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MDS Technology: An Approach for Topical, Oral Controlled and Cosmetic Formulations.

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ABSTRACT

Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin and in cosmetic preparations in order to reduce systemic exposure and it offers the potential to hold active ingredients in a protected environment minimize local cutaneous reactions to active drugs and also 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. The size of the microsponges can be varied usually from 5-300µm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. Although the microsponge size may vary, 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. This approach opens up entirely new opportunities for MDS by colon specific targeting of drugs. Microsponges are extremely small, inert, indestructible spheres that do not pass through the skin. Rather, they collect in the tiny nooks and crannies of the skin and slowly release the entrapped drug, as the skin needs it. They 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. They can be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, tablets and powder and share a broad package of benefits and thus provide formulation flexibility.

Keywords: Micro sponges, cosmetics, colon specific, Biopharmaceuticals

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INTRODUCTION

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. Moreover, the application of topical drugs has many problems like greasiness, stickiness associated with the ointments and so on, that often result in lack of patient compliance. Conventional dermatological products typically provide active ingredients in relatively high concentrations but with a short duration of action, which may lead to a cycle of short term overmedication followed by long-term under medication. Rashes or more serious side effects can occur when active ingredients penetrate the skin. It could be overcome by using a unique, versatile and novel approach Microsponge drug delivery system. Microsponge technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy.

The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc. This company developed a large number of variations of the technique and applied to the cosmetic as well as over the counter (OTC) and prescription pharmaceutical products. At present, this technology has been licensed to Cardinal Health, Inc., for use in topical products.

Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. Microsponges 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.

They can be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, tablets and powder and share a broad package of benefits and thus provide formulation flexibility[1-12].

Structure

Microsponge are uniform, spherical, porous polymeric microspheres having myriad of interconnected voids of particle size range 5-300µm (Fig.1). These microsponges have the capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens and anti-infective, etc. are used as a topical carrier system.3 Microspheres, averaging 25 µm in diameter4 and embedded in the vehicle, act like microscopic sponges, storing the active drug until its release is triggered by application to the skin surface. Micro pores within the spheres comprise a total pore density of approximately 1ml/g, and pore length 10ft for extensive drug retention. Further these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Microsponges consisting of non-collapsible structures with porous surface through active ingredients are released in a controlled manner. Release of drug into the skin is initiated by a variety of triggers, including rubbing and higher than ambient skin temperature. Their high degree of cross-linking results in particles that are insoluble, inert and of sufficient strength to stand up to the high

shear commonly used in manufacturing of creams, lotions, and powders. Their characteristic feature is the capacity to adsorb or "load" a high degree of active materials into the particle and on to its surface. Its large capacity for entrapment of actives, up to three times its weight, differentiates microsponge products from other types of dermatological delivery systems. The active payload is protected in the formulation by the microsponge particle; it is delivered to skin via controlled diffusion. This sustained release of actives to skin over time is an extremely valuable tool to extend the efficacy and lessen the irritation commonly associated with powerful therapeutic agents like α- hydroxy acids which may produce burning, stinging or redness in individuals with sensitive skin. Microsponge polymers possess the versatility to load a wide range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended wear to a wide range of skin therapies.5 When microsponge delivery system applied to the skin, the release of drug can be controlled through diffusion or other variety of triggers, including rubbing, moisture, pH, friction, or ambient skin temperature. [13,14,15]

SALIENT FEATURES/ CHARACTERISTICS OF MICROSPONGES

- MDS are stable over range of pH 1 to 11.
- These are stable at the temperature up to 130˚C.
- Microsponge formulations are compatible with the majority of vehicles and ingredients.
- Self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- These systems have higher payload up to 50 to 60% Still free flowing. [7,11,16]

