INTRODUCTION

Microsponges are porous, polymeric microspheres having a myriad of interconnected voids of particle size ranging from 5-150 µm. Microsponge Drug Delivery System (MDS) is a unique technology that provides controlled release of active ingredients [1-3]. They are mostly used for prolonged topical administration. Microsponges are designed to deliver pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release profiles [4-7]. An MDS is highly cross-linked that acquire the flexibility to entrap a wide variety of active ingredients such as emollients, fragrances, sunscreens, essential oils, anti-infective, anti-fungal and anti-inflammatory agents etc and are used as a topical carrier system. They can be incorporated into a conventional dosage form such as creams, lotions, gels, ointments, tablets, and powders and share a broad package of benefits and thus provides formulation flexibility [8-10].

The incidence of mycoses, especially superficial fungal infections is increasing and according to a recent report, more than 25% of the world’s population is affected [11, 12], disease progression is more rapid and severity increased in patients with compromised immune function [13].

Terbinafine hydrochloride (THCI) is a broad-spectrum antifungal activity against a wide variety of fungi [14-16]. It is an ally amine antifungal used in the treatment of jock itch and athletes foot. It is highly lipophilic in nature and tends to accumulate in skin and nails when applied topically and cause side effects like rash, irritation etc. Because of the size and porous polymeric structure of microsponges, they slowly release the active ingredient, thereby prevent excess build up in epidermis and dermis and reduce side effects. Terbinafine hydrochloride (THCI) has Pharmacokinetic interactions with drugs that are substrates for CYP2D6 (e.g., tricyclic antidepressants, ß-blockers, selective serotonin reuptake inhibitors [SSRIs], monoamine oxidase [MAO] inhibitors) [17, 18].

The aim of the present investigation was to design novel terbinafine hydrochloride microsponges (I-IV) with six different ratios of the drug: polymer and also to enhance stability, reduce side effects and modify drug release profiles [4-7]. Microsponges containing Terbinafine hydrochloride were obtained successfully with six different drugs: polymer ratios. The formulations were studied for particle size, physical characterization, and in vitro release.

Objective: The purpose of the present research work was to formulate and evaluate Terbinafine hydrochloride microsponges using quasi emulsion solvent diffusion technique and microsponge gel by using carbopol for controlled release of the drug and consequently avoiding its side effects.

Methods: Microsponges containing Terbinafine hydrochloride were obtained successfully with six different drugs: polymer ratios. The formulations were studied for particle size, physical characterization, and in vitro release.

The microsponges containing Terbinafine hydrochloride (THCI) was supplied as a gift sample from MSN Laboratories Ltd, Bollaram, India, Ethyl Cellulose, Polyvinyl alcohol, and Dichloromethane was purchased from SD Fine Chem Limited, Mumbai. Carbopol 940, Triethanolamine was purchased from Qualikems Fine Chem Pvt. Limited, Vadodara. Ethanol was purchased from Jiangsu Huax. International Trade Co. Ltd, China. PEG 400 purchased from Drt Biochemical reagents, Mumbai.

Preparation and characterization of THCI microsponges

Preparation of the microsponges

The microsponges containing Terbinafine hydrochloride (THCI) were prepared by quasi emulsion solvent diffusion method [19] using different drug: polymer ratios as shown in table 1. The inner phase Ethylcellulose was dissolved in dichloromethane and then added the drug to the solution under ultrasonication at 35 °C. The inner phase is then poured into the PVA solution in water. The resultant mixture was stirred at speed of 3000 rpm for 60 min and filtered to separate the microsponges. The microsponges were dried in a hot air oven at 40 °C for 12 h and weighed to determine the yield [20].

Characterization of THCI microsponges

Fourier transforms infrared (FTIR) analysis

FT-IR spectra of finely powdered pure terbinafine hydrochloride, Ethyl cellulose as well as the THCI microsponge formulation were recorded on an FT-IR spectrophotometer (Shimadzu, Kyoto, Japan) by potassium bromide (KBr) disk pellet method [21].

