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ORIGINAL ARTICLE **OPEN ACCESS**

Formulation Development and Characterization of Surface Modified Pectin Microspheres for Colon Targeting

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ABSTRACT
Colon-specific drug delivery approach through oral route exerts some obvious advantages such as enhanced drug localisation and reduction of side effects. Mesalamine (MSM) and Prednisolone (PRD) are the drugs of choice for the treatment of Inflammatory Bowel Disease (IBD) specifically in ulcerative colitis (UC) and Crohn's disease (CD). In the present study, pectin microspheres containing MSM and PRD were prepared by emulsion dehydration technique and coated with a pH-sensitive Eudragit S100 (ES100) polymer for a controlled drug release profile. Fabricated microspheres were characterized for size, shape, drug entrapment and in vitro drug release. The percentage drug entrapment in ES100 coated pectin microspheres was found to be 61.14 ± 0.5% to 75.59 + 0.96% for MSM and 70.16 + 1.27% to 81.53 + 0.73% for PRD. An initial burst release followed by sustained release profiles for MSM and PRD were observed from microspheres for a period of 14 hrs at colonic pH suggests the pH-dependent release behaviour.
KEYWORDS: *Mesalamine, Prednisolone, Microspheres, Eudragit S100, Colon targeting.*

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INTRODUCTION

A prerequisite for precise colon drug delivery systems is a drug release mechanism that only responds to the unique physiological conditions of the colon [1]. Several methods, including prodrugs [2], pH-sensitive polymer coating [3], timed release formulations [4], polymeric nanoparticles [5] and microspheres, have been examined to accomplish efficient drug delivery to the colon site [6]. Among these methods, biodegradable polymer microspheres are intensively studied for colon-targeted drug delivery [7]. However, oral drug delivery to colonic diseases is limited due to several formidable barriers in the gastrointestinal tract, such as pH, microbial flora, and solubility behavior of the drug, which may compromise the drug's effectiveness [8, 9]. Still, persistent efforts have been made to develop manipulative colon-targeted drug delivery systems with enhanced site specificity and adaptable drug release kinetics to meet a variety of therapeutic requirements [10, 11]. Ulcerative colitis is a type of IBD that affects the lining of the large intestine (colon) and rectum [12]. It is an intermittent disease characterized by periods of symptom exacerbation and periods of relative symptom relief. UC is treated as an autoimmune disease, and its management entails the effective suppression of active inflammatory response with anti-inflammatory medications. Therapeutic regimens are based upon the severity of ulcerative colitis and the extent of gastrointestinal tract involvement [13]. MSM, also known as mesalazine or 5-aminosalicylic acid, is an anti-inflammatory substance used to treat inflammatory bowel disease (IBD), such as in UC as first-line therapy and in mild-to-moderate CD. MSM reduces inflammation in the colon by inhibiting cyclooxygenase and prostaglandin production [14]. PRD is an anti-inflammatory or immunosuppressive synthetic glucocorticoid. It reduces inflammatory response by restricting capillary dilation and vascular structure permeability. The substance is the second-line treatment for UC. PRD can inhibit leukocyte infiltration at inflammatory sites, interfere with inflammatory response mediators, and suppress humoral immune responses [15, 16]. Therefore, the combination of these two drugs may have a synergistic effect in the treatment of UC and may substantially reduce the treatment failure rate and delay the development of drug resistance. It has been reported that multiparticulate systems, such as pellets, granules, and minitablets,

