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# Microsponge Mediated Targeted Drug Delivery System for the Treatment of Fungal Infection

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## ABSTRACT

The microsponge delivery system is a profoundly cross-connected permeable, polymeric microsphere, polymeric system comprising of permeable microspheres that can capture and delivery them into the skin throughout a significant stretch of time. This system furnishes broadened discharge with diminish disturbance, better resistance, worked on warm, physical and compound steadiness. The principal objective of any prescription transport structure is to achieve needed gathering of the medicine in blood or tissue, which is therapeutically incredible and non-noxious for a somewhat long period in this review different strategy for planning of microsponge drug delivery system are considered. Different benefits are likewise given which shows the significance of this strategy for the delivery of medication over the other medication delivery system. An ever increasing number of advancements in delivery system are being coordinated to enhance the adequacy and cost viability of the treatment. Microsponge innovation offer entanglement of fixing and is accepted to contribute towards lessen incidental effects, further developed strength, expanded style, and improved plan adaptability. Furthermore various examinations have affirmed that microsponge systems are not bothering, non-mutagenic, non-allergenic and non-harmful Microsponge delivery innovation is being utilized at present in beauty care products, over the counter, healthy skin, and sunscreen and remedy items.

**Key Words:** Microsponge, Target release, Topical formulation, Solvent diffusion method, Scanning electron microscopy, Drug delivery, Control release

## INTRODUCTION

A Microsponges Delivery System (MDS) is "Protected, exceptionally cross-connected, permeable, polymeric microspheres, and polymeric framework comprising of permeable microspheres that can capture wide scope of actives and afterward discharge them into the skin throughout a period and because of trigger".10-25 microns in measurement. Miniature wipe polymers have the flexibility to stack a wide scope of actives giving the advantages of improved item viability, gentleness, bearableness, and stretched out wear to a wide scope of skin treatments. A few unsurprising and solid frameworks were created for foundational drugs under the heading of transdermal conveyance framework (TDS) utilizing the skin as entry way of section. It has worked on the adequacy and security of many medications. Yet, TDS isn't commonsense for conveyance of materials whose last objective is skin itself. Hence the need exists for framework to boost measure of time that a functioning fixing is available

either on skin surface or inside the epidermis, while limiting its transdermal entrance in the body.<sup>1</sup>

The microsponge innovation was created by Won in1987, and the first licenses were appointed to Advanced Polymer Systems, Inc. This Company fostered an enormous number of varieties of the systems and those are applied to the restorative just as over-the-counter (OTC)also remedy drug items. At the current time, this intriguing innovation has been authorized to Cardinal Health, Inc., for use in effective items.<sup>2</sup>

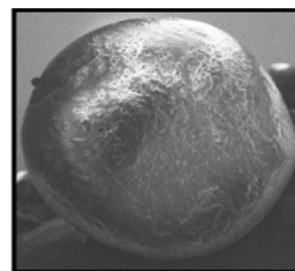


Figure 1: Typical diagram of microsponge.

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The checking electron microscopy of the microsponge molecule uncovers that its interior design as the “pack of marbles”. The porosity is because of the interstitial spaces between the marbles. The interstitial pores can entangle many wide scopes of dynamic fixings like emollients, scents, fundamental oils, and sunscreens, hostile to infective and calming specialists. These captured microsponges may then coordinated or figured into item frames, like creams, moisturizers, powders, cleansers, cases and tablets. At the point when these items are applied the ensnared material gets conveyed to the skin in a controlled time discharge design or a pre-customized way using a few distinctive triggers, scouring or squeezing the Microsponge after it has been applied to the skin, hoists skin surface temperature presenting solvents for the captured materials like water, liquor or even sweat and controlling the pace of vanishing. Dynamic fixings entangled in the permeable polymeric design show modified conduct, concerning their delivery, which is limited and delayed.<sup>2</sup>

#### ► Potential features or characteristic of microsponge drug delivery systems:

1. Microsponges show adequate soundness over pH going from 1 to 11 and at high temperatures (up to 130°C).
2. Microsponges show great similarity with different vehicles and ingredients.
3. Microsponges have high entanglement productivity up to 50 to 60%.
4. Microsponges are described by free streaming properties.
5. The normal pore size of microsponges is little (0.25 µm) in a method for forestalling the entrance of microbes, in this way they do not need cleansing or expansion of preservatives.
6. Microsponges are non-allergenic, non-bothering, non-mutagenic and non-toxic.
7. Microsponges can ingest oil up to multiple times their weight without drying.<sup>3</sup>

