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MICROSPONGES - A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Micro sponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favourably. Micro sponge technology has many favourable characteristics, which make it a versatile drug delivery vehicle. Micro sponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. The outer surface is typically porous, allowing a sustained flow of substances out of the sphere. Micro sponges are porous, polymeric microspheres that are used mostly for topical use and have recently been used for oral administration. Micro sponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release.

KEYWORDS: ***Micro sponges, transdermal delivery, controlled release, topical, effective delivery.***

INTRODUCTION

A Micro sponge drug delivery system (MDDS) is a patented, highly cross-linked, porous, polymeric microspheres polymeric system (10-25 μ) consisting of porous microspheres particles consisting of a myriad of inter connecting voids within non-collapsible structures with a large porous surface that can entrap wide range of actives (cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products) and then release them onto the skin over a time and in response

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to trigger. A typical 25µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10ft in length providing a total pore volume of about 1ml/g [1]. Micro sponge does not pass through the skin (capable of holding four times their weight in skin secretions). Rather, they collect in the tiny nooks and crannies of skin and slowly release the entrapped drug, as the skin needs it. The micro sponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. These products are typically presented to the consumer in conventional forms like creams, gels or lotions and they contain relatively high concentration of active ingredients. Micro sponges are polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents. The MDS has advantages over other technologies like microencapsulation and liposomes. Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured the actives contained within microcapsules will be released. Liposome suffer from lower payload, difficult formulation, limited chemical stability and microbial instability. (14)

Micro sponge Delivery System (MDS) technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce the systemic exposure and minimize local cutaneous reactions to active drugs. Micro sponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. (6)

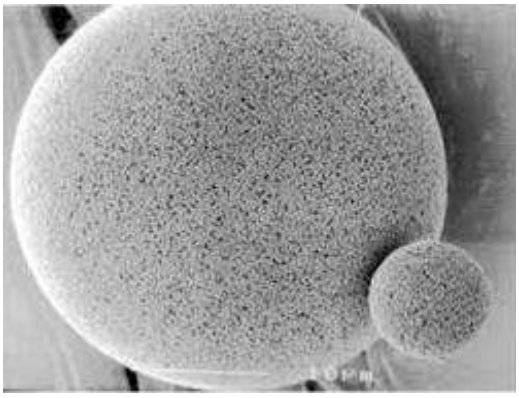

Fig 1: Ideal structure of Micro sponge (12)

History of Micro Sponges

The micro sponge technology was developed by Won in 1987 and the original patents were assigned to Advanced Polymer Systems, Inc. (Redwood City, California, US). This Company developed a large number of variations of the procedures and those are applied to the cosmetic as well as over-the-counter (OTC) and prescription pharmaceutical products. At the current time, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. (11)

Properties of the Actives for the Entrapment into Micro sponges

Active ingredients that are entrapped in micro sponges can then be incorporated into many products such as creams, gels, powders, lotions and soaps. Certain considerations are taken into account while, formulating the vehicle in order to achieve desired product characteristics:

- It should 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 should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- It should be stable when in contact with the polymerization catalyst and under conditions of polymerization.
- The spherical structure of the micro sponges should not collapse.
- Not more than 10 to 12% w/w micro sponges must be incorporated into the vehicle in order to avoid

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cosmetic problems.
 Payload and polymer design of the micro sponges for the active must be optimized for required release rate for given period of time (3)

Potential Advantages of the Microsponge Drug DeliverySystem

 Microcapsules cannot usually control the release rate of the active pharmaceutical ingredients (API). Once the wall is ruptured the API contained within the microcapsules will be released. Can the MDS can do it, is the question.
 Liposomes suffer from a lower pay load, difficult formulation, limited chemical stability, and microbial instability. Do the MDS have a wide range of chemical stability and are they easy to formulate?
 MDS have stability over a pH range of 1 – 11.
 Micro sponges have stability up to temperature 130°C.
 Micro sponge having Pay load is up to 50 – 60%.
 They have free flowing and cost effective.
 Micro sponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin. (4)

Advantages of micro sponge technology

The advantages of MSP technology were pictorially represented in fig.

