Development and Characterization of Eudragit RS 100 Loaded Microsponges and its Colonic Delivery Using Natural Polysaccharides

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Abstract

In the present work, paracetamol loaded eudragit based microsponges were prepared using quasi-emulsion solvent diffusion method. The compatibility of the drug with various formulation components was established. Process parameters were analyzed in order to optimize the formulation. Shape and surface morphology of the microsponges were examined using scanning electron microscopy. The colon specific formulations were prepared by compression coating of microsponges with pectin:hydroxypropylmethylcellulose (HPMC) mixture followed by tabletting. The in vitro dissolution studies were done on all formulations and the results were evaluated kinetically and statically. The kinetics of release study showed that the release data followed Higuchi matrix and the main mechanism of drug release from microsponges was diffusion. In vitro studies exhibited that compression coated colon specific tablet formulations started the release the drug at the 6th hour corresponding to the arrival time to proximal colon

Keywords: Microsponge, Colonic delivery, Pectin, Diffusion
**Introduction**

The requirement for an oral colonic drug delivery system is to reduce the drug release to a minimum prior to the cecum (1). Colon as a site offers distinct advantages on account of a near neutral pH, a much longer transit time, reduced digestive enzymatic activity and a much greater responsiveness to absorption enhancers (2). These criteria favour this distal part of the gastrointestinal tract (GIT) as a site for the delivery of vermicides, colonic diagnostic agents and sustained release of drugs in treatment of nectural asthma, angina and arthritis (3). A colon-specific drug delivery system should prevent drug release in the stomach and small intestine and affect an abrupt onset of drug release upon entry into the colon (4).

Various approaches have been used for delivery of drugs to the colon via oral route, which include coating with pH-dependent polymers, design of time-release dosage forms and the utilisation of carriers that are degraded exclusively by the colonic bacteria (5). Every system has advantage as well as disadvantages. The poor site-specificity of pH-dependent systems, because of large variations in the pH of the gastrointestinal tract, is very well documented. The site-specificity of timed-release dosage forms is considered poor because of large variations in gastric emptying times and passage across the ileo-caecal junction (6). However, microflora-activated systems formulated making use of non-starch polysaccharides are highly promising because the polysaccharide remain undigested in the stomach and the small intestine and can only be degraded by the vast anaerobic microflora of the colon. Further more, this strategy exploiting the abrupt increase of the bacteria population and corresponding enzyme activities will also accomplish greater site-specificity of initial drug release (7). The polysaccharides for colonic drug delivery are also inexpensive, naturally occurring and abundantly available (8).

Single unit colon targeted drug delivery systems may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the
colon. Recently much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like increased bioavailability; reduce risk of local irritation and predictable gastric emptying (9).

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge like spherical particles that consist of myriad of interconnecting voids within a non-collapsible structure with large porous surface (10). Moreover, they may enhance stability, reduce side effect and modify drug release favorably (7).

Paracetamol (PCM), an antipyretic and analgesic drug which has been widely used in clinical practice was selected as a model drug. It has a short half life in plasma about 1–4 hours.

The present study is aimed at developing microsponge based novel colon specific drug delivery system containing PCM. The microspongs of PCM were prepared and characterized. They were formulated as colon specific tablets and subjected to in vitro characterization for various attributes.

**Materials and Methods**

**Materials**

Paracetamol was purchased from Jackson Laboratories Pvt. Ltd. Amritsar (India). Eudragit RS-100 was kindly gifted by Evonic India Pvt. Ltd. Mumbai (India). Polyvinyl alcohol 30,000–70,000 (PVA), Triethylcitrate, and HPMC (100,000 cps) were purchased from Sigma-Aldrich (USA). Pectinex Ultra SP-L (26,000 FDU/mL), Pectin (from citrus fruits, methoxy content 9.4%) and Sodium carboxymethyl cellulose (Na-CMC) were procured from Sigma (USA). All chemicals used for analysis were analytical grade.

**Methods**

**Paracetamol loaded microsponge preparation**
Paracetamol microsponges were prepared by quasi-emulsion solvent diffusion method. The internal phase consisted of Eudragit RS-100 (200mg) and triethylcitrate (1% w/v) dissolved in 5 ml dichloromethane. Triethylcitrate (TEC) was used as plasticizer. This was, followed by addition of drug with gradual stirring (500 rpm). The internal phase was then poured into polyvinyl alcohol 30,000-70,000 (PVA) solution in water, the external phase. After 8 hour of stirring the microsponges were formed due to removal of dichloromethane from the system. The microsponges were filtered and dried at 40°C for 12 hours. The composition of microspunge formulations are given in Table 1.

