

FORMULATION AND EVALUATION OF CHITOSAN SODIUM ALGINATE MICROCAPSULES OF 5-FLUOROURACIL FOR COLORECTAL CANCER

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ABSTRACT

The present work describes the preparation of Sodium alginate/chitosan microcapsules containing 5-Fluorouracil (5-FU) intended for colon-specific delivery. The alginate/chitosan micro granules were prepared by the cross linking technique with calcium chloride(4%). Microscopy and Digital photography was used for morphology observation, which shows spherical shape but rough surface of the micro particles. Transmission infrared spectra of chitosan powder, 5-fluorouracil, sodium alginate pectin, and prepared microcapsules were acquired to draw information on the molecular state of chitosan and 5-fluorouracil. Differential scanning calorimetry (DSC) studies of 5-Fluorouracil, Chitosan, sodium alginate and pectin, were performed with PerkinElmer Thermal Analysis (Mettler Toledo 821Thermal analyzer) Calibrated with indium as standard. For thermogram acquisition The drug content and release profile of 5-FU was determined by UV-Vis absorption measurement at λ max 266 nm. The drug content was found to be 0.061mg of 5-FU /mg of alginate/chitosan microcapsules. The swelling behavior and release of drug was determined at two different pH conditions i.e. at pH 1.2 and pH 6.8. micro particles were swelling but did not dissolves give more sustain manner of release. In order to study the effect of alginate on drug release from microcapsules. Accordingly, three different batches (F₁, F₂ & F₃) containing 1.5% w/v, 2.0% and 2.5% w/v of alginate based microcapsules were prepared (batches A₁, A₂ and A₃). The results of in vitro studies shown 5-fluorouracil remain intact and shows minimal drug release in stomach and small intestine, it is very advantage because 5-fluorouracil the initial release it is required to be drastically minimized to avoid the sight effects associated with these agents.

Keywords: Microcapsules, Sodium alginate, Chitosan, Pectin.

INTRODUCTION^{1, 3, 4, 7}

Colon drug delivery³ has gained much interest in local as well as systemic delivery due to its prolonged residence time of luminal contents,

reduced epithelial enzymatic activity, increased tissue responsiveness to absorption enhancers and natural absorptive characteristics. Site specific delivery of drugs to the receptor site has

the potential to reduce side effects and to increase pharmacological response. The treatment of disorders of the large intestine, such as irritable bowel syndrome, ulcerative colitis, Crohn's disease, colon cancer and infectious diseases where it is necessary to attain a high concentration of the active agent, may be efficiently achieved using colon specific delivery systems. Conventional oral dosage forms are ineffective in delivering drugs to the colon due to absorption and/or degradation of the active ingredient in the upper gastrointestinal tract.

The specific delivery of drug to the colon by prodrugs, polymeric prodrug and polymeric systems has evoked great interest in recent times. Essentially there are three approaches to achieve site specificity: utilizing pH changes in the gastrointestinal tract, timed-release capsules and Azo-polymeric¹² carriers degraded by the microflora located in the colon. The mechanism of these colon-specific drug delivery systems is presumed to take place due to enzymatic cleavage by the normal colonic microflora. The rich microflora of the human colon is responsible for the conversion of laxatives such as sulistine and sennosides to active therapeutics. Another well known demonstration of the use of this mechanism is the localization of 5-amino salicylic acid in the human colon by bacterial azo- reduction of sulphasalazine and olsalazine. There are only a few studies performed on polymeric systems that could carry a variety of drugs to the colon. A more universal approach to utilize bacterial degradation of the azo bond to achieve specific release has been the synthesis of a polymer suitable for coating and the use of hydrogels with azo-aromatic cross-links.

Among the different approaches to achieve colon selective drug delivery,³ that use of polymers specially biodegradable by colonic bacteria, holds a great promise. Chitosan^{2, 5, 11,14,15,16} is a high molecular weight, cationic polysaccharide obtained by the deacetylation of chitin, the major compound of exoskeletons in the crustaceans. Because of its low production costs, bioadhesivity, biodegradability, biocompatibility, nontoxic nature and recent FDA approval, the pharmaceutical and food applications of chitosan have increased remarkably over recent years. Pharmaceutical applications include nasal, ocular, oral, parental and transdermal drug delivery. Recently, it was reported to be degraded by colonic microbial flora and it can be utilized as a polymer for colonic drug delivery.

The present investigation is aimed at using these inexpensive, naturally occurring and abundantly available polysaccharides for colon delivery of 5-fluorouracil. An attempt was made to formulate a dosage form which consisted of biodegradable polysaccharides as the main constituent, showed minimal release of 5-fluorouracil in the tracts of the upper GIT and rapid release in the tracts of the colon. 5-Fluorouracil is a pyrimidine analogue and is the drug of choice for colon cancer. It inhibits RNA function and/or processing and synthesis of thymidylate. It is administered parenterally since absorption after ingestion is unpredictable and incomplete. Targeting of 5-fluorouracil to the colon in cases of colon cancer would not only reduce the systemic toxicity of the drug but would also show the desired action in a lesser dose.

