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Formulation And Evaluation Of Microsponges For Topical Drug Delivery Of Mupirocin

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Abstract: Impetigo is a chronic, contagious bacterial skin infection caused by *Staphylococcus aureus, Streptococcus pyogenes* or both and usually treated with systemic antibiotics. Mupirocin is a medium potency, synthetic, topical antibacterial agent used in the treatment of impetigo. Percutaneous absorption is a risk associated with topically administered formulations. Controlled release of the drug to the skin could reduce the side effects while reducing percutaneous absorption. Therefore, the aim of the study was to produce mupirocin entrapped microsponges to control the release of the drug to the skin. Mupirocin microsponges were prepared using an emulsion solvent diffusion method. In order to optimize the microsponge formulation, factors affecting the physical properties of microsponges were determined. FT-IR and SEM was used to study the shape and morphology of microsponges. Mupirocin microsponges were then incorporated into a vanishing cream base for release studies. It was shown that the drug: polymer ratio, stirring rate, volume of external and internal phase influenced the particle size and drug release behavior of microsponges.

The results showed that an increase in the ratio of the drug: polymer resulted in a reduction in the release rate of Mupirocin from microsponges. Kinetic analysis showed that the main mechanism of drug release was by Higuchi matrix- controlled diffusion.

Keywords: Microsponges, Mupirocin, Eudragit [RS100], Quasi-emulsion solvent diffusion, Topical drug delivery.

1. Introduction:

Microsponges are polymeric drug 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 enhance stability, reduce side effects and modify drug release[1, 2].

Impetigo is a primary superficial bacterial skin infection, initially vesicular or bullous, and later crusted. It is caused by *Staphylococcus aureus*, *Streptococcus pyogenes* or both. Two types of impetigo are Non-bullous impetigo and Bullous impetigo[3]. The most widely used topical agents in the management of patients suffering from impetigo are highly contagious and are usually treated with systemic antibiotics[4]. Mupirocin (MUP) is a medium potency, synthetic, non-fluorinated antibiotic used in the topical treatment of impetigo[5]. Mupirocin strongly inhibits protein and RNA synthesis in *staphylococcus aureus* while DNA and cell wall formation were also negatively impacted to a lesser degree. The inhibition of RNA synthesis was shown to be a protective mechanism in response to a lack of one amino acid, isoleucine. *In vivo* studies in *Escherichia coli* demonstrated that pseudomonic acid inhibits isoleucine t-RNA synthetase (IleRS) [6].

The percutaneous absorption increases risk associated with systemic absorption of topically applied formulation. Controlled release of mupirocin from delivery system to the skin could reduce the side effects by reducing percutaneous absorption[7]. The present study was designed to formulate a delivery system based on microsponges that would reduce the side effects of the drug.

2. Materials And Methods:

2.1 Materials:

Mupirocin sample was gifted by Micro labs Pvt Ltd, Eudragit RS100 was a gift sample obtained from Roehm Pharma Polymers (Degussa), Poly vinyl alcohol from Loba chemie, Bangalore. All the chemicals used for analysis were of analytical grade.

2.2 Preparation of microsponges

The microsponges were prepared by quasi-emulsion solvent diffusion method[8, 9]. The internal phase consists of eudragit RS100 dissolved in 20 ml of dichloromethane: ethanol (1:1) under sonication. This was followed by addition of MUP with stirring. The surfactant PVA (0.75%) was weighed accurately and dissolved in 90 ml of distilled water at 60˚C. The surfactant mixture was allowed to cool to room temperature. The internal phase containing mupirocin and eudragit polymer was added drop wise with stirring at 1500 rpm. After 10 hours of stirring, microsponges were formed due to the removal of solvent from the system by evaporation. The microsponges were washed with water, filtered and dried overnight at room temperature. For the evaluation of the effect of drug: polymer ratio on the physical characteristics of microsponges, seven different ratios of the drug to eudragit RS100 (1:1, 2:1, 4:1, 6:1, 8:1, 10:1,12:1, and 14:1) were employed.

