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FORMULATION, OPTIMIZATION, DEVELOPMENT AND EVALUATION OF MICROSPONGE GEL OF FLUCONAZOLE

Rakesh Kumar*, Monu Kumar, Babita, Nidhi Saini, Neelam Kumari, Rakesh Kumar

1. Institute of Pharmaceutical Sciences, Kurukshetra University, India, Kurukshetra-136119
2. Dept. of Pharmacy, RPIIT, India, Karnal-132114
3. Dept. of Pharmaceutical Sciences and Research, BMU, India, Rohtak-124021
4. Institute of Pharmaceutical Sciences, Kurukshetra University, India, Kurukshetra-136119
5. Jan Nayak CH. Devi lal Memorial College of Pharmacy, Sirsa, 125055
6. Dept. of Pharmacy, Annamalai Nagar, Chidambaram, Tamil Nadu 608002

ABSTRACT

Aim: The aim of present investigation was to optimization, development & In vitro evaluation ethyl cellulose and Xanthan Gum containing topical microsponge gel of Fluconazole drug. The microsponges were prepared by the Xanthan gum facilitated W/O/W emulsion solvent evaporation technique. The controlled drug delivery potential of these microsponges was investigated following their incorporation into a carbopol gel base to enhance of solubility & permeation of Fluconazole. It is also helpful to reduce oral related side effect, taste and odour masking of drug. It is also protect the drug against the environment (moisture, light and oxidation). It is also decrease the side effects of drug and reduce the dose frequency so improve the bioavailability & relative stability of drug.

Study Design: The microsponges were prepared by the Xanthan gum facilitated W/O/W emulsion solvent evaporation technique. A hundred milligrams of drug were dissolved in 2 ml of acetone then 8 ml of doubly distilled water was added to the solution.. Xanthan gum was dispersed slowly into the acetone/water mixture to obtain a concentration of 0.2 % (m/V). Up to 40–50 % of acetone can be added to an aqueous solution of Xanthan gum preventing precipitation of the gum. This internal aqueous phase was emulsified into a 25 ml 1 % (m/V) solution of ethyl cellulose in dichloromethane containing 0.5 % (m/V) Span 80 using a Mechanical Stirrer for 5 min at 2000 rpm. The resulting water-in-oil (W/O) emulsion was then transferred into 60 ml of water containing 0.6 % (m/V) Tween 80 under continuous mechanical stirring at 1300 rpm to form a W/O/W type emulsion. A continuous stirring with a three- -blade propeller for 1.5 h to allow evaporation of the organic solvent and resulting microsponges were separated by filtration and finally air-dried.

INTRODUCTION

However, TDS is not practical for delivery of materials whose final target is the skin itself. To maximize the period that an active ingredient is present, either on the skin surface or within the epidermis while lowering its transdermal penetration into the body controlled mechanism is needed. Some limitations associated with topical delivery of drugs are uncontrolled evaporation of the drug moiety, unpleasant odour, lack of patient compliance as vehicles may be greasy, sticky and may cause discolorations .1,2 Carrier technology like Microparticles and nanoparticles are the novel solution to these limitations. Microspheres, liposomes, and nanoparticles etc. are some examples which dramatically alter the absorption and release kinetics of the drug. Microspheres control the release rate of drug after outer wall is ruptured by some carrier.3 Microsponge delivery system consists of a polymeric bead with a network of pores with an active ingredient held within was developed to control the release of drugs whose final destiny is the skin itself. The common method for formulation is the incorporation of the active ingredients at its maximum thermodynamic activity in an optimized vehicle and the reduction of the resistance to diffusion from the stratum corneum. Microsponge consists of noncollapsible structures with a porous surface through which active Ingredients are released in a controlled manner. Depending upon the size, the total pore length may range up to 10 feet and pore volume up to 1 ml/g. Microsponges are porous microspheres having interconnected voids of particle size range 5-300µ m. Their characteristic feature of microsponges is the capacity to absorb or "load" a high degree of active constituents into the particle and on to its surface. Active payload in the formulation is protected by the Microsponge particle and delivered to the skin via controlled diffusion. Microsponges are microscopic spherical shaped particles, capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Microsponge possesses the versatility to load a wide range of actives particles providing the benefits of enhanced efficacy, tolerability to a wide range of skin therapies 10. MDS technology is now a days used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products.4,5

Materials and method

Materials

Fluconazole was obtained from heliox pharma, Span-80, Tween-80, Acetone, Triethanolamine were obtained from Thomas baker pvt. Ltd. Mumbai, Xanthamgum obtained from Arihant trading co. Mumbai, Ethyl cellulose, Sodium hydroxide, Potassium dihydrogen, Phosphate were obtained from CDH, Octanol-1 was obtained from Finar chemicals ltd, Ahmadabad and Carbapol 980-NF was obtained from Lubrizol advanced material Europe BVBA.

