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REVIEW: A THERAPEUTIC APPLICATIONS OF MICROSPONGE DRUG DELIVERY SYSTEM

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ABSTRACT

More and more developments are being employed in the drug delivery systems to optimize its efficacy and cost-effectiveness of drug therapy. Peptides, proteins and DNA-based therapeutics can not be effectively delivered through conventional means. A Microsponges drug delivery system is a highly cross-linked, porous, polymeric system consisting of porous microspheres that can entrap and release them into the skin layers over a long period of time. Microsponges drug delivery system provides extended release with reduced irritation, improved thermal, physical and chemical stability. Microsponges drug delivery technology is used currently in cosmetics, skin care products, sunscreens and prescription products. One of the best feature of microsponge delivery system is it is self-sterilizing. Current review is focused on the method of preparation, characterization and various therapeutic applications of microsponges.

KEYWORDS: Drug delivery System, Therapeutic Applications, Microsponges, quasi-emulsion diffusion solvent method, suspension polymerization, controlled release system.

1. INTRODUCTION

There are many classes of drugs that are being evolved day by day in evolution of the drug delivery technology. Development of the new drugs delivery system with calculated predetermined rates at different sites of action is required for the drug to be effective against any disorder. Drug delivery systems are those that can control the release rates or target drugs to a specific body site, improving the efficacy of the drug, cost-effectiveness of the drug therapy and improving patient compliance. This control of the delivery rate of active pharmaceutical ingredient (API) to a required site in the human body has become a major

challenge to the pharmaceutical industry and all of the above challenges were minimized by the discovery of microsponge drug delivery system.[1]

Microsponges Delivery System (MDS) is "Highly porous, cross-linked, polymeric system consisting of porous microspheres that can entrap wide range of active ingredients into it and then release them into the skin layers in efficient manners over a time and in response to trigger it". Micro-sponge polymers possess the versatility to load the wide range of actives and providing the benefits of enhanced product efficacy, safety and product stability and extended wear to a wide range of skin therapies.[2]

The microsponge technology was developed in 1987 by Won and the original patents were assigned to Advanced Polymer Systems, Inc. Microsponges are porous microspheres polymeric delivery system composed of tiny sponge like spherical particles with large porous surface. Microsponge technology has many beneficial features, which makes it a multifaceted drug delivery vehicle, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge Systems are based on the microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances and then it can be incorporated into a formulated product such as a gel, cream, liquid or powder. MDS can provide increased effectiveness for the topically active agents with enhanced safety, extended the product stability and improved aesthetic properties in an efficient and novel manner. A typical size is about 25 µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. This results in large reservoir within each microsponge, which can be loaded with up to 6 times of its own weight of active agents like various therapeutic oils.[3]

Sizes of microsponges typically range between 5 and 300 µm in diameter with an average pore size of 0.25 µm, which is very less than the average size of various microorganisms, as a result, preventing their penetration. This is why microsponges are called as selfsterilizing and they do not need any kind of excipients for the stability of microsponges.[4]

According to recent research microsponge is suitable for topical, oral as well as ophthalmic administration of therapeutics. Several filed have patents reported use of microsponges as excipient due to its high drug loading capacity and sustained drug release behavior. Microsponges are designed to deliver therapeutic agents efficiently at minimum dose and to enhance stability and to modify drug release.[3]

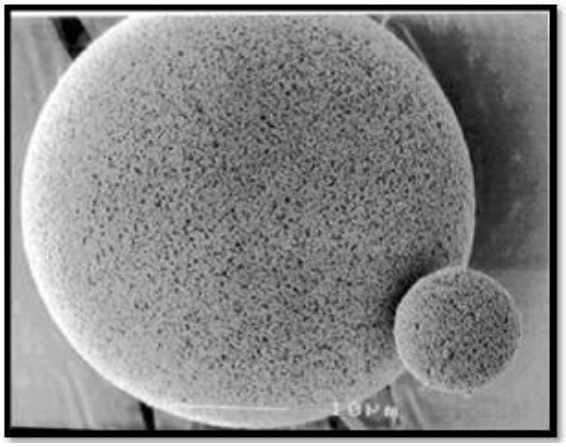

Figure 1: Porous structure of microsponge.