#### ► Advantages of microsponge drug delivery system:

- Microcapsules can't typically control the delivery pace of the dynamic drug fixings (API). When the divider is burst the API held inside the microcapsules will be delivered. Can the MDS can do it, is the issue.
- Liposomes experience the ill effects of a lower pay load, troublesome plan, restricted synthetic strength, and microbial precariousness. Do the MDS have a wide scope of compound security and would they say they are not difficult to detail?
- MDS have solidness over a pH scope of 1-11.
- Stable up to temperature 130C.
- Pay load is up to 50 60%.
- Free streaming and financially savvy.
- Microsponges are tiny circles equipped for retaining skin discharges, thusly, decreasing slickness and sparkle from the skin

- Enhanced product performance.
- Extended release.
- Diminish irritation and hence enhanced patient Compliance.
- Improved product elegancy.
- Improved oil control as it can absorb oil up to 6 times its weight without drying.
- Allows for novel product forms.
- Improves efficacy in treatment.
- Cure or control confirm more promptly.
- Further develop control of condition.
- Further develop bioavailability of same medications
- Adaptability to foster novel item shapes.
- Non-aggravating, non-mutagenic, non-allergenic and non-harmful
- Further develops steadiness, warm, physical and synthetic security
- Permits joining of immiscible items.
- Improves material processing e.g. liquid can be converted to powders.<sup>4</sup>

#### ► Application of microsponge:

Microsponge conveyance frameworks are utilized to upgrade the security, viability and tasteful nature of effective solution, over-the-counter and individual consideration items. Items being worked on or in the commercial center use the Topical Microsponge frameworks in three essential ways:

1. As repositories delivering dynamic fixings throughout a lengthy timeframe,
2. As repositories for retaining unfortunate substances, for example, overabundance skin oils, or
3. As shut compartments holding fixings from the skin for shallow activity.

Delivering of dynamic fixings from ordinary effective definitions throughout a lengthy timeframe is very troublesome. Beauty care products and skin health management arrangements are planned to work just on the external layers of the skin. The average dynamic fixing in traditional items is available in a moderately high focus and, when applied to the skin, might be quickly retained. The normal outcome is overmedication, trailed by a time of under medicine until the following application. Rashes and more genuine incidental effects can happen when the dynamic fixings quickly infiltrate underneath the skin's surface. Microsponge innovation is intended to permit a drawn out pace of arrival of the dynamic fixings, accordingly offering expected decrease in the secondary effects while keeping up with the restorative viability. Microsponges are permeable, polymeric microspheres that are utilized for the most part for effective and as of late for oral organization. Microsponges are intended to convey a drug dynamic fixing productively at the base portion and furthermore to improve steadiness, lessen incidental effects and change drug discharge. (Displayed in Table no.1)

**Table 1**

Sr. no	Active agents	Formulations
	Anti-acne	Kept up with viability with diminished skin bothering.
	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
	Anti-fungals	Sustained release of actives
	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Diminished disagreeable scent with brought down disturbance with expanded wellbeing and adequacy.
	Antipruritics	Broadened and further developed action
	Sunscreens	Dependable item viability, with further developed insurance against burns from the sun and sun related wounds even at raised fixation and with decreased irritancy and refinement
	Skin depigmenting specialists for example hydroquinone	Further created change against oxidation with additional created ampleness and slick appeal.
	Rubefaciants	Prolonged activity with reduced irritancy greasiness and odour.