tend to be more uniformly dispersed in the gastrointestinal tract and also facilitate more uniform drug absorption [17, 18]. Microspheres are microscopic spherical particles with diameters in the micrometer range (typically 1 m to 1000 m) and are also referred to as microparticles [19-22]. Pectin is primarily a linear polymer composed of -(1-4)-linked D-galacturonic acid residues and 1, 2-linked L-rhamnase residues. Pectin is appropriate for use as a colon-specific drug delivery vehicle because it is selectively metabolized by colonic microflora, resulting in minimal drug degradation in the upper gastrointestinal tract [23]. Biodegradable pectin microspheres provide a novel strategy for the development of sustained release drug delivery systems with the potential for colonic drug delivery [24]. Eudragit S100 (ES100) is a methacrylic acid and methacrylate-based anionic copolymer. Due to its distinct solubility profile, this polyacrylic resin has been suggested for use in microencapsulation for controlled-release applications. The free carboxylic acid groups render the polymer pH-sensitive; it is only soluble at pH 7 or higher; therefore, it is an ideal polymer for colon-targeted delivery [25]. In the present study, we propose a dual controlled release system, where the combination of specific biodegradability of polymer and solubility of ES100 at colonic pH creates a reliable drug delivery system that effectively releases the drug only at colonic pH. In addition, the proposed microparticulate system may increase therapeutic efficacy by extending the drug's localization in the afflicted area. Due to the fact that ES100 only dissolves above a pH of 7, this system is also expected to prevent drug loss in the upper GI tract.

MATERIALS AND METHODS

Mesalamine and Prednisolone were generously provided as gift samples by Cipla Ltd., Ratlam (India) and Kwality Pharmaceuticals Pvt. Ltd., Amritsar (India), respectively. Pectin and Fluorescein isothiocyanate (FITC) were purchased from Himedia Laboratories Limited, Mumbai. ES100 was obtained as a gift sample from Sunpharma Laboratory Ltd, India. All other chemicals and reagents utilized in this study were of analytical grades and used without further purification.

Table. 1 Optimization Parameters of Pectin Micropsheres

Formulation Code	Drug Polymer Ratio (w/w)	Surfactant Concentration (v/v)	Strrring Speed (rpm)
F1	1:1	0.5	500
F2	1:2		
F3	1:3		
F4	1:1	0.5	1000
F5	1:2		
F6	1:3		
F7	1:1	0.5	1500
F8	1:2		
F9	1:3		
F10	1:1	1.0	500
F11	1:2		
F12	1:3		
F13	1;1	1.0	1000
F14	1:2		1000
F15	1:3		1000
F16	1:1	1.0	1500
F17	1:2		1500
F18	1:3		1500
F19	1:1	1.5	500
F20	1:2		500
F21	1:3		500
F22	1:1	1.5	1000
F23	1:2		1000
F24	1:3		1000
F25	1:1	1.5	1500
F26	1:2		
F27	1:3		

Preparation of Pectin Microspheres:

According to Esposito et al. [26], the pectin microspheres were made using the emulsion dehydration method. Pectin and medications were dissolved at a ratio of 1:1 to 1:3 in 20 ml of distilled water and agitated overnight to produce a clear solution. This drug-polymer solution was dispersed in 50 ml of iso-octane containing 1.5% w/v span 85 (as a surfactant) and agitated at a predetermined speed to produce a stable water/oil (w/o) emulsion. Pectin molecules were dehydrated by abruptly cooling the above solution to 15°C and adding 50 ml of acetone. This system was then kept under mechanical agitation at a predetermined speed at room temperature for eight hours to permit the complete evaporation of the solvent. Overnight, the microspheres were freeze-dried and stored in a hermetic container for future research. Several formulations of pectin microspheres with varying parameters have been developed in order to optimize the production process and obtain the desired particle size and drug dosage (Table 1).

Characterization of Pectin Microspheres:

Size and Size Distribution: Microspheres were suspended in deionized water (50g/mL), and particle size and size distribution were determined using dynamic light scattering (DLS) techniques and a Zetasizer ZS90 (Instrument Malvern, UK). All measurements were performed in triplicate at a temperature of 25 °C.

Shape and Surface Morphology:

Using a transmission electron microscope (TEM), the shape and surface morphology of pectin microspheres and ES100-coated pectin microspheres were determined [27]. On a copper grid, one drop of the suspended microsphere was distributed and allowed to dry at room temperature. Then, each sample was analyzed with a TEM (TECNAI 200 Kv TEM, Fei, Electron Optics) instrument.