2.3 Compatibility studies:

FT-IR spectra of Mupirocin, eudragit RS100, physical mixtures of mupirocin and eudragit polymer were incorporated in KBr discs and evaluated with a Shimadzu model FT-IR Spectrometer for their compatibility.

2.4 Evaluation of prepared microspheres:

2.4.1 Determination of production yield and loading efficiency

The production yield of the microparticles was determined by calculating accurately the weight of raw materials and the weight of microsponge obtained[10] . The loading efficiency (%) was calculated according to the following equation.

$$\textbf{Loading efficiency} = \frac{Actual\ MUP\ content\ in\ microsponges}{Theoretical\ MUP\ content}$$

2.4.2 Drug content

Microsponges equivalent to 100mg of MUP were dissolved and made up to the mark in 100ml volumetric flask with methanol[11,12]. Further 10ml was diluted to 100ml with methanol and final dilutions were made using methanol to get a concentration within beer's range of 4-32µg/ml. The absorbance was measured spectrophotometrically at 222 nm using blank microsponges treated in the same manner as sample.

2.4.3 Morphology and particle size studies

The morphology and surface characterization of the microsponge formulation were evaluated by SEM analysis using JSM 840A SEM analyser after the sample had been gold sputtered coated with 25nm gold film thickness[13, 14].

2.4.4 In vitro dissolution studies

In vitro dissolution studies were carried out using USPXXI dissolution assembly (basket type) in 900 ml of pH7.4 saline phosphate buffer solution at $37^0 \pm 5$˚C and rotated at 50 rpm. Specified amount of aliquots were withdrawn at hourly intervals up to 8h. The samples were assayed at 222 nm[15].

2.4.5 Stability studies

The stability studies are carried out according to guidelines given by International Council of Harmonization (ICH guidelines). In view of the potential utility of coated, uncoated & Ethyl cellulose microsponge formulation, stability studies were carried out[16]. The formulation was tested for stability at $5^0 \pm 2^0$ C, $25^0 \pm 2\ ^0$C/ 60±5 RH, $40^0 \pm 2^0$ C/ 75±5 RH. Formulations were stored in glass bottles/vials and were evaluated after 15, 30, 45 days.

3. Results and discussion

3.1 Effect of drug polymer ratio on the physical properties of microsponges

Free flowing powder particles of microsponges were obtained by quasi-emulsion solvent diffusion method with eudragit RS100. The method seems to be promising for the preparation of MUP microsponges. The encapsulation efficiency and production yield increased with increase in drug: polymer ratio. The mean particle size ranged from 365 to 251.7µm when the drug: polymer ratio was increased from 1:1 to 14:1. The results are shown in the table no 1.

3.2 Production yield, loading efficiency and particle size analysis

The production yield, loading efficiency and mean particle size of MUP microsponge formulation are given in table no.1. It was found that production yield and loading efficiency increased with increase in the drug: polymer ratio. But the mean particle size decreased.

3.3 Characterization of microsponges

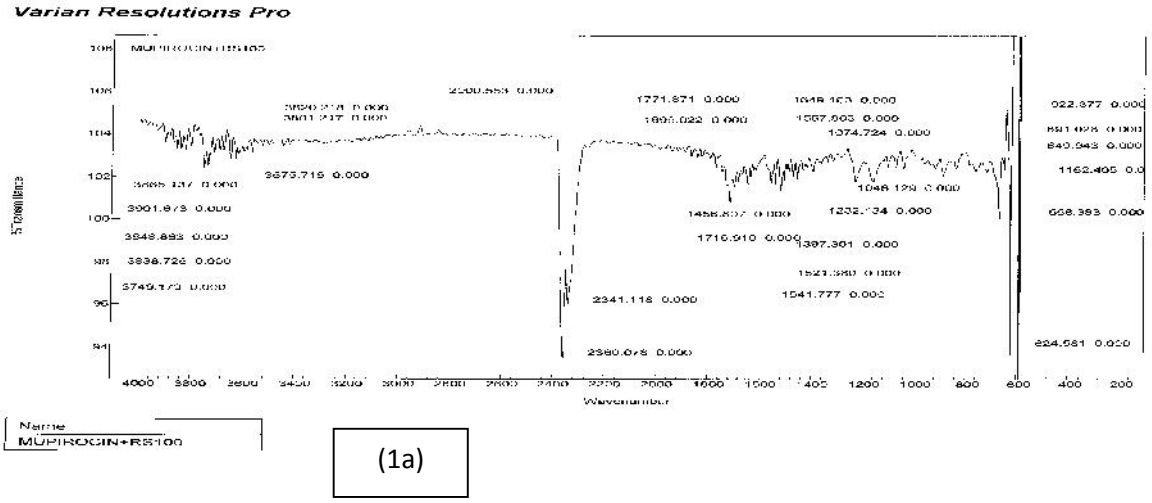
Analysis of FT-IR Spectra revealed that the peaks of pure drug and formulation were found to be identical, indicating that the drug remained in its original form without any modification when formulated as microsponge and also shows that there was no significant interaction between drug and polymer used. The spectra are shown in figure no 1.