Methods of Formulation of microsponges

Method: Modified multiple emulsion technique

The microsponges were prepared by the Xanthan gum facilitated W/O/W emulsion solvent evaporation technique. A hundred milligrams of drug were dissolved in 2 ml of acetone then 8 ml of doubly distilled water was added to the solution.. Xanthan gum was dispersed slowly into the acetone/water mixture to obtain a concentration of 0.2 % (m/V). Up to 40–50 % of acetone can be added to an aqueous solution of Xanthan gum preventing precipitation of the gum. For this reason, Xanthan gum was used in this novel process. This internal aqueous phase was emulsified into a 25 ml 1 % (m/V) solution of ethyl cellulose in dichloromethane containing 0.5 % (m/V) Span 80 using a Mechanical Stirrer for 5 min at 2000 rpm. The resulting water-in-oil (W/O) emulsion was then transferred into 60 ml of water containing 0.6 % (m/V) Tween 80 under continuous mechanical stirring at 1300 rpm to form a W/O/W type emulsion. The stirring was continuous with a three- -blade propeller for a period of 1.5 h to allow evaporation of the organic solvent. The resulting microsponges were separated by filtration and finally air-dried. Composition of different microsponges were given in a table no 1

Table no 1: Composition of Different Fluconazole microsponge

S.no.	Formulation code	Xanthum gum (% w/v)	Ethyl cellulose (%w/v)	Acetone: water	Stirring time
1	F1	0.2	-	2:8	1.5 hr
2	F2	-	1%	2:8	1.5 hr
3	F3	0.2	0.5 %	2:8	1.5 hr
4	F4	0.2	1%	2:8	1.5 hr
5	F5	0.2	1.5 %	2:8	1.5 hr
6	F6	0.2	2 %	2:8	1.5 hr
7	F7	0.2	2.5 %	2:8	1.5 hr
8	F8	0.2	3%	2:8	1.5 hr
9	F9	0.2	4%	2:8	1.5 hr
10	F10	0.2	2 %	1:9	1.5 hr
11	F11	0.2	2%	3:7	1.5 hr
12	F12	0.2	2%	4:6	1.5 hr
13	F13	0.2	2%	5:5	1.5 hr
14	F14	0.2	2%	3:7	1hr
15	F15	0.2	2%	3:7	2hr
16	F16	0.2	2%	3:7	2.5hr
17	F17	0.2	2%	3:7	3 hr

Method of Formulation of microsponge based Topical gel

After optimization of microsponge based gel the final formulation was prepared for optimization .For the preparation of microsponge based gel 1% of carbopol was dispersed in sufficient amount of water kept in dark overnight. This swelled carbopol 980 NF was then neutralised by using triethonalamine i.e. adjusting pH at 7. After this the prepared microsponge was added to the swelled carbopol followed 1% propylene glycol. Carbopol 980 NF was stirred by using mechanical stirrer. The microsponge based gel was thus formed.

Qualitative and Quantitative Evaluation:

Evaluation of formulated Microsponges

1. **Production yield:**

$$\text{Production yield} = \frac{\text{Practical mass of microsponges}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

2. Encapsulation Efficiency

The drug content in the microsponges was determined spectrophotometrically (λmax = 261 nm). A sample of microsponges (25mg) was dissolved in 25 ml of methanol. The drug content was calculated from the calibration curve and expressed as loading efficiency.

3. Particle size and Morphology

The size of microsponge was calculated using optical microscope. The morphology of microsponge was observed by scanning electron microscopy. Prepared microsponges were coated with platinum studied by scanning Electron microscopy under vacuum at room temperature.

4. Micromeritic properties

The bulk density and tapped density of each of the batches of microsponge was determined using a measuring cylinder. The flowability of the microcapsules was measured by the Carr's (consolidation) index and Hausner ratio. Furthermore, Carr's index was calculated using the equation:

$$\text{Carr's Index} = \frac{\text{Tapped Density-Bulk Density}}{\text{Tapped Density}} \times 100$$

While Hausner's ratio was calculated using the equation:

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Optimization of microsponge based gel

After optimization of the nano-emulsion formulation it was given a gel base as for topical delivery the nano-emulsion has very low viscosity. The gel was formed by varying the concentration of carbopol 980 as 0.5%, 1%, 1.5%, 2%, 3% w/v. For the preparation of gel the required amount of carbopol was dipped in sufficient amount of water for 24 hrs and the nano-emulsion formulation was added after neutralizing the pH of carbopol. The following parameters were evaluated for optimization of microsponge based gel.

1. **Viscosity**

The viscosity was studied by using Brookfield viscometer.

2. **pH**

It was analyzed by using Labindia pH meter.

3. **% Drug content**

For determination of drug content, the gels were first dissolved in methanol. Further were centrifuged 1800-2100 rpm for 1hrs. Then these samples were analysed using UV spectrophotometer scanning from 200- 400nm.

1. **In-vitro studies**

In vitro permeation studies were performed on a fabricated Franz diffusion cell with an effective diffusional area of 19.63 cm^2 and 35 mL of receiver chamber capacity using cellophane membrane. The membrane was dipped in the medium for 24hrs before use the membrane was mounted between the donor and receiver compartment of the Franz diffusion cell; on which the gel was spread completely to cover most of the area.