The present study was aimed to develop and evaluate suitable Chitosan alginate microcapsule for colon-specific delivery of 5-fluorouracil for better treatment of colorectal cancer. Microcapsules were prepared by calcium chloride cross linking method with different concentration of sodium alginate, Chitosan, and pectin.¹⁷

1. Materials

5-Fluorouracil
Potassium dihydrogen phosphate
Sodium hydroxide
Hydrochloric acid
Potassium chloride

2. Standard solution

Standard stock solution of pharmaceutical grade 5-Fluorouracil was prepared by dissolving 50mg of drug, and make up to 50 ml with acid Buffer pH 1.2 and phosphate Buffer pH 6.8 separately in order to get concentration 1mg /ml.

3. Working solution procedure

From the above standard solution a series of dilutions containing 2,4,6,8,10 and 12 µg/ml were prepared by using acid Buffer pH 1.2 and phosphate Buffer pH 6.8 separately. The absorbance of above dilutions were measured in Elico uv-visible spectrophotometer- 119 at 266 nm, using Buffer pH 1.2 and 6.8 as a blank. The concentration of 5-fluorouracil and corresponding absorbance are given in table 1. The optical densities were plotted against concentration of 5-Fluorouracil as shown in fig 1 and 2. This calibration curve was used for the estimation of 5-fluorouracil in the present work.

Formulation Development

Preparation of chitosan-alginate microcapsules Containing 5 - fluorouracil

As per method reported^{11,13} all the formulation were prepared using 20ml of sodium alginate solution containing 150mg of 5-fluorouracil and 100ml of chitosan^{15,16} solution (prepared in 2% v/v acetic acid) containing calcium chloride dihydrate.

The formulations were prepared using 20ml of sodium alginate solution containing 250mg of 5-fluorouracil and 100ml of chitosan^{15,16} solution containing calcium chloride hydrate. P^H of chitosan solution was adjusted to 5.5 with 10% sodium hydroxide solution. Sodium alginate solution was loaded into a syringe fitted with 23G needle. 100ml of chitosan-calcium chloride solution was taken in a beaker and stirred at 100 rpm. Alginate 5-FU solution was added at a constant rate of 30ml/hour to chitosan - calcium chloride solution with constant stirring. A reaction time of 10 minutes was used. After forming microcapsules, it was filtered, wash with distilled water and hardened with acetone.

Formulation I

In these formulation three different batches A₁, A₂ & A₃ were developed by using sodium alginate,

CHARACTERIZATION

a. Morphological evaluation of microcapsules³¹

Shape, surface characteristics and sizes of microcapsules were evaluated using optical microscope and digital photograph. Sizes of microcapsules evaluated using optical microscope. Since microcapsules were irregular after drying and spherical at wet condition. The longest diameter was measured. Hundred microcapsules per formulation were evaluated and the experiment was performed. Average diameter was then calculated. Strength and flexibility of microcapsules membrane was measured qualitatively.

b. Determination of percentage drug entrapment

Drug loading

50mg of microcapsules were treated with 50ml of phosphate buffer (pH 7.0) in a 100ml amber coloured vial with stirring at 250 rpm. The temperature was maintained at 37± 0.2°C. At the end of 2 hours it was filtered, filtrate was

analyzed spectrophotometrically at 266nm (UV/VIS spectrophotometer)

c. Equilibrium swelling studies³²

i). Percentage swelling of microcapsules

The sorption capacity of chitosan-sodium alginate microcapsules of 5-fluorouracil was determined by swelling the microcapsules in distilled water and SIG and SIF until equilibrium was attained. The Swollen weights of the microcapsules were determined by blotting the microcapsules with filter paper to remove adsorbed water and weighed. The weights of the swollen microcapsules were recorded every hour until there was no further increase in weight (equilibrium swelling).

$$E_{sw} = \left[\frac{(W_e - W_o)}{W_o} \times 100 \right]$$

Where

W_e = Weight of hydrogel at equilibrium.

W_o = Initial weight of the hydrogel microcapsules.

E_{sw} = Percent swelling at equilibrium.

ii). Percentage weight loss of microcapsules

The % weight loss from prepared chitosan-sodium alginate microcapsules of 5-Fluorouracil is determined by swelling the microcapsules in distilled water, simulated gastric fluid, and simulated intestinal fluid until equilibrium was attained. The swollen weights of the microcapsules were determined by blotting the microcapsules with filter paper to remove adsorbed water and weighed. The weights of the microcapsules were recorded every hour.

Percent weight of the microcapsules is calculated

$$E = \left[\frac{(W_t - W_o)}{W_o} \times 100 \right]$$

Where

W_t = is the weight of microcapsules at time

W_i = initial weight of the microcapsules

E = % of weight loss.

d. STABILITY STUDIES

Solid-state characterization

To study the molecular properties of 5-Fluorouracil, Chitosan, sodium alginate and pectin, the solid-state characterization was done by the application of thermal, infrared, and microscopy techniques. During these studies, solid-state characteristics of 5-Fluorouracil,

Chitosan, sodium alginate and pectin, were compared with those of microcapsules to reveal any changes occurring as a result of chitosan-sodium alginate microcapsules of 5-Fluorouracil preparation.

i) Differential scanning calorimetry

Differential scanning calorimetry (DSC) studies of 5-Fluorouracil, Chitosan, sodium alginate and pectin, were performed with perkinElmer Thermal Analysis(Mettler Toledo 821Thermal analyzer)Calibrated with indium as standard. For thermogram acquisition, sample sizes of 1 to 5mg were scanned with a heating rate of 10⁰C /min over a temperature range of 50⁰C to 300⁰C. In order to check the reversibility of transition, samples were heated to a point just above the corresponding transition temperature, cooled to room temperature, and reheated up to 300⁰C.