2. Potential features of microsponge drug delivery systems

When these are applied to skin, the microsponge are releases its active ingredient gradually to the skin on a time mode and also in response to stimuli such as rubbing, temperature and pH effect etc. with excellent efficacy and minimal irritation.

Characteristics of microsponges are as follows[5,6]

1. Microsponges are stable over wide range of pH 1 to 11 and stable at the temperature up to 130°C.
2. Microsponges can absorb oil up to 6 times its weight.
3. Microsponge formulations are compatible with most vehicles and active ingredients.
4. Microsponge formulations have high entrapment efficiency upto 50 to 60%.
5. Microsponge formulations are free flowing and can be cost effective.
6. It provides continuous action up to 12 hours i.e. extended release.
7. They have superior formulation flexibility.
8. Microsponges are thermal, physically, and chemically stable.
9. Liquids can be converted into powders by improving material processing.
10. Microsponge formulations are self- sterilizing as their average pore size is about 0.25µm where the bacteria cannot penetrate the pores.

3. Advantages of microsponges over other formulations

Microsponge drug delivery system provide extended and sustained release of the medicament. It improves the compliance of the patient by decreasing the irritation. Formulations containing microsponges are thermal, physically, and chemically stable. They decrease oiliness and greasiness on the skin by absorbing them.

3.1 Advantages over conventional formulations

Conventional topical formulations are only intended for the local effect, for example - cuts, wounds, bleeding on the outer layer of the skin, etc. These types of products contain high concentration of API because of their rapid absorption into the skin and productively the less outcome. Microsponges comparatively need the much lesser amount of API to show the required therapeutic action than that of conventional formulations by preventing the excessive accumulation of ingredients within the epidermis and dermis. In addition, Microsponges also significantly reduce side effects due to the accumulation of API on skin surface providing safety and increasing patient's compliance. Due to uncontrolled evaporation of API in many topical formulations and a potential incompatibility, it requires more amount of the vehicle in the formulation.[7]

3.2 Advantages over Microencapsulation and Liposomes

Microcapsules are used to reduce the dosing frequency by controlling release rate of API. When the wall ruptures whole API present in microcapsules is released, this is its potential disadvantage over microsponges. Liposomes are the spherical vesicles with phospholipid bilayer which is used as a carrier for various drugs, peptides, and nucleic acids. Microsponges are stable over a pH range of 1–11 and at high temperatures while liposomes exhibit stability-related problems. Microsponges do not require the preservatives while liposomes require preservatives. Entrapment efficiency of microsponges is about 50%–60% while that of liposomes is approximately 30%. Hence, liposomes are difficult to frmulate, commercially expensive, no microbial stability, less chemical stability, and shows lower payload compared to microsponge.[7,8]

3.3 Advantages over ointments

Ointments need a high concentration of API for the required effective therapeutic action because of their low permeation efficiency. Because of high concentrations, it leads to side effects like irritation and allergic reactions and often it is unappealing, sticky resulting in the lack of patient compliance. Moreover, they have an unpleasant odor and uncontrolled evaporation of active ingredient. Incompatibility between the drugs and vehicles may arise in these formulations. In comparison to ointments, microsponge delivery systems have improved permeation with minimum transdermal penetration into the body which enhance the retention time of drug within the superficial layers (epidermis and dermis) of skin.[7,8]

4. Techniques of microsponges preparation

1. Liquid-liquid suspension polymerization

The porous microsphere based microsponges are prepared by suspension polymerization method. In this polymerization technique the immiscible monomers are first dissolved with active ingredients in the suitable solvent and then dispersed in aqueous phases which consist of surfactant or suspending agents are used for the formation of suspension. The polymerization is then activated by increasing the temperature or irradiation or by addition of catalyst. The polymerization process continues until the reservoir form of system with spherical structure is made. After polymerization process the solvent is removed, leaving the microsponges.[9]

