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Microsponges laden gels for topical delivery: A novel approach

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Abstract
Depression is a term which state of low mood (mood disorder) and repugnance to activity that can affect a person's thoughts, behavior, feelings and sense of well-being. People with depressed mood can persistent feeling of sadness and loss of interest, worthless, anxious, empty, hopeless, helpless, guilty, irritable, ashamed or restless. They may lose interest in activities that were once pleasurable, experience loss of appetite or overeating, have problems concentrating, remembering details or making decisions, and may contemplate, attempt or commit suicide. Insomnia, aches, pains, digestive problems, excessive sleeping or reduced energy may also be present. You may have trouble doing normal day-to-day activities, and sometimes you may feel as if life isn't worth living.
Anti–Depressent increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults. Transdermal delivery of venlafaxine hydrochloride (VHCl) may result in proper patient compliance by reducing the incidence of the undesirable GI problems generally associated with its plural oral dosing. In therapeutic dosing with VHCl tablets, rapid dissolution results in rapid increase in plasma levels of active compounds shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic levels are approached after about 12 hrs, following administration, thus require additional dosing with the drug. With plural daily dosing regimen, the most common side effect is nausea, experienced by 45% of patients under treatment with VHCl. About 17% of the patients suffers from vomiting at higher doses VHCl is associated with a rise in blood pressure. There is no first pass metabolism effect on drug absorbed through transdermal route while oral drugs are metabolized in liver. Hence, this enhance the greater uniformity in plasma levels in case of TDDS and also reduces toxicity.

Keywords: Microsponges, topical delivery, novel

Introduction
Transdermal drug delivery system is not only practicable for delivery of materials which have final target skin as itself. Drug released into a control rate onto the epidermis with assurance that the drug remains primarily localized and does not enter into the systemic circulation in accurate and appropriate amount is a challenging area of research. Microsponges are highly porous micro-sized particles with a unique ability for entrapping active pharmaceutical ingredients. To control the delivery rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by researchers. Microsponges are safe biologically and offer unique advantage of programmable release. This technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. This technology is being used for topical formulations and also for oral administration. The present review describes microsponge technology including its preparation, characterization, programmable parameters and release mechanism of microsponge drug delivery system [1].
Microsponges are advanced and proposed polymeric drug delivery systems which is composed of porous microspheres. They are tiny sponge-like structure and spherical in shape with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponge 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 [2].
The ever-increasing interest among consumers with regard to skin care and skin treatment products has been fostered by the widespread use of ingredients like α-hydroxy acids and vitamins in topical products, which can induce perceivable and demonstrable benefits –

especially in aging or photo-damaged skin. Although quite useful, in many instances, these ingredients may produce irritancy; such irritancy can be perceived as burning, stinging or redness and particularly occurs in individuals with sensitive skin. Recognizing this problem, the formulators have attempted to deal with this problem in one of the two methods. They have reduced the concentration of such ingredients, but in the process, sacrificed efficacy. They have also modified the vehicle in order to make the product more emollient or skin-compatible [3]. Drug delivery systems that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system. Several predictable and reliable systems been developed for systemic drugs under the heading of transdermal delivery systems (TDS) using the skin as a portal of entry [4].

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, depending upon the degree of smoothness or after-feel required for the end formula. Although the microsponge size may vary, a typical 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 a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. The microsponge particles themselves are too large to be absorbed into the skin and this adds a measure of safety to these microsponge materials. Another safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 µm cannot penetrate into the tunnel structure of the microsponges [5]

Benefits of Microsponge Technology [6]

- Microsponge technology offers:
- Enhanced product performance.
- Extended release.
- Reduced irritation and hence improved patient compliance.
- Improved product elegancy.
- Improved oil control as it can absorb oil up to 6 times its weight without drying.
- Improved formulation flexibility.
- Improved thermal, physical, and chemical stability.