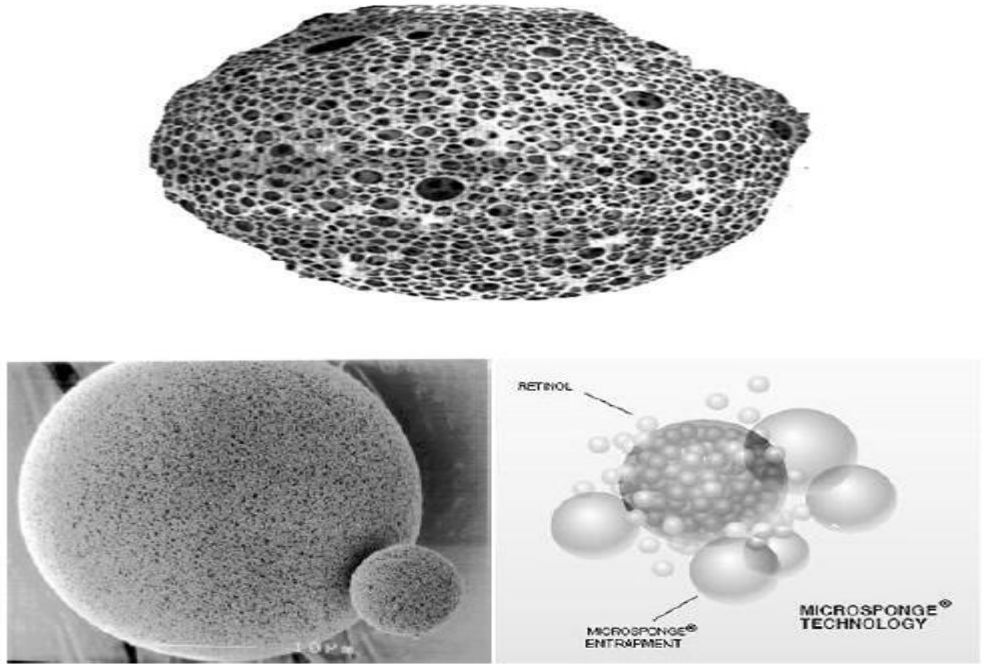

Figure 1: View of Microsponge-[27]

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CHARACTERISTICS OF MATERIALS THAT IS ENTRAPPED IN MICROSPONGES:

Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microsponges must meet following requirements.

- It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- The solubility of actives in the vehicle must be limited to avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle. Otherwise the vehicle will deplete the microsponges before the application.
- It should not collapse the spherical structure of microsponges.
- Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.
- It should be stable in contact with polymerization catalyst and conditions of polymerization [8].

Active following these criteria serves as porogen or pore forming agent. Such drugs can be entrapped while polymerization takes place by one-step process. While when the material is sensitive to the polymerization conditions, polymerization is performed using substitute porogen. The porogen is then removed and replaced by contact absorption assisted by solvents to enhance absorption rate. [9,13,17]

DRUGS EXPLORED IN MDS

- Ketoprofen
- Benzyl peroxide
- Retinol
- Fluconazole
- Ibuprofen
- Tretinoin
- Trolamine
- Paracetamol,
- Dicyclomine,
- Flurbiprofen
- Flucinolone acetonide. [12,18,19]

DRUG USED IN MICROSPONGE DELIVERY (Geeta Patel et al. 2006)

Drugs explored in Microsponge delivery system (MDS)

Dicyclomine, an anticholinergic drug, has direct smooth muscle relaxant action, and in addition to being a weak anticholinergic, it exerts antispasmodic action. Its plasma half life is 4 - 6 h. Dicyclomine causes gastrointestinal (GI) side effects like other antispasmodic drugs. The study was designed to formulate a delivery system based on microsponges that would reduce the GI side effects of the drug.

Flurbiprofen, Microsponge system containing flurbiprofen was formulated for the colonic delivery of the drug for targeted action.

Benzylperoxide, Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes foot. Skin irritation is a common side effect, and it has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, the ethyl cellulose microsponge system was formulated containing BPO which were able to control the release of BPO to the skin.

Fluocinolone acetonide, (FA) is a corticosteroid primarily used in dermatology to reduce skin inflammation and relieve itching. The percutaneous absorption increases risk associated with systemic absorption of topically applied formulation. Controlled release of drug to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, FA en-trapped microporous microparticles (microsponges) were formulated to control the release of drug to the skin.

Retinol, the use of vitamins like tocopherol, retinol in cosmetic formulations like creams, gels is limited due to high instability so oil and water soluble microsponge delivery of the retinol has been developed.