Percentage Yield:

Using the following formula, the total percentage yield of pectin microspheres was calculated. The weight of prepared microspheres was divided by the total quantity of non-volatile ingredients utilized in their preparation [28].

$$\% \text{ yield of production} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \text{ X100}$$

Estimation of Surface Drug in Microspheres:

100 mg of uncoated microspheres were suspended in 10 ml of PBS (pH 7.4) and vigorously agitated for 10 minutes, with the supernatant being set aside. Similar to the treatment of the sediment, the second supernatant was combined with the first supernatant and analyzed for the presence of pharmaceuticals at 332nm for MSM and 246nm for PRD using a UV/Visible Spectrophotometer (UV- 1800 Shizuzu, Japan). The quantity of substance adsorbed on the surface of the microspheres was determined by the amount of MSM and PRD in the mixed washings [28].

Estimation of Entrapped Drug in Microspheres:

The microspheres obtained after two washings were digested for one hour in 10 ml of 4% w/w pectinase solution. The homogenate was centrifuged for 15 minutes at 5000 rpm, and the supernatant was analyzed spectrophotometrically (UV- 1800 Shimadzu, Japan) for MSM and PRD. The percentage of drugs entrapped and drug dosage were calculated using the following formula [29].

$$\% \, Drug \; entrapment = \frac{Practical \; entrapped \; drug}{Total \; drug \; taken} \times 100$$

Swelling Ratio:

100 mg of drugs-loaded pectin microspheres and ES100 coated pectin microspheres were deposited in an enzyme-free simulated intestinal fluid (SIF, pH 7.4) and permitted to reach a constant weight at 37 oC 0.5 oC. After 4 hours, the microspheres were periodically removed, dampened with filter paper, and the change in weight was measured until a constant weight was attained. The swelling ratio (SR) was then computed using the formula below [30].

$$SR = \frac{\omega g - \omega o}{\omega o}$$

Where, SR indicates swelling ratio; ω_o, initial weight of microspheres; and ω_g, final weight of microspheres.

Preparation of ES100coated Pectin Microspheres:

The enteric coating solution was made by dissolving 500 mg of ES100 in 10 ml of a 2:1 mixture of ethanol and acetone. On the basis of particle size and drug entrapment, ES100 was used to encapsulate the optimized formulations F18, F24, and F27. Immersion of 50mg of microspheres in the coating solution, followed by solvent evaporation in a rotary evaporator, was used to encapsulate the microspheres. The procedure was repeated until a coat-to-core ratio of 5:1 was attained. Microspheres coated with ES100 were desiccated and further characterized for size and drug release study in vitro [31].

Coating Thickness:

Using a calibrated ocular eyepiece, the mean diameter of representative microsphere samples from each cohort was calculated. Difference between the mean diameters of microspheres before and after coating was used to determine the mean coating thickness.

In-Vitro Drug Release Studies in Simulated Gastrointestinal Fluids of Different pH:

The in-vitro drug release study selected and evaluated ES100-coated pectin microspheres F18, F24, and F27 based on particle size, percentage yield, and entrapment efficiency. The dissolution experiments of microsphere formulations (pectin microspheres and ES100-coated pectin microspheres) were conducted using the paddle procedure outlined in USP XXIII. Accurately weighing 100 milligram of microspheres and dispersing them in 900 ml of dissolution medium. The contents were rotated at 100 revolutions per minute and maintained at 37± 0.5 degrees Celsius using a thermostat. The condition of the sink was maintained throughout the dissolution investigation.

In order to mimic mouth-to-colon transit, drug release was studied in simulated gastrointestinal fluids (SGF) of varying pH in the following order: in simulated gastric fluid (pH 1.2) for 2 hours, followed by simulated intestinal fluid (pH 6.8) for 2 hours, and finally in simulated colonic fluid (pH 7.4) for 10 hours. After 2 hours and 4 hours, the dissolution medium was filtered through Whatmann filter paper, and the microspheres residual on the filter paper was added promptly to the next medium. Using a pipette equipped with a microfilter, samples were withdrawn from the dissolution vessel at various time intervals and analyzed spectrophotometrically. The volume of the dissolution medium was kept constant by substituting an equivalent volume of fresh SGF. On the basis of dissolution tests, formulation F24 was selected as best formulation.