ii) Fourier transform infrared spectroscopy

Fourier transform infrared (FTIR) spectra were performed for 5-Fluorouracil, Chitosan, sodium alginate, pectin, blank microcapsules on Nicolet impact 410 (Nicolet Analytical Instruments Madison, WI). Spectra of 5-Fluorouracil, Chitosan, sodium alginate and pectin, blank microcapsules were obtained using the potassium bromide disc method, in each case, spectra in the region of 400 to 4000cm⁻¹ were co-added with a resolution of 2cm⁻¹.

e. Drug release studies

In vitro Dissolution

The ability of the prepared microcapsules to retard drug release in the physiological environment of the stomach and the small intestine was assessed by conducting drug release studies in stimulated stomach and small intestinal pH, respectively. Dissolution test was conducted in USP 1 apparatus at 75 rpm and a temperature of 37⁰C. Initial drug release studies were conducted in 750ml of 0.1N HCl (p^H 1.2) for 2 hours. Then, 250ml of 0.2M trisodium phosphate was added to the dissolution media and the pH adjusted to 6.8. samples were withdrawn after regular intervals of time to evaluate drug release. These were analyzed spectrophotometrically at a wavelength of 266nm.

Modified method

Drug release studies in the presence of goat cecal content were also carried out using USP dissolution test apparatus. However, slight modification in the procedure was done. The

experiments were carried out in 250ml beaker immersed in water maintained in the jars of dissolution test apparatus. Initial studies were carried out in 150ml of 0.1N HCl (p^H of 1.2) for 2 hours. After this 50ml of 0.2M trisodium phosphate was added the dissolution media and the pH adjusted to 6.8. the study at a pH of 6.8 was continued for 3 hours. After which goat cecal content equivalent in cecal content to 4 and 8g were added to 200ml of buffer (p^H 6.8) to give a final cecal dilution of 2 and 4 per cent, respectively. Dissolution in the cecal content media was carried out till completion of 24 hours. The experiments in cecal content media were carried out in presence of continuous supply to nitrogen. At different time intervals 1 ml sample was with drawn from the dissolution media and 1 ml of cecal content (2 or 4 % as the case may be), maintained under anaerobic conditions, was replenished into the dissolution media. The volume of sample was made up to 10ml, filtered through sintered glass (G-5) filter and the filtrate was analyzed using UV spectrophotometer at 266 nm.

RESULTS AND DISCUSSION

The main objective of the present work is "Development of chitosan-sodium alginate microcapsules of 5-fluorouracil for reducing the dosing frequency, Targeting the drug release into the colon their by increase the bioavailability of the drug, by using polysaccharide and natural polymers.

On the whole a total number of three formulations F₁,F₂,F₃ were developed ,in each formulation three different batches were developed by cross-linking (with calcium chloride) method .Composition of formulations are shown in Table 2,3,4.

The following studies were conducted for chitosan-sodium alginate microcapsules of 5-fluorouracil and results are shown below.

a) Morphological evaluation of microcapsules

Shape and surface features of prepared microcapsules were studied by optical microscopy and digital photograph. It was observed that prepared microcapsules were spherical in wet conditions, irregular after drying (fig.3) and also brown in colour properly due to alginate drug core.

The chitosan membrane was transparent, porous and continuous in nature. Chitosan flakes could also be seen inside the pores suggesting the membrane was thick.

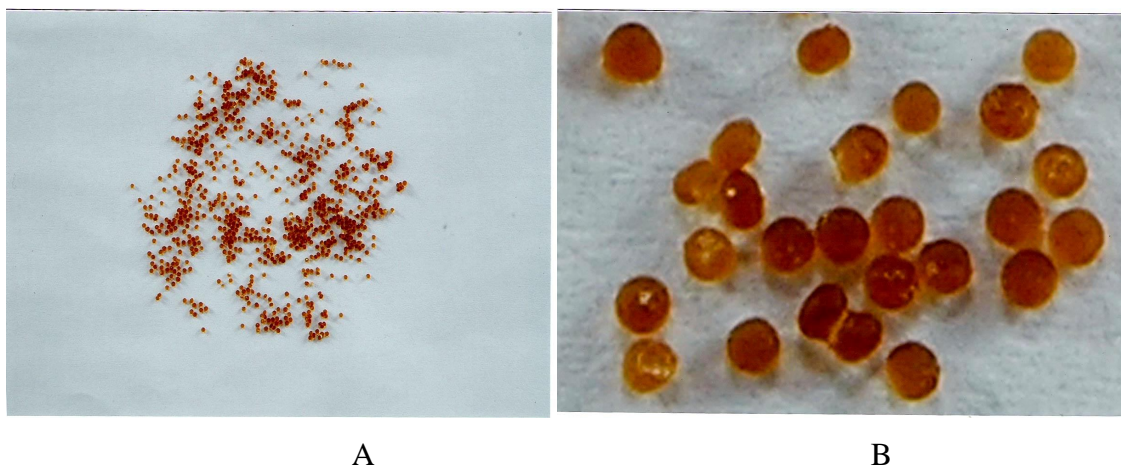
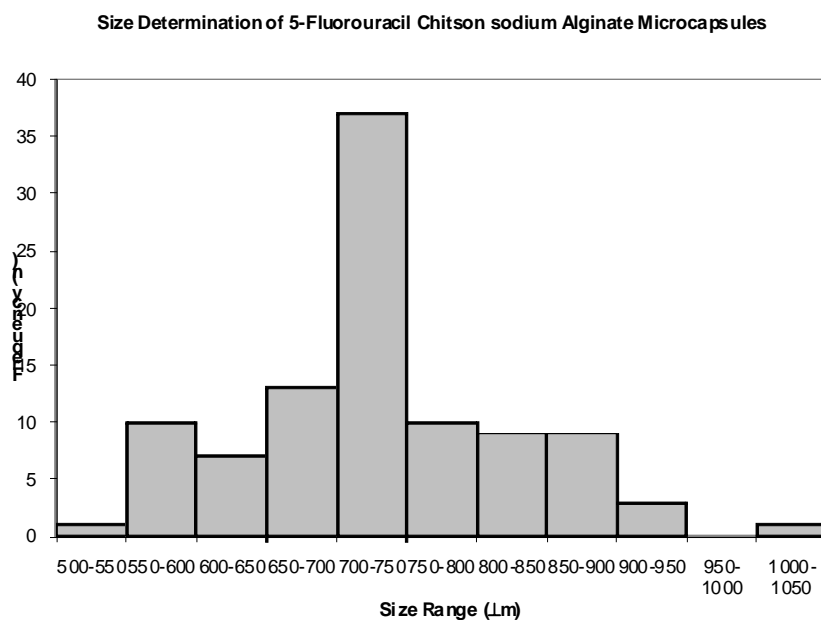


