be expected to be consisting of;

(1) pH dependent dissolution of Eudragit coating;
(2) Slow diffusion of drug through Chitosan-Eudragit complex;
(3) Mucoadhesion of Chitosan and;
(4) Biodegradation of Chitosan by colonic bacteria [34-35, 43].

The scheme of proposed mechanism of Colon specific delivery of Budesonide using Chitosan Capsule is depicted in **Fig. 4**.

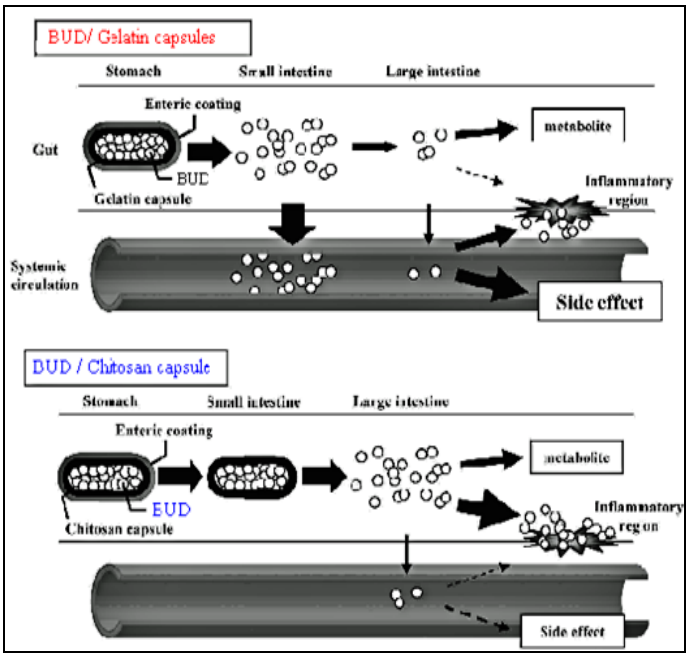

FIGURE 4: PROPOSED MECHANISM OF COLON SPECIFIC DELIVERY OF BUD USING CHITOSAN CAPSULES

IR Spectroscopy: To confirm the interaction between Chitosan and eudragit, the sample of Chitosan, Eudragit S100 / L100, & Eudragit coated Chitosan capsule were analyzed by IR spectroscopy and scanning micrographic techniques [35]. The results of analysis indicate that there has been interaction between Chitosan and eudragit. The IR spectrums are reported in **fig. 5, 6, and 7**.