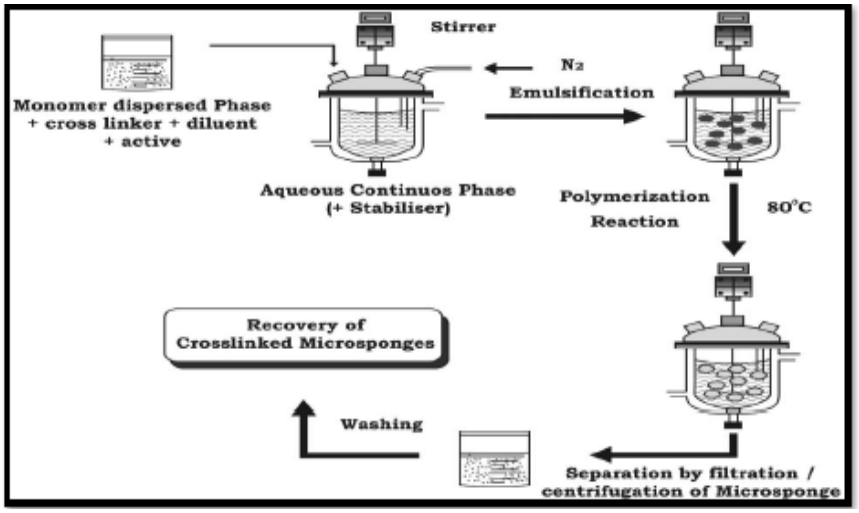

Figure 2: Suspension polymerization- system set up method.

2. Quasi-emulsion solvent diffusion

Quasi-emulsion solvent diffusion method (two-step process) is employed for the preparation of Porous microsphere (microsponges). In this method an inner phase containing polymer such as eudragit dissolved in the solvent like ethyl alcohol. The drug is slowly added to the polymeric solution, then dissolved under ultrasonication at the temperature 35°C and plasticizer such as triethylcitrate (TEC) is then added in order to assist the plasticity. The inner phase is then poured into the external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 to 3 hours. Mixture is then filter to separate microsponges. The microsponges is then washed and dried in an oven at 40°C for 10 to 12 h.[9]

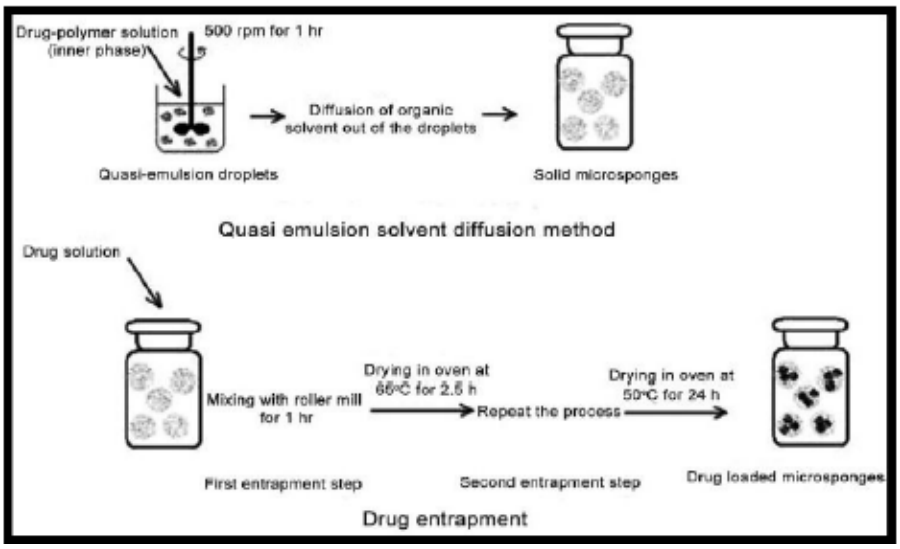

Figure 3: Preparation of microsponge by using quasi emulsion solvent diffusion technique.