3.4 In vitro drug release

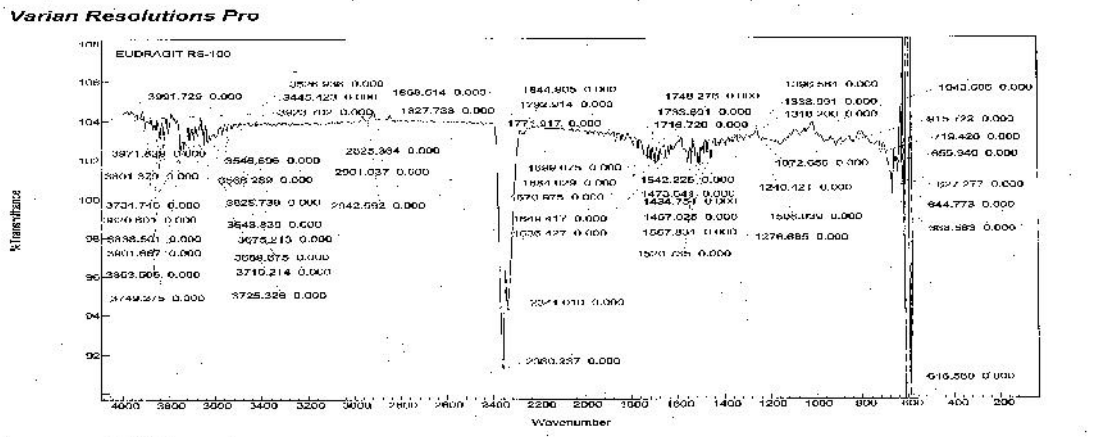
The release profiles obtained for the microsponge formulations are presented in figure no 4. The profiles showed a biphasic release with an initial burst effect, and then continuous drug release effect. In the first hour, about 27- 36% of the drug was released. Cumulative release from microsponge after 8h ranged from 62-95% and is shown in fig no 2.

Table 1: Effect of different Drug: polymer ratios on microsponge properties and the drug release from the formulations

Formulation codes	Drug:polymer ratio	Production yield %	Loading efficiency %	Mean particle size	Drug content %	% CDR
MS1	1:1	35.52	28.70	365	35.01	98.06
MS2	2:1	46.26	49.71	352.77	57.39	96.57
MS3	4:1	54.62	62.06	336.05	70.03	94.63
MS4	6:1	64.17	65.27	333.54	71.98	90.16
MS5	8:1	72.41	75.58	326.12	80.73	89.26
MS6	10:1	76.18	82.88	308.62	86.57	85.55
MS7	12:1	82.34	89.10	284.25	91.43	82.09
MS8	14:1	88.28	88.23	251.7	93.58	79.17



(1a)



(1b)