Product name Manufacturer Advantages

Carac Cream
Dermik Laboratories, Inc.
Berwyn , PA 19312 USA

Carac Cream contains 0.5% fluorouracil; with 0.35% being incorporated into a patented porous microsphere consisted of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone. Carac is a once-a-day topical prescription product for the treatment of actinic keratosis (AK) that is characterized by common pre-cancerous skin condition caused by overexposure to the sun.

Salicylic Peel 20 & 30 Biophora Salicylic acid 20%, microsponge technology has excellent exfoliation and used for stimulation of the skin for more resistant skin types or for faster results. It will considerably improve pigmentation, fine lines and acne concerns. Salicylic acid moves easily through the pores, clearing them out while reducing inflammation. This treatment effectively combats acne leaving an amazingly smooth and clear complexion.

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Line Eliminator Dual Retinol Facial Treatment.

Avon

Lightweight cream with a retinol (Vitamin A) in MDS, dual-system delivers both immediate and time released wrinkle-fighting action. Clearly diminishes appearance of fine lines, wrinkles & skin discolorations associated with aging.
Micro Peel Plus /Acne Peel Biomedic

The MicroPeel ® Plus procedure stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge® technology. These microcrystals target the exact areas on the skin that need improvement. The MicroPeel Plus aggressively outperforms other superficial chemical peels by freeing the skin of all dead cells while doing no damage to the skin.

Retinol cream, Retinol 15 Night cream
Biomedic, Sothys

A night time treatment cream with Microsponge technology using a stabilized formula of pure retinol, Vitamin A. Continued use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles, a noticeable improvement in the skin discolorations due to aging, and enhanced skin smoothness.

Lactrex™ 12%
Moisturizing Cream SDR Pharmaceuticals, Inc., Andover , NJ , U.S.A. 07821

Lactrex™ 12% Moisturizing Cream contains 12% lactic acid as the neutral ammonium salt, ammonium lactate. Microsponge® technology has been included for easy application and long lasting moisturization. Lactrex™ also contains water and glycerin, a natural humectant to soften and help moisturize dry, flaky, cracked skin.

EpiQuin Micro
SkinMedica Inc

The Microsponge® system uses microscopic reservoirs that entrap hydroquinone and retinol.The microsponges release these ingredients into the skin gradually throughout the day. This provides the skin with continuous exposure to hydroquinone and retinol over time, which may minimize skin irritation. EpiQuin Micro is a prescription moisturizing fading cream that reduces the impact of these conditions known as melasma, post inflammatory hyper pigmentation or solar lentigines. Also help in Age spots, Sun spots and Facial discoloration.
Oil free matte block spf20 Dermalogica This invisible oil-free sunscreen shields the skin from damaging UV sun rays while controlling oil production, giving you a healthy matte finish. Formulated with microsponge technology, Oil free matte block absorbs oil and preventing shine without any powdery residue.

Sports cream RS and XS Embil Pharmaceutical Co. Ltd.

Topical analgesic-anti-inflammatory and counterirritant actives in a microsponge® delivery system (MDS) for the management of musculoskeletal conditions.
Oil Control Lotion

Fountain Cosmetics A feature-light lotion with technically advanced microsponges that absorb oil on the skin's surface during the day, for a matte finish. Eliminate shine for hours with this feature-weight lotion, formulated with oil-absorbing Microsponge technology. The naturally- antibiotic Skin Response Complex soothes inflammation and tightness to promote healing. Acne-Prone, oily skin conditions.

Advantages of MDS

- Oil control: Microsponges can absorb oil up to 6 times its weight without drying.
- Extended release: It provides continuous action up to 12 hours i.e. extended release.
- Improved product elegancy.
- Lessen the irritation and better tolerance leads to improved patient compliance.
- They have better thermal, physical and chemical stability.
- These are non-irritating, non-mutagenic, nonallergenic and non-toxic.
- MDS allows the incorporation of immiscible products.
- They have superior formulation flexibility.
- In contrast to other technologies like microencapsulation and liposomes, MDS has wide range of chemical stability, higher payload and are easy to formulate.
- Liquids can be converted in to powders improving material processing.
- It has flexibility to develop novel product forms.
- MDS can improve bioavailability of same drugs.
- It can also improve efficacy in treatment.
- Site specific action produce on target organ. [6,19,20]