Characteristics of the Materials [6]

- 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.
- It should be stable in contact with polymerization catalyst and conditions of polymerization.

Fig 1: A Microsponge system (porous microsphere) [7]

Potential Advantages of the Microsponge Drug Delivery System [8]

- 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.
- Microsponges have stability up to temperature 130°C.
- Microsponge having Pay load is up to 50 – 60%.
- They have free flowing and cost effective.
- Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin.

Properties of the Actives for the Entrapment into Microsponges [8]

- 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.

Methods of Preparation of Microsponges

Liquid–Liquid Suspension Polymerization [8]

In general, a solution is made comprising of monomers and the functional or active ingredients, which are immiscible with water. This phase is then suspended with agitation in an aqueous phase, usually containing additives, such as surfactants and dispersants, to promote suspension. Once the suspension is established with discrete droplets of the desired size, polymerization is effected by activating the monomers either by catalysis, increased temperature or irradiation. As the polymerization process continues, a spherical structure is produced containing thousands of microsponges bunched together like grapes, forming interconnecting reservoirs.

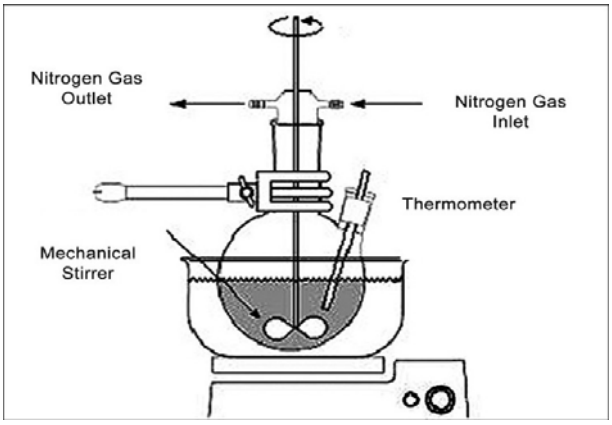

Fig 2: Reaction vessel for microsponge preparation by liquid–liquid suspension polymerization [8]

Once the polymerization is complete the solid particles that result from the process are recovered from the suspension. The particles are then washed and processed until they are substantially ready for use. The microsponge products can be made using styrene and divinylbenzene or methyl methacrylate and ethylene glycol dimethacrylate as starting materials.

Quasi-emulsion solvent diffusion

To prepare the inner organic phase, Eudragit RS 100 is dissolved in ethyl alcohol. Next, the drug is added to the solution and dissolved under ultrasonication at 35°C. The inner phase is poured into the polyvinyl alcohol solution in water (outer phase). Following 60 minutes of stirring, the mixture is filtered, to separate the microsponges. The microsponges are dried in an air-heated oven at 40°C for 12 hours [9].

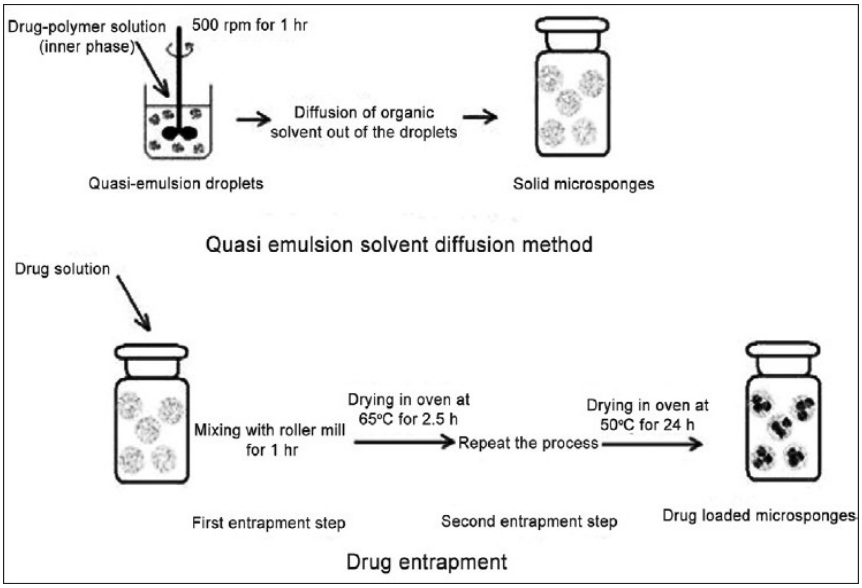

Fig 3: Preparation of microsponges by the quasi-emulsion solvent diffusion method [9]