Fig. 2: Advantages of micro sponge technology (11)

MSPS HAVE SEVERAL ADVANTAGES OVER OTHER PREPARATIONS AVAILABLE IN THE MARKET:

Advantages over Conventional Formulations

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. When compared to the conventional system, Micro sponge systems can prevent excessive accumulation of ingredient within the epidermis and the dermis significantly reducing the irritation of effective drugs without affecting their efficacy.

Advantages Over Microencapsulation and Liposomes

Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured, the actives contained within microcapsules will be released. Liposomes suffer from lower payload, difficulty in formulation, limited chemical and microbial stability, whereas micro sponge system in contrast to the above system has several advantages like stable over a pH range of 1-11 and up to temperature of 130 ^{0}C, have higher payload up to 50 to 60 %, with average pore size of 0.25 μm where bacteria cannot penetrate.

Advantages over Ointments

Ointments are often unappealing, greasy and sticky that results in lack of patient compliance. These vehicles require a high concentration of active agents for effective therapy, which results in allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient and unpleasant odour.MSP systems

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maximize the amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body (11).

Limitations

1. Use of organic solvents as pyrogen, pose an environmental hazard which may be highly inflammable.
2. In case of the Bottom-Up approach traces of residual monomers have been observed, which may be toxic and hazardous to health.
3. While the limitations seem to be serious, they can be easily overcome by using proper quality control measures coupled with optimization and standardization of procedures e. g., Post-manufacture washing (11)

Release Mechanism

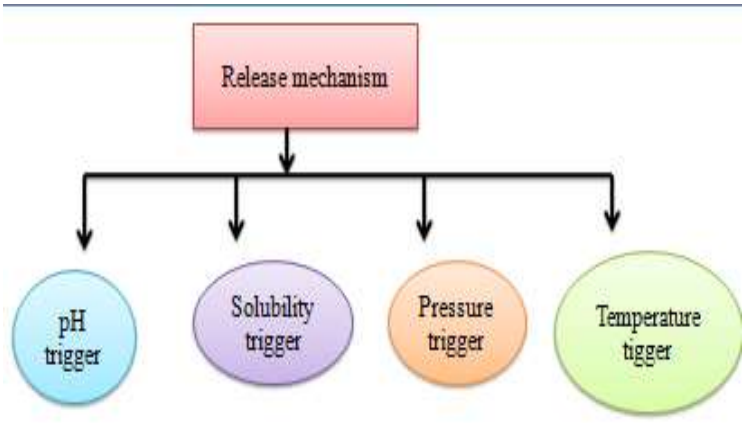

Figure 3: Programmable release from micro sponges (1)

Pressure Triggered Systems

Micro sponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon special characteristics of the sponge. The micro sponge best suited for a given application may be optimized by varying the type of material and different process variables.

Temperature Triggered Systems

Some active ingredients loaded in micro sponge can be too viscous at room temperature to flow spontaneously into the skin. The flow rate can be increased by increasing the skin temperature and hence release. So, it is possible to regulate the release of substances from the micro sponge by modulation of temperature.

pH Triggered Systems

Triggering the pH-based release of the active can be achieved by modifying the coating on the micro sponge. This has many applications in drug delivery.

Solubility Triggered System:

Micro sponge loaded with water-soluble ingredients will release the ingredient in the presence of water. The release rate of active ingredients can be triggered in the presence of aqueous medium. This release may be achieved based on the ability of the external medium to dissolve the active, the concentration gradient or the capability to swell the microspore network

Micro Sponge Delivery System: Preparation Methods

A particular encapsulation method is selected on the basis of solubility properties of the drug and polymer **have** reported the preparation of micro sponge drug delivery system can be carried out using two methods: first method is liquid-liquid suspension polymerization and another is quasi emulsion solvent diffusion techniques. These methods are based on physical as well as chemical properties of loaded drug. If the loaded drug is usually an inert non-polar material, will generate the pervious structure known as "porogen".