Fig no: 01: FT-IR Graphs Of (1a) Mupirocin+RS100 (1b) Eudragit+RS100

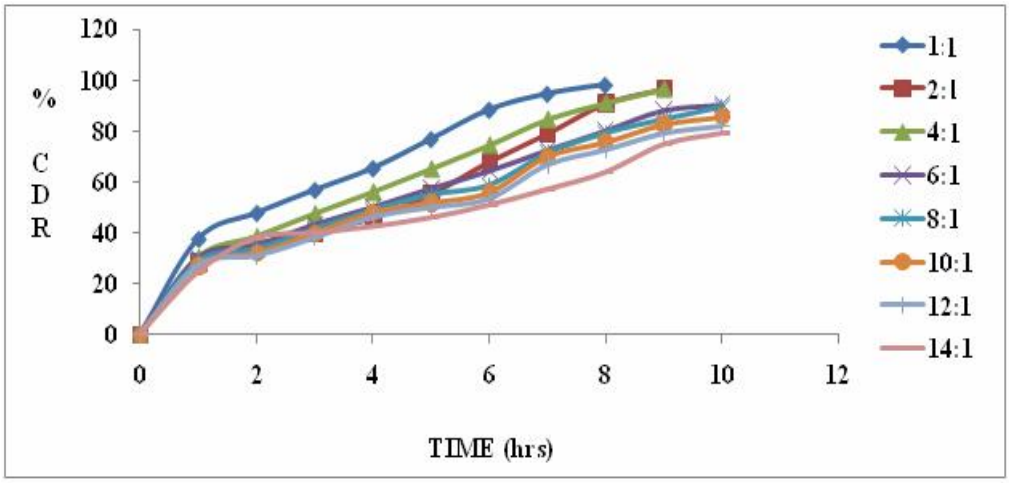
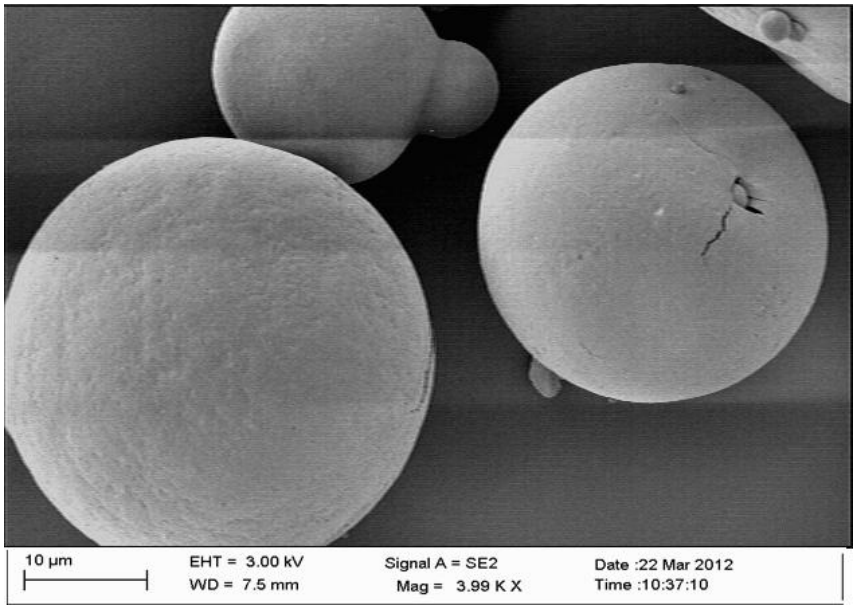
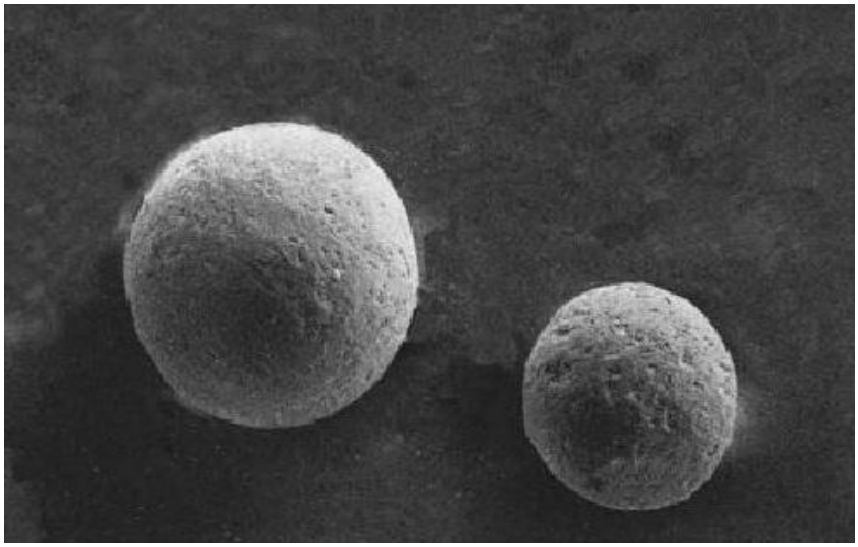


