



Research Article

TOLNAFTATE MICROSPONGES EMBEDDED BIOCOMPATIBLE GELS FOR CONTROLLED AND EFFECTIVE ANTIDERMATOPHYTIC ACTIVITY

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Article Received on: 26/05/18 Approved for publication: 22/06/18

DOI: 10.7897/2230-8407.096103

ABSTRACT

The aim of this investigation was to develop potentially efficient Tolnaftate Microsponges embedded gels for effective management of dermatophytosis, which has been highly ignored skin ailment in the current era. Immunosuppressant and patients suffering from severe diseases are highly prone to dermatophytosis. Herein Tolnaftate microsponges were prepared through quassi-emulsion solvent diffusion technique applying biocompatible polymers Eudragit RL100 and Eudragit RS100. Formulated Microsponges were embedded in Carbopol 934 and HPMC to attain controlled topically effective formulation and their physical parameters like viscosity, pH, spreadability, the in-vitro drug release kinetics were evaluated. Drug-excipient compatibility was performed by FTIR and TGA. FESEM analysis revealed micro size microsponges with numerous pores present over their surface. Several in-vitro release kinetics models were applied, and the formulated gels followed Korsmeyer Peppas model. Antidermatophytic activity against *Trichophyton mentagrophytes* revealed a distinct zone of inhibition and showed the potential role for the management of dermatophytosis.

Keywords: Dermatophytosis, Tolnaftate, Microsponges, Quassi emulsion technique, *Trichophyton mentagrophytes*

INTRODUCTION

Dermatophytosis is a superficial cutaneous infection is extremely common disease in last few decades is caused by filamentous dermatophytes. Mostly belongs to the genera *Trichophyton*, *Microsporum* and *Epidermophyton* which is keratinophilic fungi that encroaches keratinized layer of skin tissues (scalp, nail and hair) and causes several tinea diseases. They likely develop outwards on skin, forming a ring like pattern that's why also known as 'Ringworm'. These dermatophytes propagate only in the superficial layer of the epidermis (stratum corneum) and usually do not penetrate deeper tissue but encouraged by a damp and warm local environment. Although the complex immune system and internal temperature of human body largely protect from major life threatening fungal infections but excess use of antibiotics/steroids and altered physiological conditions are also worsen the cases.^{1,2} Dermatophytes are spreaded by coming in contact with affected host or by direct or indirect contact with infected skin or hair (combs, adhered in clothing, hair brushes).³

Tolnaftate is a synthetic thiocarbamate used as the topical antifungal agent, reported by Noguchi and their colleagues in 1963.⁴ It is a lipophilic in nature, has poor aqueous solubility with a high molecular weight (307.41 g/mol), shows poor permeability property and it comes under BCS class IV drugs. It acts by suppressing an enzyme squalene epoxidase, resulting deficiency of ergosterol in fungal membrane.^{5,6} Tolnaftate is active only by topical application and inactive via intraperitoneal and other routes. In market Tolnaftate is available in various topical dosage forms like spray, powder, liquid aerosol and creams.^{7,8}

Microsponges is sponge like porous polymeric delivery system that are commonly used for extended release of drug. It offers to deliver active ingredients readily at low dose and reduce allergenicity, mutagenicity, irritation and side-effects and enhanced stability and payload of drug. They are stable at variable ranges (pH 4-9).⁹⁻¹¹ The objective of the present investigation was to load Tolnaftate into microsponges by quassi-emulsion solvent diffusion technique in order to elevate the aqueous solubility and permeability and to evaluate them by formulating controlled release topical gels.

MATERIALS AND METHOD

Tolnaftate was received from Yarrow Chem. Products, Mumbai. Eudragit RS 100, Eudragit RL 100, Hydroxy propyl methyl cellulose (HPMC) and Carbopol 934 were purchased from Yarrow Chem. Products, Mumbai. PVA (poly vinyl acetic acid), PEG (poly ethylene glycol), dichloromethane, methanol and triethanolamine were purchased from S.D Fine Chem. Ltd, Mumbai. All other reagents and chemicals used for analysis were of analytical grade.