**Fourier transform infrared (FTIR) analysis**

FTIR spectra of the drug, physical mixture of drug & eudragit RS-100, formulations FPRS1–FPRS4 were recorded in potassium bromide disc using a Shimadzu Model 8400 FTIR spectrometer to ascertain compatibility.

**Differential scanning calorimetric (DSC) analysis**

Thermal analysis using DSC was carried out on drug, physical mixture of the drug & eudragit RS-100, and formulations FPRS1–FPRS4 (Shimadzu DSC-60 Thermal Analyzer). Accurately weighed samples were loaded into aluminum pans and sealed. All samples were run at a heating rate of 20°C/min. over a temperature range 40-430°C.

**Morphology**
The morphology and surface characteristics of the microsponges were studied using scanning electron microscopy (SEM). All the samples were coated with gold-palladium alloy under vacuum. Coated samples were then examined using LEO 430 SEM analyzer.

**Actual drug content and encapsulation efficiency**

The weighed amount of drug loaded microsponges (100 mg) was kept in 100 ml phosphate buffer pH 6.8 for 12 h with continuous stirring. The samples were filtered using 0.45\_m membrane filter and the samples were analyzed at 256 nm against blank using UV spectrophotometer (UV 1700, Shimadzu, Japan). The drug content and encapsulation efficiency were calculated using the following formula (7).

Actual drug content (\%) =\(\frac{M_{\text{act}}}{M_{\text{ms}}} \times 100\)

Encapsulation efficiency (\%) =\(\frac{M_{\text{act}}}{M_{\text{the}}} \times 100\)

Where \(M_{\text{act}}\) is the actual drug content in microsponges, \(M_{\text{ms}}\) is the total amount of the microsponges and \(M_{\text{the}}\) is the amount of drug added to the microsponges. All analyses were carried out in triplicate.

**In-vitro drug release studies of microspunge formulations**

The microsponges containing 250 mg of paracetamol were subjected to in-vitro drug release studies. In-vitro release studies were carried out in USP basket apparatus with stirring rate 50 rpm at 37±0.5 \(^\circ\)C. Initial drug release was carried out in 900 ml of 0.1N HCl for 2 hours followed phosphate buffer pH 6.8 for next 6 h. Samples were withdrawn at regular intervals of time. The sink conditions were maintained by adding equal amount of dissolution medium. The samples were analyzed spectrophotometrically (Shimadzu UV-1700) at a wavelength of 256 nm. Dissolution tests were performed in triplicate for each sample.
Preparation of colon specific tablet formulations

The core tablets consisting of microsponges containing 250 mg drug, Na-CMC and magnesium stearate were prepared by direct compression method. All tablet constituents were weighed and mixed in motor passel for 15 min. Final powder mixture was compressed using 10 mm round flat punches on an eight station tablet punch machine (Cambart, D-8) using 1500 kgf/cm² compression pressure. Core tablet formulations are given in Table 2.

Pectin:HPMC (80:20) mixture was used as outer shell for compression coating. The coating material used was 400 mg. Fifty percent of coating material was placed in the die cavity and the core tablet was placed in centre followed by addition of the remainder of the coating material. The coating material was compressed around the core tablet at an applied pressure of 2500 kgf/cm² using round flat punches (14 mm) on the same tableting machine.

In-vitro drug release studies of colon specific formulations

The drug release studies were done with the same method used for microsponges and core tablets. Additionally, Pectinex Ultra SP-L was added to the dissolution medium at 6th hour in order to simulate the enzymatic action of the colonic bacteria. Samples were withdrawn periodically and compensated with an equal amount of fresh dissolution media. The samples were analyzed for drug content by measuring absorbance at 256 nm using UV spectrophotometer.

Results and discussion
Quasi-emulsion solvent diffusion method was used for preparation of microsponges because of its simplicity and reproducibility. Moreover, it has advantage of avoiding solvent toxicity. The drug and polymer in the ratios 3:1, 6:1, 9:1, and 12:1 were taken to prepare different microsponge formulations namely FPRS1, FPRS2, FPRS3, and FPRS4, respectively. In each formulation, the amounts of polymer (200 mg), dichloromethane (5 ml), PVA (0.5% w/v) were kept constant. The microsponge formulations were prepared using mechanical stirrer (Remi RQ1217-D) at a stirring rate of 500 rpm for 8 hours. The composition of various microsponge formulations are depicted in Table 1.