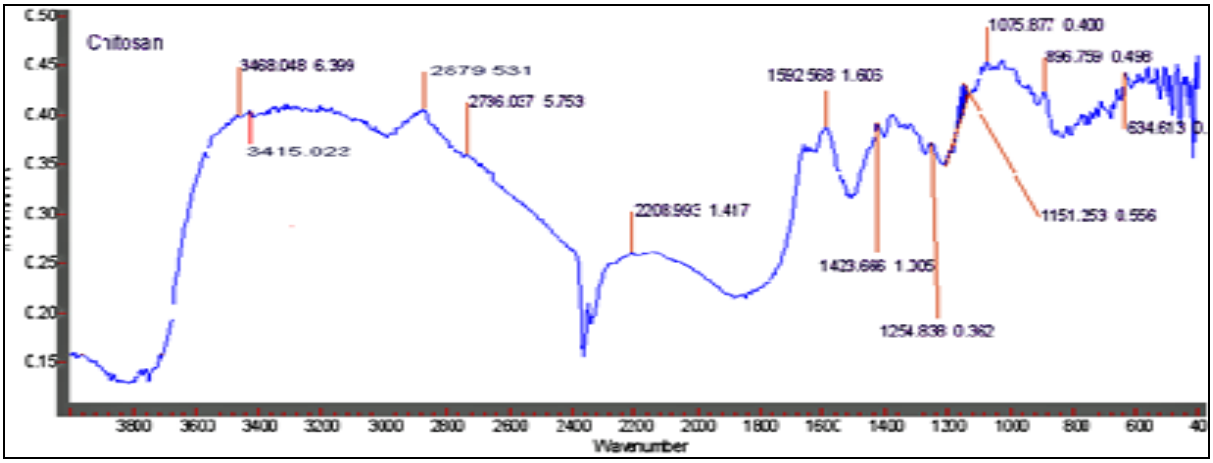

FIGURE 5: IR SPECTRUM OF CHITOSAN

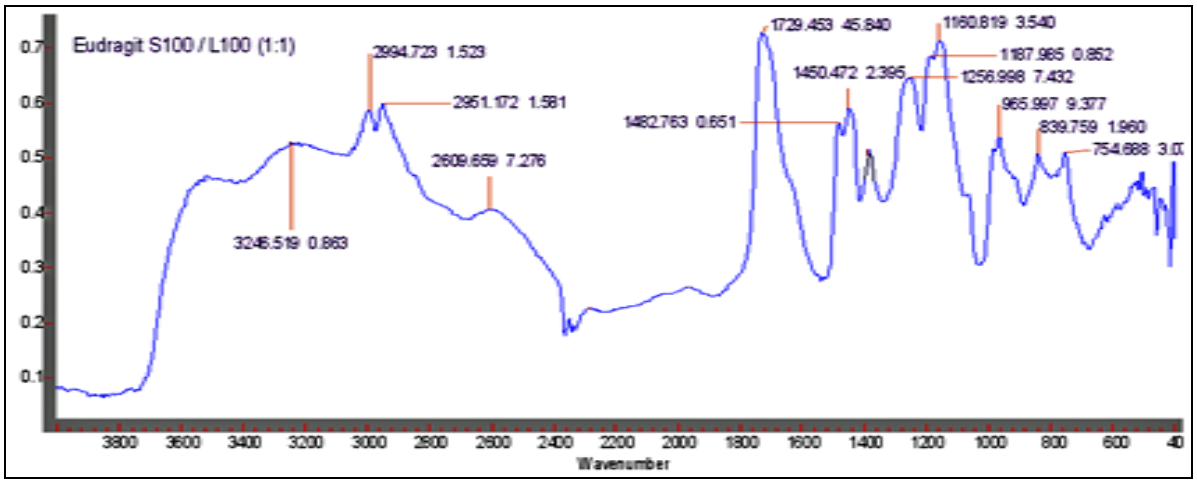

FIGURE 5: IR SPECTRUM OF EUDRAGIT S/L100 (1:1)

