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Research Article

Imipenem Loaded Pectin Microspheres for Colon Delivery

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ABSTRACT

The present studies divulge the positive upshot of Eudragit S-100 coated imipenem loaded pectin microspheres for the colon delivery. These microspheres maintain their integrity in upper part of gastro intestinal tract (GIT) and reduce the side effects of the drug caused by its absorption from the upper part of GIT when the drug is given in conventional dosage forms such as tablets and capsules. The experimental results demonstrated that Eudragit S-100 help the drug to release in the colon by degrading its coating at pH 7 results in exposure of the pectin microspheres which on enzymatic influence and due to pH sensitive nature degraded and release the drug to the colon. Thus the Eudragit coated pectin microspheres have the potential to be used as a drug carrier for an effective colon-targeted delivery system.

INTRODUCTION

Drug targeting to the colon is useful when a delay in drug absorption is desired from a therapeutic standpoint, such as the treatment of diseases with peak symptoms in the early morning, such as nocturnal asthma, angina, or arthritis, as well as the local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide medications [1].

The colon-specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon, which means that drug release and absorption should not occur in the stomach or small intestine, and the bioactive agent should not be degraded in either of the dissolution sites, but should only be released and absorbed once the system reaches the colon [2]. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons: (i) less diversity and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum, and eventually releases the drug into the ileum or colon, which leads to greater systemic bioavailability. Finally, because the colon has a long residence time of up to 5 days it is extremely sensitive to absorption boosters [3].

Several approaches are used for colonic drug delivery [4]. Among them, pH sensitive polymer coated drug delivery system for colon delivery is most prevalent. Multiparticulate dosage form consisting of a hydrophobic core coated with a pH dependent polymer for colonic drug delivery is commonly used [5].

The aim of present study is to prepare the imipenem loaded pectin microspheres. These prepared microspheres will not maintain their integrity and release the drug at upper part of GIT. To protect the drug release from microspheres, these multiparticulte systems were coated with enteric coating material i.e. Eudragit S-100. These imipenem loaded Eudragit S-100 coated pectin microspheres will not only target the drug to colon but also avoid diffusion of drug through formulation, lead to inhibit any absorption through small intestine. This concept will also maximize the drug utilization that will result lowering of the dose.

MATERIALS AND METHODS

Materials

Pectin was purchased from Central Drug House (CDH) Ltd., Daryaganj, New Delhi, India. Mylan laboratories limited Nashik (M.H.) supplied imipenem as gift sample. Eudragit S-100 and span-80 was procured from Research Lab Fine Chem Industries Mumbai India. Isooctane was purchased from Central Drug House (Mumbai, India). All other chemicals were of analytical reagent grade.

Methods

Preparation of pectin microspheres

Pectin microspheres were prepared by the method reported by Vaidya et al., (2009) with slight modification [4]. Briefly the drug-polymer solution (0.5%, in distilled water) was dispersed in 50 ml isooctane containing span 80 (1.5% w/v) and the dispersion was continuously stirred at varied speed to obtain stable water/oil emulsion. The dispersion was rapidly cooled to 10ºC followed by addition of 50 ml of acetone, for the dehydration of pectin droplets. For the complete solvent evaporation, the formulation was continuously stirred at 1000 rpm for 30 min at room temperature. The formulation containing microspheres were freeze-dried and kept in airtight container for further studies. Similarly, the pectin microspheres with varying compositions and varying formulation variables were prepared and optimized.

Optimization

Various formulation variables e.g. imipenem concentration, polymer concentration, span 80 concentration and process variables viz. stirring speed and stirring time, which could affect the preparation and properties of microspheres were identified and studied. The formulation compositions of designed pectin microspheres are given in Table 1 [6].

Optimization of process variables

Various process variables that could affect the preparation and properties of microspheres were optimized i.e. stirring speed: 1000, 1500, and 2000 rpm stirring time 20, 30, and 40 minutes and span 80 concentrations (0.5, 0.75, 1.00 and 1.25). Effect of these variables were observed on final particle size, size distribution and shape of microspheres and imipenem loading efficiency are reported in Table 1 and shown graphically in figures 1-6. On the basis of imipenem loading efficiency the optimum condition are reported in Table 2 [7].

Entrapment efficiency

The drug entrapment efficiency in microspheres was determined using the method reported by Vaidya et al., (2009) [4]. The prepared microspheres were digested in 10 ml of PBS (pH 7.4) for 12 h which contain pectinase solution (4% wt/wt) which is followed by the centrifugation at 3000 rpm for 5 min, and the supernatant obtained was assayed The digested homogenate was centrifuged at 3000 rpm for 5min, and the supernatant was assayed spectrophotometrically at 297 nm (UV- Thermo scientific) for Imipenem drug.

