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Research Article

Dicyclomine-loaded Eudragit®-based Microsponge with Potential for Colonic Delivery: Preparation and Characterization

Vikas Jain* and Ranjit Singh

School of Pharmaceutical Sciences, Shobhit University, Meerut, Uttar Pradesh, 250110, India

Abstract

Purpose: *The purpose of this work was to develop a prolonged microsponge drug delivery system containing dicyclomine.*
Methods: *Dicyclomine-loaded, Eudragit-based microsponges were prepared using a quasi-emulsion solvent diffusion method. The compatibility of the drug with formulation components was established by differential scanning calorimetry (DSC) and Fourier transform infra-red (FTIR). Process parameters were modulated to optimise the formulation. Shape and surface morphology of the microsponges were examined using scanning electron microscopy.*
Results: *The results of compatibility tests showed that no chemical interaction or changes took place during preparation of the formulations; furthermore, the drug was stable in all the formulations. In increase in drug:polymer ratio resulted in a reduction in the release rate of the drug from the microsponges. Kinetic analysis showed that the main mechanism of drug release was by Higuchi matrix-controlled diffusion. Drug release was bi-phasic with an initial burst effect with 16 – 30 % of the drug was released in the first hour. Cumulative release for the microsponges over 8 hours ranged from 59 - 86 %.*
Conclusion: *This study presents an approach for the modification of microsponges for prolonged drug release of dicyclomine. The unique compressibility of microsponges can be applied to achieve effective local action since microsponges may be taken up by macrophages present in colon.*

Keywords: *Microsponge; Dicyclomine; Quasi-emulsion solvent diffusion; Eudragit RS-100; Colonic drug release*

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*Corresponding author: **E-mail:** vikasjain11118059@rediffmail.com; **Tel:** +91-1212575724, 9219610427; **Fax:** +91-1212575724*

INTRODUCTION

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface. Moreover, they may enhance stability, reduce side effect and modify drug release favourably [1,2].

Dicyclomine, an anticholinergic drug, has direct smooth muscle relaxant action, and in addition to being a weak anticholinergic, it exerts antispasmodic action. Its plasma half life is 4 - 6 h. Dicyclomine causes gastrointestinal (GI) side effects like other antispasmodic drugs. The present study was designed to formulate a delivery system based on microsponges that would reduce the GI side effects of the drug.

EXPERIMENTAL

Materials

Dicyclomine was purchased from Jackson Laboratories Pvt Ltd, Amritsar, India. Eudragit RS 100 was a gift from Evonic India Pvt Ltd, Mumbai, India while polyvinyl alcohol (PVA, mol weight 30,000 – 70,000) and triethylcitrate were purchased from Sigma-Aldrich, USA. All the chemicals used for analysis were of analytical grade.

Preparation of microsponges

The composition of the microsponge formulations is outlined in Table 1. The microsponges were prepared by quasi-emulsion solvent diffusion method [2,3] using an internal phase that consisted of Eudragit RS-100 (200 mg) and triethylcitrate (1 %v/v) dissolved in 5 ml of dichloromethane. Triethylcitrate (TEC) was then added to enhance the plasticity of the polymer. This was, followed by the addition of dicyclomine with stirring (500 rpm). The mixture was then poured into 0.5 % w/v aqueous solution of polyvinyl alcohol (PVA) which served as the external phase. After 8 h of stirring, microsponges were formed due to the removal of dichloromethane from the system by evaporation. The microsponges were washed with water, filtered and dried at 40 °C for 12 h.

Table 1 Composition of microsponge formulations

Ingredient	Formulation			
	FDRS1	FDRS2	FDRS3	FDRS4
Dicyclomine (mg)	600	1200	1800	2400
Eudragit RS-100 (mg)	200	200	200	200
Triethylcitrate (ml)	1	1	1	1
Dichloromethane (ml)	5	5	5	5
PVA (0.5 % w/v)	0.5	0.5	0.5	0.5

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of dicyclomine, Eudragit RS 100, physical mixture(s) of dicyclomine and Eudragit RS-100, and microsponge formulations having drug:polymer ratios of 3:1, 6:1, 9:1 and 12:1 (FDRS1 – FDRS4) were incorporated in potassium bromide discs and evaluated with a Shimadzu Model 8400 FTIR spectrometer.