Scanning electron microscopy (SEM)

The morphology of microsponges was examined using a scanning electron microscope (GSED 5400, USA) operating at 20 kV. Dried microspheres were coated with gold-palladium alloy for 45s under an argon atmosphere before observation. SEM photograph was recorded at a magnification of ×500 and 1500.
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 [23].

\[
\text{Drug entrapment} = \frac{\text{Mass of drug present in the microspongnes}}{\text{Theoretical mass of } \text{THCI}} \times 100
\]

**Determination of 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 [23].

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

**Dissolution behavior of microsponges**

The drug release tests of the microsponges were carried out for 8 h at 100 rpm by the paddle method. The temperature of the dissolution medium was controlled at 32±1 °C. The microsponges equivalent to 50 mg of THCI were weighed. The dissolution medium was 150 ml of phosphate buffer (pH 7.4) to keep the sink condition for the drug. Three milliliters of the dissolution medium were sampled at certain intervals (0.5-8 h) and a fresh dissolution medium was simultaneously replaced in the apparatus to keep the volume constant. The withdrawn samples were filtered with a membrane filter (0.45 μm) and the filtrate was assayed spectrophotometrically at 274 nm.

**Preparation and characterization of terbinafine HCl microsponge gel**

**Preparation of terbinafine hydrochloride microsponge gel (THMG)**

Four gels were prepared by using the best microsponge formulation and different concentrations of carbopol 940 as shown in Table 2. An accurately weighed amount of carbopol 940 was taken and dissolved in water using the propeller. In another beaker, microsponges containing terbinafine hydrochloride (free or entrapped, equivalent to 0.1%w/v) drug dissolved in ethanol and added to carbopol solution by stirring, followed by addition of PEG 400. Neutralize the carbopol solution by slowly adding triethanolamine solution with constant stirring until the gel is formed. The pH of the final gel formed was determined [24].

**Characterization of Terbinafine HCl microsponge gel**

**Physical parameters of THMG**

Four gel formulations containing terbinafine hydrochloride microsponges were characterized for pH using pH meter, viscosity using a Brookfield digital viscometer (Model DV-III + Rheometer), spreadability and drug content [25-27].

**In vitro release study**

The in vitro release of THMG formulations was studied by membrane diffusion technique using a cellophane membrane. The dissolution medium is pH7.4 phosphate buffer, freshly prepared. Cellophane membrane previously seeded overnight in the dissolution medium was tied to one end of a specifically designed glass cylinder (open at both ends). 1g of the formulation (equivalent to 1000 mg of terbinafine hydrochloride) was accurately placed into this assembly. The cylinder was attached to stand and suspended in 200 ml of dissolution medium maintained at 37±1 °C, the membrane just touching the receptor medium surface. The dissolution medium was stirred at 100 rpm speed using Teflon coated magnetic bead. Aliquots, each of 5 ml volume were withdrawn periodically at a predetermined time interval of 15, 30, 60, 120, 180, 240, 300, 360 min and replaced by an equal volume of the receptor medium to maintain sink conditions. The aliquots were suitably diluted with the receptor medium and analyzed by UV-visible spectrophotometer at 274 nm using neutralized phthalate buffer as blank [28].

Several mathematical models attempt to correlate dissolution profiles with the mechanisms of drug release from the drug delivery system [29, 30]. In this work, zero-order first order, Higuchi and Korsmeyer-Peppas models were applied to analyze the release profile of THCI from the prepared microsponge gels [31-35].

**Antimicrobial activity**

This was determined by sabouraud dextrose medium employing "cup plate technique" using previously sterilized Petri dish. A solution of the prepared gel formulation, marketed gel and pure terbinafine hydrochloride as a standard 1 mg/ml was poured into cups bored of size 8 mm into wells of sabouraud dextrose plate previously seeded with test organism (Candida albicans Procured from MTCC, Chandigarh, Acc. No.183). After allowing diffusion of solution for 2 h, the plates were incubated at 27 °C for 48 h. The zone of inhibition measured around each cup was compared with that of marketed gel and standard [36].