Coating of pectin microspheres

The prepared pectin microspheres were coated with Eudragit S-100 using the method reported by Vaidya et al., 2009 with slight modifications [4]. Briefly, the prepared pectin microspheres (50 mg) were dispersed in 10 ml of organic solvents mixture (acetone/ ethanol, 2:1) containing Eudragit S-100 to provide 1:5, 1:10 or 1:15 core/coat ratio. This

untreated phase was added into 70ml of light liquid paraffin which hold 1% w/v span 80. After this the system was continuously stirred for 3 h at 1000 rpm in order to evaporate the solvent at room temperature. The Eudragit coated microspheres were centrifuged at 1000 rpm for 15 min for separation and washed with n-Hexane. Finally coated microspheres were lyophilized and stored in tightly capped container [8].

Table 1: Average particle size, Entrapment efficiency of uncoated pectin microspheres.

Formulation code	Variables	Values	Particle size (µm)	Entrapment efficiency (%)
PMS-P1	**Pectin concentration (%)**	1	9.17±2.28	68.42±2.28
PMS-P2		**1.5**	**9.39±1.35**	**70.61±3.19**
PMS-P3		2	10.34±1.43	73.50±2.18
PMS-D1	**Drug concentration (%)**	5	10.19±0.59	62.28±3.07
PMS-D2		**10**	**10.31±0.58**	**66.31±2.81**
PMS-D3		15	10.42±0.91	63.89±3.22
PMS-E1	**Emulsifier concentration**	0.5	10.86±1.80	70.05±3.22
PMS-E2	**[Span 80(w/v) (%)]**	0.75	10.06±1.15	71.98±2.65
PMS-E3		**1.0**	**9.18±1.19**	**72.37±2.54**
PMS-E4		1.25	8.68±2.61	71.12±3.18
PMS-R1	**Stirring speed (rpm)**	1000	13.61±1.59	72.23±3.31
PMS-R2		**1500**	**10.30±1.90**	**74.51±2.65**
PMS-R3		2000	9.89±2.09	69.01±2.31
PMS-T1	**Stirring time (min)**	20	12.30±2.44	70.21±2.87
PMS-T2		**30**	**10.89±1.60**	**71.13±3.54**
PMS-T3		40	10.30±2.15	63.89±2.99

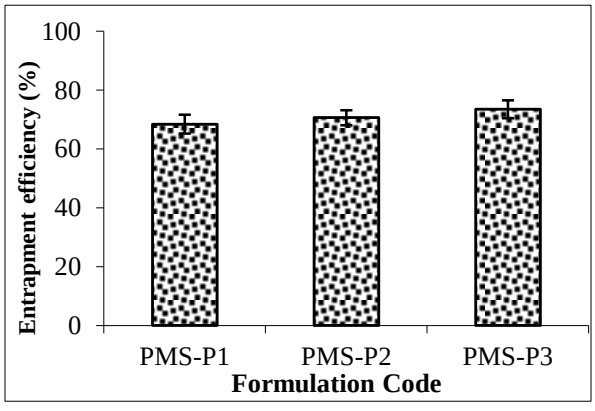

Fig. 1. Effect of pectin conc. on entrapment efficiency.

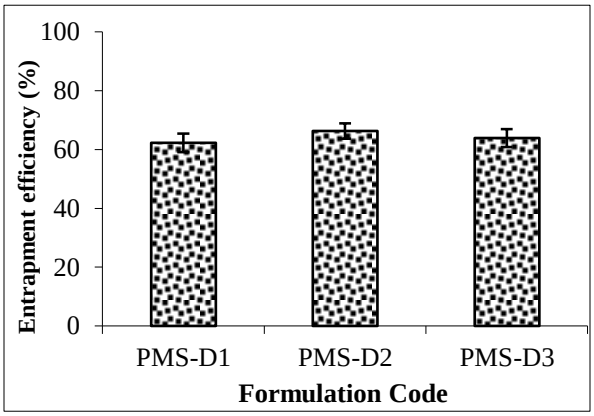

Fig. 2. Effect of drug conc. on entrapment efficiency.