ADVANTAGES OVER OINTMENTS

Ointments are often aesthetically unappealing, greasiness, stickiness etc. That often results into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odor and potential incompatibility of drugs with the vehicles, when microsponge system maximize 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. [7, 21, 24]

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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 Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the Microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy. [8, 10]

PREPARATION OF MICROSPONGES

Drug loading in microsponges can take place in two ways, one-step process or by two-step process as discussed in liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques which are based on physico-chemical properties of drug to be loaded. If the drug is typically an inert non-polar material, will create the porous structure it is called porogen. Porogen drug, which neither hinders the polymerization nor become activated by it and stable to free radicals is entrapped with one-step process. [23, 25, 28]

1) LIQUID-LIQUID SUSPENSION POLYMERIZATION:

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In their preparation, the monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase, which consist of additives (surfactant, suspending agents, etc. to aid in formation of suspension). The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation.

The various steps in the preparation of microsponges are summarized as

1. Selection of monomer or combination of monomers
2. Formation of chain monomers as polymerization begins
3. Formation of ladders as a result of cross linking between chain monomers
4. Folding of monomer ladder to form spherical particles - Agglomeration of microspheres, which give rise to formation of bunches of microspheres
5. Binding of bunches to form microsponges.

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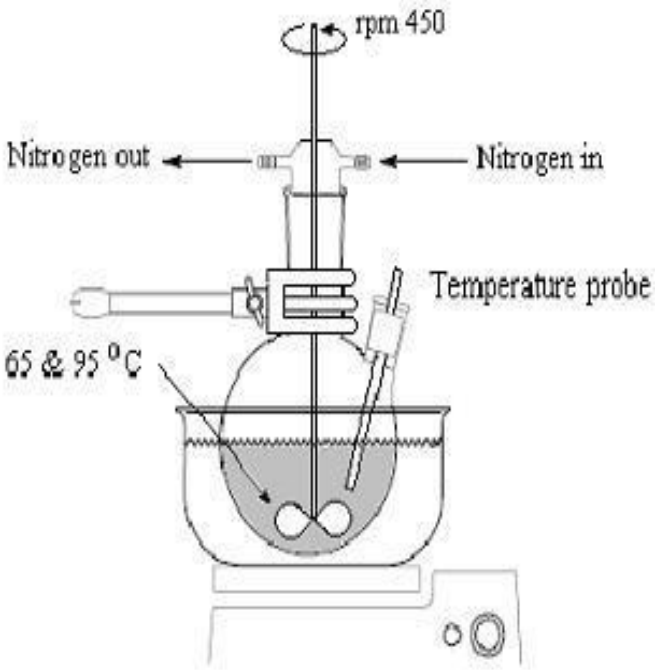

Figure 2: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization [26]

The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. In some cases an inert liquid immiscible with water but completely miscible with monomer is used during the polymerization to form the pore net-work. After the polymerization the liquid is removed leaving the porous microspheres, i.e., microsponges. Impregnating them within preformed microsponges then incorporates the functional substances. Some-times solvent may be used for faster and efficient in-corporation of the active substances. The micro-sponges act as a topical carriers for variety of function-al substances, e.g. anti acne, anti inflammatory, anti purities, anti fungal, rubefacients, etc. [18, 19, 21)]

2) QUASI-EMULSION SOLVENT DIFFUSION

All microsponges were prepared by a quasi-emulsion solvent diffusion method using an external phase of containing 200 ml distilled water and 40 mg polyvinyl alcohol (PVA) 72 000. The internal phase consisted of ketoprofen, ethyl alcohol, polymer and triethylcitrate (TEC), which was added at an amount of 20% of the polymer in order to facilitate the plasticity. At first, the internal phase was prepared at 60°C and added to the external phase at room temperature. After emulsification, the mixture was continuously stirred for 2 hours. Then the mixture was filtered to separate the micro-sponges. The product was washed and dried by vacuum oven at 40°C for 24 hours. [22, 26]