Fig. 1 A: Digital Photograph of Chitosan Sodium Alginate Microcapsules of 5-fluorouracil in dry condition, B: Zoom size digital photograph of Chitosan Sodium Alginate

Fig. 2



Determination of percentage drug entrapment

Drug loading

Drug loading was decreased with increase in the weight of either encapsulating polymer or chitosan and different coatings. (Table 1)

Table 1: Physical characteristics of prepared microcapsules of chitosan sodium alginate

S. No.	Batch code	Size (μm)	Drug loading (mg/100mg)	Strength	Flexibility
1	A ₁	422	15.000	++	+++
2	A ₂	450	12.500	++	+++
3	A ₃	465	10.500	+++	+++
4	C ₁	480	14.500	+	++
5	C ₂	495	11.200	++	++
6	C ₃	510	9.700	+++	+++
7	P ₁	520	13.500	+++	+++
8	P ₂	535	10.500	+++	+++
9	P ₃	550	9.000	++++	+++

Strength/ flexibility: + very weak / fragile, ++ weak / fragile, +++ strong / flexible, ++++ very strong / flexible.

stomach due to low swelling and in the intestine, the highly swollen. Chitosan allows the azoreductase to diffuse into the interior. This is followed by the cleavage of the azo cross-links in the gel matrix.

Percentage weight loss of microcapsules

The percent weight loss curves of the microcapsules are shown in Fig (6) chitosan – sodium alginate microcapsules weights were gradually decrease at each and even hour are shown in table (8) and finally reached to 0% weight loss at 24 hours.

e) STABILITY STUDIES

i) Fourier Transform infrared spectroscopy

Transmission infrared spectra of chitosan powder, 5-fluorouracil, sodium alginate pectin, and prepared microcapsules were acquired to draw information on the molecular state of chitosan and 5-fluorouracil Fig 7. Chitosan is an amino glucose characterized by a small proportion of amide groups via an amide linkage with acetic acid.

In the infrared spectrum, powder chitosan exhibited a broad peak at 3443.28cm^{-1} which is assigned to the N-H and hydrogen bonded O-H stretch vibrational frequencies, while a sharp (shoulder) peak at 3610cm^{-1} is that of free O-H bond stretch of glucopyranose units. Further, in the C-H stretch region of FTIR spectrum, the higher intensity peak at 2922.59cm^{-1} is assigned to the asymmetric and the lower intensity peak at 2923cm^{-1} is assigned to symmetric modes of CH_2 . In addition, the characteristic band due to CH_2 scissoring, which usually occurs at 1378.85cm^{-1} was also present in the sample. Since the grade of chitosan used in the present

study was $\geq 85\%$ deacetylated, an amide bond peak was present in the spectra and the C = O stretch of amide bond was observed at 1642.09cm^{-1} . The peaks at 1550 and 1599cm^{-1} were assigned to strong N-H bending vibrations of secondary amide, which usually occur in the range of 1640 to 1550cm^{-1} as strong band.

In the carbonyl frequency region, pectin showed strong peaks at 1639 and 1421.28cm^{-1} , which were attributed to carboxylic C=O struching.

In the infrared spectrum of sodium alginate exhibited a broad peak at 3411.46cm^{-1} which is assigned to the N-H and hydrogen bonded O-H stretch vibrational frequencies, while a sharp (shoulder) peak at 3610cm^{-1} is that of free O-H bond stretch of glucopyranose units. Further, in the C-H stretch region of FTIR spectrum, the higher intensity peak at 2922.59cm^{-1} is assigned to the asymmetric and the lower intensity peak at 2923cm^{-1} is assigned to symmetric modes of CH_2 . In addition, the characteristic band due to CH_2 scissoring, which usually occurs at 1415.49cm^{-1} was also present in the sample. Since the grade of chitosan used in the present study was $\geq 85\%$ deacetylated, an amide bond peak was present in the spectra and the C = O stretch of amide bond was observed at 1625.7cm^{-1} . The peaks at 1030.77 and 1599cm^{-1} were assigned to strong N-H bending vibrations of secondary amide, which usually occur in the range of 1640 to 1550cm^{-1} as strong band.