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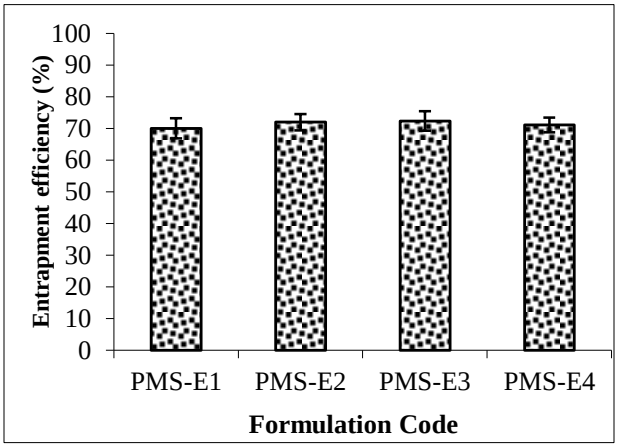

Fig. 3. Effect of emulsifying conc. on entrapment efficiency.

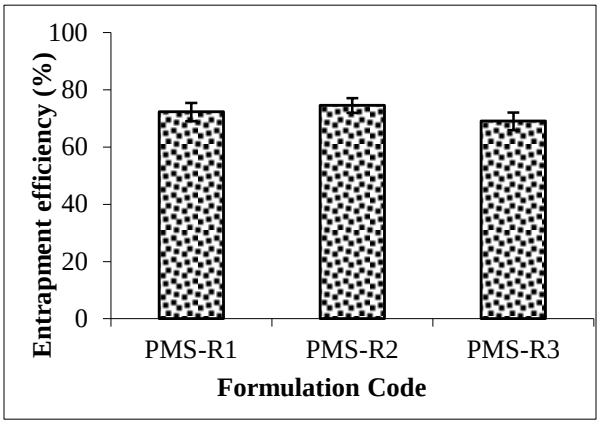

Fig. 4. Effect of stirring speed. on entrapment efficiency.

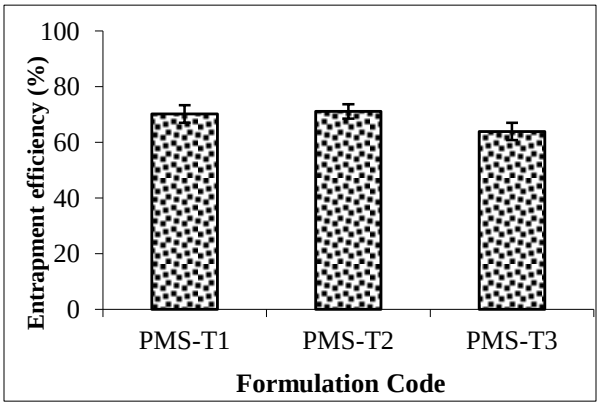

Fig. 5. Effect of stirring time on entrapment efficiency.

Characterization of pectin microspheres

Shape and surface morphology

The shape and surface morphology of the prepared pectin microspheres were studied by using scanning electron microscopy, where the microsphere powder was lightly sprinkled on a double adhesive tape which was stuck on aluminium stub. By using the sputter coater the stubs were then coated with the gold to of about 300Å thick and then observed under scanning electron microscopy (Figure 7).

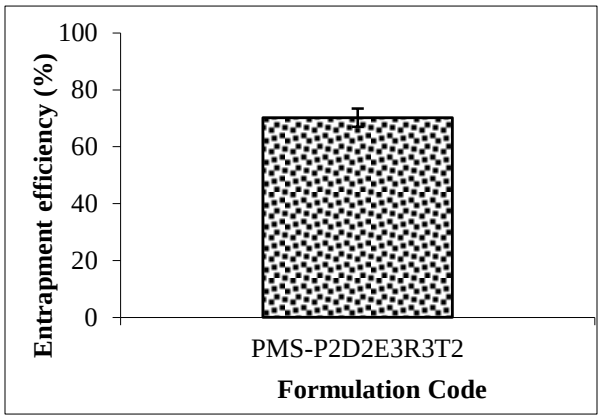

Fig. 6. Effect of optimized condition on entrapment efficiency of pectin microspheres.

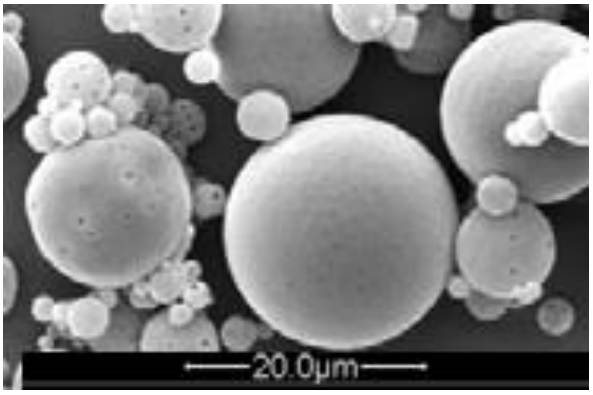

Fig. 7. SEM image of prepared pectin microspheres.