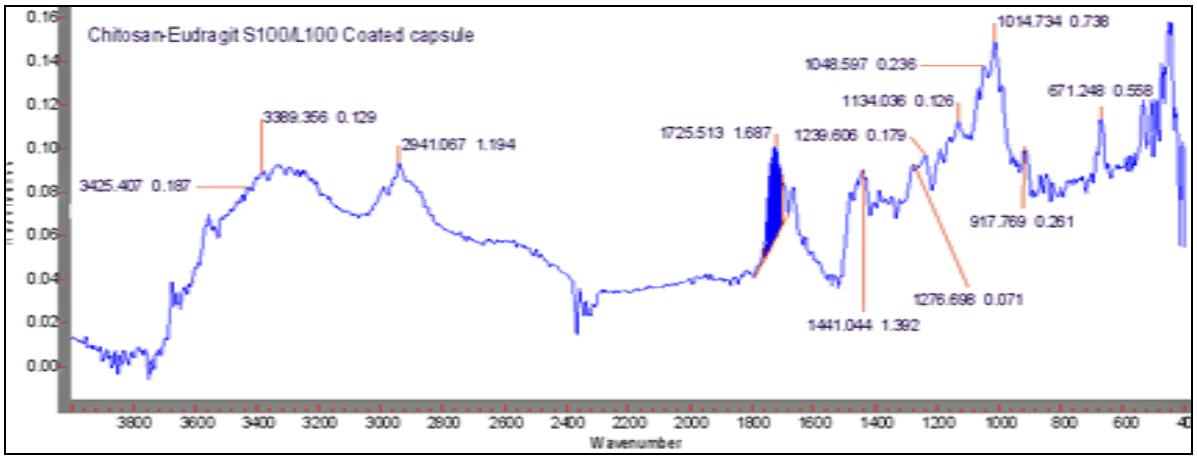

FIGURE 5: IR SPECTRUM OF EUDRAGIT S/L100 (1:1) COATED CHITOSAN CAPSULE

Chitosan showed the characteristic band of the amino groups at 1592cm^{-1}. Eudragit S/L-100 showed the characteristic band of the C=O vibrations of carboxylic groups at 1729 cm $^{-1}$ and ester vibrations at 1160, 1187 and 1256 cm^{-1}. The wide absorption range of the associated OH groups between 2500 and 3500 cm^{-1} is superimposed by CH_X vibrations at 2951, 2994 cm^{-1}. Further CH_X vibrations can be discerned at 1388, 1450 and 1,482 cm^{-1}. Carboxylic acids (R-COOH) are most readily identified as such by infrared spectroscopy. They exhibit a sharp C=O stretch between 1690 and 1760 cm^{-1} and the characteristic O-H stretch of the carboxyl group appears as a broad peak in the 2500 to 3500 cm^{-1} region [36-37]. In the case of the Chitosan Capsule coated with Eudragit S/L100, the peaks at 1592 cm^{-1} corresponding to the amine group of Chitosan has disappeared.

In addition, a significant band appeared at 1725 cm^{-1}. This peak could be attributed to the formation of a carboxylate between the –COOH groups of Eudragit and the $–NH3^{+}$ groups of CS [44-45].

The broad O-H stretching is significant in Carboxylic acid of Eudragit, which was not seen in Eudragit coated Chitosan capsule spectrum, thus lack of an O-H group confirms the formation of Carboxylate anion ($R\text{-}COO^{-}$). Consequently, it seems reasonable to conclude that Chitosan was ionically cross linked with the acrylic polymer. This is, to our knowledge, which reports an ionic cross linking process of cationic Chitosan due to its interaction with a pH sensitive anionic (acrylic) polymer [46].

Gamma Scintigraphic study-Gastrointestinal transit: The objective of the study was to assess the gastric emptying time and IC junction arrival time of budesonide containing Chitosan capsule. After gastric emptying, the 99mTc-labelled pellets spread along the small intestine. Later, the radioactivity became concentrated in the caecal region and ascending colon. It indicates that the radiolabelled pellets get concentrated at caecal region. The linear fit T ½ analysis was done. The tracer is seen in the stomach in the initial images and there is gradual emptying of the contents in the distal bowel over period of time. The tracer is seen at the IC junction between 4 and 5 hours [20-21].

From the scintigraphs taken at different time intervals, the mean gastric emptying time was found to be 1.14 h and the mean colonic arrival time was 4.27 h. Hence, the mean small intestinal transit time was found to be 1.68 h. The capsules entered the colon between 4.0 h and 4.38 h of administration in all the volunteers. This is in conformation with conducting the in vitro drug release studies in simulated gastric and intestinal fluids for 5 hour [22].

The gastrointestinal transit data, time and anatomical location of the complete disintegration of Chitosan capsule in the volunteers is shown in **Table 5 and 6** respectively.

TABLE 5: GASTROINTESTINAL TRANSIT DATA [MEAN (95% CONFIDENCE INTERVALS)]

Parameters	Healthy subjects fasting (hr)	Healthy subjects fed (hr)
Gastric emptying	1.06 (0.95, 1.16)	1.26 (1.31, 1.13)
Small intestine transit time	1.5 (1.0, 1.7)	2.0 (1.8, 2.1)
Ascending colon arrival	4.0 (4.25, 4.33)	4.4 (4.38, 4.26)

TABLE 6: TIME AND ANATOMICAL LOCATION OF THE COMPLETE DISINTEGRATION OF CHITOSAN CAPSULE IN THE VOLUNTEERS

Volunteer	Time (h)	Site of disintegration
1	12	Hepatic flexure
2	14	Transverse colon
3	15	Splenic flexure
4	13	Hepatic flexure
5	16	Splenic flexure
6	15	Descending colon

This study aimed to elucidate whether the controlled release formulation of budesonide (Chitosan capsules) differed in its rate, site and extent of uptake vs. a budesonide formulation in gelatin capsule. It was clearly shown that a delayed and more distal delivery and uptake are achieved with the controlled-release formulation by using Chitosan capsule as carrier. In addition, food has little influence on the site and extent of budesonide uptake from the controlled-release formulation.

