SHORT COMMUNICATIONS

PREPARATION AND EVALUATION OF CHITOSAN CAPSULE FOR COLON SPECIFIC DELIVERY OF CAPECITABINE

ABSTRACT

The prime objective of the present study was to develop enteric coated chitosan capsule containing capecitabine for targeting colorectal cancer cells. The study 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 HPMC K4M / Cellulose acetate phthalate provides it a special feature of releasing drug at colonic pH. The complex formation between HPMC K4M, cellulose acetate phthalate and chitosan capsule gives extended release of drug over longer period. The disintegration time of the developed enteric coated capsule (Batch F2) was found to be 78±0.86 min and drug release was observed to be 97 % at the end of 9 h in pH 8.5 buffer solution simulating the colon fluid. All the prepared batches exhibited no release of drug in the first 3 h in simulated gastric fluid pH 1.2 and intestinal fluid pH 6.8. Thus, the enteric coated chitosan capsule proved to be efficient to deliver the drug at colon in colorectal cancer disease, which minimizes the side effects, of anticancer drug in stomach and upper intestine.

Keywords: Chitosan capsule, capecitabine, Enteric coating, Colorectal Cancer

INTRODUCTION

A foremost reason of cancer death in men and women is colorectal cancer (CRC) and it affects nearly 1 million people throughout the world every year[1]. Targeting of the drug(s) specifically to the colonic region is often beneficial for the effective treatment of various diseases associated with the colon, namely, amoebiasis, Crohn's disease, ulcerative colitis, and colorectal cancer[2].

An ideal colon specific drug delivery system (CDDS) should be able to protect the drug in the route to the colon. Moreover, the bioactive agent should not undergo degradation at either of the dissolution sites, and only achieve its release and absorption once it reaches the colonic region[3]. This drug delivery system has acquired importance not only for the delivery of drugs for the treatment of local diseases of colon such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis, but also for its potential for the delivery of various proteins and therapeutic peptides including insulin[4-5]. Capecitabine, an anticancer drug exhibits short half-life which is a drawback of concern in conditions, where the localized delivery of the drugs in the colon is needed to be stable environment of upper GIT and which should reach the colon. Colon region exhibits long retention time and appears to be greatly responsive to the agents that enhance the absorption of poorly absorbed drugs[6-7]. The primary approaches include coating of drug delivery by using pH sensitive polymer to the colonic area, time controlled release (delayed) system release drug delivery to colon area and microbial trigger to colon[8].

Chitosan, is an interesting biopolymers with an ever increasing number of uses in a variety of fields. The term chitosan is usually used when the polymers are soluble in a dilute acid solution[9]. Considering the filmogenic property of chitosan, the objective was to prepare capsules of chitosan, loading of the drug, coating of drug filled chitosan capsule with pH dependent enteric polymer like HPMC / cellulose acetate phthalate and to examine its suitability for targeting the ileum and ascending colon sites which were primarily affected in Crohn's disease[10-13].

MATERIALS AND METHODS

Materials

Capecitabine was obtained as a generous gift sample from Divi's Laboratories, Andhra Pradesh, India.

METHODS

Preparation of chitosan capsule shell

The sets of moulds (made up of plastic) for cap and body parts of capsule were used. Instead of dipping the moulds in the solution, chitosan solution was poured on the moulds. 5 % w/V solution of chitosan in 2M glacial acetic

Table I: Evaluation of chitosan capsules

Formulation	Weight* (mg)	Thickness* (mm)	Locking Length*(mm)
Empty chitosan capsule	58±1.37	5.5±0.08	13.4±0.18
Uncoated filled capsule	175.05±1.21	5.5±0.04	13.4±0.18
Drug filled enteric coated capsule	186.13±0.87	5.6±0.02	13.5±0.16