Porogen drug is uncompleted to hinder the polymerization and to become it activated have been found out that other than above methods, lyophilization, water in oil in water (w/o/w) emulsion solvent diffusion and oil in oil (o/o) emulsion solvent

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diffusion

A. Liquid-Liquid Suspension Polymerization

1) Micro sponges are formulated by suspension polymerization method based on free radical suspension polymerization technique shown in Figure 4
2) In this method, the process was takes place in three naked round bottom flask with stirrer, connected with water condenser and thermometer is used to determine the temperature.

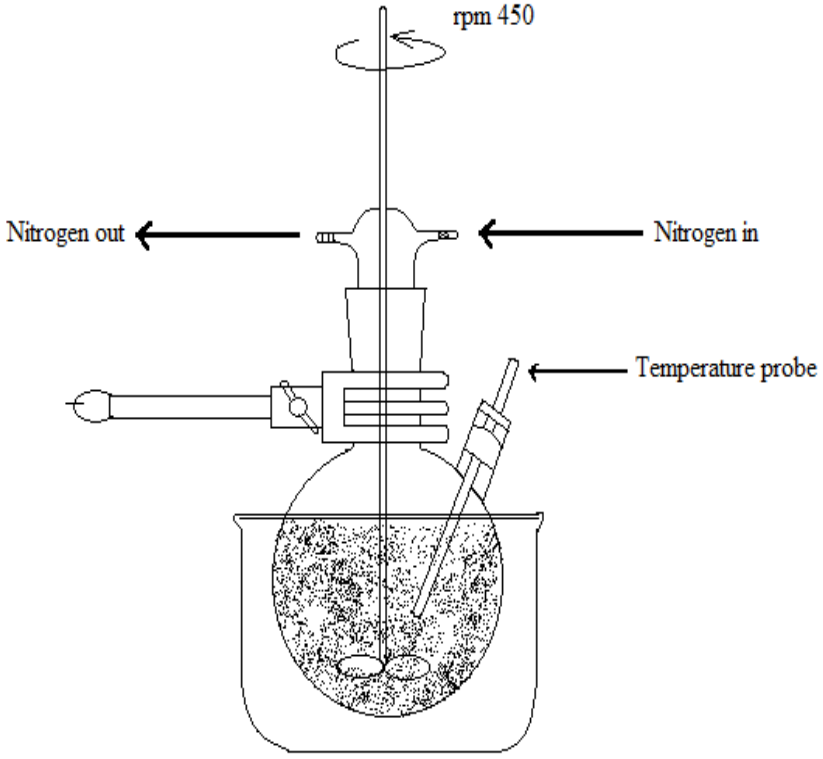

Fig. 4: Reaction vessel for micro sponge preparation by liquid-liquid suspension polymerization (13)

B. Quasi-Emulsion Solvent Diffusion

1) This is the widely used technique of micro sponge preparation.
2) Micro sponge was also prepared by second technique i.e., Quasi-emulsion solvent diffusion technique.
3) In this technique, the inner phase containing Eudragit polymer i.e., Eudragit RS 100 were dissolved in ethanol.
4) After preparation of internal phase, the drug is added slowly into solution and then it dissolved under ultrasonication at temperature 35oC.