Limitations: The preparation methods usually use the organic solvents as porogens, which pose an environmental hazard, as some may be highly inflammable, posing a safety hazard. In some cases, the traces of residual monomers have been observed, which may be toxic and hazardous to the health.[10]

5. Mechanism of action

The porous microspheres contain a complex network of interconnecting voids with non-collapsible structure. These systems can absorb the wide range of active ingredients such as emollients, volatile oils, sunscreens, perfumes, and anti-infective and antifungal agents. Depending on several factors, such as pore diameter, extent of cross-linking of the polymers, concentration difference of the active ingredient between the microspheres and vehicle in which these spheres resides, the release rate of active ingredients can be determined before they are entrapped in the microspheres.

The topical agent formulation with this technique are often prepared in many various forms like a gel, cream, or lotion. The active ingredients diffuse out of the spheres into vehicle and then onto the skin, while applying formulation topically to the desired area of the skin. The release can be initiated by many release triggers such as pressure and temperature changes, pH and solubility. The microsponges cannot pass through to the stratum corneum because of their size, so they retained into the skin surface, releasing slowly the active ingredients over a period of time. The MDS provides more control on rate of release, which potentially has an

impression on intensity of skin irritancy provoked by the topical agent. However, Microspones technology is limited, it can only entrap active ingredients with certain characteristics.[11]

6. Drug release mechanism of microsponges

Microsponge can be designed to release the given amount of active ingredients over time in response to one or more external triggers.

6.1 Temperature change: At the room temperature few entrapped active ingredients can be too viscous to flow suddenly from microsponges onto the skin. With increase in the skin temperature, flow rate is also increased and therefore release is also enhanced.[12]

6.2 Pressure: Rubbing or pressure applied can release the active ingredient from microsponges onto skin. The amount of release depends upon the resiliency of microsponge.[13]

6.3 Solubility: Microsponges loaded with water miscible ingredients like antiseptics and antiperspirants will release ingredient in the presence of water. The release can also be activated by the diffusion but taking into consideration, the partition coefficient of the ingredient between the microsponges and external system.[14]

6.4 pH triggered systems: Triggering the pH-based release of the active can be achieved by modifying the coating on the microsponge. This has many applications in the drug delivery.[15]

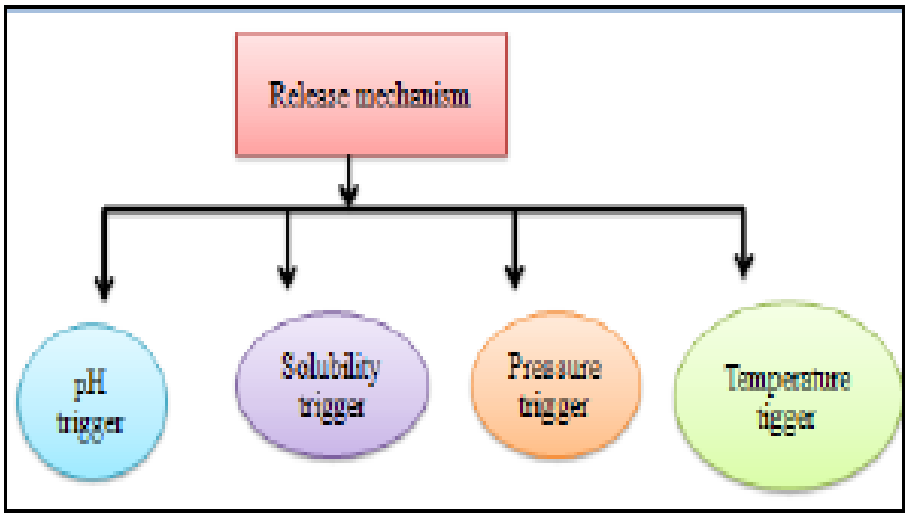

Figure 4: Programmable release mechanisms from microsponges triggered systems.