### ► Composition of microsponge:

Different polymers utilized in manufacture of microsponges for effective application bring about arrangement of a microsponge 'confine'. According to distributed writing, polymers investigated up to this point incorporate polymethacrylates or Eudragit® polymers (EudragitRS100, Eudragit RSPO, Eudragit S100), polylactide-co-glycoliccorrosive, polylactic corrosive, polydivinyl benzene, polyhydroxy butyrate and ethyl cellulose. Eudragit RS100 is the most generally concentrated on polymer, inferable from its adaptable nature. The wide scope of Eudragit polymers, contrasting in control, dissolvability further more water penetrability, considers exceptionally custom-made delivery qualities in this framework, working with a wide scope of choices to accomplish the ideal presentation. Polymers having a place with polymethacrylate classification are Food and Drug Organization (FDA) supported, protected, non-harmful and monetary excipients, generally utilized in the drug business. The adaptability to join diverse polymethacrylate polymers offers a superior control on drug discharge conduct, particularly because of medication methacrylate-polymer cooperation. Being an establishment material for microsponges, ethyl cellulose is too utilized for designing of microsponges because of its nonirritating, nontoxic and no allergenic nature. Another polymer, polydivinyl benzene, has been accounted for the creating of permeable microspheres by fluid suspension polymerization method. Albeit, a few polymers have been investigated of late, yet just couple of studies has been accounted for with biodegradable polymers. They can be potential excipients for the advancement of microsponge transporters for drug focusing on. Henceforth, there is a solid need to investigate biodegradable polymers for this conveyance framework. Adjacent to this, the decision of polymer should consider skin aggravation and dermal poisonousness potential. This being a main pressing issue in dermatological definitions, has been considered by a few gathering of analysts working in the area

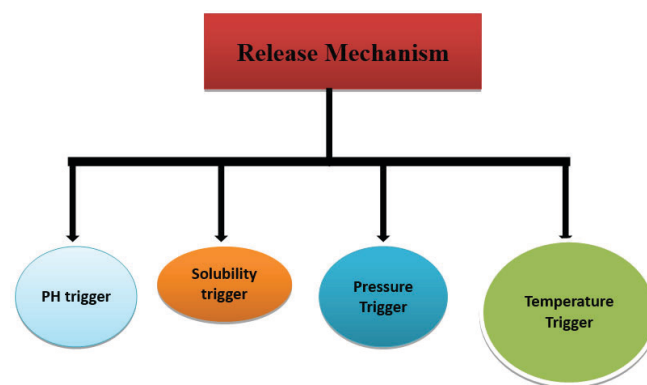
of microsponge based conveyance frameworks.<sup>5</sup>

### ► Properties of the actives for the entrapment into microsponges:

1. It ought to be either completely miscible in a monomer or equipped for being made miscible by the expansion of a modest quantity of a water-immiscible dissolvable.
2. It ought to be water immiscible or at most just marginally solvent.
3. It ought to be latent to monomers and ought not to build the consistency of the combination during plan.
4. It ought to be steady when in touch with the polymerization impetus and under states of polymerization.

The circular construction of the microsponges ought not to fall.<sup>6</sup>

► Release mechanism of microsponge Microsponge can be designed to release given amount of active ingredients over tie in response to one or more following external triggers



**Figure 2:** Release mechanism of microsponge triggered systems.

- i. Pressure: Rubbing or strain applied can set dynamic fixing free from microsponge onto skin.
- ii. Solubility: Microsponge stacked with water-solvent fixings like enemies of precipitants within the sight of water. The delivery can likewise be actuated by dissemination thinking about the segment coefficient of the fixing between the microsponge and the external framework.
- iii. Temperature change: Some entangled dynamic fixing can be excessively gooey at room temperature to stream precipitously from microsponge onto the skin. Expanded in skin temperature can bring about an expanded stream rate and thus discharge. Drug discharge from the skin semisolid plan can be examined by utilizing Franz-type static dissemination cells.

**PH set off:** Triggering the pH-based arrival of the dynamic can be accomplished by adjusting the covering on the microsponge. This has numerous applications in the medication conveyance.<sup>7</sup>

### 1. Fungal infection:

More often than not, the human species live in serene concurrence with the microorganisms that encompass them and just when the guard framework is harmed or the grouping of microbes comes to an especially high thickness, a disease might arise. Most contaminations pass by unnoticed yet now and then the tainting specialists do get a reaction of the body, which prompts clinically show signs and indications, a condition known as irresistible illness. Microbes, infections, parasites, growths, prions, worms, helminths have all been implicated in irresistible sicknesses, of which those brought about by normal infections are the most successive, and, until years and years prior, those by microorganisms the most dreaded. As procedures to control bacterial contaminations in patients improved, organisms turned into the most unsafe microorganisms. Yeasts and forms currently rank among the 10 most habitually disengaged microbes among patients in Intensive Care Units. Roughly 7% of all febrile scenes that happen during neutropenia can be credited certainly to intrusive contagious contaminations. *Candida* has turned into the fourth driving circulatory system detach in medical clinics in the USA, outperforming numerous generally infamous bacterial microbes. Since the eighties an expanded rate of intrusive contagious contaminations in patients who are not in an end phase of their fundamental sickness was observed. Moreover, because of the universal low dissection rate their rate is likely misjudged on the grounds that signs and manifestations are rarely trademark, which makes that numerous obtrusive parasitic diseases are not recognized while the patient is alive.<sup>8</sup>