The peaks present in 5-fluorouracil pure drug, chitosan, sodium alginate, pectin or aslo present in physical mixture and formulation of chitosan sodium alginate microcapsules of 5-fluorouracil. Hence there is no drug interaction between drug, polymer and excipients.

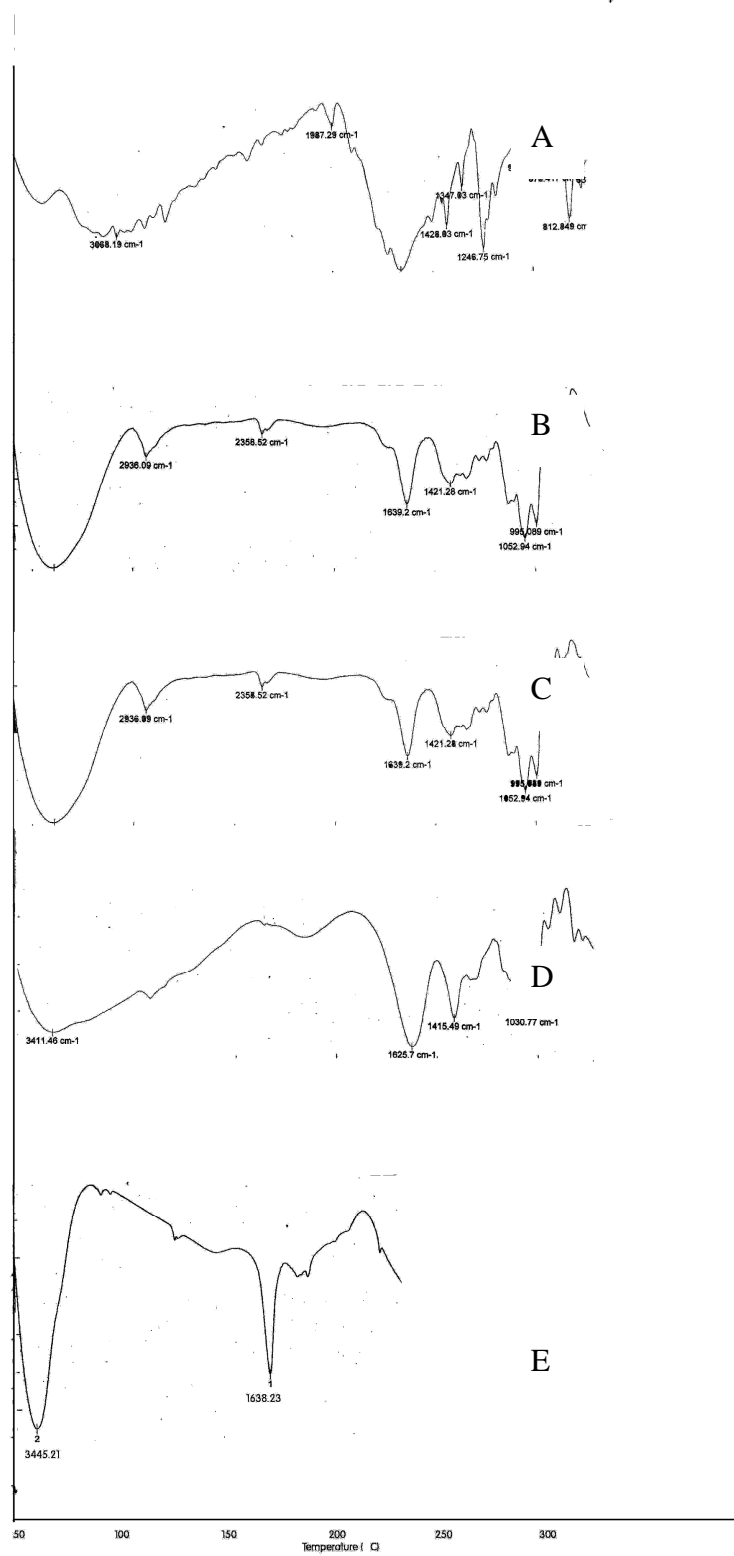


Fig. 3: Comparison FT-IR Spectrum of 5-Fluorouracil, Chitosan, Pectin, Formulation

ii) Differential scanning calorimetry

The DSC thermograms of 5-fluorouracil, sodium alginate, chitosan, pectin, blank microcapsules, chitosan-sodium alginate microcapsules of 5-fluorouracil are shown in figure. And the observed thermal events are summarized in table 2.

Table 2

S.No.	Sample	Peak I		Peak II		Peak III	
		T (°C)	ΔH (J/g)	T (°C)	ΔH (J/g)	T (°C)	ΔH (J/g)
1.	5-Fluorouracil	285.166	212.54	-	-	-	-
2.	Sodium alginate	102.000	217.685	236.166	173.396	259.333	16.127
3.	Chitosan	68.2	145.63	-	-	-	-
4.	Pectin	157.666	23.536	-	-	-	-
5.	Physical mixture	94.666	174.928	185.833	10.326	233.833	66.130
6.	Formulation P ₃	99.000	148.575	200.333	233.833	-	-

Thermogram of 5-fluorouracil shows different endotherms, which are fused together at 270°C. Presents of endotherms in this region may be due to the reasons: melting (with decomposition) of 5-fluorouracil in the temperature range of 250°C to 285.166°C, and removal of the residual solvents from the pure drug. Peak transition temperature for melting of the drug was about 287°C.