Ingredients can be entrapped in microsponge polymers either at the time of synthesis, or if too labile to withstand polymerization conditions, they can be post-loaded after the microsphere structure has been pre-formed. In general, the latter process is the preferred mode, as many cosmetic ingredients, and most pharmaceutical ones, would decompose at the temperatures employed for polymerization.

Pseudo Mechanism of Action

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (i.e., 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, when the vehicle becomes saturated. 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 microsponge particle into the vehicle, and from it to the skin, until the vehicle is either dried or absorbed. Even after that the microsponge particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with microsponge entrapments. If the active is too soluble in the desired vehicle during compounding of the finished products, the products 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 microsponge entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives. This principle is contrary to the conventional formulation principles usually applied to topical products. For these conventional systems it is normally recommended to maximize the solubility of the active in the vehicle. When using microsponge entrapments, some solubility of the active in the vehicle is acceptable, because the vehicle can provide the initial loading dose of the active until release from the microsponge is activated by the shift in equilibrium from the polymer into the carrier. Another way to avoid undesirable premature leaching of the active from the microsponge polymer is to formulate the product with some free and some entrapped active, so the vehicle is pre-saturated. In this case there will not be any leaching of the active from the polymer during compounding. The rate of active release will ultimately depend not only on the partition coefficient of the active ingredient between the polymer and the vehicle (or the skin),

but also on some of the parameters that characterize the beads. Examples of these include surface area and primarily, mean pore diameter [10] Release can also be controlled through diffusion or other triggers such as moisture, pH, friction or temperature.

Oral Drug Delivery Using Microsponge Technology

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. As these pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increases the rate of solubilization. Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, eudragit RS, by changing their intraparticle density [11]. Sustained release formulation of chlorpheniramine maleate, using powder-coated microsponges, is prepared by the dry impact blending method, for oral drug delivery [12]. Controlled oral delivery of Ketoprofen prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterwards tablets of microsponges were prepared by the direct compression method. Results indicated that compressibility was much improved in the physical mixture of the drug and polymer; due to the plastic deformation of the sponge-like microsponge structure, producing mechanically strong tablets. Colon-specific, controlled delivery of flurbiprofen, was conducted by using a commercial Microsponge® 5640 system. *In vitro* studies exhibited that compression-coated colon-specific tablet formulations started to release the drug at the eighth hour, corresponding to the proximal colon arrival time, due to addition of the enzyme, following a modified release pattern, while the drug release from the colon-specific formulations prepared by pore plugging the microsponges showed an increase at the eighth hour, which was the point of time when the enzyme addition was made [13].

Microsponges loaded Gels [14, 15]

The term 'gel' was introduced in the late 18th century to name some semisolid or semi liquid material according to their physiological characteristics rather than molecular composition. A gel is consist of two-component, physically or chemically cross linked three-dimensional network consisting of structural materials interspersed by an adequate but proportionally large amount of liquid to form an infinite rigid network structure. This leads to gel classification into chemical and physical gel systems, respectively. Chemical gels are associated with permanent covalent bonding while physical gels result from relatively weaker and reversible secondary intermolecular forces such as hydrogen bonding, electrostatic interactions, dipole dipole interactions, Vander Waals forces and hydrophobic interactions.