#### ► Mycology:

Parasites are momentous organic entities and they establish a different realm for reasons for characterization. Parasites

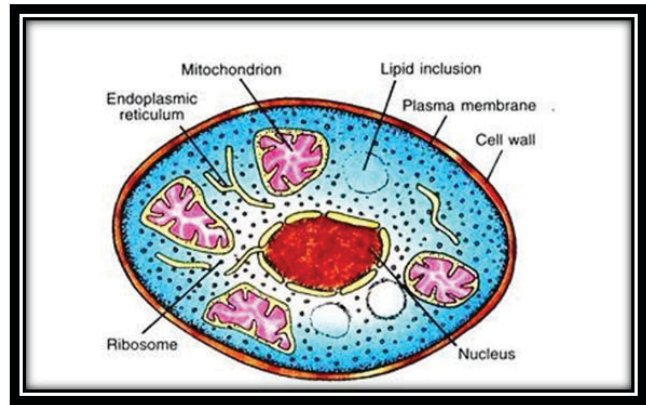


Figure 3: The fungus.

are eukaryotes; they have a film encompassing their core, their cells are a lot bigger than microorganisms and their sub-atomic cycles intently look like those of plants and creatures. In any case, in contrast to mammalian cells, growths quite often have an unbending cell divider made out of chitin items that encompass their plasma layer (see figure no.4). A growth is a vegetative organic entity and is most certainly not a plant either on the grounds that parasites don't blend chlorophyll. It is non-motile living thing and its fundamental primary unit comprises of either a chain of round and hollow cells (hyphae) or a unicellular structure, or both. The most widely recognized species like *Aspergillus* and *Candida* are tracked down wherever on the planet. Gardens, jungle gyms, houses, lodgings, emergency clinics and surprisingly the skin and mucous layers have been recognized as wellsprings of organisms that caused hazardous diseases.<sup>9</sup>

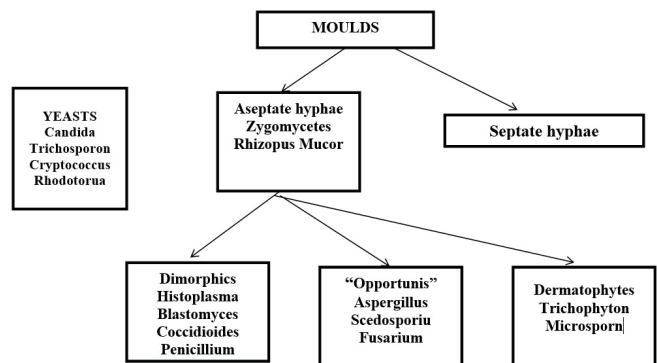


Figure 4: Classification of fungus.

#### ► Pathophysiology of fungal infections:

A couple of the organisms pathogenic for people are adequately harmful to contaminate a sound host. Most are relatively innocuous except if they experience an immune-compromised patient, in whom a debilitated guard framework grants them to attack the body. Under typical conditions, the unblemished epithelial surfaces of the gastrointestinal lot will

forbid attack by miniature living beings and the mucociliary hindrance of the respiratory parcel forestalls goal of parasitic cells and spores, while, interestingly, dead or harmed tissue might transform into a favorable place for contamination. Therefore intrusive contagious diseases must be positioned among the commonly crafty contaminations.<sup>10</sup>

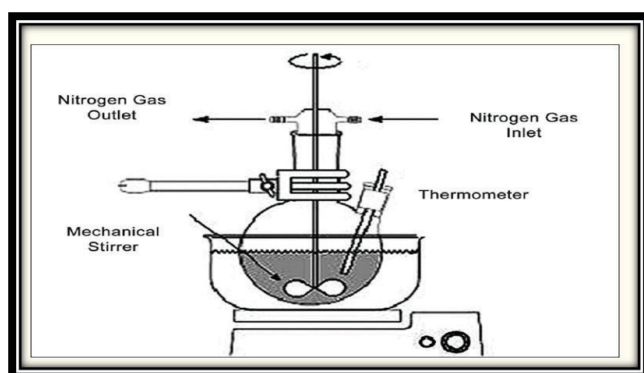
### Method of preparation of microsponges:

The microsponge is formulated by two ways the one step process or by two step processes discussed in liquid-liquid suspension polymerization and Quasi emulsion solvent diffusion method which are based on the physiochemical properties of the drug.