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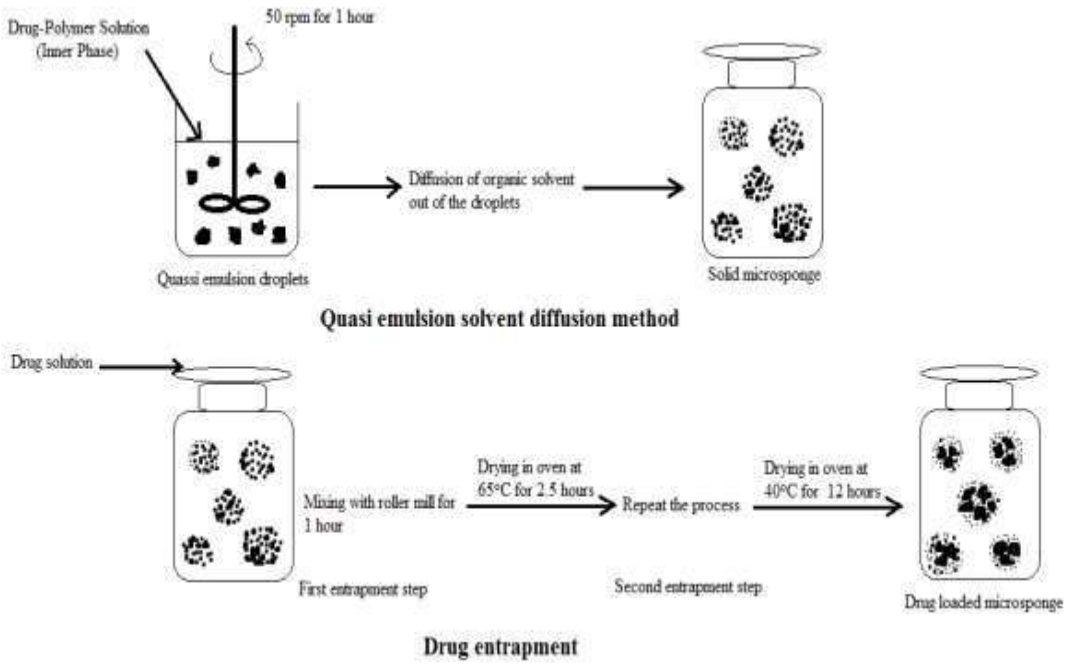

Fig. 5: Preparation of micro sponges by quasi emulsion solvent diffusion(13)

C. Lyophilization

Lyophilization is novel technique was prepared by gelation technique used for converting the microspheres to porous microspheres. In this technology, the microparticles were incubated in the Chitosan HCl solution and lyophilized. Rapid elimination of solvent leads to formation of pores in the microspheres. This method is quick and rapid. But due to rapid elimination of solvent, there are broken or shrunken microparticles are produced. This is the disadvantage of lyophilization method.13

D. Water in oil in water (w/o/w) emulsion solvent diffusion

Another novel technique named w/o/w emulsion solvent diffusion was developed to prepare biodegradable porous microparticles. In this method, an internal water phase was dispersed in organic polymeric solution. The internal phase consists of an emulsifying agent such as span, stearyl amine and polyethyleneimine. After that, this w/o emulsion was again dispersed in external aqueous phase which contain PVA to form a double
emulsion. The advantage of this method is the entrapment of both water soluble and water insoluble drugs.13

HYPOTHETICAL MECHANISM OF ACTION

In Topical Formulations

The active ingredient is added to the vehicle in an entrapped form. As the micro sponge particles have an open structure (they do not have a continuous membrane surrounding them), the active is free to move in and out from the particles and into the vehicle until equilibrium is reached. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the MSP particle into the vehicle and from it to the skin, until the vehicle is either dried or absorbed. The MSP particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time was shown in fig. 6. If the active is too soluble in the desired vehicle during compounding of the finished product, it will not provide the desired benefits of gradual release. Instead, they will behave as if the active was added to the vehicle in a free form. Therefore, while formulating MSP entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives.11

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In Oral Formulations

MSPs with<200 µm may efficiently be taken up by the macrophages present in the colon, thus exhibiting effective localized drug action at the desired site They can also increase the lag time for absorption of the drug as these get entrapped on the surface of the colon and thus have the potential for being developed as a colon-targeted drug delivery system (11)

Characterization of Micro Sponges(6):

Various methods are used for the evaluation of the MDS. These are following-

1. Particle size determination

Particle size analysis of loaded and unloaded micro sponges can be performed by laser light diffractometry or any other suitable method. The values can be expressed for all formulations as mean size range.

