

# Formulation and Evaluation of Antifungal Microsponge Loaded Gel

Pankaj Singh Khanka<sup>1</sup>, Kashif Hussain<sup>2</sup>

<sup>1</sup>Student, Department of Pharmacy, Gyani Inder Institute of Professional Studies, Dehradun, India

<sup>2</sup>Professor, Department of Pharmacy, Gyani Inder Institute of Professional Studies, Dehradun, India

**Abstract:** The purpose of present study aims to designs novel drug delivery system containing an antifungal drug and to prepare microsponge gel. Microsponge delivery system is unique technology for controlled release of active agents. Many formulations are available in market for treatment of topical fungal infection but drawback is effect is limited time period. As compare to conventional formulation, the microsponge gel is expected to remain on the skin for a longer time, gradually releasing drug over the time. Fungal infection is a common in these days, fungle infection occur when an individual fungus takes over an area of the body and is too much for the immune system to handle. Fungi can live in the air, soil, water, and plants. There are some fungi that live naturally in the human body.

**Keywords:** Antifungal Microsponge, Loaded Gel

## 1. Introduction

Microsponge is polymeric delivery system composed of porous microspheres. They are tiny sponge like spherical particles with a large porous surface. It is a novel technique of drug delivery mainly for control release and target specific drug delivery system.

Currently a lot of evaluation in delivery systems are being used to optimize the drug efficacy and cost-effectiveness of the drug, Microsponge delivery system (MDS) has been successively addressed for the controlled release of drugs onto the outer layer of skin (epidermis). Drug loaded microsponge consist of microporous beads, typically 10-25  $\mu\text{m}$  in diameter that possess a versatility to entrap wide range of active agents (medicine or therapeutic active agents). Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substance or material. Microsponge technology entrap drug substance and reduces harmful effects, improved stability, increased smoothness, and enhanced formulation flexibility. A numerous studies have proved that microsponge system are nonirritating, no allergenic in nature. This method is also being used now days in cosmetics skin care, sunscreens or clinical care. One of the best feature is it is self-sterilizing, it also useful in oral drug delivery, bone and tissue engineering. The unique properties of MDS made it ideal carrier of various drugs with shorter half-lives and drugs which are affected from first pass metabolism.

Main objective of microsponge is to minimizes or reduces drug dose and also minimizes side effects of drug and enhance

the stability. Now-a-days microsponge are one of the most popular because of their use of controlled release and targeted drug delivery system. Microsponges has ability to retain in skin cell or tissue and prevent the dose dumping in blood circulation, which may cause side effects. Microsponge system offers entrapment of active ingredients, improved stability, reduced side-effects, enhanced preparation and formulation flexibility. According to different studies microsponges system are non-allergic, nonirritating, non-mutagenic and non-toxic in nature. This method now involves in cosmetics, skin care, sunscreens and clinical prescription products.

### A. Characteristics of Microsponge drug delivery system

- Microsponge are stable over the pH from 1.5 to 11.
- Microsponges are stable up to 130 c temperature.
- Microsponges are compatible with many of active therapeutic material and excipients.
- Average pore size of microsponge is 25 $\mu$ , So there no specific need of sterilization.
- Approximately 38 to 62 % of drugs may entrapped in microsponge.
- Microsponges must be either fully miscible in a monomer or capable of being made miscible by the addition of a small amount of a water-immiscible solvent
- It must be inert with monomers and should not increase the viscosity of the mixture or formulation.
- It must be stable when in contact with the polymerization catalyst and under environment of polymerization.

### B. Advantages of Microsponges:

- It improves the flexibility of the formulation
- This formulation can extend the release pattern of drug; it can release the loaded drug up to 12 hours continuously.
- Microsponges are non-allergic
- It increases the patient compliance
- Drug directly applies on target organs or area.
- Drug loading capacity is higher than other topical preparations.
- Stable up to temperature 130c

- They are stable against the thermal, physical and chemical conditions.
- Improving physiological and pharmacological response.