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

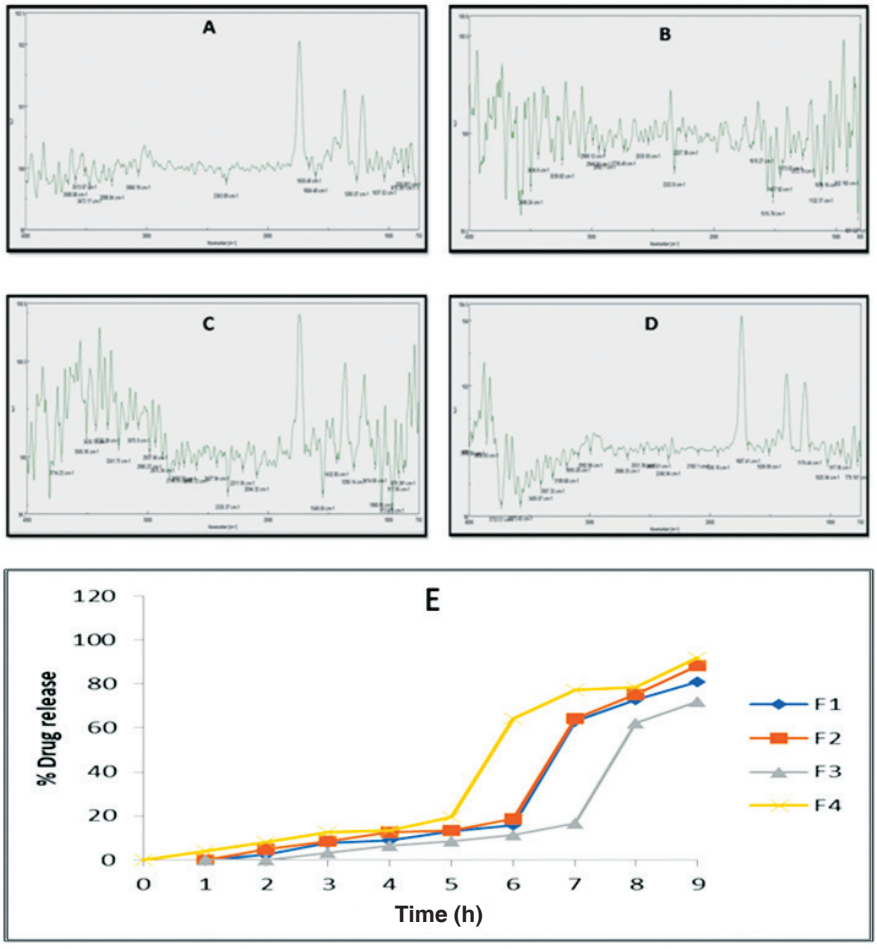

Fig. 1: : FTIR spectra of A) Capecitabine B) Chitosan C) HPMC K4M D) Cellulose Acetate Phthalate E) % Drug release of Capecitabine from different batches

acid was used. After pouring the solution on moulds, it was dried at 40 ^{0}C to 50 °C till it set on the mould. Then, the shells were stripped off and cut to a suitable length. The cap and body sections were then joined.

Preparation of the coating dispersion

CAP was weighed accurately and dissolved in a mixture of methanol and acetone (1:1V/V) (Solution I). Titanium dioxide was homogenized in rest quantity of acetone (Solution II). Solution I was added to Solution II with stirring. HPMC K4M was added in the aforesaid solution with stirring[14]. Four different batches were prepared with varying quantities of HPMC K4M and CAP.

EVALUATION PARAMETERS

Melting point determination

Melting point of drug was determined by using capillary tube method.

IR Spectroscopy

Dry sample of capecitabine was mixed and triturated with dry KBr. This mixture was analyzed by using IR. The infrared absorption spectrum was recorded and the spectrum was compared with the reference spectrum of capecitabine.

UV spectroscopy

10 mg of capecitabine was accurately weighed and was first dissolved in 0.1N HCl (pH 1.2), pH 6.8 phosphate buffer and pH 8.5 buffer solutions to plot spectrum and calibration curve in respective solutions. UV spectrum was recorded in the wavelength range 200-400 nm to get spectrum. λmax and calibration curve of capecitabine in 0.1 N HCl, pH 6.8 phosphate buffer and pH 8.5 buffer solutions, respectively .

