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Microsponges: An Approach to Novel Drug Delivery System-A Review

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A B S T R A C T

Microsponges, the drug release technology has become more spirited and rapidly on the rise. Different drug delivery systems are being incorporated to optimize the efficiency and cost-effectiveness of the rehabilitation. In malevolence of presence of these technologies the drug delivery systems are unsuccessful to reach the systemic circulation in adequate amounts in control manner in few cases like Peptides and proteins. Conventional topical formulations have also many problems, such as producing a highly concentrated layer of active ingredient resulting irritation and allergic reactions etc. To control the delivery rate of active agents to a encoded site in human body has been one of the major challenges for drug industry. This review article focus on the Novel approaches to product formulation incorporating Microsponges technology may offers better entrapment of ingredients, reduced side effects, increased elegance, and enhanced formulation flexibility.

Keywords: Microsponges, Drug delivery system, drug release technology, topical

A R T I C L E I N F O

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1. Introduction

To control the delivery rate of active ingredients to a predetermined site in human body has been one of the biggest challenges faced by drug industry. Several conventional and consistent systems were developed for systemic drugs under the heading of transdermal drug delivery system (TDDS) using the skin as portal of entry. It has improved the efficacy and safety of many drugs that may be better administered through skin. But TDS is not practical for delivery of materials whose final target is skin itself. Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is an area of research that has only recently been addressed with success. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis. Application of topical drugs suffers many problems such as ointments, which 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 odour and potential incompatibility of drugs with the vehicles. Thus the need exists for system to 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. The microsponge delivery system fulfills these requirements. A Microsponge® Delivery System (MDS) is "Patented, highly cross-linked, porous, polymeric microspheres polymeric system consisting of porous microspheres that can entrap wide range of actives and then release them onto the skin over a time and in response to trigger"[1]. It is a unique technology for the controlled release of topical agents and consists of microporous beads, typically 10-25 microns in diameter, loaded with active agent. When applied to the skin, the MDS releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc). MDS technology is being used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. Delivery system comprised of a polymeric bead having network of pores with an active ingredient held within was developed to provide controlled release of the active ingredients whose final target is skin itself. The system was employed for the improvement of performance of topically applied drugs. The common method of formulation remains same; the incorporation of the active substance at its maximum thermodynamic activity in an optimized vehicle and the reduction of the resistance to the diffusion of the stratum corneum. Application Solubility enhancement Site specific action produced on the target organ Increase stability of drug Targeted drug delivery Controlled release drug delivery Topical drug delivery Oral drug delivery Bone tissue engineering Cardiovascular engineering Reconstruction of vascular wall. Microsponges are porous, polymeric microspheres that can suspend or entrap a wide variety of active ingredients such as fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents and can be incorporated into a formulated product such as a gel, cream, liquid or powder.[2]They are used mostly for topical use and have been recently used for oral administration. Microsponges 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[3]. The microsponges technology was developed by Won in 1987, and applied to the cosmetic and OTC product. At the present time, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products. The size of the microsponges can be varied, usually from 5-300 μm in diameter having large pores as a reservoir within each microsponge[4]. Several systems have been developed for systemic drugs delivery such as microcapsules, microsphere and liposome etc, but they have some limitation such as microcapsules cannot usually control the release rate of the active drug once the wall is ruptured and liposome suffer from a lower pay load, difficult formulation, chemical stability, and microbial instability. Thus there is need of a system to maximize the amount of time that an active ingredient is present either on the skin surface or within the epidermis with minimizing its transdermal penetration into the body[3]. Microsponges have stability over a pH range of 1-11 and also stable up to temperature 130°C. Microsponges are microscopically spherical, free flowing, and better entrapment efficiency to reduced side effects, increased elegance, non-irritating etc. Currently microsponges are used in cosmetics, over-the-counter (OTC) skin care, sunscreens products. The detailed applications of microsponges and list of marketed products are enumerated in table no. 3 and table no. 4.

