RESEARCH ARTICLE

Formulation and evaluation of pectin-hydroxypropyl methylcellulose coated curcumin pellets for colon delivery

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High molecular weight hydroxypropyl methylcellulose (HPMC) and biodegradable pectin were used for coating the pellets containing curcumin, to be released in the colon. The prepared pellets were free flowing. *in vitro* release of curcumin remained intact up to pH 3.0, disintegrated at pH 7.2, and released up to 12 hours. The ideal batch (1:3) showed minimum release at pH 1.2 and maximum release at pH 6.8, and an increased amount of curcumin in the blood stream(1.287 µg/ml) was achieved when compared with pure curcumin (0.5 µg/ml). The drug release was retarded by the high concentration and greater thickness of the coating of HPMC on the pellets. Release kinetics of the preparation shows a non-Fickian or anamolous diffusion or matrix erosion.

Key words: *Colon drug delivery, curcumin, pectin, pellets*

INTRODUCTION

Targeting of drugs to the colon via the oral route can be achieved by different approaches including different formulation systems, for which the drug release is controlled by different pH conditions, transit time, and intestinal microbial flora.[1] Specific targeting of drugs to the colon is recognized to have several therapeutic advantages. The colon is an ideal site for both systemic and local delivery of drugs.[2] To reach the colon and absorb the drug there the dosage forms must be formulated taking into account the obstacles of the gastrointestinal tract (GIT). Various strategies have been developed to achieve this goal, such as, use of specific characteristics of the organ, for example, pH, microbial flora, enzymes, reducing medium, and transit time.[3] A number of serious diseases of the colon, for example, colorectal cancer, ulcerative colitis, and other inflammatory conditions could be treated more effectively if drugs are targeted to the colon.[4-6] The colonic site is being investigated as a potential site for the delivery of proteins, peptides, vaccines, and other drugs such as nifedipine, theophylline, and isosorbide.[7-11]

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Due to a comparatively longer transit time than in the stomach, colonic absorption of poorly absorbed drugs can be improved.[12] Methods for drug delivery to the colon have recently been discussed.[13]

The presence of certain enzymes in the colon, which have been involved to specifically cleave certain types of drugs attached to another molecule or a polymer, has been studied by a number of authors.[14-16] Colon cancer, one of the serious diseases, can also be treated by means of effective targeting of anticancer drugs to the colonic region.[17] The pH of the GI tract gradually increases as it moves down the GI tract from the stomach (pH 1.5-3) to the terminal ileum (pH 7-8). Khan *et al*. developed a single coating system for mesalazine based on the combination of polymers.[18] Optimization of two factors (coating composition and thickness) is useful to achieve the best pH-dependent colonic drug delivery.[19]

Curcumin a bioactive natural product with an antioxidant, anti-tumor promoter, and anti-inflammatory properties, displays COX-2 inhibition for the chemoprevention of colon cancer. The mechanism of curcumin to inhibit COX-2 activity is through the regulation of transcription factors like the aryl hydrocarbon receptor (AHR).[20] From the perspective of drug delivery, it would be preferable to deliver smaller quantities of the antineoplastic drug directly to the tumor site, which would improve the prospects for a successful treatment outcome.

Hence an attempt has been made to deliver bioactive curcumin to the colon to treat cancer, using pectin and hydroxypropyl methylcellulose as release modifiers. Pectin, a polysaccharide, remains intact in the physiological environment of the stomach and small intestine, but is degraded by the bacterial inhabitants of the human colon. Being soluble in water, pectin is not capable of shielding its drug load effectively during its passage through the stomach and small intestine. A coat of considerable thickness is required to protect the drug (bioactive curcumin) core in simulated *in vivo* conditions. Hence HPMC, a hydrophilic rate-controlling polymer, can be used to overcome this problem. The adjustment of the polymer concentration, viscosity grade, and addition of different types and levels of excipients to the HPMC matrix can modify the drug release rate.[21] The main reason for selecting pellets as formulation is rapid gastric emptying. Hence it was decided that with the positive contribution of HPMC — pectin would be a good candidate for designing the colonic delivery of bioactive curcumin through pellet formulation.

MATERIALS AND METHODS

Materials

Curcumin (Hi Media Ltd, India), hydroxypropyl methylcellulose (Gift from Fourts India Ltd., India), Pectin (Hi Media Ltd., India), sodium starch glycolate (Sigma), avicel PH 101 (Signet Corporation Ltd., Mumbai), sodium carboxymethyl cellulose (sigma), trisodium ortho phosphate (SD Fine Chem. Ltd., India), methanol, diethyl ether, and acetonitrile (SD Fine Chem. HPLC-grade). All the ingredients used in the study were of analytical grade.