### Table 1: Composition of the prepared THCI microsponge systems

| Constituents      | Microsponges formulation |
|-------------------|--------------------------|
|                   | MS I | MS II | MS III | MS IV | MS V | MS VI |
| Terbinafine hydrochloride (g) | 1    | 1     | 1      | 1    | 1    | 1     |
| Ethyl cellulose (g)    | 0.1  | 0.2   | 0.3    | 0.4  | 0.5  | 0.6   |
| Dichloromethane (ml)  | 5    | 5     | 5      | 5    | 5    | 5     |
| PVA (g)              | 0.05 | 0.05  | 0.05   | 0.05 | 0.05 | 0.05  |
| Distilled water (ml) | 200  | 200   | 200    | 200  | 200  | 200   |

### Table 2: Formulation of gels containing THCI microsponges

| Ingredients         | THMG-1 | THMG-2 | THMG-3 | THMG-4 |
|---------------------|--------|--------|--------|--------|
| Microsponge Eqv to THCI 0.1% w/v | 1      | 1      | 1      | 1      |
| Carbopol1940(g)      | 0.25   | 0.35   | 0.45   | 0.55   |
| Ethanol(ml)          | 15     | 15     | 15     | 15     |
| PEG 400(g)           | 15     | 15     | 15     | 15     |
| Triethanolamine(g)   | 5      | 5      | 5      | 5      |
| Water up to (ml)     | 100    | 100    | 100    | 100    |
In vivo study

Male guinea pigs (250-350 g) were used. The hair was removed from their flanks with an electrical clipper. The area of skin (20 mm diameter) on each flank was scarified with coarse sandpaper. Scarified skin was infected with few drops of the culture of *Candida albicans*. Infected guinea pigs were housed individually in wire bottom cages and were provided food and water *ad libitum*. The fungal infection was induced on the guinea pig for the first 3 d, on the 4th day; the skin of guinea pig was scraped and was cultivated in sabouraud dextrose agar media plates. The inoculated plates were incubated at 27 °C for 48 h. The colonies were measured after incubation. On the 4th day, treatment was initiated by topical application to the infected sites with gel formulation for another 4 d. On the 8th and 11th day skin was again scraped and cultured on sabouraud dextrose agar plate respectively and further treatment was done. The inoculated plates were incubated at 27 °C for 48 h and examined for growth of colonies [36,37].

RESULTS AND DISCUSSION

In the quasi-emulsion solvent diffusion method, the formation of microsponges could be by the rapid diffusion of dichloromethane (A good solvent for the polymer and drug) into the aqueous medium, might reduce the solubility of the polymer in the droplets, since the polymer was insoluble in water. The instant mixing of dichloromethane and water at the interface of the droplets induced precipitation of the polymer, thus forming a shell enclosing the dichloromethane and the dissolved drug. The finely dispersed droplets of the polymer solution of the drug were solidified in the aqueous phase via diffusion of the solvent [38].

FTIR spectra of pure Terbinafine hydrochloride, Ethylcellulose and mixture were shown in fig. 1, 2 and 3. Fundamental peaks of terbinafine It clearly indicates that the FTIR spectra of pure Terbinafine hydrochloride were compatible with Ethylcellulose polymer.

![Fig. 1: FTIR spectra of Terbinafine hydrochloride](image1)

![Fig. 2: FTIR spectra of Ethylcellulose](image2)

![Fig. 3: FTIR spectra of microsponge formulation](image3)

The scanning electron photograph of the microsponge is shown in fig. 4. It was observed by SEM analysis that the microsponges were finely spherical and uniform. Microscopy studies showed that THCI microsponges contained pores. The pores were induced by the diffusion of the solvent from the surface of the microparticles. The appearance of the particles was such that they were termed microsponges.
Changing drug: polymer ratio has a considerable effect on the size of the prepared THCI microsponge. Increasing the polymer fraction significantly increased the particle size as shown in table 3. This could probably be due to increasing the amount of polymer available per microsponge, hence larger particle size was obtained.

The loading efficiency of terbinafine hydrochloride microsponge formulations is given in table 3. The loading efficiency calculated for all microsponges ranged from 85.5 to 92%. The highest loading efficiency was found for the MS IV formulation, where a greater amount of drug was encapsulated. The production yield of Terbinafine hydrochloride microsponge formulations is given in table 3. Production yield calculated for all microsponges ranged from 65.75 to 78.66%. From the production yields of Terbinafine hydrochloride microsponge formulations, it was indicated that increasing the drug: polymer ratio to some extent increased the production yield.