Differential scanning calorimetry (DSC)

DSC analysis was carried out on the drug, Eudragit RS 100, physical mixtures of the drug and polymer, and formulations FDRS1-FDRS4, using a Shimadzu DSC-60 Thermal Analyzer. Samples (approximately 2 mg) were placed in aluminum pans and sealed and run at a heating rate of 20 $^{\circ}$C/min over a temperature range 40 - 430 $^{\circ}$C.

Morphology and particle size studies

The morphology and surface characterization of the microsponge formulations were

evaluated by SEM analysis using LEO 430 SEM analyzer after coating the microsponges with gold–palladium under vacuum.

In-vitro dissolution studies

In-vitro dissolution studies were carried out using USP XX1V dissolution assembly (basket type, Electrolab TDT-08L) in 900 ml of 0.1N HCl at a stirring rate of 50 rpm and temperature of 37±0.5 $^{\circ}$C. Initial drug release was monitored for 2 h; thereafter, the dissolution medium was replaced with 900 ml of phosphate buffer (pH 6.8) and drug release monitored for another 6 h. Samples (5 ml) were withdrawn at regular time intervals and sink conditions were maintained by replacing an equal amount of fresh dissolution medium. The samples were analyzed spectrophotometrically (Shimadzu UV-1700) at a wavelength of 420 nm. Dissolution tests were performed in triplicate.

The dissolution data were subjected to various release models, namely, Zero order, First order, Higuchi and Korsmeyar-Peppas

Statistical analysis

The data obtained from each experiment were subjected to statistical analysis by Student t-test and one-way analysis of variance (ANOVA) using Graph Pad Instat software. $P < 0.05$ was considered to be indicative of significance.

RESULTS

Effect of stirring rate on microsponge

The effect of stirring rate on the size of microsponges was studied. As the stirring speed was increased, microsponges of smaller size were obtained, as shown in Table 2. When the rate of stirring was increased from 300 to 500 rpm, the mean particle size decreased from 67.23±4.45 to 60.25±5.67 μm but this was not statistically significant.

Effect of volume of internal phase on microsponges

It was observed that when the volume of internal phase (dichloromethane) was increased from 5 to 10 ml, microsponges were not formed. Good microsponges were produced only when 3 to 5 ml of internal phase was used.

Effect of amount of emulsifying agent on microsponge

Increase in the amount of PVA (emulsifying agent) incorporated in the microsponges decreased production yield and increased the particle size.

Effect of drug/polymer ratio on microsponges

The microsponges were spherical and uniform with no drug crystal on the surface, as shown in Figure 1. Drug/polymer ratio had an effect on the morphology and size of microsponges with increase in drug:polymer ratio leading to a decrease in particle size. The mean particle diameters for the drug/polymer ratios of 3:1 and 12:1 were 60.25±5.67 μm and 43.66±6.20 μm, respectively (see Table 2).

The production yield, actual drug content, encapsulation efficiency, and mean particle size of the microsponge formulations were 70 – 77 %, 62 – 80 %, 81 – 88 %, and 44 - 60 μm, respectively, as given in Table 2. On subjecting the data obtained for production yield, actual drug content, and encapsulation efficiency to statistical analysis, no significant difference was observed amongst the formulations ($p < 0.05$).

Characterization of microsponges

Analysis of the FTIR spectra (see Fig 2) of the drug (dicyclomine), physical mixture of drug and Eudragit RS-100, and formulations FDRS1–FDRS4 indicate a characteristic C=O stretching band at 1716.53 cm^{-1} for the drug,
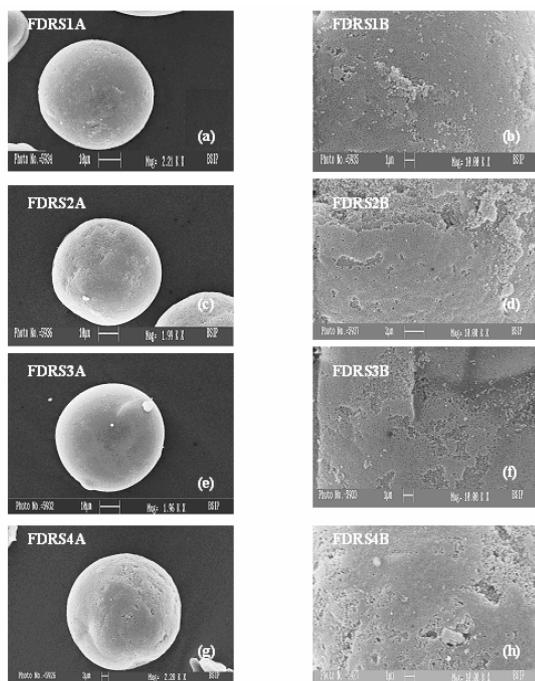
Figure 1: SEM of microsponge formulations. (**Note:** Photographs in the left column represent whole images of microsponge while those in the right column show their surface morphology; FDRS1, FDRS2, FDRS3 and FDRS4 denote formulations with drug to polymer ratios of 3:1, 6:1, 9:1, and 12:1, respectively).