C. Limitations

- The preparation uses organic solvents as porogens, which pose an environmental hazardous as some may be highly inflammable, posing a safety hazardous
- In some cases, the traces of residual monomers observed these are toxic and hazardous to health.

D. Gel

Gel is a semi solid formulation that has a pair of components which is liquid phase in rich. It has a character the continuous structure show like slid properties. After the application of gel the liquids are drying by the evaporation and, gels of drug are covering the skin.

Gels are as compare to the creams and other ointments give better drug release. These are highly bio-compatible that's why minimum risk of adverse reaction and inflammation. The dermatological use of gels has many property as thixotropic, easily remove, non- greasy, desirable spreadable, non-staining, emollients, compatible with the many excipients. Topical drug delivery systems are applying as directly on the body surface as external part by spraying, rubbing, spreading. The topical rout of administration is very common and it is use as treatment of skin disorder and local effects. Gels are often topically applied as emollients, or as occlusive dressing and also as protective for the local and systemic medication. Gels are defined as significant extent dilute cross linked system that is in the steady state no flow. Gels are sometimes called jellies.

E. Methods of Preparation of Microsponges

Mainly two types of preparation methods are used to prepare microsponges.

1. Liquid-liquid suspension polymerization
2. Quasi-emulsion solvent diffusion

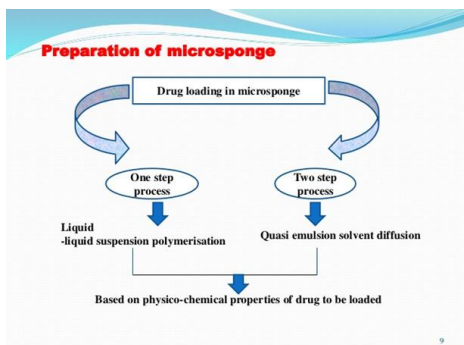


Fig. 1. Microsp sponge preparation types

1) Liquid-liquid suspension polymerization

A solution is prepared in which monomers and the API added, it should be considered that API should be immiscible in water. Then this phase is suspended in an aqueous phase

containing additive like surfactants and dispersant. This is agitated appropriate so that suspension can be promote. As the establishment of discrete droplets of desired sized found, catalyst is added so that monomer activates and polymerization effected. Monomer also can be activated by increasing the irradiation or temperature. As the polymerization process continues, a spherical structure is formed which containing thousands of microsponges bunched together like grapes, and forming interconnecting reservoirs.

After completion of the polymerization process the solid particles that formed by the process are recovered from the suspension. Then these solid particles are washed and processed until they are substantially ready for use. To produce the microsp sponge styrene and divinyl benzene or methyl methacrylate and ethylene glycol dimethacrylate can be used as a starting materials.

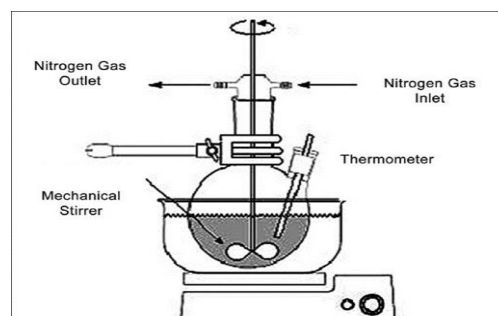


Fig. 2. Liquid-liquid suspension polymerization

2) Quasi-emulsion solvent diffusion

Dissolve the Eudragit RS 100 in ethyl alcohol to prepare inner organic phase, and then drug is added to this inner organic phase and then it is processed under ultra-sonication at 35°C for dissolving.

The inner phase is transfer into the polyvinyl alcohol solution in water (external phase). It is stir for 60 minutes and then this mixture is filter and microsp sponge separates. Microsponges are dry by placing it in an air-heated oven for 12 hours at 40°C. At the time of synthesis Ingredients can be entrapped in microsp sponge polymers, or if API is not able to withstand in polymerization conditions then preparation of the microsp sponge structure the ingredients can be loaded.