Preparation of Tolnaftate loaded microsponges

Tolnaftate microsponges were prepared by Quassi-emulsion solvent diffusion technique. The method consists of two step process. In first step, internal phase was prepared and in second step external phase was prepared. Internal phase was prepared by dissolving Eudragit RL 100, Eudragit RS 100 separately and their combinations, in different ratio in dichloromethane followed by addition of PEG (which was added to facilitate the plasticity),

then after Tolnaftate added into the solution and allowed for ultrasonication at 35°C. Then after external phase was prepared by dissolving PVA in deionized water and the process is carried out at room temperature. Then at room temperature, internal phase was poured into the external phase. After the completion of emulsification process, the mixture was stirred continuously for 6-7 hours at 5000 rpm. Prepared Microsponges MF1 and MF2 were separated by filtration, washing and dried in vacuum oven at 40°C for 12 hours.¹²⁻¹⁴

Evaluation of Tolnaftate loaded microsponges

Drug-Polymer compatibility studies

The samples of pure drug, physical mixture and Microsponges were recorded. Sample was prepared by triturating samples with KBr and samples were analyzed. Each spectrum was measured over a frequency range from 500 – 3500 cm⁻¹.¹⁸

DSC analysis

Samples were loaded in aluminium and the DSC thermographs were recorded at a heating rate of 10 °C/min in range of 0°C to 600°C. Nitrogen gas was purged for maintaining inert atmosphere at rate of 50ml/min. DSC thermograms were obtained using the instrumental software.¹⁹

Surface Morphology analysis

The morphology of microsponges was examined by SEM. The dried sample was mounted on aluminium grooved edge stub and properly coated with gold (15 nm) for one minute. The coated sample was then scanned and their images were taken.²¹

Particle size analysis

The particle size was done by using an optical microscopy by using calibrated eye piece and stage micrometer. A little amount of microsponges (MF1 and MF2) were spread on glass slide and average particle size was calculated by counting atleast 100 particles of each batch.²⁰

Determination of Production yield

The production yield of prepared Tolnaftate loaded microsponges (MF1 and MF2) was determined by using following equation (1).²²

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

Determination of Drug content

A specific quantity (10 mg) Tolnaftate loaded microsponges (MF1 and MF2) were taken, triturated and dissolved it in 100 ml of phosphate buffer solution (pH 6.8). The volumetric flask containing microsphere solution was shaken in order to get complete solubility of drug. This solution is filtered and estimated spectrophotometrically at 257 nm using phosphate buffer solution as blank.²³

In-vitro diffusion study

In-vitro diffusion study of Tolnaftate loaded microsponges were carried out by dialysis bag method using dialysis membrane in freshly prepared phosphate buffer solution (pH 6.8). Dialysis membrane was soaked overnight in the diffusion medium facilitate opening of pores for proper diffusion process.

Accurately weighed Microsponges equivalent to 10 mg Tolnaftate was added in dialysis bag and allowed to hang in same diffusion media for in-vitro drug analysis. The release/diffusion profile of the drug was obtained by sampling 5ml of aliquots from the diffusion medium at predetermined interval for 8 hours. The sampled aliquot was every time replaced by fresh diffusion medium of the same quantity, to maintain the sink condition. Aliquots were analyzed through UV spectrophotometer and release kinetics were interpreted by applying DDSolver software.²⁴

Preparation of Tolnaftate loaded microsphere based gel

Hydroxy propyl methyl cellulose (HPMC) and Carbopol 934 were selected for providing final form of topical gel formulation. Tolnaftate microsponges were dispersed in water and added to the drug solvent system. Triethanolamine was added dropwise in this mixture with slowly stirring, taking consideration that air bubble should not form. Prepared Tolnaftate gel was stored in an air tight collapsible tube for further study.¹⁵⁻¹⁷

Evaluation of Tolnaftate loaded microsphere based gel

Physical examination of gels

The prepared Tolnaftate microsphere based gel formulations was examined visually for its color and appearance.²⁵ The pH of the prepared microsphere gel formulations were measured by digital pH meter.²⁶

Spreadability

Spreadability of gel formulations was determined by using horizontal plate method. A glass plate was stationed on the surface and an excess of gel (1g) were allocated in the slide. The gel was sandwiched between the slide and another glass slide having the fixed dimension was placed over it. A 125 g weight was positioned over the upper slide for specific time (5 min.) to expel and to provide a uniform film of the gel between the slides.²⁷ The spreadability was then calculated using the following formula

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

Where, S= spreadability, M= weight placed on the upper slide, L= length moved by the glass slide, T= time

Viscosity measurement

Viscosity measurement was carried out by using Brookfield viscometer. Sufficient sample was placed in a cylindrical tube and measured the reading at 37°C ± 2°C and rotating the spindle no. 63 at 1.5 rpm.²⁸

Extrudability

The prepared gel formulation was filled in clear, collapsible aluminum tubes. Afterward, the extrudability of gel formulations was estimated in weights in gram required to extrude out through tip of the tube.²⁹