7. Therapeutic applications of microsponges

Microsponges have been investigated for the various therapeutic applications. It provides a novel suitable carriers system for therapeutic agents and able to modify and control the release behavior of the drugs. Microsponges are vastly spreading their domain, starting from topical formulations for treatment of various skin diseases and disorders and expanding up to the oral formulations which release drug in predetermined release rates in target sites. Because of safety and efficacy of the drug administration microsponges play a very important role in creating 3D porous scaffold for bone tissue engineering. As microsponges are self-sterilizing in nature (because of its pore size) it is also playing a major role in cardiovascular engineering, where biodegradable graft material containing collagen microsponges are used preparing a patch from it, which is for regenerating autologous tissue in cardiovascular surgery.[16,17]

Some advances in microsponges like nanosponges, nanoferrosponges, and porous microbeads, β-Cyclodextrin nanosponges are prepared by modifying the preparations steps. They can be used for the delivery of various types of drugs including the hydrophilic and hydrophobic drugs orally or topically, and for delivery of gaseous particles, for treating the cancerous cells and delivery of siRNA and RNA.[18,19,20]

7.1 Microsponges in psoriasis

Psoriasis is an autoimmune chronic skin disorder characterized by itchy, scaly and disfiguring skin lesions. It is manifested by the altered keratinocyte differentiation, hyper proliferation, and increased epidermal thickness. It reduces the quality of life of infected person. Microsponges have been studied for their application in the treatment of psoriasis, Rekha et al. formulated the microsponges of the drug Mometasone furoate by the emulsion solvent diffusion method. Mometasone furoate is used in the inflammatory and pruritic disorders such as psoriasis. Microsponges were prepared using emulsion solvent diffusion method. The release profiles showed biphasic release with an initial burst effect. The seven formulations was prepared that showed 29%–36% drug release in the first hour and 78%–95% cumulative release after 8 hr. The another one example for the use of microsponges in psoriasis is, Sumbul and his coworkers formulated the microsponge gel containing Clobetasol Propionate for treatment of psoriasis to reduce number of application due to the prolonged release of drug. They observed drug release upto 12 hr compared to that of 2.5 hr of the conventional form.[21]

7.2 Microsponges in arthritis

In arthritis, for the delivery of diclofenac the Topical application of microsponge has been studied. Diclofenac is most used NSAID for relieving the pain and swelling associated with arthritis and other musculoskeletal diseases but its oral administration is associated with problems such as first pass metabolism and gastric irritation. Thus, topical formulation containing microsponges of diclofenac can be used to overcome these problems. Osmani et al. formulated the microsponges gel of diclofenac diethylamine using quasi-emulsion solvent diffusion method to obtain a prolonged release for arthritis therapy. They compared their results with marketed formulation, that is, Voltaren Emulgel 1.16% w/w. The drug release studies have shown that gel release 81.11% of drug up to 4 hr only while microsponge-based gel showed prolonged release upto 8 hr.[16]

There is also one another study done by Karthika et al. formulated microsponges containing lornoxicam as active agent for treating the arthritis and incorporated them into tablet form and found prolonged drug release, that is, 86%–96% to 12 hr.[22]

Microsponge loaded with mafenamic acid formulated for topical delivery in the treatment of rheumatoid arthritis by Shuhaib B. et al. 2018. Drug loaded microsponge was obtained from ethyl cellulose as polymer and polyvinyl alcohol as stabilizer using quasi-emulsion solvent diffusion technique. FTIR spectrum revealed no interaction between the drug and excipients. The formulated microsponges were evaluated for the production yield, drug content, entrapment efficiency and mean particle size. The prepared microsponge incorporated in HPMC and light liquid paraffin emulgel. The In-vitro diffusion of drug across egg membrane was assessed using modified Keshary-Chein (K-C) cell. The results were revealed sustained diffusion of drug over the period of 8 hours. Finally authors concluded the suitability of microsponge based topical drug delivery system over conventional delivery of mafenamic acid.[23]