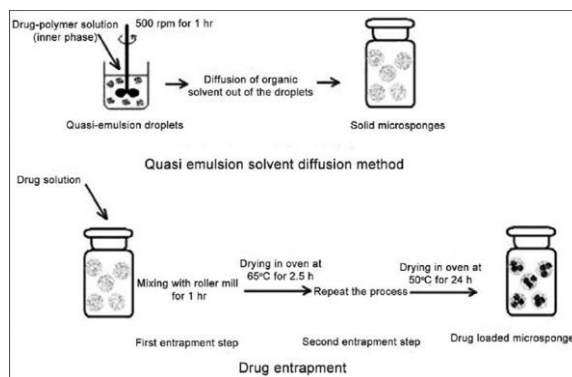


Fig. 3. Quasi-emulsion solvent diffusion

#### F. Evaluations

- Drug and excipients morphology and surface topography
- Determination of true density
- Loading efficacy and production yield
- Characterization of pore structure
- Drug release study
- Particle size determination

#### G. Preparation of drug loaded Microsponges

Microsponges were prepared by quasi emulsion solvent diffusion. The required amount of drug and polymer were weighed accurately and dissolved in 5ml of Dichloromethane: Ethanol (1:1) under sonication. Polyvinyl alcohol was weighed accurately and dissolved in distilled water at 60°C. The surfactant was allowed to cool to room temperature. The internal phase containing drug and polymer was added drop wise with the aid of syringe with stirring at 800 rpm until the complete diffusion of the external phase i.e. about 8 h. After complete diffusion of the external phase, the microsponges were filtered and dried overnight at room temperature.

### 2. Characterization of microsponges

- Particle Size and Size Distribution Analysis
- Shape and Surface Morphology of Microsponges
- Drug entrapment efficiency
- Production Yield
- In Vitro Drug Release Studies

#### A. Preparation of Microsponge loaded Topical gel

Gel formulation was developed using carbopol® 934 as gelling agent. The accurately weight quantity of carbopol® 934 (1% w/v) was dispersed in beakers containing adequate amount of water under constant stirring and allowed to hydrate for 24 h at room temperature. Later, glycerine and optimized microsponges formulation containing drug was incorporated into the carbopol gel with the help of mechanical stirrer at 25 rpm. Then, water was added to gel under constant stirring. The dispersion was neutralized using triethanolamine (0.5% w/w). The gel was allowed to stand overnight to remove entrapped air. The formulation was transferred to a suitable container and stored for further studies.

### 3. Evaluation of microsponges loaded gel formulations

The prepared gels were evaluated for different parameters such as pH, appearance, viscosity, spreadability, drug content and drug release, in vitro antifungal activity and stability studies with the aim of checking the efficacy of microsponges loaded gel formulations.

- *Appearance*: The prepared gel bases were inspected visually for clarity, colour and presence of any particles. Transparent gel was found in microsponges loaded carbopol gel.
- *pH*: 1g of microsponges loaded gel formulation was

dissolved in 100 ml water and the pH was determined with the help of digital pH meter. All the gels were tested for pH three times and average of three determinations was calculated.

#### A. Rheological Studies

- *Spreadability*: The spreadability studies of microsponges loaded gel formulations were carried out by keeping gel between two horizontal glass slides of standard dimension. 100 g weight was placed on top of the two slides so that the formulation gets uniformly spread. The weight was removed and excess formulation was scraped out [20]. The experiment was carried out in triplicate.

$$S = m. l / t$$

Where,

m = weight kept on the upper slide

l = length of glass slide

t = time taken in seconds.