Initially, the donor compartment was empty and the receiver chamber was filled with 30% Ethanolic phosphate buffer (pH 7.4). The receiver fluid was stirred with a magnetic rotor at a speed of 100 rpm, and the temperature was maintained to 37±2o C (n=3). The study was carried out for 12 hrs.

2. **Drug release kinetics**

The release kinetic was studied by various kinetic models as zero order plot, first order plot, higuchi plot and korsmeyer-peppas. To study the release kinetics of optimized Microsponge gel, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order as cumulative amount of drug releases Vs time, first order as log cumulative percentage of drug remaining Vs time, Higuchi model as cumulative percentage of drug released Vs square root of time. The best fit model was confirmed by the value of correlation coefficient near to 1.

3. **Zero Order Model**

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q0 - Qt = K0t \quad (1)$$

Rearrangement of equation (1) yields:

$$Qt = Q0 + K0t \quad (2)$$

Where Qt is the amount of drug dissolved in time t,

Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and K0 is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released versus time.

Application: This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc.

4. First Order Model

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

$$\log C = \log C0 - Kt / 2.303$$

Where C0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303.

Application: This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

5. Higuchi's Model

Graph was plotted between cumulative percentages of drug released Vs square root of time.

$$Q=K1/2$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence drug release rate is proportional to the reciprocal of the square root of time.

Application: This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

6. Korsmeyer – peppas model

Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-peppas model.

$$Mt / M\infty = Ktn$$

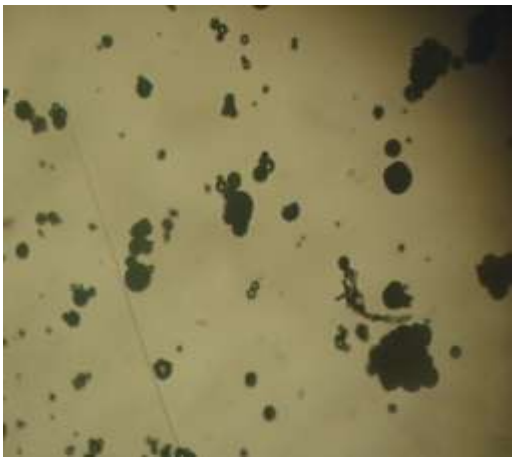
where Mt / M∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. For the case of cylindrical tablets, 0.45 ∞ n corresponds to a fickian diffusion mechanism, 0.45 < n < 0.89 to non-fickian transport, n = 0.89 to Case II (relaxational) transport, and n > 0.89 to super case II transport. To find out the exponent of n the portion of the release curve, where Mt / M∞ < 0.6 should only be used. To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.

Result and Discussion

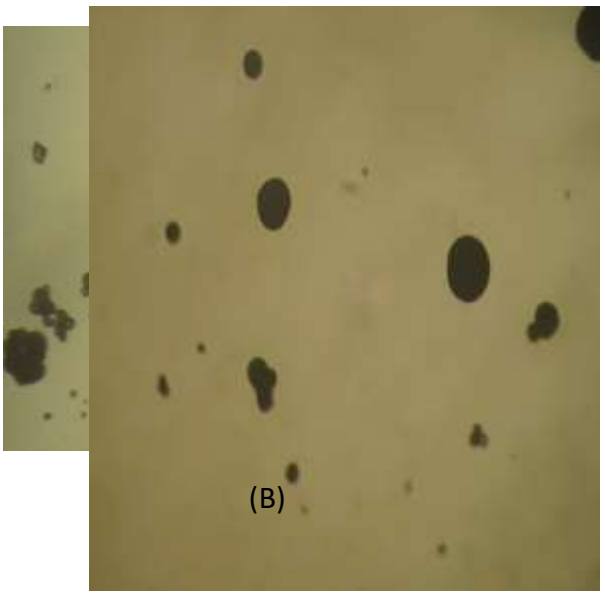
Table No 2: Appearance of different microsponges formulations

S.no.	Formulation code	Appearance
1	F1	Microsponge not form
2	F2	Microsponge not form
3	F3	Microsponge not form
4	F4	Irregular and Spherical shape microsponge shape
5	F5	Spherical microsponge formed
6	F6	Spherical microsponge formed
7	F7	Irregular and Spherical microsponge formed
8	F8	Irregular shape microsponge formed
9	F9	Agglomeration structure was formed
10	F10	Spherical microsponge formed
11	F11	Spherical microsponge formed
13	F12	Irregular and Spherical microsponge formed
14	F13	Irregular shape microsponge formed
15	F14	Irregular and Spherical microsponge formed
16	F15	Spherical microsponge formed
17	F16	Irregular shape microsponge formed
18	F17	Irregular shape microsponge formed

From table no 2 it was found that some formulations were spherical in shape and some formulation had irregular structure and some formulation showed agglomeration formation.
Optical microscope image of Formulations F5, F6, F10, F11, F15



(A)



(B)

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(D)