RESULTS AND DISCUSSION

Using a reported emulsion dehydration method, pectin microspheres were effectively created. The preparation method was optimized for the drug-to-polymer ratio, surfactant concentration, and agitation speed in order to produce microspheres of small and uniform size. Figure 1 depicts the proportions derived from various parameters. The average diameter of pectin microspheres ranged from 3.7± 0.235 m to 258.78± 2.78 m when the concentration of pectin was altered from 1% to 3%. For further characterization, formulations with particle size less than 25 m were chosen based on their small particle size. The % yield was calculated for formulations selected on basis of particle size and it was observed that the formulations F6 (66.5 ± 0.9), F16 (68.5 ± 1.5), F18 (76.74 ± 1.8), F22 (76 ± 2.2), F23 (71 ± 2.1), F24 (79.05 ± 1.6), F25 (74± 1.6), F26 (73.96 ± 2.1), F27 (73.0 ± 2.3) only shown good yield. The % drug concentration and swellability ratio of the chosen formulations were further characterized. According to the results of the swellability ratio, the swelling characteristics of microspheres range from 0.95 for formulation F16 to 1.61 for formulation F27. The percentage of drug entrapment in ES100-coated pectin microspheres ranged from 61.41± 0.5% to 74.95 ± 1.6% for MSM and from 70.64 + 1.02 % to 80.93 + 1.6% for PRD (Figure 1) All other formulations fell between these categories; therefore, formulations F18, F24, and F27 were selected, coated with ES100, and further characterized for coating thickness and in-vitro drug release study based on the above results. Coating of pectin microspheres with ES100 via solvent evaporation with a coat-to-core ratio of 1:1 and size increase indicated successful coating of pectin microspheres. The thickness of formulations F18, F24, and F27 was studied, and it was determined that formulation F24 had the thickest coating at 4.36± 0.782 m.

Using DLS and TEM, the Z-average diameter for a representative formulation (F24) was determined to be 19.07± 1.64 m for uncoated and 25.82± 1.282 m for coated with PDI values of 0.865±0.023 and 0.927±0.018, respectively. TEM analysis of the developed microspheres corroborate the dimensions and suggest that the obtained microspheres are nearly spherical in shape.

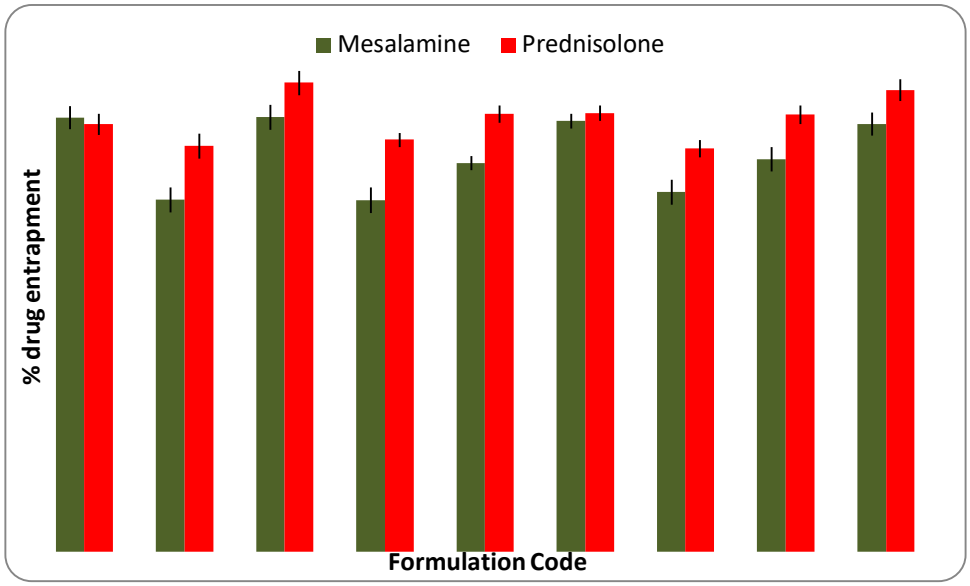

Fig. 1: Percentage Drugs Entrapment of Pectin Microspheres Optimized Formulations

In vitro drug release study of ES100 coated pectin microspheres was performed at different pH at 37ºC ± 0.5ºC. The cumulative % drug release suggested the achievement of desired release profile as minimum drug release was observed in first four hrs (i.e. 2 hrs at pH 1.2 and then 2 hrs at pH 4.5). However, at colonic pH 7.4, an accelerated release in sustained manner was observed for MSM and PRD for next 10hrs with ES100 coated pectin microspheres. Formulation F24 demonstrate 69.98 ± 2.2 % release for MSM and 88.91±2.7% release for PRD, which is found to be better in comparison to formulation F18 and F27 in terms of sustained release (Fig. 2,3 and 4). This release profile confirms the pH dependent control drug release from ES100 coated pectin microspheres.