Table 3: Particle size, production yield and loading efficiency of THCI microsponges

| Formulation code | Particle size (µm) | Production yield (%) | Drug loading (%) |
|------------------|--------------------|----------------------|------------------|
| MS I             | 43.8±0.15          | 65.75±0.45           | 85.5±0.64        |
| MS II            | 44.8±0.34          | 67.33±0.54           | 86.5±0.32        |
| MS III           | 45.6±0.65          | 68±0.76              | 90.5±0.54        |
| MS IV            | 48.2±0.54          | 78.6±0.65            | 92±0.45          |
| MS V             | 46.2±0.32          | 72.5±0.78            | 91.5±0.32        |
| MS VI            | 48.5±0.43          | 70.57±0.24           | 90±0.45          |

The THCI release from the microsponge formulations is shown in fig. 5 and table 4. The fig. shows that, generally, the release rate was high during the first two hours then the microsponges were able to sustain the release of THCI for more than 8 h in most formulations as shown in table 4. THCI release kinetics of microsponges on the basis of the highest $r^2$ can be explained by Higuchi diffusion mode (data not shown). Based on the above characterization MS IV (having acceptable yield, particle size, high entrapment efficiency, and slow-release profile) was chosen as candidate formula and was subjected further in gel formulations.
observed for 6 h and was depicted in fig. 6 and table 6. The total amount of drug release was 75.63%, 79.4%, 69.4%, 64.9% and 58.8% observed at different time intervals for a period of 6 h for THMG I-IV and Marketed formulation (MF) respectively. The gel formulation (THMG II) showed the best release i.e. total amount of drug release was 79.4 %. From the logarithmic plot of the release data log Q versus log t of THMG II, the diffusion exponent (n) and the kinetic constant (k) have been calculated, as shown in table 5. The results showed that n value of microsponges loaded gel is less than 0.5. This indicates that the mechanism of drug release is Fickian diffusion, and is controlled by the porosity of the microsponges.

The four gel formulations showed physical characteristics like spreadability, viscosity, pH and drug content, as given in table 5. The drug content of the formulations showed that the drug was uniformly distributed in the gels.

![Fig. 6: In vitro release profile of terbinafine hydrochloride from gel formulation (Values are expressed as mean±SD, n=3)](image)

| Time (h) | Formulation code | Spreadability (g, cm/s) | Viscosity(cps) | pH | Drug content (%) |
|---------|------------------|-------------------------|----------------|----|-----------------|
| THMG-I  | 17.6±0.13        | 3860±5                  | 6.7±0.3        | 82.8±0.28 |
| THMG-II | 18.1±0.24        | 3960±4                  | 6.2±0.2        | 87.6±0.87 |
| THMG-III| 16.5±0.26        | 4005±6                  | 6.8±0.4        | 85.2±0.71 |
| THMG-IV | 15.8±0.18        | 4206±2                  | 6.4±0.5        | 83.6±0.57 |
| Marketed Formulation | 18.3±0.33 | 3963±4                  | 6.2±0.1        | 88.9±0.85 |

(mean±SD, n=3)

The in vitro release profile of four THCI microsponge gels was observed for 6 h and was depicted in fig. 6 and table 6. The total amount of drug release was 75.63%, 79.4%, 69.4%, 64.9% and 84.8% observed at different time intervals for a period of 6 h for THMG I-IV and Marketed formulation (MF) respectively. The gel formulation (THMG II) showed the best release i.e. total amount of drug release was 79.4 %. From the logarithmic plot of the release data log Q versus log t of THMG II, the diffusion exponent (n) and the kinetic constant (k) have been calculated, as shown in table 5. The results showed that n value of microsponges loaded gel is less than 0.5. This indicates that the mechanism of drug release is Fickian diffusion, and is controlled by the porosity of the microsponges.

| Time (min) | Formulation code | MF | THMG-1 | THMG-2 | THMG-3 | THMG-4 |
|-----------|------------------|----|--------|--------|--------|--------|
| 0         | 0                 | 0  | 0      | 0      | 0      | 0      |
| 15        | 18.3±0.29         | 0  | 17.5±0.23 | 17.6±0.31 | 18.5±0.54 | 19.3±0.45 |
| 30        | 25.9±0.45         | 0  | 18.9±0.75 | 23.6±0.54 | 26.6±0.36 | 24.3±0.25 |
| 60        | 32.1±0.76         | 28.4±0.85 | 29.6±0.43 | 31.0±0.76 | 28.6±0.73 |
| 90        | 40.2±0.34         | 32.49±0.75 | 38.63±0.41 | 36.8±0.64 | 36.3±0.64 |
| 180       | 55.3±0.65         | 46.55±0.53 | 47.3±0.74 | 43.3±0.83 | 42.6±0.87 |
| 240       | 65.2±0.39         | 53.21±0.88 | 58.8±0.65 | 55.6±0.67 | 49.8±0.36 |
| 300       | 71.1±0.76         | 64.21±0.59 | 69.3±0.27 | 63.3±0.87 | 55.8±0.64 |
| 360       | 84.8±0.56         | 75.63±0.61 | 79.4±0.29 | 69.4±0.56 | 64.9±0.77 |