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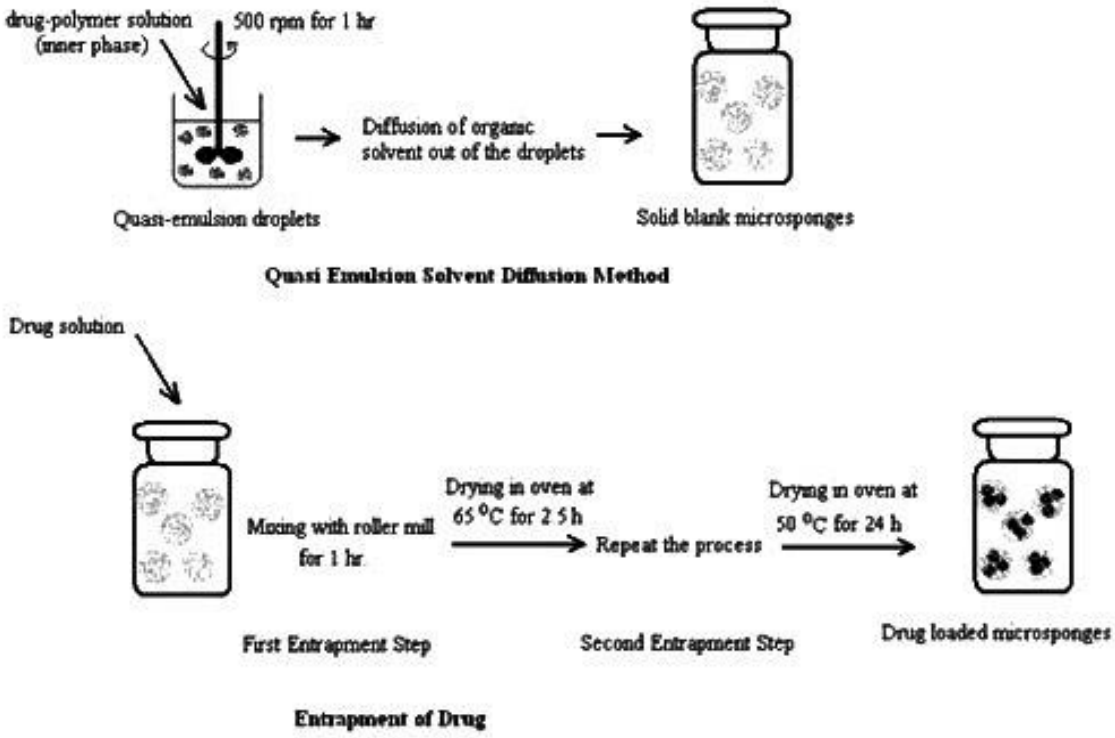

Fig 3: Preparation of Microsponges By Quasi-Emulsion Solvent Diffusion Method [28]

RELEASE MECHANISMS:

By proper manipulation of the before mentioned programmable parameters, microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers.[25]

PROGRAMMABLE RELEASE

(i)Pressure triggered systems:

Microsponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon various characteristics of the sponge. By varying the type of material and different process variables, the microsponge best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect. The duration of emolliency was also much more for the microsponge systems.

(ii)Temperature triggered systems

Some entrapped active ingredients can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an

increased flow rate and hence release. So it is possible to modulate the release of substances from the microsponge by modulation of temperature. For example, viscous sunscreens were found to show a higher release from microsponges when exposed to higher temperatures; thus a sunscreen would be released from a microsponge only upon exposure to the heat from the sun.

(iii) 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 drug delivery.

(iv)Solubility triggered system

Microsponges loaded with water-soluble ingredients like antiperspirants and antiseptics will release the ingredient in the presence of water. Presence of an aqueous medium such as perspiration can trigger the release rate of active ingredients. Thus release may be achieved based on the ability of the external medium to dissolve the active, the concentration gradient or the ability to swell the microspore network.

Various factors that are to be considered during development of such formulations includes,

1. Physical and chemical properties of entrapped actives.
2. Physical properties of microsponge system like pore diameter, pore volume, resiliency etc.
3. Properties of vehicle in which the microsponges are finally dispersed.
4.Particle size, pore characteristics, resiliency and monomer compositions can be considered as programmable parameters and microsponges can be designed to release given amount of actives in response to one or more external triggers like; pressure, temperature and solubility of actives. [23]

FORMULATION CONSIDERATIONS:

Actives entrapped in MDS can then be incorporated into many products such as creams, lotions, powders and soaps. When formulating the vehicle, certain considerations are taken into account in order to achieve desired product characteristics.