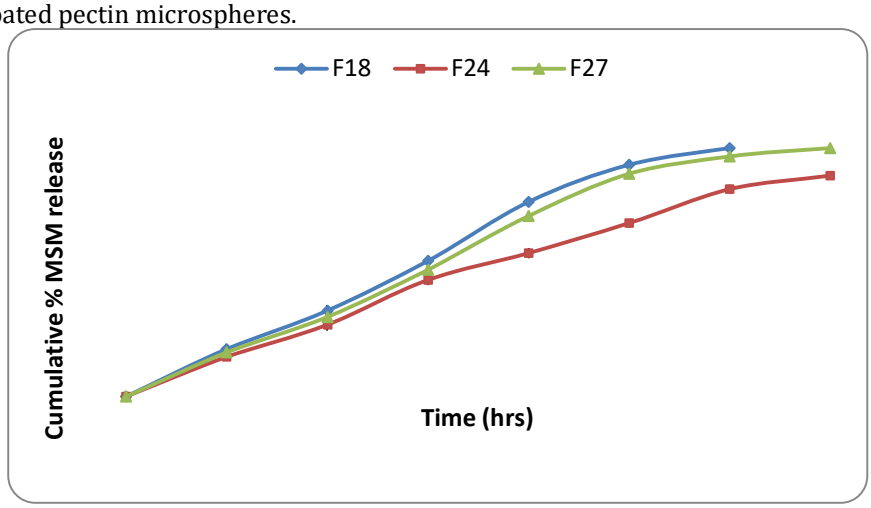

Fig. 2: Percent Cumulative Drug Release of MSM from Optimized Formulations of ES100 Coated Pectin Microspheres in PBS (pH 7.4)

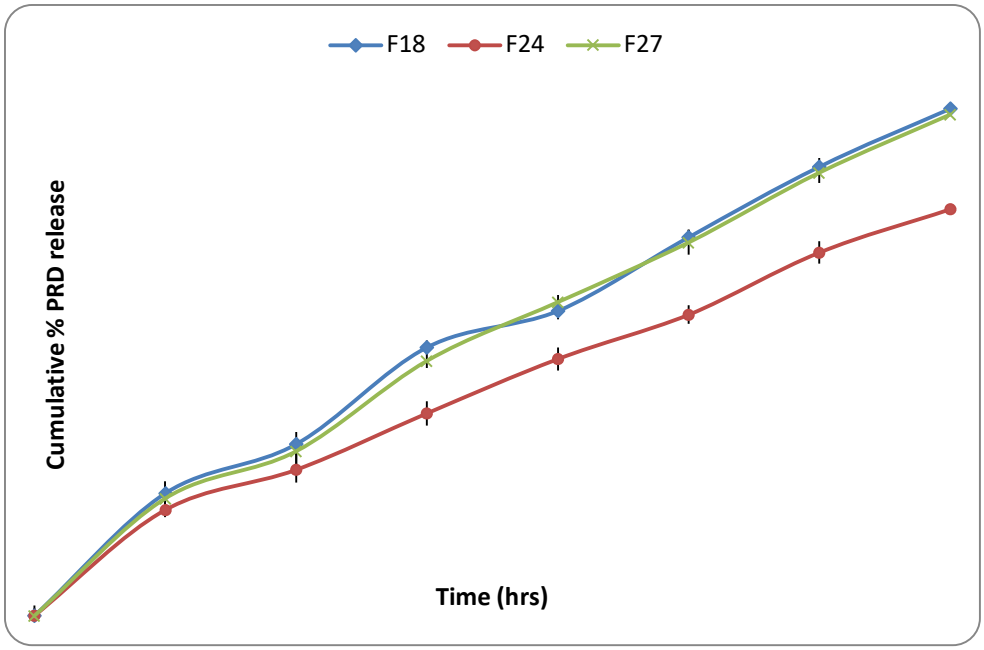

Fig. 3: Percent Cumulative Drug Release of PRD from Optimized Formulations of ES100 Coated Pectin Microspheres in PBS (pH 7.4)