Characteristics of Microsponge

Microsponges formulations are stable over range of pH 1-11; Microsponge formulations are stable at temperature up to 130°C.Microsponge formulations are self-sterilizing as their average pore size 0.25μm where bacteria cannot penetrate. Microsponge formulation have higher payload (50-60%), still free flowing and can be cost effective. The Microsponge technology is a proprietary system of microparticles that can entrap a very wide range of pharmaceutical and cosmetic active ingredient to enhance their performance in topically applied dermatological products. This technology has been introduced in topical drug products to ensure the controlled release of active drug into the skin in order to reduce systemic availability and reduce local cutaneous reaction to active drug.

A Novel Drug Delivery System

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. Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability. While microsponge system in contrast to the above systems are stable over range of pH 1 to 11,

temperature up to 130oC; compatible with most vehicles and ingredients; self sterilizing as average pore size is 0.25µm where bacteria cannot penetrate; higher payload (50 to 60%), still free flowing and can be cost effective. 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.
- It should be stable in contact with polymerization catalyst and conditions of polymerization.

Advantages:

- Controlled drug release
- Site specific action produce on target organ
- Enhanced drug stability
- High drug loading capacity Improve therapy
- Compatible with vehicle and ingredients
- Stable over the range of 1 -11 pH.
- Solution Free flowing and cost effective
- Improve thermal, physical, and chemical stability
- Flexibility to develop novel product forms

Preparation Method of Microsponge:

The active material should be water immiscible or at most only slightly soluble, inert to monomers (Table no.2). It should be also stable when in contact with the polymerization catalyst and under conditions of polymerization. The spherical structure of the microsponges should not collapse [5].

Polymerization Method:

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 and the solution of monomers is dispersed in the aqueous phase containing surfactant etc [6]. The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation[7].

Quasi-Emulsion Solvent Diffusion Method

Microsponges were prepared by a quasi-emulsion solvent diffusion method using an external phase of containing distilled water and polyvinyl alcohol (PVA) 72000.The internal phase consists of drug, ethyl alcohol, polymer and triethyl citrate 20% of the polymer. 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 microsponges. The product was washed and dried by vacuum oven at 40°C for 24 hours[8].

- **Properties for the Entrapment into Microsponges** 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 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.
- It should be stable when in contact with the polymerization catalyst and under conditions of polymerization.
- The spherical structure of the microsponges should not collapse.

2. Evaluation

Evaluations of microsponges are carried out by various methods which are given in table no. 1.

Table: Evaluation of Microsponges

Parameters	Methods
Particle size (Microscopy), size distribution and polydispersity	Diffractometry[9]
Morphology & surface topography	Electron microscopy[10]
Density	Displacement method [11]
Pore structure	Mercury intrusion porosimetry [11]
Drug polymer interaction	FTIR [12]
Crystallinity	XRD studies [13]
Drug release study from topical formulation	Franz diffusion cell [14]

Table 2: Drug used in microsponge delivery system

Drugs	Polymer	Offering Benefits
Mupicin	Ethyl cellulose and dichloromethane as a solvent which contained PVA as emulsifying agent	Enhanced retention in the skin indicating better potential of the delivery system for treatment of primary and secondary skin infections [15]

Benzyl Peroxide	Ethyl cellulose and dichloromethane as a solvent.Suspension polymerization of styrene and methyl methacrylate	Reduce the side effect by reducing percutaneous absorption and control the release BPO to the skin.[16]
Fluconazole	liquid-liquid suspension polymerization of styrene and methyl methacrylate	Reduce the side effect and controlled the release. [17]
Flurbiprofen	Eudragit RS 100 and pore plugging of microsponges with pectin: HPMC mixture followed by tabletting	Microsponge system containing flubiprofen was formulated for the colonic delivery of the drug for targeted action.[18]
Dicyclomine	Eudragit RS 100	System based on microsponges that would reduce the GI side effects of the drug. [19]
Hydroxyzine HCl	Eudragit RS-100 microsponges	Controlled release of the drug from a delivery system to the skin could reduce the side effects while reducing percutaneous absorption. [20]
Diclofenac sodium	Xanthan gum-facilitated ethyl cellulose microsponges	At the lowest drug/polymer ratio could be useful for controlled release of Diclofenac sodium to the skin. [21]
Paracetamol	Eudragit S-100 based microsponges. tablets were prepared by compressing the microsponges followed by coating with pectin: hydroxyl propyl methyl cellulose (HPMC) mixture	Colonic delivery of the drug for targeted action. [22]

Application of Microsponge

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

- 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.
- Pay load is up to 50 –60%.
- Free flowing and cost effective.
- Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin.