Drug content study

Tolnaftate microsphere embedded gel (100 mg) was accurately weighed and dissolved in 100 ml of Phosphate buffer solution (pH 6.8), sonicated for 10-15 minutes. The solution was filtered and absorbance was estimated by using UV/Vis Spectrophotometer at 257 nm.³⁰

In-vitro diffusion study

In-vitro release of microsphere based gel containing Tolnaftate was studied by using membrane diffusion technique. The gels equivalent to 10 mg Tolnaftate was kept in the dialysis bag. The temperature of medium as maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. Aliquots of 5 ml volume of each formulation were withdrawn periodically, and medium was then replaced by equal volume. The samples were analyzed at 257 nm by UV/Vis Spectrophotometer.³¹

Anti-fungal activity

On the basis of in-vitro drug release profile the gel was selected for antifungal activity. Antifungal activity of formulated gel was carried out by Agar well diffusion method. A defined volume of *Trichophyton mentagrophyte* suspension were poured into Potato dextrose agar media (PDA) and allowed to solidify. Later the wells were made using a sterilized cork borer over that plate. The prepared wells were filled with standard solution having equal strength of control gel, Tolnaftate microsphere loaded gel. Then the petri plates were incubated at 37°C for 24 hours.³² The zone of inhibition were obtained, and diameter were measured.

Table 1. Tolnaftate Microsphere Formulations Prepared by Quasi-Emulsion Solvent Diffusion Method

Constituents	Microsphere formulations	
	MF1	MF2
Tolnaftate (gm)	0.25	0.25
Eudragit RL 100 (gm)	0.05	0.15
Eudragit RS 100 (gm)	0.15	0.05
Dichloromethane (ml)	5	5
Polyvinyl alcohol (gm)	0.08	0.08
Polyethylene glycol (ml)	0.5	0.5
Deionized water (ml)	10	10

Table 2. Formulation of Tolnaftate Gels Containing Microspheres Entrapped Drug

Ingredients	TMG 1	TMG 2
Tolnaftate microsphere equivalent 100 mg drug (mg)	100	100
HPMC (gm)	0.3	
Carbopol 934 (gm)		0.3
Polyethylene glycol (ml)	2	2
Ethanol (ml)	3	3
Triethanolamine (ml)	2	2
Methyl paraben (mg)	0.8	0.8
Deionized water q.s. (ml)	50	50

Table3. Production Yield, Drug Content, Particle Size And % Cumulative Drug Release of Microsphere Formulations

Formulation code	Production yield (%)	Drug content (mg)	Particle size (μm)	% Cumulative drug release
MF 1	68.9	27.3	0.8	70.4
MF 2	71.7	39.3	1.0	89.2

Table 4. Physical Evaluation of Gel Characteristics for Prepared Gel Formulations

Formulation code	pH	Spreadability (g cm/sec)	Extrudability (g/cm ²)	Viscosity (cp)	Drug content (mg)	% Cumulative drug release
TMG 1	6.74	18.33	0.97	6079	29.50	69.3
TMG 2	6.92	24.81	1.03	6059	15.22	60.1

Table 5. Release Kinetic Models for Tolnaftate Microsphere Gel Formulations

Formulation Code	Zero order		First order		Korsmeyer Peppas		Higuchi	
	K ₀	R ²	K ₁	R ²	N	R ²	K _h	R ²
TMG 1	0.205	0.878	0.004	0.896	0.423	0.974	3.721	0.968
TMG 2	5.75	0.899	0.003	0.805	0.478	0.973	3.174	0.946

Table 6. Observation of in-vitro Antifungal activity

Antifungal Strain	Formulation	Zone of inhibition (mm)
<i>T. mentagrophytes</i>	Control gel	-
<i>T. mentagrophytes</i>	TMG1	8.8 ± 0.7

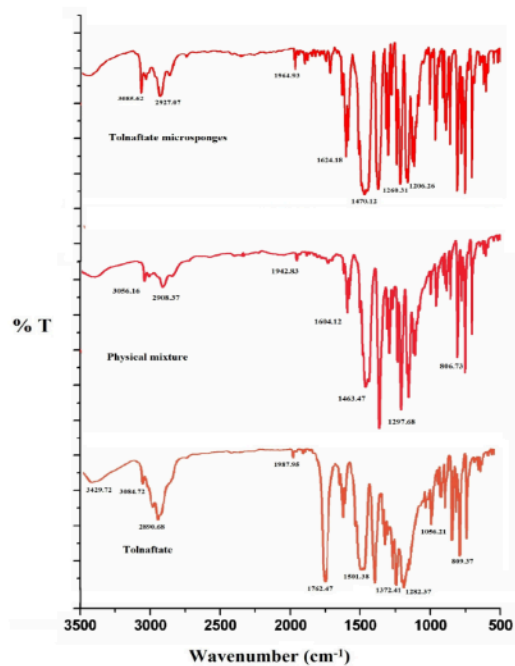


Figure 1. FTIR Spectra of Tolnaftate, Physical Mixture and Tolnaftate Microsponge