2. Morphology and surface topography of micro sponges

For morphology and surface topography, prepared micro sponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the micro sponges can be studied by scanning electron microscopy (SEM). SEM of a fractured micro sponge particle can also be taken to illustrate its ultra structure.

3. Determination of loading efficiency and production yield

The loading efficiency (%) of the micro sponges can be calculated according to the following equation: Loading efficiency = (Actual Drug Content in Micro sponges /Theoretical Drug Content) X 100

The production yield of the microparticles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the micro sponge obtained. Production Yield= (Practical mass of micro sponges / Theoretical mass (Polymer + drug) X 100.21

4. Characterization of pore structure Pore volume and diameter: This are vital in controlling the intensity and duration of effectiveness of the active ingredient. Pore diameter also affects the migration of active ingredients from micro sponges into the vehicle in which the material is dispersed. Mercury intrusion porosimeter can be employed to study effect of pore diameter and volume with rate of drug release from micro sponges.

5. Determination of true density: The true density of microparticles is measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations. 6.. Polymer/monomer composition Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the micro sponge system and hence have direct influence on the release rate of entrapped drug. Release of drug from Micro sponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time.

6. Resiliency (viscoelastic properties)

Resiliency (viscoelastic properties) of micro sponges can be modified to produce beadles that is softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release.

7. Dissolution studies Dissolution profile of micro sponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consist of 5µm stainless steel mesh. The speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical method at various intervals.

8.. Drug release from the semi solid dosage forms and drug deposition studies

Drug release from the semi solid dosage forms are performed by the Franz- type static diffusion cells. In this epidermal side of the skin was exposed to ambient condition. While dermal side was kept facing the receptor solution. Receptor compartment containing 20 mL phosphate buffer pH 5.8 was thermo stated at 32±0.5°C and stirred at 600 rpm. Skin was saturated with diffusion medium for 1 h before the application of sample. A 200-mg of sample was applied on the donor compartment. For determination of drug deposited in the skin, the diffusion cell was dismantled after a period of 4, 8, 16, and 24 h. The skin was carefully removed, and drug present on the skin surface was cleaned with distilled water.

9. Compatibility studies Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC).

10. In-vitro diffusion studies The in vitro diffusion studies of prepared micro sponge gel were carried out in Keshary–Chien diffusion cell using through a cellophane membrane. 100 ml of phosphate buffer was used as receptor compartment, and then 500 mg of gel containing 10 mg of drug was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.50C. The solution on the receptor

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side were stirred by externally driven Teflon coated magnetic bars at predetermined time intervals, pipette out 5 ml of solution from the receptor compartment and immediately replaced with the fresh 5 ml phosphate buffer. The drug concentration on the receptor fluid was determined spectrophotometrically against appropriate blank. The experiment was carried out in triplicate.

SAFETY CONSIDERATION

Safety studies of micro sponges can be established by:

- Eye irritation studies in rabbits.
- Skin irritation studies in rabbits.
- Mutagenicity in bacteria.
- Oral toxicity studies in rats.
- Allergenicity in guinea pigs.3

FUTURE EXPECTANCY

Micro sponge is the present-day novel technology, which is the mostly developed for the topical delivery system and recently for oral administration. It provides various kinds of advantages. Micro sponges are carefully designed pharmaceutical active ingredient that deliver the drug effectively at the target site with the minimum dose and also to enhance stability, reduce side effects and control drug release. The real face off in the future is the development of the delivery system for the oral peptide delivery by altering the ratio of polymers. Micro sponges will be an excellent drug delivery system. Micro sponges drug delivery system that can accurately control the release rates to the specific sites of the body will be sought in great detail in the years to come that have an immense on the health care system and. Some micro sponge related products are already approved; several products are currently under development and clinical assessment. 1

Applications (3)

Micro sponges are used mostly for topical and recently for oral administration as well as biopharmaceutical delivery. It offers the formulator a range of alternatives to develop drug and cosmetic products. These are developed to deliver an active ingredient efficiently at the low dose and also to enhance stability, reduce side effects and modify drug release