#### 1. Liquid-liquid suspension polymerization:

As a general rule, an answer is made involving monomers and dynamic fixing which are immiscible with water. This stage is then suspended with fomentation in a watery stage, ordinarily it containing added substances, like surfactant and dispersants, to shape a suspension. When the suspension is set up with discrete beads of the ideal size, polymerization is affected by enacting the monomers either by catalysis, increment temperature or illumination.

In polymerization process in which it delivered 1000 of microsponge confine which are round in structure interconnected with one another its appear as though a grapes bundle. On consummation of polymerization delivered strong particles were recuperated from the suspension. Particles are washed and dried for additional utilization.<sup>11</sup>

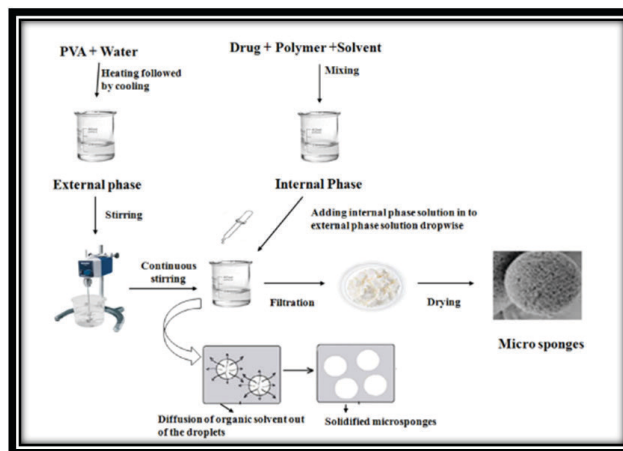


**Figure 5:** Microsponge preparation by liquid-liquid suspension polymerization.

#### 2. Quasi-emulsion solvent diffusion:

This technique is by and large having two stages, initial step is arrangement of the inward stage and second step is the development of outer stage. This strategy is by and large utilized for the planning of oral and effective microsponges. In the internal natural stage first and foremost polymer is disintegrated in ethyl liquor and medication is broken up in this arrangement by ultra-sonication at room temperature. The

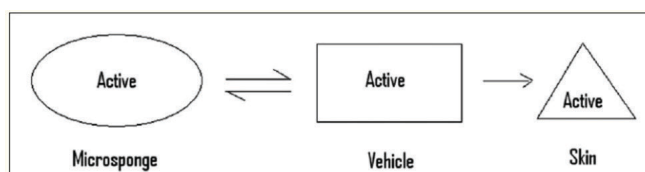
external stage comprises PVA arrangement in water. The arrangement is blended and separated for additional utilization. The inward stage is blended in the external stage drop astute with the assistance of mechanical stirrer. After the blending the semi emulsion drop was shaped which might facilitate dissipation of natural dissolvable produces the strong microsponges confine. The pre-arranged microsponge are sifted and dried in stove for 12 hr.<sup>12</sup>



**Figure 6:** Microsponge is prepared by Quasi-emulsion solvent diffusion method.

#### Mechanism of action:

For the active material to emerge from the matrix of the Microsponge particle at a pre-determined rate, a number of parameters can be modified taking into consideration the physical-chemical characteristics of the active agent and the environment. The vehicle in which the polymer resides plays an important role in the release rate of active agent from the system. Initially, there is equilibrium between the concentration of active agent in the polymer and in the vehicle as the skin depletes the concentration of the active agent from the vehicle, the MDS releases more active agent in response to the demand caused by the shift in the equilibrium. A continuous and steady release of active agent onto the skin is accomplished with such a system. In addition, as opposed to conventional topical formulations, the MDS can act as a reservoir and continue to release active agent to the skin even after the vehicle has been absorbed by the skin or has dried out.<sup>13</sup>



