Research Article

Formulation, Development and *In-vitro* Evaluation of Terbinafine HCL Microscope Gel.

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ABSTRACT

Microsponges containing THCl were prepared using Eudragit RSPO as a polymer by quassi-emulsion solvent diffusion method. To optimize the microsponges formulation, factors affecting the physical properties of microsponges were evaluated. It was observed that the polymer Eudragit RSPO and stabilizing agent PVA concentration influenced the particle size and drug content of formed microsponges. The production yield, loading efficiency, surface morphology and particle size analysis was performed. The surface morphology including the pore structure of microsponges was evaluated using scanning electron microscopy. Microparticles were then incorporated in Carbopol 934 gel base and In-vitro permeation studies of formulations were performed in Franz diffusion cell. Surface morphology by scanning electron microscopy showed micro-porous nature of microsponges. Drug release was observed comparison with marketed formulation.

Keywords: Microsponges; Terbinafine HCl; Quassi-emulsion solvent diffusion method; controlled release.

INTRODUCTION

Controlled release of drugs onto the epidermis assures that the drug remains primarily localized and does not enter into the systemic circulation in significant amounts. 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. The development of novel microsponge based on the drug delivery systems, in order to modify and control the release behavior of the drugs.[1,2]

Microsponges are microscopic spheres capable of absorbing skin secretions, therefore reducing oiliness from the skin. Spherical particles composed of clusters of even tinier spheres are capable of holding four times their weight in skin secretions. Microsponge particles are extremely small, inert, indestructible spheres that do not pass through the skin.

The size of the microsponges can be varied, usually from 5 - 300 µm in diameter. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. Microsponges are prepared by several methods utilizing emulsion system as well as suspension polymerization in a liquid-liquid system. The most common emulsion technique used is emulsion solvent diffusion method.[3,4]

Terbinafine is an allylamine which has a broad spectrum activity in fungal infection of hair and skin. It inhibits the biosynthesis of the ergosterol, an important component of fungal cell, and thus results in antifungal activity. Terbinafine has oral bioavailability 40% which increases the dosing frequency of the drug which leads to some systemic side effects, and also its topical use may cause side effects like itching, oedema, and skin irritation. Thus the aim of the present investigation was to design microsponges as novel carriers for topically controlled delivery of Terbinafine and to decrease the side effects related to skin.

This investigation consisted of preparation, optimization, and evaluation of Terbinafine microsponges in semisolid vehicle base (gel) to obtain acceptable topical product.[5,6]

MATERIALS AND METHODS

Materials

The Terbinafine hydrochloride (B.P) was received as a gift sample from ABIL chempharma Pvt. Ltd. India. Eudragit RSPO was purchased from Evonik Pharma, Mumbai. Carbapol (934), Poly vinyl alcohol was purchased from Loba chemie, Mumbai. All other reagents used were of A.R grade.

Method

THC microsponges were prepared by an Emulsion solvent diffusion method. The inner phase, Eudragit RSPO was dissolved in dichloromethane and then drug was added to solution under ultrasonication at 35°C and was then gradually added into external phase, which contained PVA as emulsifying agent. This mixture was stirred mechanically at 1000 rpm for 3 hours at room temperature to remove dichloromethane from the reaction flask. The formed microsponges were filtered, washed with distilled water and dried at room temperature. Microsponges were weighed, and production yield (PY) was determined.[7]

Effect of Variables on Formulation of Microsponges

Drug concentration and stirring speed of 1000 rpm for a period of 3 hours was kept constant for all the experiment and effect of different variables such as surfactant concentration, polymer concentration was observed. The formed microsponges were evaluated for

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their physical characteristics, % entrapment efficiency, drug content and particle size.[8]

RESULTS AND DISSCUSSION

Characterization and Evaluation of Microsponge Formulations

Drug Content

Microsponges equivalent to 100 mg of THCl were dispersed in phosphate buffer (pH 5.5) in 10 ml volumetric flask. 1 ml of this solution was diluted to 10 ml with acetate buffer (pH 5.5) to get concentration within Beer's range.

The absorbance was measured spectrophotometrically at 222.3 nm using placebo microsponges to determine the drug content.[9]

Drug Loading Efficiency

A sample of Terbinafine microsponges (10 mg) was dissolved in 100 ml of acetate buffer, freshly prepared (pH 5.5) and the drug content in the microsponges was determined spectrophotometrically at 222.3 nm.

The drug content was calculated from the calibration curve and expressed as actual drug content in microsponge. The loading efficiency (%) of the microsponges was calculated according to following equation,[10]

$$Loading\ Efficiency = \frac{Actual\ drug\ content\ in\ microsponge}{Theoretical\ drug\ content} \times 100$$

Production Yield

The production yield of the microsponge was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained.