Method

Formulation of curcumin pellets

An accurately weighed quantity of the bioactive material curcumin (60%), sodium starch glycolate (5%), and microcrystalline cellulose (MCC PH 101,33%), in the optimal ratio were mixed thoroughly and moistened with 2% binder solution (sodium carboxymethyl cellulose) to form a viscoelastic mass. The prepared wet mass was extruded through a roller extruder (Plate 1) and the extrudates spheronized in a spheronizer (Plate 2) at 1000 rpm speed and rounded off into spherical particles. The pellets were dried at 50°C in a hot air oven for one hour and the dried pellets were stored in an airtight container, in a dark place. The prepared pellets were coated using a fabricated coating pan as per the formula.[22,23]

Characterization of curcumin pellets

The formulated pellets were evaluated for their percentage yield, particle size, bulk density, angle of repose, compressibility, friability, and drug content. The results have been shown in Table 1.

The particle sizes were determined by using the optical microscopy method. The diameter of the minimum number of 50 pellets in a batch was calculated.[24] A scanning electron microscope (SEM) was used to examine the morphology and appearance of the curcumin pellets [Figure 1].

***In vitro* dissolution study**

In vitro release profiles were performed using a system based on the general drug release standard for delayed release formulations (enteric coated). *In vitro* release was studied by following the method used by Sarasija and Hota, by making slight modifications with the addition of another pH medium, based on the different transit times from the stomach to the colon (using basket apparatus USP-XXIII-dilution method). Hence different pH conditions similar to *in vivo* conditions (pH 1.2 for two hours, pH 3.0 for one hour, pH 7.2 for one hour, and pH 6.8 for up to eight hours) were maintained for the entire study. About 500 ml of pH 1.2 medium was placed in the basket followed by placing the pellets and stirred at 75 rpm, with a temperature of 37°C maintained in the basket. After one hour, a specified quantity of 0.1 M tri sodium phosphate was added, to change the pH of the test medium to pH 3.0, without stopping the dissolution process.

***In vivo* study**

In vivo studies were carried out using albino rabbits, approved by the animal ethical committee of JSS College of Pharmacy. (No: JSSCP/ IAEC/ M.PHARM/ PH. CEUTICS/ 01/ 2007 – 2008).

Table 1: Cumulative percentage release of coated curcumin pellets

pH	Time in hours	Pectin: HPMC (0.5:1)	Pectin: (1%)	Pectin: HPMC (1:0.5)	Pectin: HPMC (1:1)	Pectin: HPMC (1:2)	Pectin: HPMC (1:3)	Pectin: HPMC (1:3)
	0	0	0	0	0	0	0	0
1.2	1	17.06	11.73	5.62	4.08	3.20	0.19	-
	2	20.57	16.91	10.52	5.28	4.88	0.33	-
3	3	42.39	43.49	19.75	9.10	7.56	0.33	-
7.2	4	58.82	63.57	61.39	38.43	37.47	19.72	-
6.8	5	65.43	90.37	65.58	42.33	40.24	23.41	28.72
	6	80.87	98.97	88.27	43.91	42.85	32.12	35.67
	7	98.62	-	98.66	61.23	51.64	36.79	57.24
	8	-	-	-	65.57	55.94	45.84	65.32
	10	-	-	-	88.29	74.08	53.31	74.53
	12	-	-	-	97.35	79.63	58.62	89.91