The ability of the controlled-release formulation of budesonide to provide targeted deposition in the ileum and throughout the colon was tested under different conditions: in healthy controls with and without food. The gastric emptying curve is depicted in **Fig. 8**.

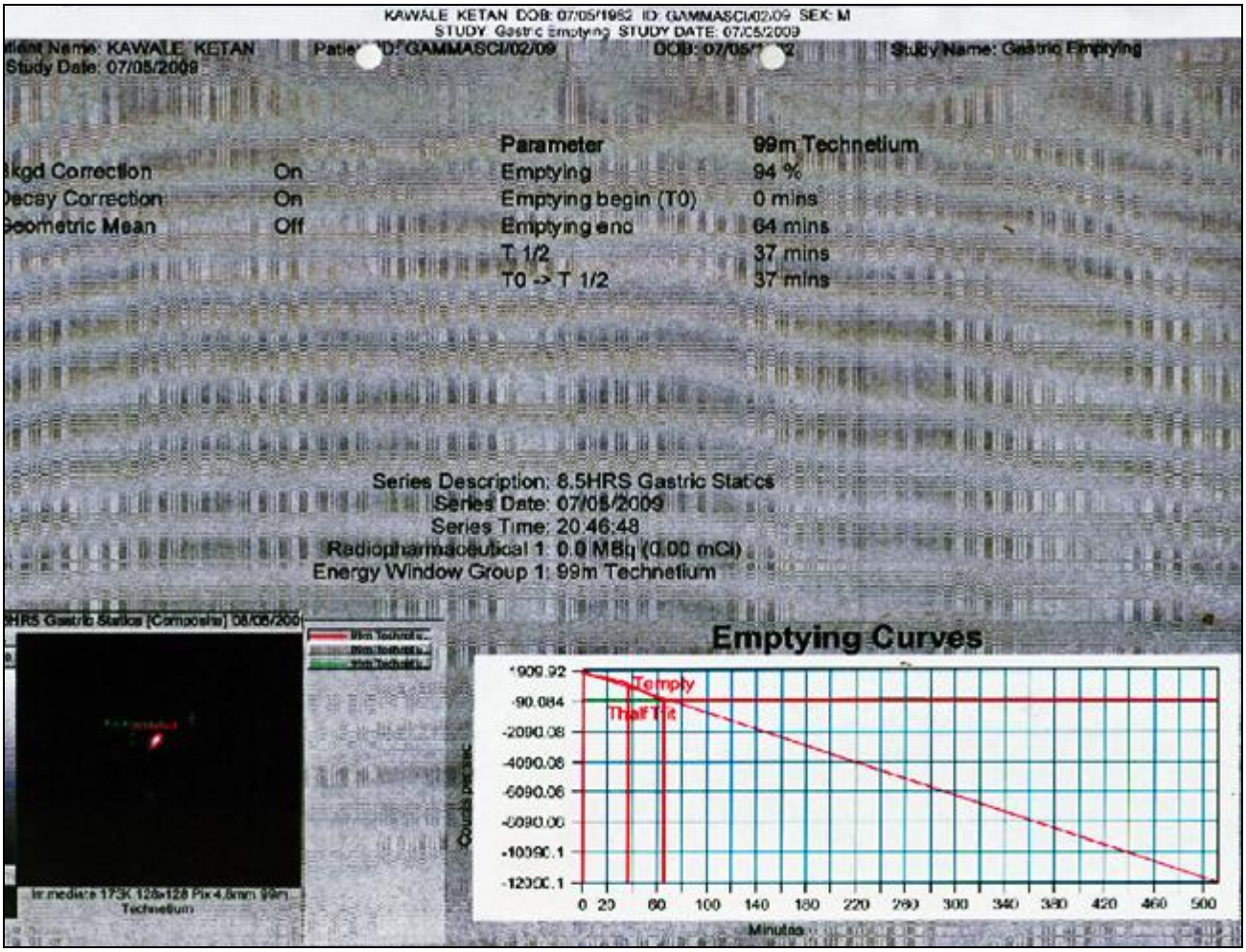

FIGURE 8: GASTRIC EMPTYING CURVE AND GASTRIC EMPTYING TIME

CONCLUSION: The main objective of the studies described was to develop enteric coated Chitosan capsule containing budesonide for targeting the ileum and ascending colon sites which were mainly affected in Crohn's disease. As a new oral drug delivery system for colon targeting, enteric coated Chitosan capsule were developed by coating enteric polymer on surface of Chitosan capsule containing budesonide as a model drug.

The characterization of budesonide was carried out by FTIR and UV spectroscopic techniques. From the IR data it was concluded that the drug was budesonide and the wavelength of maximum absorbance (λ_{max}) was found to be 248 nm.

This work describes a new colonic drug delivery system utilizing capsule shells prepared from Chitosan. Coating of drug filled Chitosan capsule with pH dependent enteric polymer like Eudragit S100 / L100 (1:1) provides it a special feature of releasing drug at colonic pH (Acetate buffer pH 3.5).

Moreover it results in complex formation of Eudragit and Chitosan through which the drug release could be sustained .Another important finding in this work is that, Chitosan can be used in the form of capsule shell for such work which is relatively simple and economic when compared with microspheres, microcores, and micro-encapsulation methods using Chitosan. Industrial scaling and batch to batch reproducibility of the proposed method would be comparably well.