EVALUATION OF ENTERIC COATED CHITOSAN CAPSULE

Capsule weight variation, locking length and thickness

The individual weight variation according to USP/NF was performed by weighing 20 capsules individually, The capsule locking length and thickness of both uncoated and coated chitosan capsule were measured by digital micrometer.

Disintegration time

Analysis of the disintegration of the capsule was carried out using a disintegration tester. Media temperature was set to 37 °C. Media used was 0.1N HCl for 2 h.

In vitro drug release study

In vitro release testing was performed according to the procedure mentioned in the Indian Pharmacopoeia (IP- I) basket method (100 rpm). Three different kinds of media, namely, simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 6.8) and pH 8.5 buffer solution simulating the colon fluid were used during the course of the study. The temperature of the media was maintained at 37±0.5 ^{o}C and the speed of the rotation of basket was set at 100 rpm. 5 mL of the aliquot were taken every 30 minute for the first four hours and then after every 60 minutes up to the end of experiment. The amount of capecitabine released from the capsule was determined spectrophotometrically by measuring absorbance at 240 nm[15-23].

RESULTS AND DISCUSSION

Melting point determination

The melting point of capecitabine was determined by using capillary tube method and it was found to be 116 ^{0}C.

IR spectrum interpretation

FTIR spectroscopy was performed to identify the supplied pure drug. FTIR spectrum of capecitabine is shown in Fig. 1A. The peaks at 3288.04, 1604.48, 1265.07, 1037.52, and 838.88cm^{-1} were observed due to the functional group namely O-H, C=C, C-O, C-F and C-H respectively. The IR of chitosan was reported in Fig. 1B. The peaks obtained at 1272.79, 1074.16, 912.165, 821.527cm^{-1} were observed due to the functional groups like C-N stretching, C-O stretching, =C-H bending and C-H. The IR spectrum of HPMC K4M is represented in Fig.1C The peaks at 1128.15, 2950.56 cm^{-1} are due to the functional groups like C-O and C-H. The IR spectrum of cellulose acetate phthalate is shown in Fig. 1D. The peaks at 3307.32, 1745.25 and 1255.24cm^{-1} are due to the functional groups like O-H, C=O and C-O. From the FTIR spectroscopic study of drug and polymers, it can be concluded that polymers under study show the entire characteristics peaks and no significance differences were observed in the spectra as compared to standard.

Physical evaluation of chitosan capsules

The empty chitosan capsule, uncoated filled chitosan capsule and the drug filled enteric coated chitosan capsules were evaluated for different parameters, namely, weight variation, thickness and capsule locking length. The data of these entire tests are presented in Table I. All the formulations showed acceptable pharmacopoeial limits for weight variation and locking length. Disintegration study showed results 100±0.957427, 78±0.866025, 120±0.866025 and 85±0.408248 minutes for F1, F2, F3 and F4 batches, respectively. Dissolution study showed 97 % of drug release of optimized F2 batch, as shown in Fig. 1E

CONCLUSION

The objective of the study was to develop enteric coated chitosan capsule containing capecitabine for targeting the ileum and ascending colon sites which were mainly affected in the Crohn's disease. As a new oral drug delivery system for colon targeting, enteric coated chitosan capsules were developed by coating enteric polymer on surface of chitosan capsule containing capecitabine as a model drug. 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 HPMC K4M / cellulose acetate phthalate provides it a special feature of releasing drug at colonic pH (buffer pH 8.5). *In vitro* release study also suggests the extended release of drug over a long period of time due to complex formation between HPMC K4M, cellulose acetate phthalate and chitosan capsule. This complexation was proved by IR spectroscopy. From the above research, it was found that the optimized formulation shows 97 % drug release after 9 h targeted to colon area with the help of HPMC K4M and cellulose acetate phthalate.

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