Table 3: Applications of Microsponge **[**23]

Active agents	Applications
Sunscreens	Improve efficacy & protection against sunburns and sun related injuries
Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization
Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response
Anti-fungal	Sustained release of actives
Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odor with lowered irritation with extended safety and efficacy
Rubefacients	Prolonged activity with reduced irritancy
Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy

Table 4: List of marketed products [24]

Product name	Advantages
Retin-A-Micro™	0.1 And 0.04% tretinoin entrapped in MDS, for topical treatment of acne vulgaris.
Carac cream 0.5%	Carac cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsponge composed of

	methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone.
Line eliminator dual retinol facial treatment	Lightweight cream with a retinol (Vitamin A) in MDS, delivers both immediate and time-released wrinkle-fighting action.
Retinol cream	The retinol molecule is kept in the microsponge system to protect the potency of vitamin A. This helps to maximize the retinol dosage, while reducing the possibility of irritation. Retinol is a topical vitamin A derivative, which helps maintain healthy skin, hair, and mucous membranes.
Retinol 15 night cream	A night time treatment cream with Microsponge system. The formula contain of pure retinol. Continuous use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles, and improve in skin discolorations.
EpiQuin micro	The Microsponge® system entraps hydroquinone and retinol. The microsponges release these ingredients into the skin gradually throughout the day, which may minimize skin irritation
Sports cream RS and XS	Topical analgesic-anti-inflammatory and counterirritant actives in a Microsponge® Delivery System (MDS) for the management of musculoskeletal conditions
Salicylic peel 20 and 30	Deep BHA peeling agent: Salicylic acid 20% and 30%, Microsponge Technology, Excellent exfoliation and stimulation of the skin for more resistant skin types or for faster results. Will dramatically improve fine lines, pigmentation, and acne concerns.
Micro peel plus	The MicroPeel® Plus, stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge® technology.The MicroPeel® Plus aggressively outperforms other superficial chemical peels by freeing the skin of all dead cells, while doing no damage to the skin.
Lactrex™ 12% moisturizing cream	It contains 12% lactic acid as the neutral ammonium salt and ammonium lactate. Lactrex™ also contains water and glycerin, a natural humectant, to soften and help moisturize dry, flaky, cracked skin
Dermalogica oil control lotion	It is a feather-light lotion, formulated with oil absorbing Microsponge® technology and hydrating botanicals. The naturally antiseptic skin response complex helps soothe and purify the skin.
Ulta guard	Microsponge system that contains dimethicone to help protect a baby's skin from diaper rash

3. Advance Development

These drug delivery systems were originally developed for topical delivery of drugs. They can also be used for tissue engineering and controlled oral delivery of drugs using biodegradable polymers. It provides a wide range of formulating advantages. Liquids can be transformed into free flowing powders. Formulations can be developed with otherwise incompatible ingredients, with prolonged stability, without the use of preservatives. Therefore, microsponges will be an ideal drug delivery system related to formulations like the transdermal delivery system[24]. As we realize the nanosized particles have immense advantages like a very high surface area to size ratio and a greater potential to modulate the release of actives compared to micro-sized particles. While inorganic nanosponges have many applications in electronics, the first pharmaceutical nanosponges based on cross linked cyclodextrins have been reported[25].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 and also colors entrapped in Microsponges may be used in a variety of colored cosmetic products such as rouge or lipsticks to make them long lasting [26].

4. Conclusion

This drug delivery system is a unique technology for the controlled release of macro porous beads, loaded with active agent, offering a potential reduction in side effects, while maintaining their therapeutic efficacy. The Microsponges drug delivery system offers entrapment of its ingredients. In addition, numerous studies have confirmed

that Microsponges systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. This technology is being used currently in cosmetics, over-the-counter skin care, sunscreens, and prescription products. This kind of drug delivery technology may lead to a better understanding of the healing of several diseases. Hence, the microsponge-based drug delivery technology is likely to become a valuable drug delivery matrix substance for various therapeutic applications in the future.

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