- *Viscosity*: Viscosity of microsponges loaded gel formulation was determined using Brookfield viscometer with spindle No. 6 at 10 rpm at temperature 37±0.5°C [21].
- *Drug content*: 1 gram of gel formulation containing drug equivalent to 10 mg of drug was extracted and the volume was made up to 50 ml with ethanol. The resulting solution was filtered. Suitable dilutions of the filtrate were prepared with filtered phosphate buffer pH 5.5 and absorbance was measured at specific wavelength using UV spectrophotometer (Shimadzu UV-1208). All readings were taken in triplicate and average was calculated.
- *In vitro drug release studies*: The drug release studies of loaded microsponges were carried out using basket dissolution apparatus (USP Type I apparatus). 900ml of fresh phosphate buffer saline was used for the release studies. The temperature of the dissolution medium was controlled at 32±1°C with 150 rpm rotation speed. Microsponges equivalent to 50 mg of drug were weighed. At fixed time intervals, aliquots of samples were withdrawn and replaced by an equal volume of fresh dissolution medium to maintain the sink conditions. After suitable dilution, the samples were analyzed spectrophotometrically at specific nm (Shimadzu UV-1208) against blank.

The release studies were carried out for 12 h. Based on the evaluation characteristics, the optimized formulation of each polymer was incorporated into suitable gel bases and evaluated further. All the readings were repeated three times.

#### B. In vitro Drug Diffusion Studies

In vitro diffusion study was conducted using Keshary Chien (K-C) cell with an effective diffusion area of 2.0 cm<sup>2</sup> and a cell volume of 25 mL. Phosphate Buffer Saline (pH 5.5) was used as dissolution medium, and system was there More gulated with a water jacket at 37±1°C under constant stirring. The cellophane membrane (0.45 µm) previously soaked overnight in dissolution medium was mounted onto K-C cell. Microsponges loaded gel formulation was assessed for diffusion study. 1ml of

sample aliquots were withdrawn at predetermined time intervals and subsequently replenished with an equal amount of phosphate buffer. The samples were filtered, diluted and analyzed using UV spectrophotometer at 272nm against blank. The release studies were carried out for 10 h and the release data were analyzed by means of diverse mathematical models to know release kinetics.

### C. *In vitro* Antifungal Study

For antifungal studies, sabouraud's dextrose agar was utilized. The media was taken in a 250 ml conical flask and dissolved in 100 ml of distilled water. The pH was adjusted to  $5.6 \pm 0.2$ . The medium was sterilized in an autoclave at 15 lbs (121oC) for 15 min. After sterilization, the medium was allowed to cool down at room temperature and poured into presterilized petridishes inside a laminar airflow unit with layer of uniform thickness. Medium filled petridishes were kept in laminar airflow unit for solidification, after which a loop of diluted suspension culture (*Candida albicans*) in nutrient broth was added on to the surface of solidified agar and was spread uniformly with the help of spreader. Culture was then stabilized, subsequent to which 6mm diameter cups were punched using sterile cork borer and scraped out from the petridish.

Microsponges loaded gel formulation and marketed formulation of same drug was fed into the cup separately. The petridishes were then incubated for 24 h at 37 °C. After incubation the zone of inhibition was measured.

### D. Release Kinetics

Data obtained from release studies of gels was subjected to kinetic treatment such as zero order drug release, first order drug release, Higuchi's square root plot and Korsmeyer-Peppas model to obtain the order of release and release mechanism.

### E. Stability studies

Optimized gel formulation was subjected to stability testing as per ICH guidelines. Gel was filled in clean, glass vials and various replicates were kept at  $5^{\circ}\text{C} \pm 2$ ,  $25^{\circ}\text{C} \pm 2$  and  $40^{\circ}\text{C}/75\%$  RH in a humidity chamber for a period of 60 days. Gel was assessed for change in appearance and drug content at an interval of 7, 15, 30, 45 and 60 days.

## 4. Result and discussion

Antifungal drug loaded microsponges were successfully formulated using quasi-emulsion solvent diffusion technique. The technique used for the fabrication is very simple, replicable and quick. Polymer and polyvinyl alcohol were used as microsponges forming polymer and surfactant respectively. 23 factorial design was applied for the optimization of formulation parameters and process variables. Prior to application of factorial design, a broad range optimization was carried out so as to widely select the parameters for further experimentation. Stability studies results of optimized microsponges formulation loaded carbopol gel displayed no significant changes in the

physical appearance and drug content which clearly suggest that the formulations are stable at  $5^{\circ}\text{C}$  and  $25^{\circ}\text{C}$ . However, some drug degradation was observed at  $40^{\circ}\text{C}/75\%$  RH.