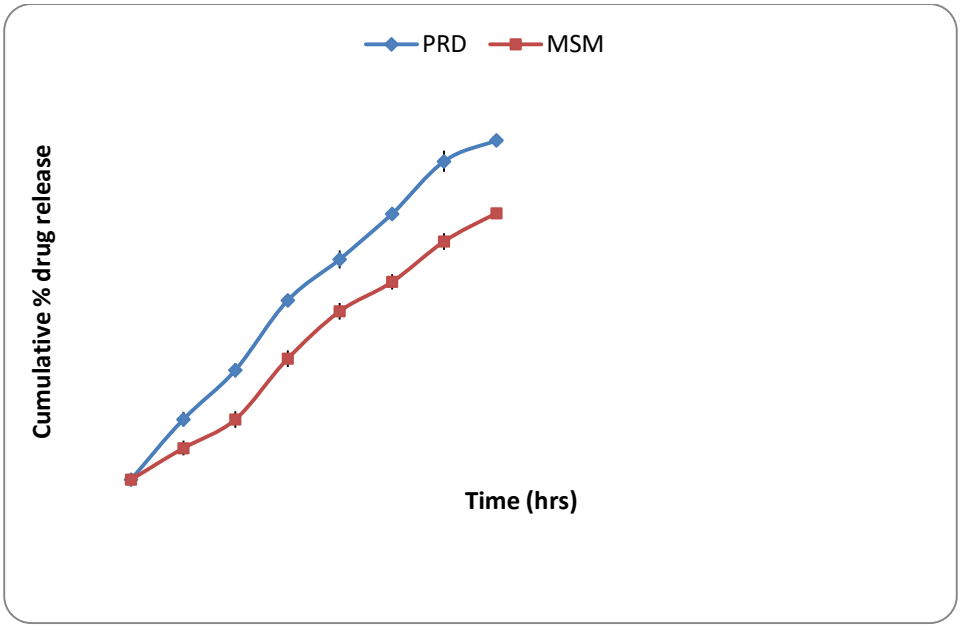

Fig. 4: Percent Cumulative Drug Release of MSM and PRD from Optimized Formulation of ES100 Coated Pectin Microspheres (F24) in PBS (pH 7.4)

ES100 coated pectin microspheres have the potential to be an efficient, viable, safe and cost-effective system for administration of MSM and PRD on account of their biodegradability, biocompatibility, and suitability for oral applications. The biodegradable natural polymers like pectin can be degraded by the colonic microflora. These polymers have limited swelling characteristics at acidic pH but swells in natural pH of colon and release the drug. Several studies have shown that pH dependent approach of drug release appears to have the lowest risk of treatment failure for crohn's disease.

Hence in the present study pH sensitive pectin microsphere as drug carrier were formulated and optimized. In order to protect pectin microsphere during intestinal transit ES100coating was applied. ES100belongs to pH sensitive group of polyacrylates that recudes the premature release of entrapped microspheres in upper parts of ileum.

CONCLUSION

ES100coated pectin microspheres of MSM and PRD are expected to deliver the drug selectively to the colon. This drug delivery system allows the desired microsphere formulation to be released at inflamed tissue area with high efficiency with reduced systemic side effects as the drug release is pH dependent. Moreover, a reduction of adverse effects is possibly due to more locally focused delivery of the drugs. The experiment results demonstrated that ES100coated pectin microspheres have potential to be used in the treatment of ulcerative colitis.

AUTHOR CONTRIBUTIONS

Dr Ashish Kumar Parashar reviewed and examined the work. Rashmi Bagri and Seemu Singh conducted the research work. Gaurav Kant Saraogi wrote the initial draft of the research article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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