JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

PREPARATION AND EVALUATION OF CONTROLLED RELEASE MICROSPHERE OF CLOBETASOL PROPIONATE

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ABSTRACT

We aim to develop a new topical delivery system in order to provide the prolonged release of Predinisolone and to reduce systemic absorption and side effects of the drug. Predinisolone loaded Eudragit microspheres were prepared by 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 formulations were subjected to *in vitro* release studies and the results were evaluated kinetically and statically. The *in vitro* release data showed a biphasic pattern with an initial burst effect. In the first hour drug release from microsponges was found to be between 15.1±0.56 to 20.37±0.41 %. The cumulative percent release at the end of 8th hour was noted to be between 52.22± 2.32 to 59.32± 2.01%. The release kinetics showed that the data followed Higuchi

model and the main mechanism of drug release was diffusion. All the result showed that prepared microsponge is a potential vehicle for improved topical delivery of Predinisolone for better treatment of skin disease.

KEY WORDS: Microsponge, emulsion solvent diffusion, predinisolone, Eudragit.

1. INTRODUCTION

Now a day the major challenge to the pharmaceutical industry is to control the delivery rate of active pharmaceutical ingredient to a pre-determined site in human body. So researcher focused on designing different controlled release drug delivery systems to improve efficacy and patient compliance[1]. Topical formulations are most useful drug delivery systems for both local and systemic treatment. Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is an area of research that has only recently been addressed with success. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis[2]. Application of topical drugs suffers many problems such as ointments, which are often aesthetically unappealing, greasiness, stickiness etc. That often results into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles. Thus the need exists for system to maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body. The microsponge delivery system fulfils these requirements[3]. Microsponge delivery system comprised of a polymeric bead having network of pores with an active ingredient held within was developed to provide controlled release of the active ingredients whose final target is skin itself. The system was employed for the improvement of performance of topically applied drugs. The incorporation of the active substance at its maximum thermodynamic activity in an optimized vehicle facilitates the reduction of the resistance to the diffusion of the stratum corneum. Microsponges consisting of noncollapsible structures with porous surface through which active ingredients are released in a controlled manner[4].

Predinisolone is a highly lipophilic corticosteroid used for the treatment of skin disorders such as psoriasis. Corticosteroid has been used extensively in topical therapy for the treatment of mild to moderate psoriasis. Their clinical effectiveness in the treatment of psoriasis is related to their vasoconstrictive, anti-inflammatory, immunosuppressive, and anti proliferative effects[5, 6].

2. MATERIALS AND METHODS

2.1 Materials

Eudragit RS100 was kindly provided by Evonik Industries (Mumbai, India) and Predinisolone were purchased from Shalkash Pharmaceuticals (New Delhi, India) and Ethyl acetate, Polyvinyl Alcohol (PVA), Glycerin were purchased from Loba chemie Pvt. Ltd. (Mumbai, India).

2.2 Compatibility studies

Predinisolone and Eudragit RS100 and their physical mixture were examined by Fourier Transform Infrared (FT-IR) spectra. The spectra were recorded in a Shimadzu 8400S FT-IR spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions[7].

2.3 Preparation of Microsponge

Predinisolone microsponge was prepared by emulsion solvent diffusion method. The organic internal phase containing drug and Eudragit RS100 in Ethyl acetate was gradually added in external phase, which contained PVA as emulsifying agent. The mixture was stirred at 500-1500 rpm for 3hr at room temperature to remove ethyl acetate from the reaction flask. The formed microsponge was filtered, washed with distilled water, and dried at room temperature[8,9].

3. Characterization of microsponges

3.1 Surface morphology

Surface morphology of microsponge was performed by Scanning Electron Microscopy (SEM) AIIMS, New Delhi. Appropriate samples of microsponge were mounted on metal stubs, using double-sided adhesive taps. Samples were gold coated and observed for morphology and size, at acceleration voltage of 15 KV.

3.2 Particle size determination

The size and zeta potential of microsponge is useful for assessment of physical stability of dispersion. The size and zeta potential of different of microsponges were measured by using Malvern Zetasizer.

3.3 Determination of Entrapment efficiency[10]

Entrapment efficiency determined by 20 mg of microsponge was dispersed in 10 ml solvent methanol followed by agitation with a magnetic stirrer for about 30 min to dissolve the polymer and to extract the drug. After filtration, the drug concentration in the methanol phase was determined by taking absorbance of the solution spectrophotometrically at 255nm. Entrapment efficiency values for all microsphere formulations were calculated according to the equations given below

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Weight of drug in microspheres} \times 100}{\text{Weight of fed drug}}$$

3.4 Production yield

The production yield of the microsponges can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained. The Production yield of the microsponges can be calculated according to the following equation:

$$\text{Production Yield} = \frac{\text{Practical mass of microsponges X 100}}{\text{Theoretical mass (Polymer + drug)}}$$