and an ester C=O stretching peak around 1726.17 cm^{-1} for Eudragit RS 100, as has also been reported in the literature for this acrylate polymer [2]. All the characteristic peaks of dicyclomine were observed in the spectra of all the microsponges (FDRS1 – FDRS 4), thus indicating that no chemical interaction or changes took place during the preparation of the formulations and that the drug was stable in all the formulations.

In the DSC studies (see Fig 2), the thermogram of the drug alone showed a sharp endothermic peak at 175.97 °C which corresponds to the melting point of drug in the crystalline form. In each of the DSC thermograms of the physical mixture of drug and polymer, and microsponge formulations FDRS1 – FDRS4, respectively, the characteristic endothermic peak of the drug was also observed, thus indicating that there was compatibility between the drug and polymers used.

In vitro drug release

The release profiles obtained for the microsponge formulations are presented in Figure 4. The profiles showed a bi-phasic release with an initial burst effect. In the first hour, about 16 – 30 % of the drug was released. Cumulative release for the mocrosponges after 8 h ranged from 59 - 86 %. Drug release from the formulations decreased with increase in the amount of polymer in the microsponges.

Table 2: Production yield, drug content, encapsulation efficiency, and mean particle size of the microsponge formulations (±SD, n=3)

Formulation	Drug: polymer ratio	Production yield (%) ± S.D	Theoretical Drug Content (%)	Actual drug content **(%) ± S.D.**	Encapsulation efficiency (% ± S.D.)	Mean particle size (µm) ± S.D.
FDRS1	3:1	79.01±0.57	75.0	62.05±0.01	82.73±0.45	60.25±5.67
FDRS2	6:1	70.65±0.28	85.7	70.12±0.01	81.91±0.04	53.62±7.11
FDRS3	9:1	76.60±0.56	90.0	75.32±0.08	83.68±0.23	49.34±6.45
FDRS4	12:1	70.48±0.78	92.3	80.69±0.03	87.42±0.56	43.66±6.20

* FDRS1, FDRS2, FDRS3 and FDRS4 denote microsponge formulations with drug to polymer ratios of 3:1, 6:1, 9:1, and 12:1, respectively.
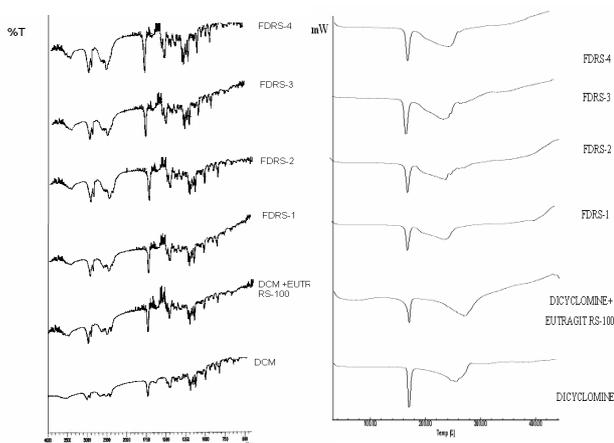
Figure 2: FTIR spectra (left) and DSC thermograms (right) of dicyclomine (DCM), physical mixture of DCM & Eudragit RS-100, and microsponge formulations (FDRS 1 – 4).
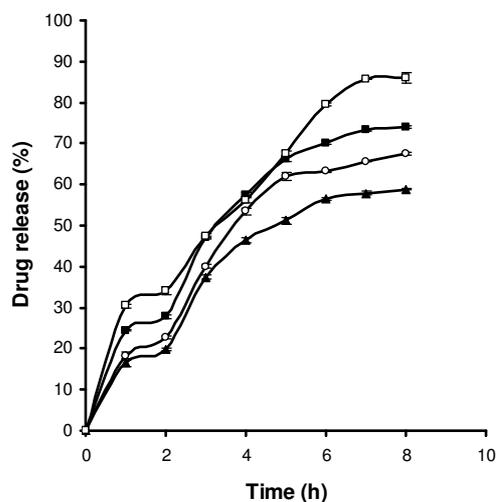
Figure 4: *In vitro* drug release profile of microsponge formulations.