The results also showed that enteric coated Chitosan capsule, comprising of a sugar pellets containing budesonide, effectively delivered to colon showing acid resistance in stomach and pH-dependent released functions on in vitro dissolution study.

In-vitro release study also suggests the extended release of drug over a long period of time due to complex formation between eudragit and Chitosan capsule. This complexation was proved by IR spectroscopy and SEM analysis.

The *in-vivo* study involves the Gamma scintigraphic evaluation of enteric coated Chitosan capsule. The transit time measurement by this method justify that enteric coated Chitosan capsule reaches the IC junction with no content release. Afterwards, the enteric coated polymer get dissolves at pH 6.8 and biodegradation of Chitosan capsule by colonic bacteria takes place. Thus, release of budesonide from Chitosan capsule occurs at IC junction, ascending colon and transverse colon which is the target site in Crohn's diseases. Thus enteric coated Chitosan capsule proved to be efficient to deliver the drug at ileum and ascending colon in Crohn's disease.

Chitosan a biopolymer is both biodegradable and nontoxic and has good film forming property hence can be used safely as capsule shell material. Chitosan being self-preservative, there is no need of adding preservative in its capsule shells. Chitosan capsule shells can be effectively protect photosensitive drugs. Chitosan capsule shells may be used for sustained release of water soluble drugs.

Thus, Chitosan capsule may be prove to be a suitable alternative to traditionally used gelatin as a capsule shell material at least for delivery of certain classes of drugs.

REFERENCES:

1. Akira Yamamoto: Study on the colon specific delivery of prednisolone using Chitosan capsule. The Pharmaceutical Society of Japan, 2007; 127: 621- 630.
2. Ferreira M.C., Morvac M.R., Durate M.L. and Nunes T.: Chitin world. Wirtchftsveriag NW Bremerhaven 1994; 480-488.
3. Ferreira M.C., Morvac M.R., Durate M.L. and Nunes T.: Chitin world. Wirtchftsveriag NW Bremerhaven 1994; 476-479.
4. E. McConnell., S. Murdan., A. Basit. : Chitosan and Cross-linked Chitosan for Colonic Specific Drug Delivery. AAPS 2007; 002076.
5. Flory, P.J.: Principles of Polymer chemistry. Ithaca, Cornell University Press 1993.
6. George, A. Roberts, F.: Chitin handbook, (Muzzarelli, R.A.A and peter, M.G., Eds) European Chitin Society 1997; 127-132.
7. Daniel C Baumgart.: Treatment of Inflammatory Bowel Disease: A Review of Medical Therapy. World J Gastroenterology 2008; 14(3): 354-377.
8. AstraZeneca Canada Inc.1004, Middle gate road, Mississauga, Ontario: Product monograph -Entocort®, (budesonide) controlled ileal release capsules, "Glucocorticosteroid for the treatment of Crohn's disease affecting the ileum and/or ascending colon"; 2007.
9. Chellan & Vijay S. Raghavan.: An in Vitro and in vivo investigation into the suitability of bacterially triggered delivery system for colon targeting. Chem. Pharm. Bull. 2007; 50: 892-895.
10. Tsutomu Suzuki; Kenichi Hashiudo; Takayuki Matsumato: Large intestinal dissociative hard capsule. Aicello chemical co. Ltd., Toyohashi, Japan: US Patent 5283064, 1994.
11. Hideki Kashiwagi, Kenichi Yukawa, Uehon-machi Tennoji-ku.: A Hard Capsule Made of Chitosan was shown to Disintegrate in Colon. Osaka-city 543–0001, Japan 2006; 20:13–17.
12. Peter Gruber, Hans Joachim Lach, Norbert Otterbeck: Budesonide pellets with a controlled released pattern and process for producing the same. Dr. Falk Pharma GmbH, Germany: US Patent-5, 1999; 932,249.
13. Richard N. Fedorak., Lana Bistritz: Targeted Delivery, Safety, and Efficacy of Oral Enteric Coated Formulations of Budesonide. Advanced Drug Delivery Reviews 2005; 57:303– 316.
14. H. Bando., J. McGinity. : Physicochemical Properties of Enteric (Eudragit® S100/L100) Films prepared under Organic and Aqueous Conditions. Eur. J. Pharm. and Biopharm 2001; 51:183-190.
15. M. Ray., & S. Basu: Design of Eudragit® Coated Chitosan Beads for Colon Specific Drug Delivery. AAPS 2005; 000843.
16. Indian Pharmacopeia: Budesonide-Identification 2007: 817-819.
17. British Pharmacopeia. General Notices part III, Budesonide: Ph Eur monograph (pp.1075).
18. Hideyuki Tozaki & Tomokazu Odoriba: Chitosan capsules for colon-specific drug delivery: enhanced localization of 5-aminosalicylic acid in the large intestine accelerates healing of TNBS-induced colitis in rats. J.Control. Release 2002; 82:51–61.
19. Libo Yang: Colon specific drug delivery: new approach and in vitro/in vivo evaluation. Int. J. Pharm 2002; 235:1-15.
20. Hodges, L.A. & Et.al.: Scintigraphic evaluation of colon targeting pectin-HPMC tablets in healthy volunteers. International Journal of Pharmaceutics 2008; doi:10.1016/j.ijpharm.2008.12.002.
21. Y.S.R. Krishnaiah S. Satyanarayana, Y.V. Rama Prasad: Gamma scintigraphic studies on guar gum matrix tablets for colonic drug delivery in healthy human volunteers. Journal of Controlled Release 1998; 55:245–252.
22. S. Edsbacker, B. Bengtsson, P. Larsson., P. Lundin., A. Nilsson: A Pharmacoscintigraphic Evaluation of Oral Budesonide Given As Controlled Release (Entocort) Capsules. J Aliment Pharmacology Therapy 2003; 17:525–536.
23. Raymond C Rowe., Paul J Sheskey and Sian C Owen: Handbook of Pharmaceutical Excipients. Pharmaceutical press, Fourth Edition 2000:410-418.
24. Raymond C Rowe., Paul J Sheskey and Sian C Owen: Handbook of Pharmaceutical Excipients. Pharmaceutical press, Fourth Edition 2000: 1992-1996.
25. Raymond C Rowe., Paul J Sheskey and Sian C Owen: Handbook of Pharmaceutical Excipients. Pharmaceutical press, Fourth Edition 2000: 736-751.
26. Raymond C Rowe., Paul J Sheskey and Sian C Owen: Handbook of Pharmaceutical Excipients. Pharmaceutical press, Fourth Edition 2000:1616-1626.
27. Raymond C Rowe., Paul J Sheskey and Sian C Owen: Handbook of Pharmaceutical Excipients. Pharmaceutical press, Fourth Edition 2000: 2032-2039.
28. Raymond C Rowe., Paul J Sheskey and Sian C Owen: Handbook of Pharmaceutical Excipients. Pharmaceutical press, Fourth Edition 2000: 2072-2079.