Size determination

The size of both uncoated and Eudragit coated microspheres was appraised using Laser diffraction based particle size analyzer (1064L, Cilar, Marcoussis, France).

In vitro drug release

In vitro drug release studies were performed according to Vaidya et al., 2009 extraction technique using USP dissolution test apparatus Type 2 (Paddle type). The dissolution studies were achieved in 900 ml dissolution medium, with continuously stirring at 100 rpm at room temperature.

The scheme for using the simulated gastrointestinal fluids at different pH was as follows:

1st hour: Simulated gastric fluid (SGF) of pH 1.2.

2nd and 3rd hours: Mixture of simulated gastric and intestinal fluid of pH 4.5.

4th and 5th hours: Simulated intestinal fluid (SIF) of pH 6.8.

6th and 7th hours: Simulated intestinal fluid of pH 7.5.

8th to 24th hours: Simulated colonic fluids (SCF) of pH 7.5.

Aliquots of samples were periodically withdrawn and balanced with an equal amount of fresh dissolution media. The spectrometric measurement at 297 nm (UV-Thermo scientific) (Figure 8).

Table 2: Optimized condition for preparation of microspheres.

Formulation Code	% Pectin solution	% Drug concentration	% Span80	Stirring speed	Stirring time
PMS-P2D2E3R3T2	1.5	10	1.0	1500	30

Table 3: Effect of optimized conditions on pectin microspheres size, shape and entrapment efficiency.

Formulation Code	Diameter (µm)	Shape	Entrapment efficiency
PMS-P2D2E3R3T2	10.24	Spherical	70.25±2.04

Table 4: Effect of core: coat ratio on size and shape of microspheres.

Formulation Code	Core: Coat ratio	Average Diameter (µm)	Shape
PMS-P2D2E3R3T2C1	1:5	13.34±1.90	Uncoated Particles seen, coating insufficient
PMS-P2D2E3R3T2C2	**1:10**	**16.32±1.22**	**Spherical with uniform coating**
PMS-P2D2E3R3T2C3	1:15	17.78±1.76	Coating material found in solution showing over concentration

Table 5: *In vitro* percent drug release from uncoated and Eudragit S 100 coated pectin microsphere.

Formulation Code	pH 1.2	pH 4.5		pH 6.8		pH 7.5				
	1 h	2h	3h	4h	5h	6h	7h	8h	12h	24h
PMS-P2D2E3R3T2	12.4	18.9	29.6	37.4	43.2	51.4	59.7	88.6	97.3	98.9
PMS-P2D2E3R3T2C2	0	2.1	4.3	6.8	11.4	21.1	29.7	48.4	83.7	96.2

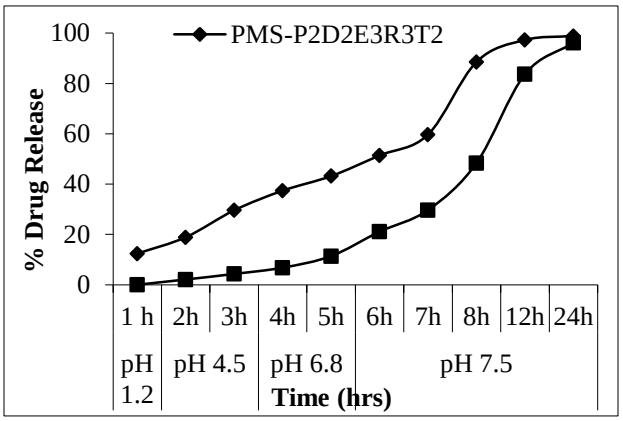

Fig. 8. *In vitro* percent drug release from uncoated and Eudragit S 100 coated pectin microsphere

RESULTS AND DISCUSSION

Pectin microspheres bearing imipenem were prepared by solvent evaporation method. There were several formulations and process variables viz, pectin concentration, span 80 (emulsifier concentration), stirring time and stirring speed which were optimized to obtain spherical microspheres with optimum particle size and maximum drug entrapment efficiency.