[▲ = FDRS1(3:1); ○ = FDRS2 (6:1); ■ = FDRS3 (9:1); □ = FDRS4 (12:1)]

Table 3: Kinetic data from *in vitro* drug release models for the microsponge formulations

Code	Zero order		First order		Higuchi		Korsmeyar-Peppas	
	R	K (mg/h)	R	K (h^{-1})	R	K ($mg/h^{-1/2}$)	R	'n'
FDRS1								0.7476
	0.9538	7.4595	0.9748	0.1181	0.9783	23.322	0.9389	
FDRS2	0.9529	8.587	0.9745	0.1506	0.9755	26.796	0.9436	0.7596
FDRS3	0.9520	9.1038	0.9835	0.1787	0.9847	28.706	0.9540	0.6825
FDRS4	0.9733	10.351	0.9854	0.2575	0.9884	32.043	0.9932	0.6989

DISCUSSION

The quasi-emulsion solvent diffusion method used for the preparation of the microsponges was simple, reproducible, and rapid. Furthermore, it was observed that as drug:polymer ratio increased, particle size decreased. This is probably due to the fact that at higher relative drug content, the amount of polymer available per microsponge to encapsulate the drug becomes less, thus reducing the thickness of the polymer wall and hence, smaller microsponges [4]. The smaller size of microsponges obtained at

higher stirring rate may be attributed to better dispersion at higher stirring rates [2].

Failure to form microsponges on increasing the volume of internal phase from 5 to 10 ml may be due to incomplete removal of internal phase solvent with the result that the droplets could not solidify as most of the internal phase remained in the droplets [5]. This warrants the use of internal phase solvent in an appropriate amount to ensure the formation of quasi emulsion droplets, and solidification of the drug and polymer thereafter. Increase in the amount of emulsifying agent resulted in decreased

production yield. This may be due to the development of some hydrophobic regions which probably dissolved some of the drug and polymer. Furthermore, the increase in microsponge particle size as the amount of emulsifying agent increased could be due to increased viscosity leading to larger droplets which, in turn, resulted in larger microsponges [1].

On analysing the *in vitro* dissolution data with various release models, the highest regression coefficient showing the best fit was found for the Higuchi model. The n value for Peppas model was between 0.5 and 1.0 which is indicative of non-Fickian diffusion. Statistical analysis using ANOVA yielded a p-value of 0.5930 for all the formulations, thus indicating that there was no significant difference among them.

CONCLUSION

This study presents an approach for the production of dicyclomine microsponges with prolonged release characteristics. The unique compressibility of microsponges offers an alternative way for producing mechanically strong tablets. This is significant since colon-specific tablets based on microsponges could provide effective local action, since microsponges can be taken up by macrophages present in colon.

ACKNOWLEDGMENT

REFERENCES

1. Jelvehgari M, Siahi-Shadbad MR, Azarmi S. The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies. Int J Pharm 2006; 308:124-132.
2. Orlu M, Cevher E, Araman A. Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. Int J Pharm 2006; 318: 103-117.
3. Omo˘glu CT, G¨on¨ul N, Baykara, T. Preparation and in vitro evaluation of modified release ketoprofen microsponges. Il Farmaco 2003; 58:101–106.
4. Nokhodchi A, Jelvehgari M, Siahi MR. Factors affecting the morphology of benzoyl peroxide microsponges. Micron 2007; 38: 834–840.
5. Yang M, Cui F, You B. Preparation of sustained-release nitrendipine microspheres with Eudragit RS and Aerosil using quasi-emulsion solvent diffusion method. Int J Pharm 2003; 259: 103-113.