7.3 Microsponges in colon cancer

Microsponges can also be used for oral drug delivery to obtain the sustain release and decrease toxicity. Othman et al. developed microsponges of Eudragit RS100 based 5-Fluorouracil to treat colon cancer. 5-FU has an anticancer activity toward the several solid tumors. 5-FU activity can be improved by increasing relative accumulation in the tumor regions. With this, the toxicity also reduces. Microsponges were prepared using oil in oil emulsion solvent diffusion method. On performing release studies, the pure 5-FU was found

to be released in just 20 min, while that from the microsponges was first found to be an immediate burst release and then a moderately slow release upto 5 hr. Cell viability has shown that MS loaded 5-FU is more effective than that of 5-FU. Results have shown that 5-FU microsponges can substitute the oral anticancer treatment of 5-FU.[24]

7.4 Microsponges in hyperpigmentation

Deshmukh et al. have successfully formulated glabridin microsponge for the effective management of hyperpigmentation disorder. Microsponges were prepared by a quasiemulsion solvent diffusion technique using ethyl cellulose as polymer. The prepared microsponges were evaluated with respect to particle size, drug content, thermal stability and FTIR spectroscopy. Porosity parameters of microsponges were determined using the mercury intrusion porosimetry. For ease of topical application, the prepared microsponges were incorporated into the Carbopol gel. Skin whitening effect of glabridin microsponge based gel was assessed in guinea pigs. UV B radiation was used to induce hyperpigmentation in guinea pigs. After the completion of therapy, the animal skin was subjected to histopathological evaluation. The effective reduction in melanin density was reported in animal treated with microsponge based gel. Finally authors proved role of microsponge effective treatment of hyperpigmentation disorder.[25]

7.5 Microsponges in treatment of gastric ulcer

The famotidine loaded gastro-retentive microsponges for treatment of gastric ulcer have successfully prepared by Charagonda et al., 2016. The floating microsponges were prepared by quasi-emulsion solvent diffusion technique using different proportions of Eudragit RS100 as a polymer and polyvinyl alcohol as stabilizer. The prepared microsponges were evaluated with respect to the particle size, drug content, thermal stability, surface morphology, powder characteristics and in-vitro drug release study. In-vitro drug release behavior was assessed in acidic medium (0.1N HCl) by using USP Type II apparatus. The microsponges were reported to release drug sustained manner for period of 12 hrs. and reported to follow zero order kinetics.[26]

7.6 Microsponges in diabetic wound healing

Pandit et al. formulated nebivolol-loaded microsponges and then incorporated them into a gel which provide adequate moist wound management environment during the last stages of the closure of wound. Nebivolol is an antihypertensive drug, which shows vasodilation through nitric oxide pathway that reduces the diabetic neuropathy and restores endothelial function in

diabetic wounds. On performing in vitro studies, it was found that 80% of the drug was released within 8 hr. Microsponge gel were showed prolonged release of the drug due to the entrapped form in the porous structure of formulation due to which significant and fast wound healing and closure in diabetic rats is observed.[27]

7.7 Microsponges formulation for antifungal

Microsponges of terbinafine hydrochloride which is an antifungal agent formulated by Anju et al. *In-vitro* studies of drug loaded microsponge based gel were conducted and compared with the drug-loaded plain gel. Drug-loaded plain gel showed drug release of 96.65% upto 6 hr, while the microsponge loaded gel showed optimum sustained release of drug around for 10 hr. Thus, Terbinafine hydrochloride loaded microsponge gels had shown the sustained drug release as compared to plain gels.[28]