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

Particle Size Determination

The particle size was determined using an optical microscope.

Preparation of Microsponge Gel

Carbopol was accurately weighed and by using water as a vehicle, sodium benzoate as preservative gel was prepared. Terbinafine HCl microsponges equivalent to 100mg of drug were dispersed into the gel base. The pH was adjusted with triethanolamine which resulted in a translucent gel; further formed gel was stored in air tight container for further study.[11]

Homogeneity

The prepared gels were visually inspected for clarity, colour and transparency. The prepared gels were also evaluated for the presence of any particles. Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness.[12]

pH of the Gels

The pH of gel was determined after diluting and dispersing it in distilled water using digital pH meter.[13]

Spreadability

Spreadability was determined by glass slides and a wooden block, which was provided by a pulley at one end by using the basis of *'Slip and Drag'* characteristics of gels. A ground glass slide was fixed on this block. An excess of gel (about 1gm) of different formulations were placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 20gms, lesser the time taken for separation of two slides better the Spreadability.[13]

Spreadability was then calculated using the following formula:

$$S = M \times \frac{L}{T}$$

Where,

S = is the spreadability,

M = is the weight in the pan (tied to the upper slide),

L = is the length moved by the glass slide

T = represents the time taken to separate the slide completely from each other.

Viscosity

Viscosity of prepared gel was measured by using Brookfield viscometer.

Extrudability Study

It is a usual empirical test to measure the force required to extrude the material from tube.[13]

Drug Content

Prepared gel formulation (100mg) was dissolved in methanol, filtered and the volume was made upto 100ml with methanol. This resulting solution diluting 10 times with methanol and measuring the absorbance at 222.3nm using UV Visible spectrophotometer after that the drug content was determined.

In-vitro Permeation Study

In vitro diffusion study of gel containing Terbinafine HCl microsponge was observed the total amount of drug release at different time intervals for a period of 12h. Acetate buffer of pH 5.5 was used as receptor medium. Cellophane membrane previously soaked overnight in the dissolution medium was used in modified Franz Diffusion Cell. The gel sample equivalent to100mg microsponge was applied on cellophane membrane and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained acetate buffer (100ml) of pH 5.5. The temperature of diffusion medium

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was thermostatically controlled at 37°C ± 1°C by surrounding water in jacket and the medium was stirred by magnetic stirrer at 50rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 222.3 nm using acetate buffer (pH 5.5) as blank.[14]

Stability Study

According to ICH guidelines the stability studies are carried out. The formulation was tested for stability at 5°C ± 2, 25°C ± 2 /60 ± 5 RH, 40°C ± 2/75 ± 5 RH. Formulation was stored in aluminium tubes and evaluated after 30, 60, 90 days.

Table 1: The composition of formulation (2^3 factorial design) for the preparation of THCl microsponge systems

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Terbinafine HCl(mg)	500	500	500	500	500	500	500	500	500
Eudragit RSPO(mg)	900	700	500	900	700	500	900	700	500
PVA(%w/v)	1	1	1	0.75	0.75	0.75	0.5	0.5	0.5
Dichloromethane(ml)	20	20	20	20	20	20	20	20	20
Distilled Water (ml)	80	80	80	80	80	80	80	80	80

Evaluation of Microsponge

Table 2: Evaluation of Microsponge

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Formation of microsponges	+	+	+	+	+	+	_	_	_
Average particle size (µm)	8.6	12.5	17.35	**14.93**	**15.8**	**13.53**	22.71	16.13	21.01
Production yield (%)	93.33	93.15	90	**99.33**	**98.33**	**96**	90.20	89.88	81.79
Drug Loading (%)	95.49	90.51	82.09	**99.70**	**98.2**	**96.09**	90	84.41	79.68