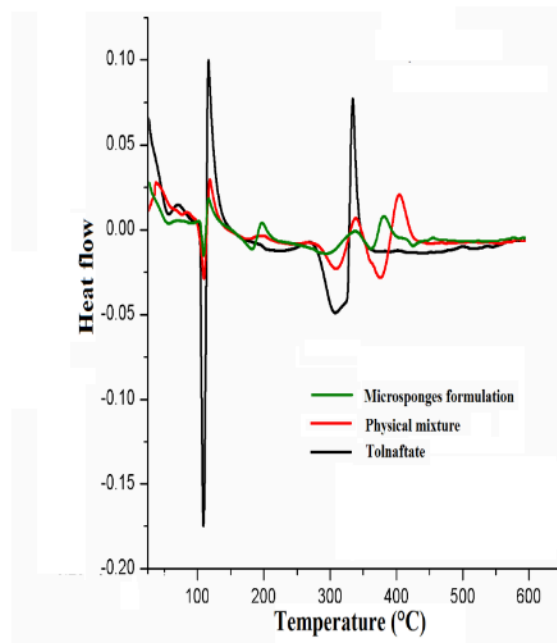


Figure 2. DSC thermogram of Tolnaftate (Drug), Physical Mixture and Microsponge Formulation

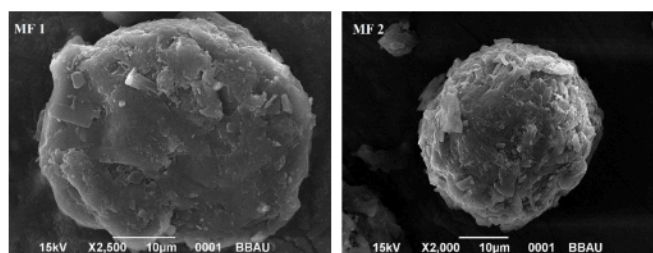


Figure 3. SEM Images of Tolnaftate Microsponges (MF1 and MF2)

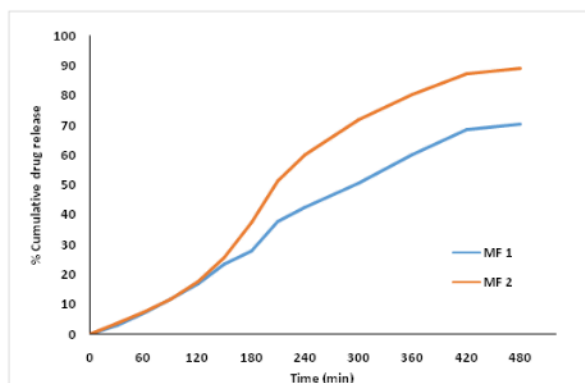


Figure 4. Drug Release Profile of Tolnaftate Microsponge Formulations

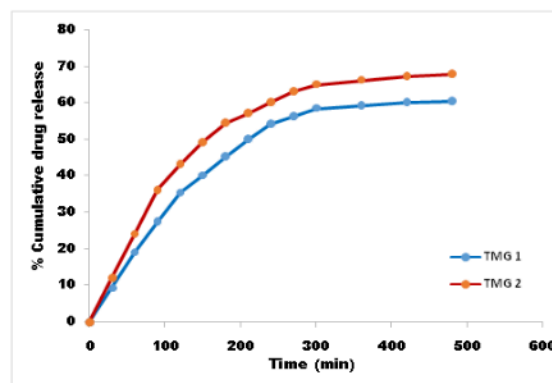


Figure 5. % Cumulative Drug Release of Tolnaftate Microsponge Gel Formulations

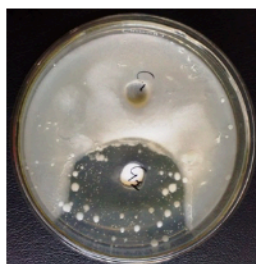


Figure 6. In-vitro antifungal activity against *T. mentagrophytes*

RESULTS AND DISCUSSION

Evaluation of Tolnaftate loaded microsponges

Drug polymer compatibility study

Drug polymer compatibility study was done by FTIR spectroscopy. The FTIR spectrum of pure drug, physical mixture and microsponges were obtained and compared to identify specific peaks by virtue of respective functional groups present in their chemical structures. Distinctive peaks of asymmetric C-H stretching at 3084.72 cm⁻¹, symmetric C-H stretching at 2890.68 cm⁻¹, C-N-C stretching vibration at 1501.38 cm⁻¹, O-H stretching peak at 1282.37 cm⁻¹ and C-O-H stretching vibration at 1056.21 cm⁻¹ were seen. It shows that there was no chemical interaction between the drug and the polymers. This illustrated that Tolnaftate was compatible with polymers and it was stable in microsphere formulations.