Dombe et al. formulated a microsponges of oxiconazole nitrate by using quasi-emulsion solvent diffusion method and then incorporated them into the gel. Oxiconazole nitrate is also an antifungal agent which has a poor aqueous solubility, side effects, and adverse reactions. Results have shown that this method of preparation was suitable technique for preparation of microsponges because microsponges formed were spherical shaped and discrete, having a good production yield of 61.44% to 80.45%. The highest drug release was found to be 87.77% for 8 hr. The microsponge gel showed the controlled release of drug for 12 hr.[29]

7.8 Microsponges in melanoma

Grimes formulated a microsponges containing hydroquinone 4% and retinol 0.15% for the treatment of melanoma and postinflammatory hyperpigmentation (PIH). Microsponges were formulated to release hydroquinone in sustained manner with minimum skin irritation. An open-label study was performed. Improvement in the disease symptoms and the intensity of pigmentation was observed to be statistically significant at weeks 4, 8, and 12 as compared to baseline ($p < .001$). Lesion area measurements was significantly improved at each visit ($p < .001$). The formulation was well tolerated and only one patient in the study discontinued because of the occurrence of an allergic reaction, which was not found to be serious.[30]

7.9 Microsponges in skin infections

Microsponges are also used in the form of creams or gels for various skin infections such as eczema and atopic dermatitis. Mupirocin which is an antibiotic agent used topically for treatment of skin infections. Amrutiya et al. formulated mupirocin microsponges for the

sustained effect against skin infections. They formulated mupirocin microsponges using emulsion solvent diffusion method and then incorporated into emulgel base. Drug release studies using cellulose dialysis membrane have shown controlled release and drug deposition studies on the rat abdominal skin showed a significant amount of drug in the skin up to 24 hr. Draize patch test proved that optimized formulations were stable and nonirritant to the skin. Ointment shoed the drug release up to 4 hr, while the microsponge gel showed up to 10 hr.[31]

7.10 Microsponges in acne

Acne is one of the major skin problems and associated with skin irritation. Benzoyl peroxide is a most common drug used for the treatment of acne. Jelvehgari and his coworkers prepared microsponges of benzoyl peroxide to control the release of benzoyl peroxide on to the skin. Drug release studies have shown that drug release was higher in 4 hr and then remained constant for next 7 hr, may be due to presence of nonencapsulated drug and when this drug released completely, release became constant which indicates the release of the entrapped drug.[32]

Osmani et al. formulated microsponges containing cream of miconazole nitrate, which is an anti-acne agent, to obtain prolonged release. They prepared Eudragit RS-100 microsponges by using quasi emulsion solvent diffusion method. Prepared microsponges were incorporated into a cream. Drug release studies have shown that drug-loaded microsponges gave prolonged drug release of 78.28% upto 8 hr, whereas the conventional creams got exhausted at the end of 4 hr releasing 83.09%.[33]

7.11 Microsponges in skin protection

Sunscreens are used to prevent the UV rays which are responsible for the sunburns and various types of cancer such as basal carcinoma, malignant melanoma. To increase the effect, microsponges can be formulated. Pawar et al. prepared microsponges for topical delivery of Oxybenzone which is broad-spectrum sunscreen agent. They formulated it using quasi-emulsion solvent diffusion method. In lotion and cream form, oxybenzone show skin irritation, dermatitis, and systemic absorption. They optimized the effect of ethyl cellulose and dichloromethane using 32 factorial designs and then dispersed it into hydrogel for further evaluation. The entrapment efficiency of the optimized formulation was found to be 96.9 _ 0.52%. The gel has shown controlled release and it was nonirritant to the rat skin. On performing the creep recovery test, it showed the highest recovery which indicates high elasticity. The formulation had more sun protection factor and lesser irritation, toxicity as

compared to the one available in the market. The microsponge gel had SPF 25 while the marketed lotion had SPF 20, which could be due to the slower release of drug from the microsponge gel, thus proving prolonged oxybenzone retention.[34]

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