1. The solubility of actives in the vehicle must be limited. Otherwise the vehicle will deplete the microsponges before the application.
2. To avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle.
3. Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period. There remains equilibrium between microsponge and vehicle and microsponge releases drug in response to the depletion of drug concentration in the vehicle. Drug concentration in the vehicle is depleted by absorption of the drug into skin. Hence continuous and steady release of actives onto the skin is accomplished with this system.

Drug release from the topical semisolid formulation can be studied by using Franz-type static diffusion cells.[24]

PHYSICAL CHARACTERIZATION OF MICROSPONGES

(i) Particle size determination

Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values can be expressed for all formulations as mean size range. Cumulative percentage drug release from microsponges of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30µm can impart gritty feeling and hence particles of sizes between 10 and 25µm are preferred to use in final topical formulation.[21]

(ii) Morphology and surface topography of micro sponges

For morphology and surface topography, prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy (SEM). SEM of a fractured microsponge particle can also be taken to illustrate its ultra structure.[21]

(iii) Determination of loading efficiency and production yield

The loading efficiency (%) of the microsponges can be calculated according to the following equation:

Loading efficiency =

$$\frac{\text{Actual Drug Content in Microsponges}}{\text{Theoretical Drug Content}} \times 100 \ldots\ldots (1)$$

The production yield of the micro particles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the micro sponge obtained. [20].

$$\text{Production Yield} = \frac{\text{Practical mass of microsponges}}{\text{Theoritical mass (Polymer+drug)}} \times 100 \ldots\ldots (2)$$

(iv) Determination of true density

The true density of micro particles is measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations. [20]

(v) Characterization of pore structure

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

Porosity parameters of microsponges such as intrusion–extrusion isotherms pore size distribution, total pore surface area, average pore diameters, interstitial void volume, percent porosity, percent porosity filled, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry. [29]

(vi)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). For DSC approximately 5mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15oC/min over a temperature range 25–430oC in atmosphere of nitrogen.

(vii) Polymer/monomer composition

Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microspheres. Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence have direct influence on the release rate of entrapped drug. Release of drug from microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time.

(viii) Resiliency (viscoelastic properties)

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

(ix) Dissolution studies

Dissolution profile of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisted 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.

(x) Kinetics of release

To determine the drug release mechanism and to compare the release profile differences among microsponges, the drug released amount versus time was used. The release data were analyzed with the following mathematical models:

$$Q = k_1 t^n \text{ or } \log Q = \log k_1 + n \log t \ldots. (3)$$

Where Q is the amount of the released at time (h), n is a diffusion exponent which indicates the release mechanism, and k1 is a constant characteristic of the drug– polymer interaction.

From the slope and intercept of the plot of log Q versus log t, kinetic parameters n and k1 were calculated.

For comparison purposes, the data was also subjected to Eq. (4), which may be considered a simple, Higuchi type equation.

$$Q = k_2 t^{0.5} + C \ldots\ldots (4)$$

Eq. (4), for release data dependent on the square root of time, would give a straight line release profile, with k_2 presented as a root time dissolution rate constant and C as a constant.

APPLICATIONS OF MICROSPONGE SYSTEMS

Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. 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.

1. 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
2. Pay load is up to 50 – 60%.
3. Free flowing and cost effective.

4. Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin.

Sr.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 pyri-thione, selenium sulfide	Reduced unpleasant odor with lowered irritation with extended safety and efficacy.
6.	Antipruritics	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.

Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter and personal care products.

Products under development or in the market place utilize the Topical Microsponge systems in three primary ways:

1. As reservoirs releasing active ingredients over an extended period of time,
2. As receptacles for absorbing undesirable substances, such as excess skin oils, or
3. As closed containers holding ingredients away from the skin for superficial action.

Releasing of active ingredients from conventional topical formulations over an extended period of time is quite difficult. [14, 16, 17, 19]

1. Microsponge for topical delivery

The Microsponge systems are based on microscopic, polymer-based microspheres that can bind, suspend or entrap a wide variety of substances and then be incorporated into a formulated product, such as a gel, cream, liquid or powder. A single Microsponge is as tiny as a particle of talcum powder, measuring less than one-thousandth of an inch in diameter. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure that can accept a wide variety of substances. The outer surface is typically porous, allowing the controlled flow of substances into and out of the sphere.