Thermogram of sodium alginate showed an initial endothermic (shoulder peak) at 102.000°C (peak I Fig) due to removal of absorbed moisture (or nonstructural water followed by two endothermic peaks at 236.166°C and 259.333°C (peak II and III fig) was observed, which is due to the presence of small amounts of dihydrate in the sample finally a sharp exothermic peak obtained as a result of decomposition.

Peak I, II and III are due to transition / melting with thermogram of chitosan showed an initial endothermic peaks at 180-200°C (peak I fig) due to transitions (or) melting and followed by a sharp exotherm due to decomposition at 350°C (peak II).

Thermogram of pectin showed an initial endothermic peak at 157.666 (peak I - fig) due to transitions (or) melting of the compound and

exothermic event occur at 300°C (peak II fig) due to decomposition of the compound.

Both physical mixture of chitosan – sodium alginate, pectin contain 5-fluorouracil chitosan–sodium alginate microcapsules of 5- fluorouracil exhibited 3 endothermic and one exothermic peaks in DSC thermograms.

The transition of sodium alginate occurred at 94.666°C and 233.833°C (peak I, III fig) with no appreciable shift. Other peaks in the regions of 185.833°C (peak II) due to transition to pectin have resulted from loss of moisture on heating. In 5 – fluoroacil loaded microcapsules peak represented endotherm at 99.000°C due to transition of SA and peak at 200.333°C due to transition of pectin. On other endotherm at 274°C to 280°C (III) due to transition of chitosan and followed by peak at 285.166°C due to decomposition of 5-fluorocil peak (IV).

DSC pattern of pure drug showed a characteristic exothermic peak which was also obtained in the physical mixture of the drug and polymer indicating no interaction b/w them in physical state. However, drug loaded MC was show the characteristic drug peak indicating no possible ionic interaction between drug, polymers and excipients.

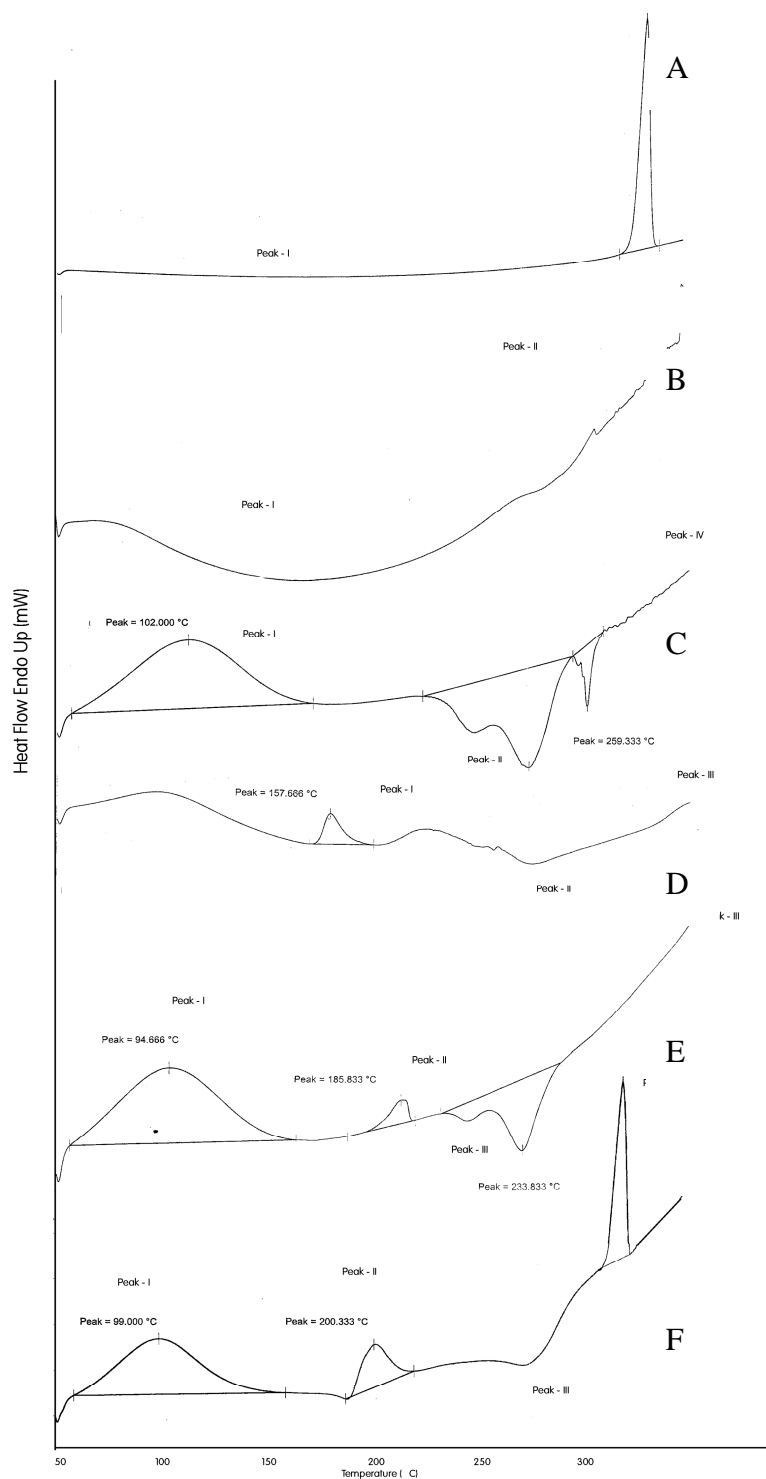


Fig. 4: Comparison DSC Graphs of 5-Fluorouracil, Chitosan, Pectin, Physical Mixture and Formulation

f) In vitro drug release studies

For drug delivery systems designed for colon targeting, it is desirable that the system remains intact and shows minimal drug release in the

physiological environment of the stomach and the small intestine and triggers in the tracts of the colon. For chemotherapeutic agents, for example, 5-fluorouracil the initial release is

required to be drastically minimized to avoid the side effects associated with these agents. Hence 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 outer coating was designed to undergo bacterial degradation in the colon.