29. Raymond C Rowe., Paul J Sheskey and Sian C Owen: Handbook of Pharmaceutical Excipients. Pharmaceutical press, Fourth Edition 2000: 1445-1462.
30. Raymond C Rowe., Paul J Sheskey and Sian C Owen: Handbook of Pharmaceutical Excipients. Pharmaceutical press, Fourth Edition 2000: 1469-1490.
31. Dong, Y.M., Qiu, W.B., Ruan, Y.H., Wu, Y.S., Wang M.A., Xu, C.Y.: Influence of molecular weight on critical concentration of Chitosan/ formic acid liquid crystalline solution. Polym. J. 2001; 33:387-389
32. Bigucci, F., Luppi, B., Cerchiara, T., Sorrenti, M.: Chitosan / pectin polyelectrolyte complexes: selection of suitable preparative conditions for colon-specific delivery of vancomycin. Eur. Journal of Pharm. Sci., doi:10.1016/j.ejps.2008.09.004.
33. Gihan Fetih. & Sara Lindberg: Improvement of absorption enhancing effects of n-dodecyl-d maltopyranoside by its colon-specific delivery using Chitosan capsules. International Journal of Pharmaceutics 2005; 293:127–15.
34. Jain N.K.: Controlled and Novel drug Delivery.CBS publication, New Delhi, Edition 1, 2002: 89-111.
35. K. Kaur & K. Kim: A New Colon-Specific Multi-Layered Delivery System for Prednisolone. AAPS 2005; 002490.
36. Kost J, Langer R.: Responsive polymeric delivery systems. Adv.Drug Delivery Rev. 2001; 46:125-148.
37. Linshu Liu., Fishman L. Joseph Kost., Kevin. B Hicks. B.: Pectin base systems for colon specific drug delivery via oral route. Biomaterials 2002; 24:3333.
38. Ole Ostergaard Thomsen., Antoine Cortot. & et.al: A Comparison of Budesonide and Mesalamine for Active Crohn's disease. The New England Journal of Medicine 1998; 339(6):371-374.
39. Manjeet S. Chinnan. & Thawien Bourtoom: Preparation and properties of rice starch Chitosan blend biodegradable film. LWT - Food Science and Technology 2008; 41:1633-1641.
40. Radi Hejazi. & Mansoor Amiji: Chitosan-Based Gastrointestinal Delivery Systems. Journal of Controlled Release 2003; 89:151–165.
41. Sayeh F. Ahrabia: Development of pectin matrix tablets for colonic delivery of model drug ropivacaine. European Journal of Pharmaceutical Sciences 2000; 10:43–52.
42. Sorlier, P. Denuziere A., A., Viton, C., Domard, A: Relation between the degree of acetylation and the electrostatic properties of Chitin and Chitosan. Biomacromol 2001, 2:765-772.
43. V. R. Sinha: In vivo evaluation of time and site of disintegration of polysaccharide tablet prepared for colon-specific drug delivery. Int. J. Pharm. 2005; 289:79-85.
44. Vishal K. Gupta: A novel pH-and time-based multi-unit potential colonic drug delivery system. Int. J. Pharm. 2001; 213:83-91.
45. W. A. Chan: Comparison of the release profiles of a water soluble drug carried by Eudragit coated capsules in different in-vitro dissolution liquids. Powder Technology 2001; 119:26-32.
46. Yogita Krishnamachari., Parshotam Madan., Senshang Lin: Development of PH and Time-Dependant Oral Microparticles to Optimize Budesonide Delivery to Ileum and Colon. Int. J. of Pharmaceutics 2007; 338:238-247.

How to cite this article:
Wakure WS, Yadav AV, Bhatia NM and Salunke MA: Development of Chitosan capsule for Colon specific delivery of Budesonide. *Int J Pharm Sci Res* 2013: 4(8); 3239-3249. doi: 10.13040/IJPSR. 0975-8232.4(8).3239-49