Several primary characteristics, or parameters, of the Microsponge system can be defined during the production phase to obtain spheres that are tailored to specific product applications and vehicle compatibility. Microsponge systems are made of biologically inert polymers. Extensive safety studies have demonstrated that the polymers are non-irritating,

nonmutagenic, non-allergenic, non-toxic and non-biodegradable. As a result, the human body cannot convert them into other substances or break them down. Although they are microscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products[21].

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne, with skin irritation as a common side effect. It has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, microsponge delivery of Benzoyl peroxide was developed using an emulsion solvent diffusion method by adding an organic internal phase containing benzoyl peroxide, ethyl cellulose and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol and by suspension polymerization of styrene and divinyl benzene [22, 23,24] .The prepared microsponges were dispersed in gel base and microsponge gels are evaluated for anti-bacterial and skin irritancy. The entrapped system released the drug at slower rate than the system containing free BPO. Topical delivery system with reduced irritancy was successfully developed. [14]

Amrutiya *et al* developed microsponge based topical delivery system of mupirocin by an emulsion solvent diffusion method and evaluated for sustained release and enhanced drug deposition in the skin. The effect of formulation and process variables like stirring speed and internal phase volume on the physical characteristics of microsponges was analyzed on optimized drug/polymer ratio by 32 factorial designs. The optimized microsponges were incorporated into an emulgel base. Several parameters were studied i.e. *in-vitro* drug release, *ex-vivo* drug deposition and *in-vivo* antibacterial activity of mupirocin-loaded formulations. Prepared microsponges were spherical and porous and found no interaction between drug and polymer molecules. Emulgels containing microsponges were showed preferred physical properties. Diffusion-controlled release pattern were showed by drug release through cellulose dialysis membrane and drug deposition studies using rat abdominal skin has been exhibited significant retention of actives in skin from microsponge based formulations by 24 h. Draize patch test demonstrated that the optimized formulations were stable and nonirritant to skin. Microsponges based emulgel formulations showed extended efficacy in mouse surgical wound model infected with S. aureus. Mupirocin was stable in topical emulgel formulations and showed enhanced retention in the skin demonstrating superior potential of the delivery system for the treatment of primary and secondary skin infections i.e. eczema, impetigo and atopic dermatitis.

Di Sapio Aj,*et al* reported that microporous polymeric particles fill up the skin's creases and valleys. This means that an even and effective spread is achieved. It also states that another important advantage of the microporous system is that it can prevent the degradation of actives such as retinol. Retinol, in high concentrations is used to reduce the appearance of lines and wrinkles on the skin. But, the formulation of high concentrations becomes difficult due to the instability of the molecule to oxygen. Interestingly, some emulsions facilitate decomposition by diffusion of oxygen. In such a case, the microsponge system not only helps to

shield retinol but also helps to improve the effectiveness of the antioxidant system of the formulation.

Sunscreens:

Melanosponge-α which contains genetically engineered melanin, is designed to spread this melanin evenly and hence give a superior sun protective effect against UV-A as well as UV-B48

Antidandruff:

Microsponges may be very useful in the odour masking of malodorous actives. The unpleasant odour and irritation associated with antidandruff actives, namely zinc pyrithione and selenium sulphide, were masked and an increase in the efficacy was reported.

Anti-acne:

Many anti-acne actives cause severe skin irritation and therefore a controlled release would help overcome the toxic effect caused by such actives. A reduction in the irritation caused by benzoyl peroxide when entrapped in the microsponges has been reported and it is available commercially
in form of a cream.