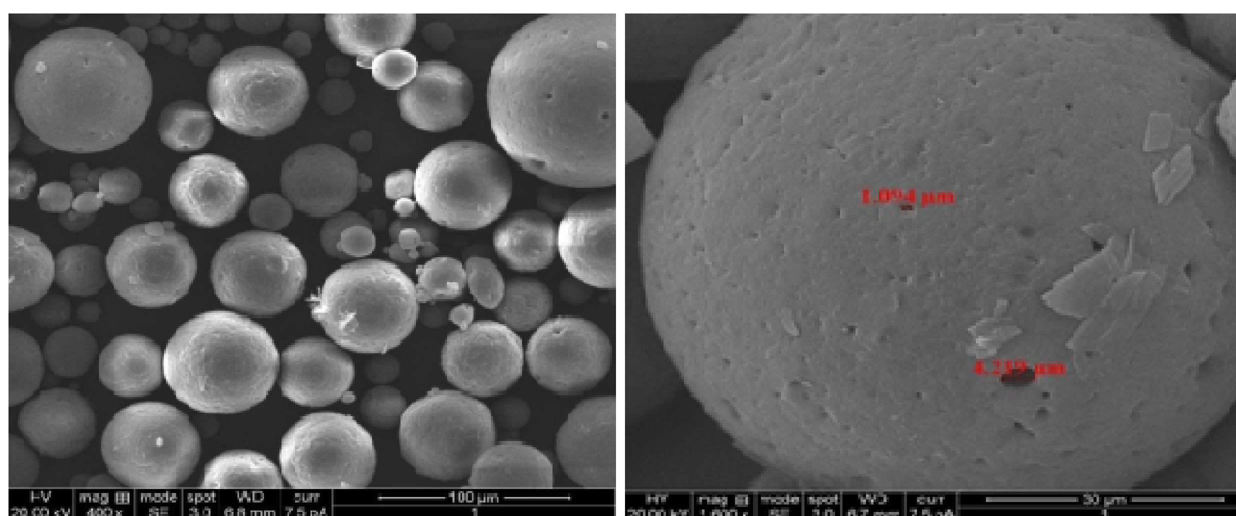

Figure 1: SEM images of Microsponge

Table 3: Suitable variables for formulation of Microsponges are

S. No	Variables	Essential Consideration
1	Internal phase	Dichloromethane
2	External phase	Water
3	Terbinafine hydrochloride	500mg
4	Concentration of polymer	900mg
5	Surfactant concentration	0.75(%w/v)
6	Internal volume	20ml
7	External volume	80ml
8	Stirring speed	1000rpm
9	Stirring time	3h

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Evaluation of Developed Microsponge Gel

Table 4: Formulation of Microsponge Gel

S. No.	Ingredient	Quantity
1.	Microsponges equivalent to 100 mg of Terbinafine HCl	0.5%
2.	Carbopol 934	1.5 %
3.	Distilled water	100 ml
4.	Triethanolamine	q.s.

Table 5: Evaluation of Microsponge Incorporated Gels

Batches	F4	F5	F6
Appearance	White color microsponges suspended in transparent gel base	White color microsponges suspended in transparent gel base	White color microsponges suspended in transparent gel base
p^H	5.50	5.48	5.55
Spreadability (gm.cm/sec)	14.58	15.38	15.33
Homogeneity	***	**	**
Viscosity(cps)	9000	6000	7600
Extrudability	***	**	**
% Drug Content	97.36	94.55	95.34

** denotes good, ***denotes excellent.

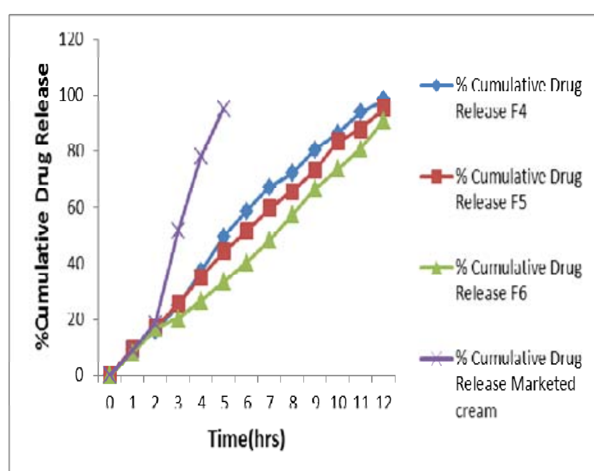

Figure 2: drug release profile of Terbinafine HCl from its microsponge gel formulation at 12 hrs

CONCLUSION

The present study was to design, develop, and evaluate the microsponge incorporated gel for topical drug delivery of Terbinafine HCl for extended release. Mixture of Eudragit RSPO and drug in DCM act as internal phase. Solution of PVA in water used as external phase. Terbinafine HCl is easily inactivated by the gastric environment and produce gastric disturbances such as diarrhoea, nausea, abdominal pain and vomiting. The best formulation F4 was incorporated into gels and gels were evaluated for physical parameters and showed extended release upto 12h.

Stability studies at room temperature showed that there was no noticeable change in the homogeneity, pH, spreadability, extrudability, viscosity, drug content and *in-vitro* release at the end of three months. Thus it was concluded that the optimized microsponges further can be incorporated into gel for topical application use as antifungal purpose.

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