The U.S.P. *defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gels consist of two phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains.*

Gel Forming Substances

Polymers are used to give the structural network, which is essential for the preparation of gels. Gel forming polymers are classified as follows:

1. Natural polymer

a. Proteins- i. Gelatin ii. Collagen

b. Polysaccharides- i. Alginic acid ii. Agar iii. Tragacanth iv. Sodium or Potassium carrageenan v. Pectin vi. Gellum Gum vii. Xanthin viii. Cassia tora ix. Guar Gum

2. Semisynthetic polymers

a. Cellulose derivatives- i. Hydroxyethyl cellulose ii. Methylcellulose iii. Hydroxypropyl methyl cellulose iv. Hydroxypropyl cellulose v. Carboxymethyl cellulose

3. Synthetic polymers- a. Carbomer- i. Carbopol -941 ii. Carbopol -940 iii. Carbopol -934 b. Poloxamer c. polyvinyl alcohol d. Polyacrylamide e. Polyethylene and its co-polymers

4. Inorganic substances- a. Bentonite b. Aluminium hydroxide

5. Surfactants- a. Brij-96 b. Cetostearyl alcohol

Evaluation of Gel [14, 15]

Measurement Of pH

The pH of gel formulations can be determined by using digital pH meter. One gram of gel is dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of formulation is done in triplicate and average values are calculated.

Drug Content

1 g of the prepared gel is mixed with 100ml of suitable solvent. Aliquots of different concentration are prepared by suitable dilutions after filtering the stock solution and absorbance was measured. Drug content is calculated using the equation, which is obtained by linear regression analysis of calibration curve.

Viscosity Study

The measurement of viscosity of the prepared gel is done with a Brookfield Viscometer. The gels are rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading is noted. The viscosity of the gel is obtained by multiplication of the dial reading with factor given in the Brookefield Viscometer catalogues.

Spreadability

It indicates the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic potency of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel which is placed in between the slides under the direction of certain load. Lesser the time taken for the separation of two slides, better the spreadability.

It is calculated by using the formula:

$S = M. L / T$

Where, M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slide

Extrudability Study

After the gels are set in the container, the formulations are filled in the collapsible tubes. The extrudability of the formulation is determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

Skin Irritation Study

Guinea pigs (400-500 g) of either sex are used for testing of skin irritation. The animals are maintained on standard animal feed and had free access to water. The animals are kept under standard conditions. Hair are shaved from back of guinea pigs and area of 4 cm2 was mark done both the sides, one side served as control while the other side is test. Gel is applied (500 mg / guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any, is graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

***In Vitro* Diffusion Studies**

The diffusion studies of the prepared gel can be carrying out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5g) is taken in cellophane membrane and the diffusion studies were carried out at 37 ± 1° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five milliliters of each sample is withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 h and each sample is replaced with equal volume of fresh dissolution medium. Then the samples were analyzed for the drug content by using phosphate buffer as blank.

Stability

The stability studies are carried out for the gel formulation by freeze - thaw cycling. Here, by subjecting the product to a temperature of 4°C for 1 month, then at 25°C for 1 month and then at 40°C for 1 month, syneresis is observed. After this, the gel is exposed to ambient room temperature and liquid exudate separating is noted.

Homogeneity

After the gels have been set in the container, all developed gels are tested for homogeneity by visual inspection. They are tested for their appearance and presence of any aggregates.

Grittiness

All the formulations are evaluated microscopically for the presence of any appreciable particulate matter which is seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

Conclusion

The microsponge delivery system is a distinctive or eccentric applied science for the controlled release of microspheres, loaded with active agent, it offers a possible reduction in side effects, while maintaining their therapeutic efficacy, improved stability, increased smoothness, and enhanced formulation liquidity. Various no. of studies have confirmed that microsponge systems are more effective and less side-effects are non-irritating, non-mutagenic, non-allergenic, and non-toxic. Microsponge systems is being used currently in cosmetics, over-the-counter skin care, sunscreens, and for diseases while prescribed. 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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