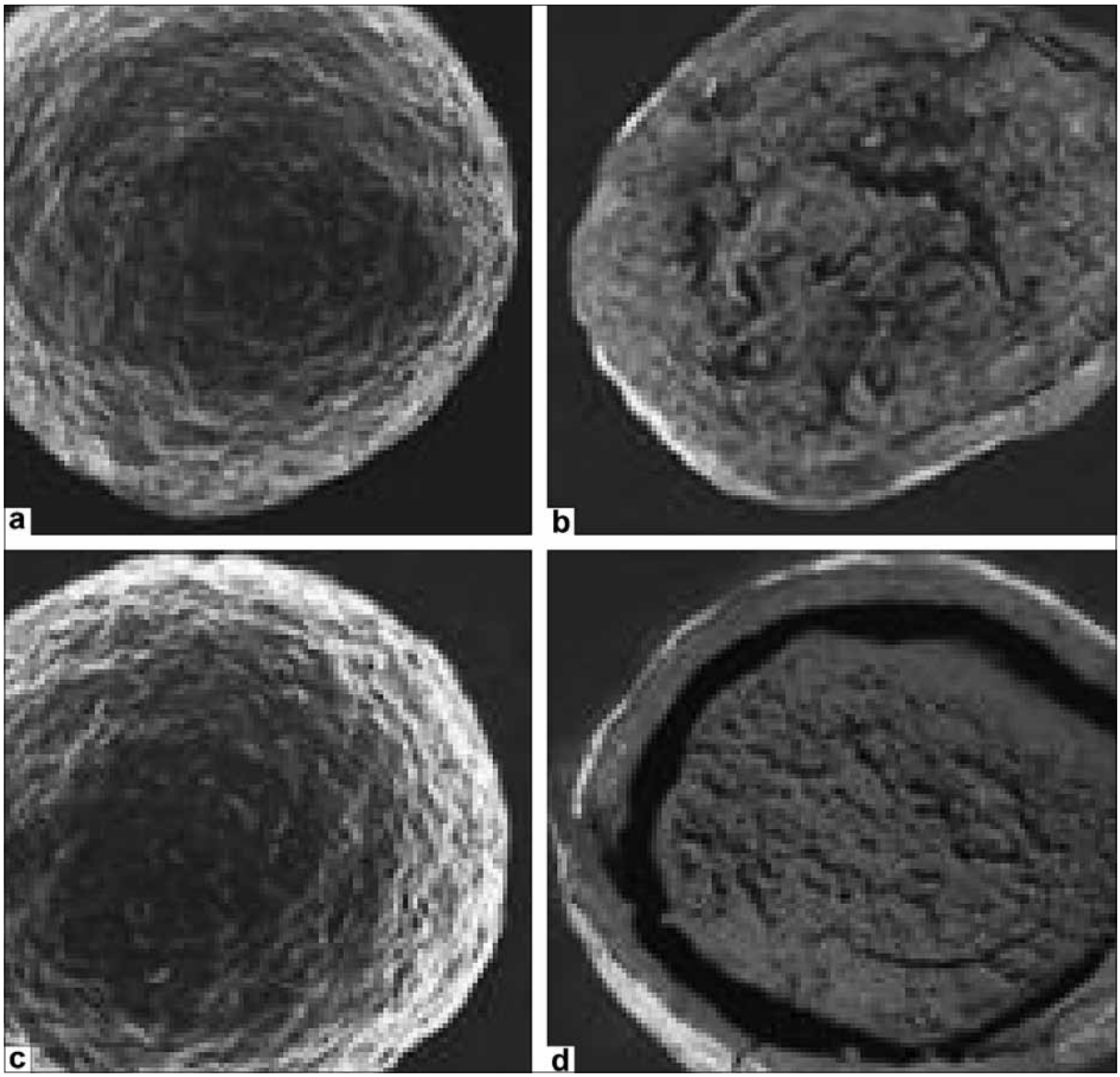

Figure 1: Scanning electron micrographs of pectin–HPMC (1:3) coated pellets: (a) coated pellet (surface); (b) cross-section; (c) After 12-hour incubation in control phosphate buffer conditions (surface); (d) cross section

About 100 mg/kg of curcumin plain and coated curcumin pellets were administered to albino rabbits, in a group of three animals, in fasting conditions. The plasma samples were liquid – liquid extracted and stored in the deep freezer until they were used for analysis by schimadzu HPLC[25] (LC 10 AT_{VP}).

Preparation of animal plasma samples

At the time of analysis the samples were removed from the deep freezer and transferred to room temperature and allowed to thaw. A sample of 0.5 ml was pipetted into a 5.0 ml test tube, and to this 500 μl of internal standard solution was added (100.0 μ/ml) and vortexed for 5 minutes followed by the addition of 5 ml ethyl acetate. The samples were placed on a reciprocating shaker at 100 rpm for 20 minutes and then centrifuged for 10 minutes. The supernatant of 4 ml was transferred to a dry test tube and evaporated to dryness. The residue was reconstituted with 250 μl of mobile phase and used for the study.