The effect of various variables like drug/polymer ratio, stirring rate, volume of internal phase, amount of emulsifying agent on the nature of microsponges was studied.

**Effect of drug-polymer ratio on microsponges**

The morphology of the microsponges was studied by scanning electron microscopy (SEM). The representative photographs of the microsponges are shown in Figure 1. The microsponges were observed to be spherical and uniform with no drug crystals on the surface. The figure 1 shows that drug-polymer ratio has considerable effect on the morphology and size of microsponges. It was observed that as the ratio of drug to polymer was increased, the particle size decreased. This could probably be due to the fact that in high drug to polymer ratios, the amount of polymer available per microsponge was comparatively less. Probably in high drug-polymer ratios less polymer amounts surround the drug and microsponges with smaller size were obtained (11).

Production yield, actual drug content, encapsulation efficiency, and mean particle size of formulations FPRS1-FPRS4 are presented in Table 3. The production yield, actual drug content, and encapsulation efficiency of FPRS1-FPRS4 formulations was found to be between 72-75%, 73-91% 98-99%, respectively.

The data obtained for various formulations in respect to production yield, actual drug content, and
encapsulation efficiency were subjected to t-test at 95% level of significance. No significant difference in relation to these parameters was observed amongst various formulation at p <0.05.

**Effect of stirring rate on the morphology and yield of microsponges**

The effect of stirring rate on the morphology of microsponges is shown in Figure 2. The formulation with the lower drug to polymer ratio (i.e., 3:1) was chosen to investigate the effect of stirring rate on the morphology of microsponges. The stirring rate was varied in the range of 300 to 500 rpm. The dispersion of the drug and polymer into the aqueous phase was found to be dependant on the agitation speed. As the speed was increased the size of microsponges was reduced and the microsponges were found to be spherical and uniform (12). When the rate of stirring was increased up to 500 rpm the spherical microsponges were formed with mean particle size of 62.34±6.89 µm.

It was noted that at higher stirring rate the production yield was decreased. Possibly at the higher stirring rates the polymer adhered to paddle due to the turbulence created within the external phase, and hence production yield decreased (13).

**Effect of volume of internal phase on the production of microsponges**

It was observed that on increasing the volume of internal phase from 5 to 10 ml microsponges were not formed. This may be due to the decrease in viscosity of internal phase (14). As the amount of dichloromethane was increased, the finely dispersed spherical quasi-emulsion droplets were seen in solvent under the agitation, but as the stirring was discontinued emulsion droplets adhered together and coalesce. Consequently, no microsponges could be formed. The result suggests that the amount of dichloromethane
need to be controlled within an appropriate range to effect not only the formation of quasi-emulsion droplets at the initial stage but also the solidification of drug and polymer in the droplets. The good microsponges were produced when 3 to 5 ml of dichloromethane was used.

**Effect of amount of emulsifying agent on the production yield and particle size of microsponges**

An increase in amount of emulsifying agent resulted in decreased production yield and increased mean particle size. As the emulsifier was non-ionic in nature and possibly formed some hydrophobic region which dissolved some of the drug and polymer. The molecules might have associated away from the oil-water interface at higher concentrations resulting in alternative hydrophobic region which dissolved some portion of drug resulting in a reduction in production yield of microsponges (13). On the other hand increase in the amount of emulsifying agent resulted in increased larger microsponges. This could be due to the increased viscosity wherein larger emulsion droplets formed resulting in larger microsponges. The dispersion of the solution of the drug and polymer into droplets was effected by the concentration of polyvinyl alcohol in the external phase. When the concentration of PVA was increased in dispersion phase, the size of microsponges was found to be decreased (18). The results of the effect of emulsifying agent on production yield and mean particle size are shown in table 4. The production yield and mean particle size was greatly effected by the amount of emulsifying agent. As increased amount of emulsifying agent decreased the production yield from 72 to 67 and increased the mean particle size from 62 to 66 µm.