DSC study

In DSC thermogram of pure drug, at 25 °C the endothermic peak was seen which indicated the glass transition of the drug, an exothermic peak was also observed at 355 °C which showed the crosslinking and the sharp endothermic peak was also observed at 111 °C which is corresponding to the melting point of the drug reflecting the purity of drug and its crystalline form. In DSC thermograph of physical mixture and formulated microsponges, exothermic peak at 111 °C were observed.

Surface morphology analysis

The morphology and surface topography were observed by Scanning electron microscopy (SEM) MIRA3 TESCAN. The scanned images of formulated microsponges are shown in Figure 3 and it revealed that microsponges were spherical in shape, smooth and porous. The surface topography study revealed that microsponges consisted tiny pores. From the surface of microsponges diffusion of volatile solvent induced pores.

Particle size analysis

Particle size of the formulated microsponges varied due to the change in the concentration of polymers. The average particle size distribution of formulated microsponges of MF1, MF2 was 0.8 µm & 1.0 µm respectively.

Determination of Production yield

The production yield of Tolnaftate microsphere formulations was determined and it ranged from 63.4 to 71.7%. From the production yield of Tolnaftate microsphere formulations, it was indicated that on increasing the ratio of drug: polymer production yield was also increased.

Determination of Drug content

The drug content of Tolnaftate microsponges was determined and reported in Table 3. The obtained drug content were in ranges of 27.3-39.3 mg. The results revealed that drug was distributed in microsponges.

In-vitro diffusion study

In-vitro diffusion profile of the formulated Tolnaftate microsponges are presented in Table 3 and Figure 4. Amongst the formulated microsponges after 8 hours, MF2 exhibited prolonged release i.e. 89.2 %. This may be due to higher permeability of

Eudragit RL 100 owing to high concentration of quaternary ammonium compound in their chemical structure with respect to Eudragit RS 100.

Evaluation of Tolnaftate loaded microsphere gels

Physical examination of gels

Formulated gels (TMG1 and TMG2) were subjected for evaluations i.e. color, appearance, pH, spreadability, viscosity, extrudability and drug content. Both formulated gels were white in color, gel prepared from HPMC (TMG1) was translucent, having skin compatible pH of 6.74 and sufficient spreadability (Table 4).

In-vitro drug release study

In-vitro drug release profile of TMG1 and TMG2 gels are being shown in figure 5. The diffusion study showed enhanced release of drug in TMG1 as compared to formulation TMG2. Microsphere loaded gel having HPMC exhibited higher amount of drug diffusion as compared to formulation having Carbopol for 8 hours. The results of various drug release kinetic models are shown in Table 5.

Antifungal activity

In-vitro antifungal activity of formulated Tolnaftate loaded microsphere gel (TMG1) against control are shown in figure 6. The gel TMG1 was selected for activity on the basis of in-vitro release profile. The formulated gel showed promising antifungal activity (Zone of inhibition of gel was 8.8 ± 0.7 mm) against selected dermatophyte *T. mentagrophyte*.

CONCLUSION

The present study concluded successfully formulation of Tolnaftate loaded microsphere by using quasi-emulsion solvent diffusion technique. The implemented technique was found to be easy, reproducible and rapid. Formulated microsponges were spherical in shape, have porous and regular surface. Varied ratio of drug-polymer showed remarkable effects on drug content, particle size, entrapment efficiency and drug release. The in-vitro drug release study of formulated Tolnaftate microsphere loaded gel TMG1 followed Korsmeyer-Peppas kinetic model on their regression (r²) values. The in-vitro antifungal study of gel showed effective results against *T. mentagrophyte* dermatophyte. Thus, it found to have potential management of nosocomial infections for better patient compliances.

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Cite this article as:

Prashant Pandey et al. Tolnaftate microsponges embedded biocompatible gels for controlled and effective antidermatophytic activity. *Int. Res. J. Pharm.* 2018;9(6):128-133 <http://dx.doi.org/10.7897/2230-8407.096103>

Source of support: Nil, Conflict of interest: None Declared

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