RESULTS AND DISCUSSION

The disk speed of 1500 ± 250 rpm and residence time of 30 minutes was found to be optimum to get spheroids. Slow speed and lower residence time failed to provide the necessary densification and rounding of particles and yielded dumbbells and rods, which indicated that spheronization was not complete. Higher disk speed yielded spheres, but more fines were generated and also agglomeration of pellets occurred. Longer residence time resulted in surface drying due to evaporation of water leading to irregular-shaped pellets. An optimal wet condition (often water) and proportion of binders for extrusion was necessary for the

formation of round-shaped pellets. Less wet extrudates lead to anisometric rod-like particles and over-wet extrudates lead to an uncontrolled granule growth during spheronization. The formulated batches of pellets had yielded 46.42% w/w, which could be considered as a satisfactory product yield value. The particles were found to possess a narrow range of size distribution and had the average particle size in the range 1.185 mm. SEM was taken to examine the microstructure of the surface of the pellets [Figure 1]. The bulk densities of the pellets were found to be in the range of 0.63-0.71 gm/cm^3. Since the low values of compressibility (15%) and the angle of repose less than 25° signify good flowability of the spheroids [Table 2], it showed that the pellets had smooth flow properties ensuring homogenous filling capacity. Friability of pellets was found to be less than 1% w/w. The drug content of curcumin in pellets was determined by a visible spectrophotometer at 425 nm.

Based on the different transit times present from the stomach to the colon, the release profile was carried out with different pH conditions similar to *in vivo* conditions as shown in Table 1 (at 37 ± 1°C). Coated curcumin pellets showed a complete release from six to eight hours. They were found to remain intact up to pH 3.0, disintegrated at pH 7.2, and released up to 12 hours. More than 60% drug release was found in colonic pH 6.8. Batches prepared using 1:3 ratio (Pectin: HPMC) showed a minimum release of 0.19% at pH 1.2 and maximum release of 89.91% at pH 6.8 [Table 1], and this batch was selected as an ideal, and used for the *in vivo* study.

The main parameters of pectin-HPMC coated curcumin pellets were obtained with the help of the HPLC method and compared with free curcumin. Maximum concentration (*C* max) and time to reach maximum concentration (*T* max) are the values obtained directly from the concentration – time curve. Time taken to release the drug was found to be three hours. Peak serum concentration of 0.5 μg/ml was attained rapidly, within one hour, when pure curcumin was administered. However, in case of coated pellets the peak concentration (1.287 μg/ml) appeared at the fourth hour and the concentration was much higher than pure curcumin. The higher concentration was also maintained for a longer period of time before dropping down [Figure 2]. The Peppas plot shows the n values of 2.833, which imply that it is a non-Fickian or anomalous diffusion or a matrix erosion type of release characteristic.

CONCLUSION

Pectin: HPMC coated pellets offer a greater degree of protection from premature drug release in the upper GI tract than pectin alone. The pectin is still available for enzymatic degradation, which allows greater drug release under conditions that may be expected to pertain in the colon. It is possible by careful formulation of the pellet core to achieve different drug release profiles, whereby an increase in the

Table 2: Evaluated parameters of curcumin pellets

% Product yield	% drug content	Speed (rpm)	Average particle size (mm)	Angle of repose	% compressibility
46. 42	98.77	1500	1.18	21.01°	15

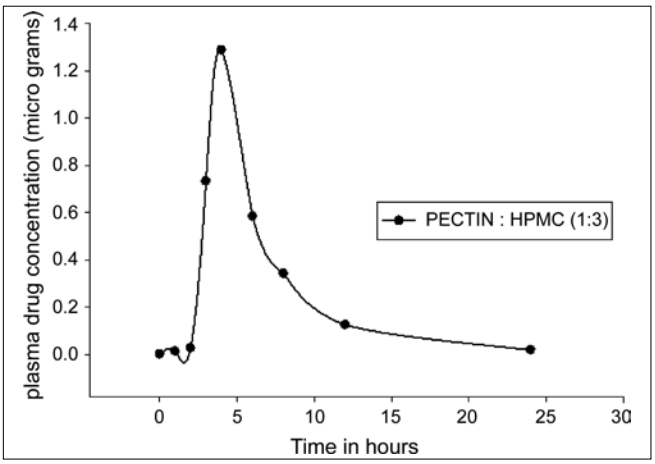

Figure 2: *In vivo* plasma concentration-time profile

amount of drug released can be induced by the action of pectinolytic enzymes. By changing the other variables such as the pectin and HPMC ratio or the molecular weight of the polymers, it may be possible to produce a system with a release profile, which is tailored to meet the particular requirements of any individual drug. From the results it can be concluded that pectin: HPMC coated pellets could be used to treat the inflammatory conditions of the colon.

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