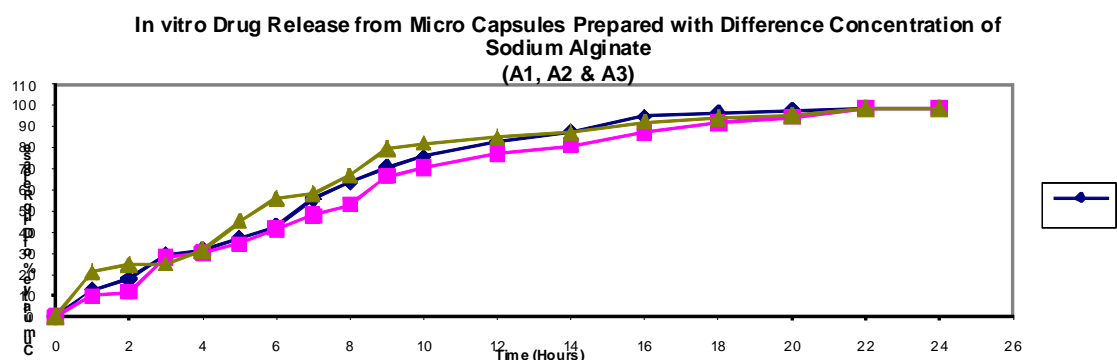
The cross linked microcapsules released the drug over a period of 24 hours. The concentration of cross-linking agent was found to have a significant effect on the release of the drug from the microcapsules.

The release of drugs from the gels depends on the structure or their chemical properties in response to environmental p^H . It was observed that 11 percent of drug was released in the 1 hour showing burst effect and as the polymeric hydrogel reaches the stomach the gels will be

exposed to acidic p^H . The gels have swollen to a very low degree in this environment. As the gel passes down the gastrointestinal tract, the p^H will be at a higher range and the degree of swelling increases slowly. The drug release during this phase of passage through the gastrointestinal tract may be attributed to the release of the surface entrapped drug. The alkaline environment present in the large intestine also contributes to the swelling of hydrogels and the cross-links will be accessible for cleavage. Easy penetration of azoreductase into the bulk of the swollen hydrogels occurs, effectively cleaving the azo cross-links will be accessible for cleavage. Easy penetration of azoreductase into the bulk of the swollen hydrogels occurs, effectively cleaving the azo linkages. This causes loosening of the polymeric matrix resulting in the release of entrapped drug in the colon.