## 5. Conclusion

For the existing era and future prospects, sustained drug delivery by means of polymer based systems has been recommended to exist owing to frequent probable benefits for technical and cost effective grounds. The notion behind the development of polymer based microsphere delivery system was to release the active in a recurrent approach for wide time period to cut the dosing frequency and to improve bioavailability. The technique executed was emulsion solvent diffusion that was found to be simple, reproducible and rapid. Fabricated microsponges were spherical in shape and have porous texture. Microsphere based gel reflected Higuchi release kinetics and controlled by non fickian release mechanism. Thus, gel comprising microsponges was found as a potential drug delivery system presenting prolonged release of antifungal drug in the treatment of diaper dermatitis.

## References

- [1] Michael J. Rathbone, Jonath Hadgraft, 'Modified Release Drug Delivery technology- Dermal and Transdermal delivery, Marcell Dekkar, New-York, 2002, page no. 471-475.
- [2] Nayak S. H, Nkhat P. D, Yeole P. G. The Indian Pharmacist. 2004; 3(27): 7-14.
- [3] Jain N, Sharma P. K, Banik A. Recent advances on microsphere delivery system.2011; (8): 2.
- [4] Nacht S and Katz M. The microsphere – A novel topical programmable delivery system. In: Osborne DW and Amman AH, editors. Topical Drug Delivery Formulation. Marcel Dekker. NewYork Basel 1990;299-325.
- [5] Pavani V, Vinod M and Anantha P: Design, formulation and invitro evaluation of microsponges based gel for topical delivery of Luliconazole. Int J Pharm Sci Res 2017;8(10): 4222-29.
- [6] Roop K Khar, SP Vyas, Farhad J Ahmad, Gaurav K Jain. The theory and practice of industrial pharmacy. CBS Publishers. 4<sup>th</sup> edition. 2013; 714-756.
- [7] Rangasamy M, Parthiban K G. Recent advances in novel drug delivery systems. International Journal of Ayurveda and Pharmacy. 2010; 1(2): 316-326.
- [8] Chein Y W. Novel drug delivery systems. Second Indian edition. Published by Marcel Dekker INC, 2007; (50):1-42.
- [9] Amer RI, Elosaily GH. 2016. Formulation and Evaluation of Pulsatile Drug Delivery of Melatonin Using Pulsincap Technology. Global Journal for Research Analysis, 5(4):101-1065.,
- [10] Avhad PS, Patil PB. 2016. A new era in topical formulations microsphere drug delivery system. International Journal of Pharmaceutical Sciences and Research, 7(7): 2756- 2761.
- [11] Karpe MS ,Bagde SA, Jadhav NC, Kadam VJ. 2016. Formulation and evaluation of topical microsphere based gel of bifonazole. Indo American Journal of Pharmaceutical Research, 6(4): 5307-5319.
- [12] Bhandare CR, Katti SA. 2016. Formulation of microsponges of risperidone HCL. International Journal of Research in Pharmacy and Chemistry, 6(3): 518-527
- [13] Shah V. P., (1989) Determination of In-vitro Release from Hydrocortisone Creams. International Journal of Pharmaceutics. 53: 53-59.
- [14] Vikas Jain and Ranjit Singh, Dicyclomine-loaded Eudragit®-based Microsphere with Potential for Colonic Delivery: Preparation and Characterization, Tropical Journal of Pharmaceutical Research, February 2010; 9 (1): 67-72.