3.5 *In Vitro* Drug Release[11]

An in-vitro release study was carried out in Franz diffusion cell using treated Semi permeable membrane in between donor and receiver compartment. The normal surface of the Franz diffusion cells which were used was 5.53 cm2 and receiver compartment had a capacity of approximately 100 ml. In this drug release studies Semi permeable membranes were mounted in Franz diffusion cells and the membrane surface dosed with 1gm Predinisoloneloaded microsponge. Receptor fluid composed of Methanol/Phosphate buffer pH 6.2 (8:2) was added to the cell and temperature maintained at 37 °C ± 10C. The dissolution medium was stirred at 50-100 rpm speed using Teflon coated magnetic bead. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of 1, 2, 3, 4, 5, 6, 7, and 8 hour and replaced by an equal volume of the receptor medium. The aliquots were analyzed by UV spectrophotometer at 240 nm using Methanol/ Phosphate buffer pH 6.2 as blank. Absorbance of these samples was measured at λmax 240 nm using UV. Cumulative percentage drug release was calculated using an equation obtained from the standard curve.

4. Result and discussion

4.1 Compatibility studies

The FTIR spectrum of Predinisolone, Eudragit RS100 and mixture Predinisolone with Eudragit RS100 are shown in Fig. 1, 2 & 3. The peak at 3300.94 cm-1for C-H Alkynes stretching, 2943.17 cm-1 for C-H Alkanes stretching, 2362.64 cm-1for O-H (hydroxyl) stretching, 1731.96 cm-1 for C=O (carbonyl) stretching, 1661.56 cm-1 for C=C Alkenes stretching, 888.16 cm-1 for -C-H Alkenes stretching (Table 1). These are the major peaks of the Predinisolone. All this peaks are almost same in the spectra of mixture Predinisolone with Eudragit RS100 and thus this conform that the drug did not interact to the polymer.

4.2 Characterization of microsponges

4.2.1 Surface morphology

The microsponges of Predinisolone with Eudragit RS100 were smooth, porous, grossly, discrete spherical. Scanning electron photomicrographs of the formulation CE-6 are shown in Figure 4.

4.2.2 Particle size

The size and zeta potential of microsponge is useful for assessment of physical stability 0f dispersion. The size and zeta potential of different of microsponges were measured by using Malvern Zeta seizer which are as show in Fig. 5 and Table 2. The mean particle size for the formulation CE1 to CE6 was to be found in range 61.12 to 78.72 µm. Minimum particle size (61.12 µm) is found with formulation CE-6. Drug/polymer ratio had an effect on the morphology and size of microsponges, with increase in drug: polymer ratio and stirring speed decrease in particle size.

4.2.3 Determination of Entrapment efficiency

The entrapment efficiency of predinisolone microsponges are given in Table 2. Entrapment efficiency is varied by changing the ratio of drug and polymer. Entrapment efficiency of different formulation CE1 to CE6 was calculated and the entrapment efficiency was found in range 58.70%- 89.18%. Maximum Entrapment efficiency (89.18%) is found with formulation CE-6. It was found that Entrapment efficiency increases with increase in drug: polymer ratio.

4.2.3 Production yield

The Production yield of predinisolone microsponges are given in Table 2. Production yield is also varied by changing the drug polymer ratio and stirring speed. Maximum Production yield is achieved with the formulation CE-6 that is 79%.

4.2.4 *In Vitro* Drug Release

The drug release profiles of the microsponge formulations are shown in Figure 6 and Table 3. *In-vitro* release study was carried out for 8th hour with all six microsponges' formulations. Drug release of all formulations in ascending order is CE-1> CE-5> CE-3 > CE-2 >CE-4> CE-6>. Among all microsponge formulations CE-1 having highest drug release at 8th hour, i.e. 59.32± 2.01%. Formulation CE-1 having lowest drug release at 8th hour, i.e. 52.22± 2.32 % which show the sustained release of the formulation. *In vitro* drug release profile of the formulations was carried out using Franz diffusion cell. Formulation CE-1, CE-2, CE-3, CE-4, CE-5, CE-6 show drug release of 59.32± 2.01, 53.4± 2.09, 55.45± 2.31, 53.25± 2.32, 59.11± 2.24 and 52.22± 2.32, respectively at 8 hr. This data shows that microsponge slowed down the release of drug from the formulation.

5. Conclusion

Microsponge based novel delivery system has been developed to provide topical delivery of Predinisolone. The formulations showed controlled release of drug through skin, indicating better potential of delivery system. If this process can be scaled-up to manufacturing level; this technology has the potential to provide the topical Predinisolone microsponge with better patient compliance. On the grounds of efficacy and improved patient compliance due to reduced frequency of application, microsponge formulations will have significantly better role in treatment of skin disease.

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