Shape and surface morphology of pectin microspheres were observed using SEM. Shape of pectin was found to be spherical with smooth surface while in the case of enteric coated pectin microspheres with the rough surface due to the Eudragit S-100 coating.

The particle size and percent entrapment efficiency of pectin microspheres increases from 9.17±2.25 µm to 10.34±1.43 µm and 68.42±2.28 %to 73.50±2.18% respectively, as the polymer concentration was increases from 1% to 2%. The optimized polymer concentration was 1.5% with the particle size of 9.39±1.35 µm and entrapment efficiency 70.61±3.19%, as on increasing the polymer concentration, no significant increase in the entrapment efficiency observed. The high polymer concentration is more viscous so it is difficult to formulate the uniform pectin microspheres.

In optimization of drug concentration which is varied from 5 to 15%, as the drug conc. increased the particle size also increased from 10.19±0.59µm to 10.42±0.91µm and entrapment efficiency also increased from 62.28±30.07% to 73.89±3.22% respectively. The optimized drug concentration was 10% with particle size 10.31±0.58µm and entrapment efficiency was 66.31±2.81%.

On optimizing the span 80 (emulsifier) concentration, it was found that on increasing the concentration from 0.5 % to 1.25%, particle size decreased from 10.86±1.80 µm to 8.68±2.61µm and the entrapment efficiency increased from 70.05±3.22% to 75.12±3.18%. The optimum span 80 conc. was 1.0% and particle size was 9.18±1.19 µm and 72.37±2.54% was optimum entrapment efficiency.

On optimizing the stirring speed, the stirring speed was increased from 1000 rpm to 2000 rpm which results the decreased particle size from13.61±1.59 µm to 9.89±2.09 µm and first increased and then gradual decreased entrapment efficiency from 72.23±3.31% to 69.03±2.31%.The optimum stirring speed considered was 1500 rpm with 10.30±1.90 µm particle size and 74.51±2.65% entrapment efficiency.

The particle size and the entrapment efficiency decreased from 12.30±2.44 µm to 10.30±2.15 µm and 70.21±2.87% to 63.89±2.99% with the increase in the stirring time from 20 mins. to 30 mins. The optimum speed was 30 mins. with the particle size and entrapment efficiency was 10.89±1.60 µm and 71.13±3.54%.

Further the plain pectin microspheres were coated with Eudragit S-100 and core:coat ratio was optimized to achieve the a uniform coated pectin microspheres, When the core:coat ratio was increased from 1:5 to 1:15 the average diameter was increased from 13.34±1.90 µm to17.78±1.76 µm. The optimized core: coat ratio was found at 1:10 with the avg. particle diameter was 16.32±1.22µm.

In vitro drug release from optimized uncoated and Eudragit S-100 coated pectin microspheres were carried out in different medium (pH- 1.2, 4.5, 6.8, 7.5) similar to the simulated pH of GIT fluids, that is with and without enzymatic medium. It showed significant difference in the release profile of the plain pectin microspheres and enteric coated pectin microspheres.

The drug release studies were carried out in SGF for 1-3 hrs, SIF for 4-7 hrs and CIF for 8-24 hrs to ensure the efficacy of the formulation to withstand the physiological environment of stomach, small intestine, and colon. There was regular

difference in drug release between uncoated and coated pectin microspheres. After 1hr there was 12.4 % drug release from uncoated formulation whereas no release was observed from the enteric coated microspheres after 1h. Consequently the drug release after 8hrs from uncoated formulation was 88.6% and from coated formulation was 48.4%. This data explained Eudragit S-100 coated formulation shown delayed released as compare to uncoated microspheres. This delayed release was due to Eudragit S-100 polymer coating contains carboxyl group which gets ionized from neutral to alkaline media. At pH 7.4 in small intestines, the coating dissolves and the pectin microspheres were released, results in polymer material swelling and erosion, thus drug was released.

CONCLUSION

The current experiments demonstrated the beneficial effects of Eudragit S-100 coated imipenem-loaded pectin microspheres for colon administration. These microspheres maintain their integrity in the upper part of the GIT, reducing the negative effects of the medicine produced by their absorption from the upper region of the GIT when given in conventional dosage forms such as tablets and capsules. The testing results showed that Eudragit S-100 aids drug release in the colon by disintegrating its coating at pH 7, exposing pectin microspheres that, under enzymatic influence and due to their pH sensitive nature, disintegrate and release the medication into the colon. Thus, Eudragit-coated pectin microspheres have the potential to be employed as a medication carrier.

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None

CONFLICT OF INTEREST

None

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