(mean±SD, n=3)
Table 5: Kinetic treatment of the release data of THCl from microsponge loaded carbopol gel (THMG II)

| Release order | Correlation coefficient |
|---------------|------------------------|
| Zero-order    | 0.945                  |
| First-order   | 0.930                  |
| Diffusion     | 0.978                  |
| Peppas        | 0.842                  |

Antifungal activities for gels are shown in Table 6. Formulation THMG II showed a zone of inhibition 15.8 mm in comparison with the marketed formulation and pure drug with 16.0 and 19.2 mm respectively.

Table 6: Results of the antifungal study

| Formulation | Zone of Inhibition |
|-------------|--------------------|
| THMG-I      | 14.3±0.16          |
| THMG-II     | 15.8±0.23          |
| THMG-III    | 13.5±0.45          |
| THMG-IV     | 12.5±0.47          |
| MF          | 16±0.65            |
| Pure drug   | 19.2±0.25          |
| Control     | .....              |

(mean±SD, n=3)

The results of the in vivo antifungal activity on guinea pig skin are shown in table 7. The fungal infection was induced on the guinea pig for the first 3 d, on the 4th day, the skin of guinea pig was scraped and was cultivated in sabouraud dextrose agar media plates and colony count was observed more than 50 for formulation THMG I-IV, MF and control respectively.

The treatment of the gel formulation was started from 4th day applying for the next 4 d and studied with the effectiveness of gel on fungal inhibition. After 8th day the skin of the guinea pig was again scraped and checked for the growth of the colony in sabouraud dextrose agar plate. Colony count was observed 40, 30, 38, 35, 32 and more than 50 for formulation THMG I-IV, MF, and control, respectively. Similarly, on the 11th day, the skin of guinea pig was again scraped and checked for the growth of the colony in sabouraud dextrose agar plate. Colony count was observed 21, 13,19,15,12 and more than 50 for formulation THMG I-IV, MF, and control, respectively.

Antifungal study and in vivo study results showed that formulation THMG II showed good inhibition of fungal infection in comparison with the marketed formulation and control. These studies were carried out in the Pharmacology laboratories of the College of Pharmaceutical Sciences, Andhra University which is approved by the institutional animal ethics committee and CPCSEA (Regd. No. 516-01/A/CPCSEA) for experimentation on animals.

Table 7: In vivo antifungal study on the guinea pig

| Formulation | Colonies | 4th day | 8th day | 11th day |
|-------------|----------|---------|---------|----------|
| THMG-I      | >50      | 40      | 21      |
| THMG-II     | >50      | 30      | 12      |
| THMG-III    | >50      | 38      | 19      |
| THMG-IV     | >50      | 35      | 15      |
| MF          | >50      | 32      | 13      |
| Control     | >50      | >50     | >50     |

8th day inhibition of colony after application of formulated gel THMG-II, marketed formulation and control.
CONCLUSION

Microsphere based delivery system has been developed using quasi emulsion solvent diffusion method to provide a sustained release medication for topical delivery of Terbinafine Hydrochloride. The drug entrapment efficiency and the size of the prepared microspheres were affected by the drug: polymer ratio. Microsphere formulation MS IV which showed good results incorporated in different concentrations of carbopol and formulated as gels THMG I-IV. Among the four gels, THMG II showed better antifungal activity. A fickian diffusion which is controlled by the porosity of the microspheres is the mechanism of the drug release from the carbopol gel loaded with the selected microsphere formulation. As the gel has sustained-release characteristics the side effects have been minimized.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICTS OF INTERESTS

All the authors hereby declare that there are no conflicts of interest

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