Skin de-pigmentation products:

Typical Skin de-pigmentation products like hydroquinone are known to be highly susceptible to oxidation. Entrapment of hydroquinone into microsponges was shown to improve the stability of hydroquinone, besides improving efficacy

Application in oral care cosmetics: a new height in cosmetic world:

An interesting application of the microsponge technology could be in oral cosmetics, such as to sustain the release of volatile ingredients, thus increasing the duration of the 'fresh feel'. Microsponges of such volatile ingredients may be easily incorporated in tooth pastes or mouth washes. [19]

2. The Microsponge for Oral Delivery:

A Microsponge 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 Microsponge system has been shown to increase the rate of Solubilization of poorly water soluble drugs by entrapping such drugs in the Microsponge 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 Microsponge system to traverse the small and large intestine is significantly increased thus maximizing the amount of drug that is absorbed. Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, eudragit RS, by changing their intraparticle density. The release of ketoprofen incorporated into modified release ketoprofen microsponge 200 mg tablets and Profenid Retard 200 mg was studied in vitro and in vivo. The formulation containing ketoprofen microsponges yielded good modified release tablets. An in vivo study was designed to evaluate the pharmacokinetic parameters and to compare them with the commercially available ketoprofen retard tablets containing the same amount of the active drug. Commercial ketoprofen retard tablets showed a more rapid absorption rate than modified release tablets and peak levels were reached within almost 3.6 h after administration. However, the new modified release tablets showed a slower absorption rate and peak levels were reached 8 h after administration.[29]

3. Micro sponges for biopharmaceuticals delivery:

The micro sponge delivery system (MDS) is employed for both in the delivery of biopharmaceuticals as well as in tissue engineering. Matsuda *et al* has been studied the biodegradable polymer with collagen microsponge serves as a new bioengineered cardiovascular prosthesis. Biodegradable materials with autologous cell seeding had gaining much interest as potential cardiovascular grafts. Though, pretreatment of biodegradable materials require an invasive and complicated procedure that carries the risk of infection. The main aim of the study is to develop a biodegradable graft material containing collagen microsponge that would allow the regeneration of autologous vessel tissue in order to avoid these problems. The capability of this material to hasten in situ cellularization with autologous endothelial and smooth muscle cells was tested with and without precellularization.

Poly (lactic-co-glycolic acid) has been used as a biodegradable scaffold which was compounded with collagen microsponge to form a vascular patch material. The poly (lactic-co-glycolic acid)–collagen patches with or without autologous vessel cellularization were used to patch the canine pulmonary artery trunk. Biochemical and histology assessments were performed 2 and 6 months after the implantation. The results showed that there was no thrombus formation in either group but the poly (lactic-co-glycolic acid) scaffold was approximately completely absorbed in both groups. Histologic results showed the formation of an endothelial cell monolayer, a parallel alignment of smooth muscle cells, and reconstructed vessel wall with elastin and collagen fibers.

The cellular and extra-cellular components in the patch had enlarged to levels analogous to those in native tissue at 6 months. The study concluded that poly (lactic-coglycolic acid) collagen microsponge patch with and without pre-cellularization showed good histologic result

and durability. This patch also shows promise as a bioengineered material for promoting in situ cellularization and the regeneration of autologous tissue in cardiovascular surgery.

4. Microsponge for Bone and Tissue Engineering:

Bone-substitute compounds were obtained by mixing pre polymerized powders of polymethylmethacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyapatite powders. The final composites appeared to be porous and acted as microsponges. Basic fibroblast growth factor (bFGF) incorporated in a collagen sponge sheetwas sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix, and exhibited local angiogenic activity in a dose-dependent manner. The injection of collagen microsponges incorporating bFGF induced a significant increase in the blood flow, in the murine ischemic hind limb, which could never have been attained by the bolus injection of bFGF. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of bFGF.[17]

CONCLUSION

Ease manufacturing, simple ingredients and wide range actives can be entrapped along with a programmable release make microsponges extremely attractive. MDS is originally developed for topical delivery of drugs like anti-acne, anti-inflammatory, anti-fungal, anti-dandruffs, antipruritics, rubefacients etc. Now days it can also be used for tissue engineering and controlled oral delivery of drugs using bio erodible polymers, especially for colon specific delivery. Microsponge delivery systems that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. MDS holds a promising future in various pharmaceutical applications in the coming years by virtue of their unique properties like small size, efficient carrier characteristics enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical, and chemical stability so flexible to develop novel product forms. New classes of pharmaceuticals, biopharmaceuticals (peptides, proteins and DNA-based therapeutics) are fueling the rapid evolution of drug delivery technology. Thus MDS is a very emerging field which is needed to be explored**.**

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