The Micro sponge for Oral Delivery

A Micro sponge system offers the potential to hold active ingredients in a protected environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract, where it will be released upon

exposure to specific enzymes in the colon. This approach if successful should open up entirely new opportunities for MDS. In oral applications, the micro sponge system has been shown to increase the rate of solubilization of poorly water-soluble drugs by entrapping such

drugs in the micro sponge system's pores. Because these pores are very small, the drug is in effect reduced to microscopic particles and

the significantly increased surface area thus greatly increases the rate of solubilization. An added benefit is that the time it takes the micro sponge system to traverse the small and large intestine is significantly increased thus maximizing the amount of drug that is absorbed

Micro Sponge for Topical Delivery

Microphonic Delivery of Fluconazole for Benzoyl peroxide (BPO) is mainly used in the treatment of mild to moderate acne and athlete's foot and the most common side effect associated with BPO is skin irritation and it has been shown that controlled release of BPO from a delivery system to the skin could lessen the side effect while reducing percutaneous absorption. Topical delivery system with reduced irritancy was successfully developed studied factors affecting the morphology of benzoyl peroxide (BPO) micro sponges. It has been revealed that encapsulation and controlled release of BPO can lessen the side effect while, when administered to the skin it also reduces percutaneous absorption. The goal of the study was to design and formulate a suitable encapsulated form of BPO using micro sponge technology and investigate the parameters affecting the morphology and other characteristics of the resulting products with the help of scanning electron microscopy (SEM). Benzoyl peroxide particles were prepared by an emulsion solvent diffusion method by including an organic internal phase containing benzoyl peroxide, dichloromethane and ethyl cellulose into a stirred aqueous phase containing polyvinyl alcohol (PVA). Different concentrations of BPO micro sponges were incorporated in lotion formulations and the drug release from these formulations were studied. The SEM micrographs of the BPO micro sponges used for the measurement of their size and showed that they were porous and spherical. Results showed that the morphology and particle size of micro sponges were affected by drug: polymer ratio, amount of emulsifier used and stirring rate. The results obtained also showed that with increase in the ratio of drug: polymer resulted in a reduction in the rate of release of BPO from the micro sponges. The release data showed that the

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highest and the lowest release rates were obtained from lotions containing plain BPO particles and BPO micro sponges with the drug: polymer ratio (13:1) respectively. Kinetics studies showed that the release data followed peppas model but diffusion was the main mechanism of drug release from BPO micro sponges.

\EXAMPLE OF MICROSPONGES DDS

TOLNAFTATE MICROSPONGES EMBEDDED BIOCOMPATIBLE GELS FOR CONTROLLED AND EFFECTIVE ANTIDERMATOPHYTIC ACTIVITY. (9)
MARKETED FORMULATION

TABLE NO. 1 Applications of micro sponges (6)

S. No.	*Active agents*	*Applications*
1	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated Concentration and with reduced irritancy and sensitization.
2	Anti-acne e.g., Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
3	Anti-inflammatory e.g., hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
4	Anti-fungal	Sustained release of actives.
5	Anti-dandruffs e.g., zinc parathion, selenium sulfide	Reduced unpleasant odor with lowered irritation with extended safety and efficacy.
6	Antipruritic	Extended and improved activity
7	Skin depigmenting agents e.g., hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
8	Rubefacients	Prolonged activity with reduced irritancy greasiness and odor.

CONCLUSION

MDS holds significant potential in both pharmaceutical as well as cosmetic industries because of its release technique is novel and its ease of administration with fewer side effects, more research works are carried out to optimize its efficacy for the therapy. It is a unique technology for the sustained release of topical agents which act locally. It is originally developed for topical delivery of drug like anti-acne, anti-inflammatory, anti-fungal, anti-dandruffs, antipruritic, and rubefacients. Micro sponge's delivery system that can release its active ingredient on stimuli. Therefore, a micro sponge has got a lot of potential in drug delivery technology today.

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