**Characterization of microsponges**

DSC studies were carried out to confirm compatibility (15). The thermal behavior of drugs, physical mixture of drug and polymer, and formulations FPRS1–FPRS4 was studied. In the thermogram, the drug showed a sharp endothermic peak (at 174.23 °C) which corresponds to the melting point of drug in the
crystalline form. In the DSC curve of physical mixture of drug and polymer, and formulations FPRS1–FPRS4, the characteristic peaks of drug(s) were observed. The result showed that there is no incompatibility between drug and polymers. Microspponge production process did not change the nature of drug in microsponges. The thermal behavior of the drug, physical mixture of drug & eudragit RS-100 and formulations FPRS1–FPRS4 are presented in figure-3.

FTIR spectra were recorded to assess the compatibility of the drug and excipients (16). FTIR spectra of drug, physical mixture of drug & Eudragit RS-100 and formulations FPRS1–FPRS4 were examined. In FTIR spectra of paracetamol powder, characteristic N-H stretching band at 3325 cm\(^{-1}\), O-H stretching band at 3161.11 cm\(^{-1}\), and carbonyl stretching band at 1654 cm\(^{-1}\) were seen. Eudragit RS 100 showed an ester C=O stretching peak around 1726.17 cm\(^{-1}\). All characteristic peaks of paracetamol were observed in the FTIR spectra of FPRS1–FPRS4 formulations. The results showed that no chemical interaction or changes took place during preparation of the formulations and the drug was found to be stable in all the formulations. The FTIR spectra of the drug, physical mixture of drug & eudragit RS-100 and formulations FPRS1–FPRS4 are presented in figure-4.

**In-vitro release studies of the microspunge formulations**

The microspunge formulations were subjected to in-vitro release studies using USP XX1V dissolution assembly at the stirring rate at 50 rpm and temperature at 37±0.5 °C. Initially drug release was carried out in of 0.1N hydrochloric acid for 2 hours followed by phosphate buffer pH 6.8 for next 6 hours.

The release profiles obtained for the formulations FPRS1–FPRS4 are presented in Figure 5. It was observed that the drug release decreased with increase in the amount of polymer for each formulation. This may be due to the fact that the release of drug from the polymer matrix takes place after complete swelling of the polymer and as the amount of polymer in the formulation increases the time required to swell also increases. The release showed a bi-phasic pattern with an initial burst effect. In the first hour drug release
was found to be 17-30%. This may be attributed to the drug present in the pores of the microsponges or improper entrapment of drug (17). The cumulative percent release for FPRS1-FPRS4 at the end of 8 h was found to be 54-83%. The microsponge formulations were subjected to in-vitro dissolution studies and the data was analyzed using various mathematical models. Based on highest regression value the best fit was observed for Higuchi matrix. The n value for Peppas model was found to be between 0.5-1 indicative of non-fickian diffusion.

The in-vitro dissolution data was subjected to statistical analysis using ANOVA. The p value was found to be 0.5207 indicating no significant difference in the release behaviour (p>0.05).

**In-vitro dissolution studies of the colon specific tablet formulations**

In order to prepare the compression coated tablet formulations, core tablets were prepared as the first step. The homogenous granular characteristic of microsponges is due to their highly porous structure and in these means, microsponges have the compressibility to produce strong tablets and 1000–2000 kgf/cm² pressure did not cause the structure deformation of microsponges (19). In vitro drug release studies of the colon specific tablet formulations were carried out using USP basket apparatus with stirring rate 50 rpm at 37±0.5 °C. The release profiles obtained for the formulations CPRS1-CPRS4 are presented in figure-6. No drug was released in the first 6 hours. After this lag time of 6 hours, the drug release started at the beginning 7th hour due to the addition of the Pectinex Ultra SP-L and continued up to 14th hour for CPRS1 (68.65%), 14th hour for CPRS2 (88.23%), 13th hour for CPRS3 (92.45%) and 12th hour for CPRS4 (95.76%).

The results of in vitro drug release showed that the ratio of Pectin: HPMC (80:20) protected the cores up to 6th hour corresponding to the time to reach the colon and after that under the influence of the enzyme, the system could be degraded faster and deliver the drug to the proximal colon that forms the main site of
bacterial carbohydrate metabolism. So, the results were in accordance with the triggering mechanism due to the very active metabolism in the proximal part compared with the distal part of colon and pectin could find the appropriate environment to be degraded.