**Figure 7:** Schematic representation of the distribution of the loaded material (active) on skin.

## Evaluation of microsponge:

The microsponge are evaluated by the following parameters

- Particle size and size distribution analysis
- Drug content
- Entrapment efficiency
- Angle of repose
- Compressibility index
- Hausner's ratio
- Determination of density:
  - i. Bulk density
  - ii. Tapped density

### ► Production yield:

Microsponge production yield was determined by formula mentioned below.

$$\text{Production yield (PY)} = \frac{\text{Practical mass of microsponge} \times 100}{\text{Theoretical mass (Polymer + Drug)}}$$

### ► Scanning electron microscopy:

The surface topography and morphology of prepared microsponge were examined with a scanning electron microscope. For this method using double adhesive tape, samples were mounted on a metal stub and coating with platinum/ palladium alloy under vacuum was done.

### ► Particle size analysis:

Microsponge particle size analysis was studied by using particle size analyzer. Prepared microsponge are dispersed in double distilled water before running the sample in instrument to ensure the light scattering signal was within the sensitivity range of the instrument. The analysis of microsponge was carried out at room temperature, keeping the angle of detection at 90°.

### ► Infrared spectroscopy:

Infrared spectroscopy was determined by Fourier transform Infrared Spectrophotometer with KBr pellet method.

### ► Differential scanning calorimetry (DSC):

To find the interaction between the drug and excipients thermal analysis is an important evaluation technique.

The interaction can be identified by with any changes in the thermogram. The thermogram of drug was obtained using the DSC instrument. The powder sample of microsponge was kept in the aluminum pan and heated at a constant rate of 100 C/ min over a temperature range of 300 C to 3000 C under a nitrogen atmosphere of the flow rate of 20 ml/min.<sup>14</sup>

### ► Evaluation of microsponge loaded gel formation:

The microsponge prepared gel was evaluated by different parameters such as pH, appearance, viscosity, spreadability,

drug content and drug release, *in vitro* antifungal activity and stability studies.

- Appearance: The microsponge prepared gel bases were inspected visually for clarity, color and presence of any particles. Microsponge loaded carbopol gel shows transparent gel.
- PH: Microsponge loaded gel formulation was dissolved in water and the pH was determined with the help of digital PH meter. All the gels are tested for pH three times and average of three determinations was calculated.
- Spreadability: The microsponge gels are keeping between two horizontal glass slides of standard dimension. 100g weight was placed on the top of the two slides so that the formulation gets uniformly spread. The weight was removed and excess formulation was scraped out.

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

Where,

m = weight kept on the upper slide

l = length of glass slide

t = time taken in second

- Viscosity: Viscosity of microsponge loaded gel formulation was determined using Brookfield viscometer with spindle no 6 at 10 rpm at 37 0 C temperature.

**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 filtrated phosphate buffer pH 5.5 and absorbance was measured at specific wavelength using UV spectrophotometer.<sup>15-16</sup>

### ► *In vitro* release of microsponges gel:

The *in vitro* release microsponges gel was performed using a modified Franz diffusion cell with Spectra Pore dialysis membrane molecular weight cut off with an effective diffusion area of 3 cm. The release medium was 100 ml acetate buffer pH 4 containing 1% SLS. One gram gel or powder was placed on the dialysis membrane which was previously soaked overnight in the release medium. The receptor medium was stirred at 50 rpm and maintained at 34°C. Aliquots of 3 ml were withdrawn at predetermined intervals over 6 h and replaced by an equal volume of the fresh medium to maintain sink conditions. The samples were analyzed spectrophotometrically at 270 nm for content and drug flux through the membrane was calculated. In order to investigate the mechanism of drug release form microsponge, zero order, first order, Higuchi, and Korsmeyer-Peppas models were applied on the release profile of microsponges gel.<sup>17</sup>

### ► **In vitro antifungal activity:**

Antifungal activity was evaluated against *Candida albicans* utilizing disc diffusion method using 100 µL of suspension containing of yeast spread on Sabourand dextrose agar (SDA). Later the media had cooled and solidified, the circles which have been impregnated with 100 mg of microsponge gel, the market item, without drug gel and gel containing unencapsulated drug were set on the agar surface. Circles impregnated in arrangements (50 mg/mL) were utilized as controls. The gave plates were then struggled for 24 h at 37 °C, later which the zone of not actually settled Antifungal movement was introduced as the measurement of the hindrance zone in millimeters.<sup>18</sup>

### ► **In vivo evaluation of therapeutic efficacy:**

- **Animal:**

Grown-up Wistar rodents (280 ± 10 g) of either sexual orientation are getting. The creatures were housed in huge, open polyacrylic confines at a surrounding room temperature with 12-h light/12-h dull cycle. Rodents had free admittance to water and rat pellets diet.