FORMULATION I

Fig. 5



FORMULATION II

Fig. 6

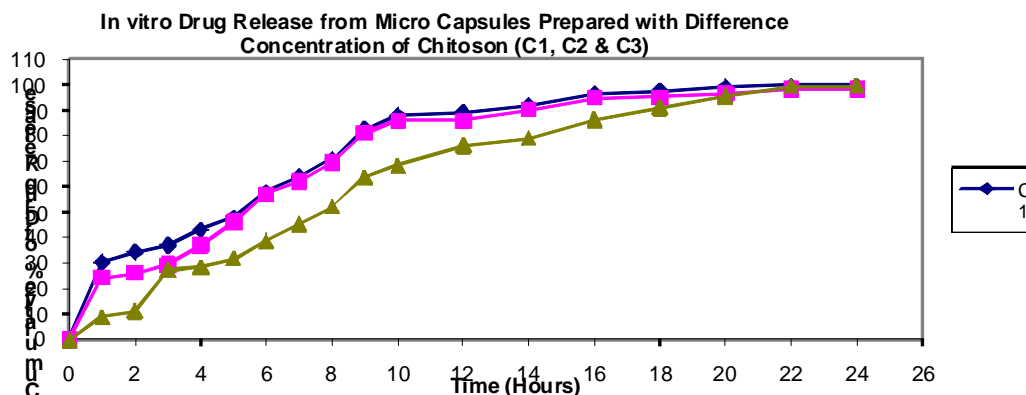
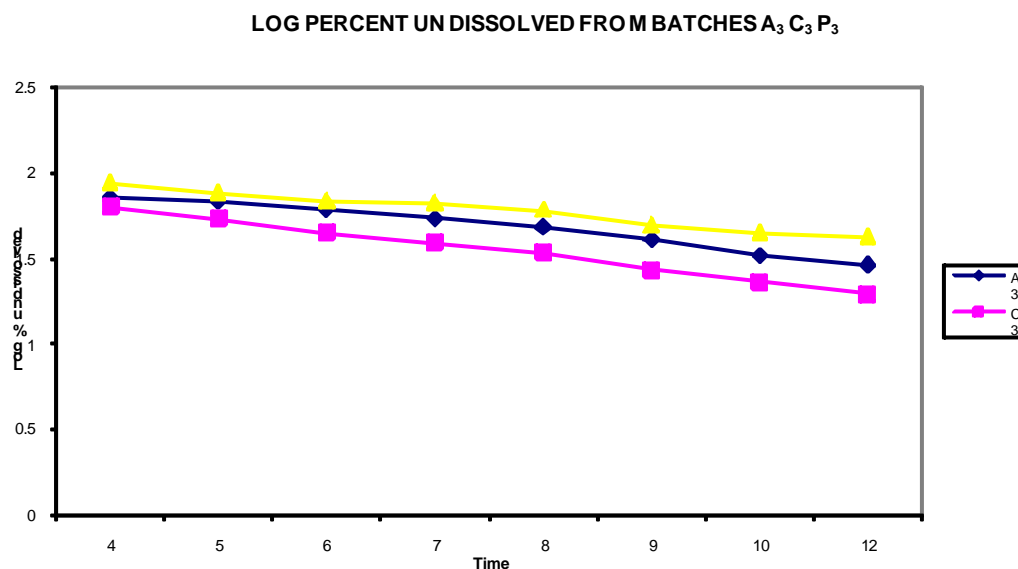
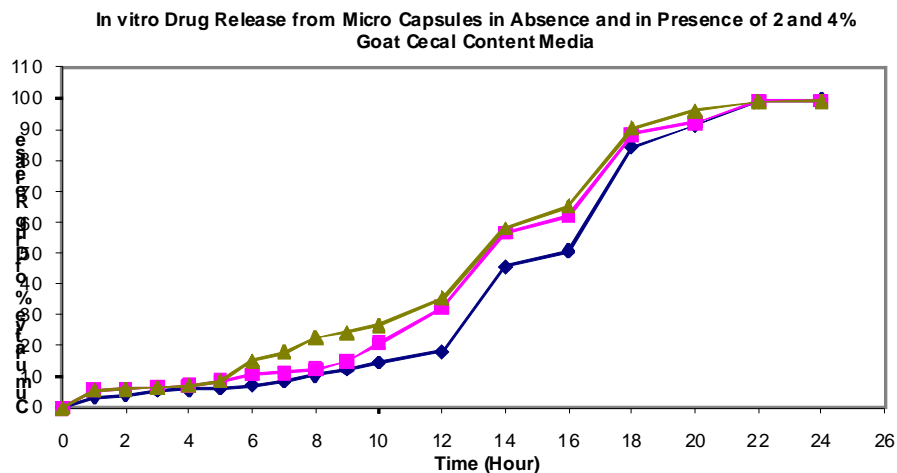


Fig. 7



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Fig. 8: Drug release from micro capsules in presence and absence of goat cecal content media



In vitro drug release study was conducted by using three different alginate concentrations. In order to study the effect of alginate on drug release from microcapsules. Accordingly, three different batches (Table 1) containing 1.5% w/v, and 2.5% w/v of alginate based microcapsules were prepared (batches A₁, A₂ and A₃). The

results (Fig. 1) of in vitro study indicated that amount of drug release decreased significantly with an increase in alginate concentration, and is attributed to increase in the densities of the microcapsules core and also increase in the diffusional path length, which the drug molecules have to traverse. Attempt to raise the alginate

concentration above 2.5% were unsuccessful, as the solution become too viscous to extrude through 26G needle during preparation of microcapsules.

In vitro drug release were also found to be marginally decreased with increasing the chitosan concentrations (Table 2) 0.2% w/v, 0.3% w/v and 0.4% w/v (batches C₁, C₂ and C₃). With alginate drug core, drug molecules already have to traverse increased diffusion path length and again they have to cross thicker chitosan membrane, so drug release was cross further retarded. (Fig. 2)

In vitro drug release were also found to be marginally decreased with increasing the outer Coating pectin concentration 0.2%, 0.4%, 0.5% (Batch P₁, P₂ and P₃) gave comparatively lesser release in acidic medium pH 1.2, but with the increase in elution medium P^H (P^H 6.8), it showed higher drug release. (Fig. 3)

In vitro release in anaerobic conditions (in presence of goat cecal contents) showed steep increase in the drug release in 2%, 4%. This may be due to degradation of chitosan by the microbial flora of the colon.

Among the three formulations, coating with pectin (P₃) gave much lower drug release (In 6 hours only 38%) as compare to other batches. And further are a significant increase in drug release after 6 hours in presents of goat cecal contents, exhibiting thereby more colon specific drug release in presence of an- aerobic microorganism.

CONCLUSION

Based on above observations, it was inferred that by adjusting microcapsules core compositions, coating thickness and giving further coatings; one could formulate more colon specific drug delivery. But uch increase the concentration of sodium alginate (abow 2.5%) it is very difficult to extrude through 26G needle, and also decrease the percentage entrapement of drug. Among the three fomulations coating with pectin (p₃) gave much lower drug release as compare to other batches (A₃, C₃) and there is no drug interaction between drug, polymers and excipients. Prepare chitosan-sodium alignate microcapsules of 5-fluorouracil remain intact and shows minimal drug release in stomach and small intestine, it is very advantage because 5-fluorouracil the initial release it is required to be drastically minimized to avoid the sight effects associated with these agents. Thus, chitosan-sodium alginate microcapsules of 5-fluorouracil gave better colon specific delivery and can be of

significant use in better treatment of diseases like colorectal cancer.

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