**Conclusion**

This study presents new approach for the preparation of modified microsponges. The prepared microsponges exhibited characteristics of an ideal delivery system for colon targeting. The unique compressibility of microsponges offers a new alternative for producing mechanically strong tablets. Further colon specific tablets based on microsponges could provide effective local action as microsponges may selectively be taken up by the macrophages present in colon.

**Acknowledgement**

The authors are thankful to the Director, School of Pharmaceutical Sciences, Shobhit University, Meerut for providing necessary facilities.
References


Table-1

Composition of various microsponge formulations

Table-2

Core tablet formulations of PCM microsponges

Table 3

Production yield, actual drug content, encapsulation efficacy, and mean particle size of various microsponges formulations (n=3)
Table 4

The effect of emulsifying agent on microsponges formulation

Table 5

In vitro drug release models for different microsponges formulations.
Figure 1 (a-h) SEM photograph of microsponge formulations (drug: eudragit RS-100). The photograph coded ‘A’ represents whole image; ‘B’ represents surface photographs.

Figure 2 SEM Photograph of drug: eudragit RS-100 microsponges prepared at different stirring rates of (a) 300 rpm; (b) 400 rpm; (c) 500 rpm

Figure 3 DSC Thermogram of Paracetamol, Physical mixture of drug & Eudragit RS-100, and FPRS1-FPRS4 microsponges formulations

Figure 4 FTIR spectra of Paracetamol, Physical mixture of drug & Eudragit RS-100, and FPRS1-FPRS4 microsponges formulations

Figure 5 In vitro drug release profile of different formulations of microsponges (FPRS1-FPRS4)

Figure 6 In vitro drug release profile of drug from different colon-specific formulations (CPRS1-CPRS4)
<table>
<thead>
<tr>
<th>Components</th>
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<th>FPRS2</th>
<th>FPRS3</th>
<th>FPRS4</th>
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<td>1200</td>
<td>1800</td>
<td>2400</td>
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<td>Eudragit RS-100 (mg)</td>
<td>200</td>
<td>200</td>
<td>200</td>
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<td>Triethylcitrate (ml)</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<td>Dichloromethane (ml)</td>
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Table 2 Core tablet formulations of PCM microsponges

<table>
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<th>Core tablet formulation codes</th>
<th>Microspones formulations (mg)</th>
<th>Na-CMC (mg)</th>
<th>Magnesium stearate (mg)</th>
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<tr>
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<td>CPRS4</td>
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Table-3 Production yield, actual drug content, encapsulation efficacy, and mean particle size of various microsponges formulations (n=3)

<table>
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<tr>
<th>Formulation</th>
<th>Drug:Polymer Ratio</th>
<th>Production yield (%) ± S.D.</th>
<th>Theoretical drug content (%)</th>
<th>Actual drug content (%) ± S.D.</th>
<th>Encapsulation efficiency (%) ± S.D.</th>
<th>Mean particle size (µm ± S.D.)</th>
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<td>FPRS1</td>
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<td>75.02±0.60</td>
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<td>External Phase</td>
<td>Yield (%)</td>
<td>Mean Diameter µm ± S.D.</td>
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<tr>
<td></td>
<td>PCM (mg)</td>
<td>Polymer (mg)</td>
<td>Dichloromethane (ml)</td>
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Table 5 In vitro drug release models for different microsponges formulations.
<table>
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<th>Zero Order K (hr⁻¹)</th>
<th>First order R (mg/hr)</th>
<th>First order K (hr⁻¹)</th>
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<th>Higuchi /model K</th>
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Fig. 1 (a-h) SEM photographs of microsponge formulations (drug: eudragit RS-100). The photographs coded ‘A’ represent whole images, ‘B’ represents surface photographs.
Figure 2 SEM photograph of drug: engraved RS-100 microsponges prepared at different stirring rates of (a) 300 rpm, (b) 400 rpm, (c) 500 rpm.
Figure 3 DSC thermogram of Paracetamol, physical mixture of drug & Eudragit RS-100, and FPRS1–FPRS4 microsponge formulations.
Figure 4 FTIR Spectra of Paracetamol physical mixture of drug & Eudragit RS-100, and FPRS1–FPRS4 microsponges formulations
Figure 5 In vitro drug release profile of different formulations of microsponges (FPR51-FPR54)

Figure 6 In vitro drug release profile of drug from different colon specific formulations (CPRS1-CPRS4)