### **Acute toxicity testing:**

The female rodents were utilized for the intense poisonousness testing. Hair present in the dorsal surface of the creature (2 X 2 cm) was eliminated by applying hair remover and cleaned with liquor. The screening is was stamped (1 X 1 cm) and 0.5 g of a microsponge improved gel was applied to the outer layer of a creature's skin during the perception time frame (14 days), signs, for example, erythematic and edema were surveyed.<sup>19</sup>

### ► **Evaluation of therapeutic efficacy:**

The male rodents were utilized for the test. The rodents were separated into the four gatherings viz., typical benchmark (group I), *Candida glabrata* control (bunch II), standard treatment (bunch III) and microsponges enhanced gel treatment (bunch IV). Bunch II to IV creatures were changed with intravenous methyl prednisolone (5mg/kg) for 3 days for enlistment and support of cell-interceded immune suppression (Organisms from stock disengages were put away in supplement agar at 27°C, streaked onto supplement stock, and brooded at 37°C for 24 h and included culture was utilized for additional trial). *Candida glabrata* culture was weakened with PBS and cleaned in smooth muscle of rodent pennies and permitted to develop for 3 days until the development of *Candida* was seen on ischiocavernosus smooth muscle. The settlement development was affirmed by counting province framing unit. The creatures which as cfu worth of more than 3 cfu/ml product remembered for the review. The creatures were treated for week time frame and outwardly noticed its actual changes. The swab culture was gathered on starting day, fourth and seventh day of the analysis for microscopical

assessment. End of the trial the creatures were forfeited and ischiocavernosus smooth muscle was gathered from every one of the trial creatures and protected in 10% formalin.<sup>20</sup>

## **DISCUSSION**

Microsponges have a discrete advantage over the current ordinary effective dose structures for the treatment of dermatological sicknesses. A Microsponge Delivery System can capture wide scope of actives and afterward discharge them onto the skin throughout a period and in light of trigger. It is exceptional innovation for the controlled arrival of effective specialists and comprises of microporous dabs stacked with dynamic specialist for effective and furthermore use for oral just as biopharmaceutical drug conveyance. It gives a wide scope of figuring benefits; Fluids can be changed into free streaming powders. MDS is initially produced for effective conveyance of drugs like enemy of skin break out, calming, against contagious, enemies of dandruffs, against pruritics, rubefacients and so forth Plans can be created with contrary fixings with delayed security without utilization of additives. Security of the bothering and sharpening medications can be expanded and modified delivery can control how much medication delivery to the designated site. Henceforth, the microsponge drug conveyance framework center as a significant device for future developments in controlled drug conveyance framework. In this manner, microsponge has a great deal of imminent and is an exceptionally best in class field which is should have been investigated.

## **CONCLUSION**

The microsponge conveyance framework is an extraordinary innovation for the controlled arrival of macroporous dots, stacked with a functioning specialist, offering a likely decrease in aftereffects while keeping up with their helpful viability. The microsponge drug conveyance framework offers ensnarement of its fixings and is accepted to contribute toward decreased aftereffects, further developed security, expanded tastefulness and upgraded detailing adaptability. Furthermore, various investigations have affirmed that microsponge frameworks are non-disturbing, non-mutagenic, non-allergenic, and non-poisonous. This innovation is being utilized at present in beauty care products, over-the-counter skincare, sunscreens, and remedy items. This sort of medication conveyance innovation might prompt a superior comprehension of the recuperating of a few infections. Consequently, Microsponge-based medication conveyance innovation is probably going to turn into a significant medication conveyance lattice substance for different helpful applications later on.

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### Authors' Contribution:

The concept and Design of the study were done by Alim Momin, Shubhrajit Mantry. Data acquisition and analysis were done by Alim Momin. Manuscript preparation, editing done by Alim Momin.

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