- [15] Sato T, Kanke M, Schroeder G, Deluca P. Porous biodegradable microspheres for controlled drug delivery. I: Assessment of processing conditions and solvent removal techniques. *Pharm Res.* 1988; 5:21 -30.
- [16] Rajnish K, Sanjay K, Manish J, Nawaz A. (2006). Microsponge Drug Delivery Systems for Novel Topical Drug Delivery. *International Journal of Pharmaceutical Sciences*, 42(2), 299-30
- [17] Roop k khar, S P vyas, Farhad J Ahmad, Gaurav K Jain. *The theory and practice of industrial pharmacy.* CBS Publishers. 4<sup>th</sup> edition. 2013; 714-756.
- [18] Rangasamy M, Parthiban K G. Recent advances in novel drug delivery systems. *International Journal of Ayurveda and Pharmacy.* 2010; 1(2): 316-326.
- [19] Chein Y W. *Novel drug delivery systems.* Second Indian edition. Published by Marcel Dekker INC, 2007; (50):1-42.
- [20] Nino M, Calabro G, Santoianni P. Topical delivery of active principles: The field of dermatological research. *Dermatology online Journal.* 2010 16(1):4.
- [21] Ramadevi B, Ramesetti RD, Srinath N, Chaitanya DSP. Microsponges: as a novel imperative for drug delivery system. *RJPT* 2013; 13-14.
- [22] Upadhye SS, Kothali BK, Apte AK, Patil AA, Danole AB. A review on microsponge drug delivery system. *IJPRBS.*2016; 5(1) 152-166.
- [23] Patel EK and Oswal RJ. Nanosponges and microsponges: a novel drug delivery system. *IJRPC.* 2012; 2(2):237-244.
- [24] Mohite PB, Khanage SG, Harishchander VS, Shirsath Y. Recent advances in microsponges drug delivery system. *J Crit. Rev.* 2016; 3(1):9-16.
- [25] Pradhan SK. Microsponges as versatile tool for drug delivery system. *IJRPC.* 2011; 1(2):243-258.
- [26] Kadam VV, Patel VI, Karpe SM, Kadam VJ. Design, development and evaluation of celecoxib- loaded microsponges- based topical gel formulation. *Applied clinical research. Clinical trial and regulatory affairs.* 2016; 3(1):44-55.
- [27] Saboji JK, Manvi FV, Gadad AP, Patel BD. Formulation and evaluation of ketoconazole microsponge gel by quasi emulsion solvent diffusion. *J Cell Tissue Res.* 11(1), 2011, 2691-2696.
- [28] Mayur K, Ramesh K, Nitin J, Prashant P, Rajendra G, Jeevan N, Ethyl cellulose based microsponge delivery system for antifungal vaginal gels of tioconazole, *J Drug Deli Therap.* 2013; 3(6), 14-20.
- [29] Jain V and Singh R. Development and characterization of Eudragit RS 100 loaded microsponges and its colonic delivery using natural polysaccharides. *Acta Pol. Pharm. Drug Res.* 2010; 67, 407-415.
- [30] Rao NGR, Rao KP and Muthalik S. Clinical studies and antimicrobial activity of ciprofloxacin hydrochloride medicated dental gels for periodontal infection. *Asian J Pharm.* 2009; 3(2): 125-134.
- [31] Loganathan V, Manimaran S, Sulaiman A, Reddy MVS, Senthil BK and Rajaseskar A. The effect of polymers and permeation enhancers of flubiprofen from gel formulations. *Indian J Pharm Sci.* 2001; 63(3): 200-204.
- [32] Hussain H, Dhyani A, Juyal D, Bahuguna A. Formulation and evaluation of gel-loaded microsponges of diclofenac sodium for topical delivery. *The Pharma Innovation Journal* 2014; 3(10): 58-63.
- [33] Rizkalla Z, Latif Aziz CM, Soliman R. In-vitro and invivo evaluation of hydroxyzine hydrochloride microsponges for topical delivery. *AAPS Pharm. Sci. Technol.* 2011; 12, 989-1001.
- [34] Shetgaonkar T, Narayana Charyulu R. Microsponge Drug Delivery of Terbinafine Hydrochloride for Topical Application. *Int J Pharm Sci Rev Res.* 2015;33(1):48-54.
- [35] Dash S, Murthy PN, Nath L, Chowdhury P, Kinetic modeling on drug release from controlled drug delivery systems. *Acta Poloniae Pharmaceutica Drug Res.* 2010; 67(3): 217-223.