Fig no: 02: Cumulative % Drug Release for MUP: ERS100 Microsponge Formulations

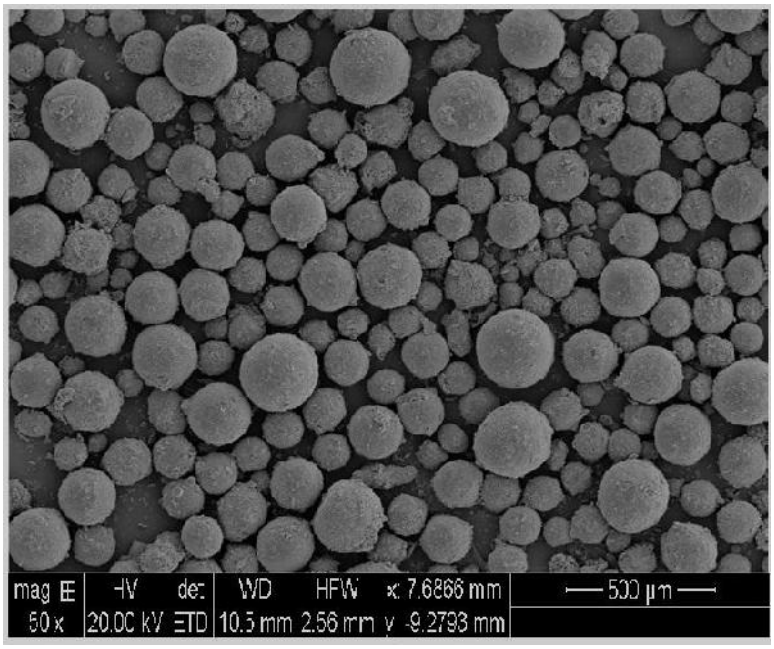
SEM PHOTOGRAPHS:



(Fig no: 03)



(Fig no: 04)



(Fig no: 05)

SEM photo of MUP: ERS 100 ratios as following:

Fig no: 03) 6:1
Fig no: 04) 8:1 and
Fig no: 05) 10:1

4. Conclusion:

Quasi –emulsion solvent diffusion seems to be a promising method for the preparation of MUP microsponges as it is a rapid, easy, reproducible method and has an advantage of avoiding solvent toxicity. In this method there is formation of quasi-emulsion droplets. The rapid diffusion of solvent into the aqueous medium might reduce the solubility of polymer in the droplets, since the polymer is insoluble in water. The instant mixing of the ethanol and water at the interface of the droplets induce precipitation of the polymer thus forming a shell enclosing the solvent and dissolved drug. Counter diffusion of solvent and water through the shell promotes further crystallization of the drug in the droplets of the polymer from the interior core. The finely dispersed droplets of the polymer solution of the drug were solidified in the aqueous phase via diffusion of solvent[17].

Furthermore, from SEM photography (fig no: 03, 04& 05) 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[18]. From FT-IR studies (fig no: 1A & 1B) we can conclude that there is no incompatibility between drug and polymers used.

The drug release profile of the microsponge formulation showed that cumulative percent drug release was maximum in the 1st hour for all formulations. Burst release was observed (fig no: 02) which could be due to the surface adsorbed drug and porous nature of microsponges which provides a channel for the release of the drug[19].

5. Acknowledgment:

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6. References:

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