

Title: Microsponge : A Novel drug delivery system

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Abstract

Microsponges are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. 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. 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. It is regarded as safe, due to less bacterial contamination as it doesn't require preservatives in the formulation. Therefore it is used in various sterile formulations like ophthalmic, parenteral etc. This review provides an overview of microsponge technology with its methodology, preparation, mechanism and recent data on marketed formulations, their application, and evaluation of microsponges in various aspects. Microsponge are frequently used for topical application but recently used for oral also.

Key word: polymeric drug delivery, parenteral, microsponge.

MICROSPONGE

Points to be covered in this topic

- Definition
- Ideal properties
- Preparation of microsponge
- Mechanism of drug release from microsponge
- Microsponge drug delivery system
- Advantages of microsponge based on drug delivery system
- Evaluation of microsponges
- Factor affecting drug release from microsponge

1.0 Introduction

Microsponge particles are microscopic, inert, and indestructible spheres that do not penetrate the skin. Instead, they collect in the tiny nooks and crannies of the skin and slowly release the trapped drug as the skin needs it. The micro-sponge system avoids excessive accumulation of ingredients in the epidermis and dermis. Potentially, the microsponge system could significantly reduce the irritation of effective drugs without reducing their effectiveness. The hollow spheres were then washed by subsequent cleaning. In the past few years, considerable emphasis has been placed on the development of novel microsponge drug delivery systems to modify and control drug release behavior. By incorporating it into a delivery system, it is possible to alter the therapeutic index and duration of action of the drug. The growing consumer interest in skin care and treatment products has been driven by the widespread use of ingredients such as α -hydroxy acids and vitamins in topical products. This ingredient can be very effective, especially for aging or sun-damaged skin. While very helpful, in many cases, these ingredients can cause irritation. Such irritation can be seen as burning, stinging, or redness and occurs mainly in people with sensitive skin. Realizing this problem, the formulas tried to solve this problem by one of two methods. They reduced the concentration of these ingredients, but in the process sacrificed efficiency

1.0.1 Definition:-Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin.

Micro sponges are polymer delivery systems containing porous microspheres ranging in size from 5 to 300 μm . With the ability to trap a wide variety of active ingredients, microsponges are a granular drug delivery system made up of a porous nature. They are small porous particles resembling spherical particles with a large porous surface. In addition, they can increase stability by altering drug release patterns with reduced side effects. Microsponges are microporous particles, used primarily for topical application and, more recently, for oral administration.

1.2 Ideal Properties of MDS

1. The structure of the microsponges must not collapse, that is, it must retain its structural integrity.
2. It must have the property of slightly dissolving in water.
3. It must be stable when exposed to a polymerization catalyst and under polymerization conditions.
4. It must not react with the monomer used in the formulation.
5. MDS should not increase the viscosity of the mixture during preparation.
6. Micro sponges have particle sizes ranging from 10 to 25 μm in diameter.

1.3 Preparation of microsponges

Drug loading into the microspong can take place in two ways, a one-step process (liquid-liquid suspension polymerization) or a two-step process (a quasi-emulsion solvent diffusion method) based on physicochemical properties. of drugs. If the drug is generally a non-polar inert substance, a porous structure will be created and this structure is called Porogen. A foaming agent does not prevent polymerization or is not activated by it and is stable to free radicals.

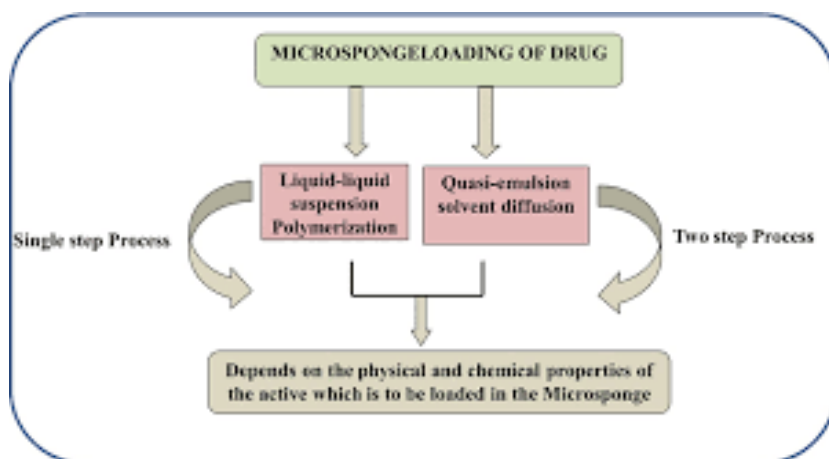


Fig. no. 1 One step and two step preparation of microsponges.⁵

1. Liquid-liquid suspension polymerization

In general, monomers are first dissolved together with the active ingredients in a suitable solvent solution of the monomer. It is then stirred in the aqueous phase, which often contains additives, such as surfactants and dispersants, to promote suspension. After the suspension was established with individual droplets of the desired size,

polymerization was initiated by activating the monomers by catalysis or by increasing temperature or irradiation. As polymerization continues, a spherical structure is produced containing thousands of microscopic sponges grouped together like grapes, forming interconnected reservoirs (Hainey et al., 1991). After the polymerization was complete, the solid particles were washed and stored.

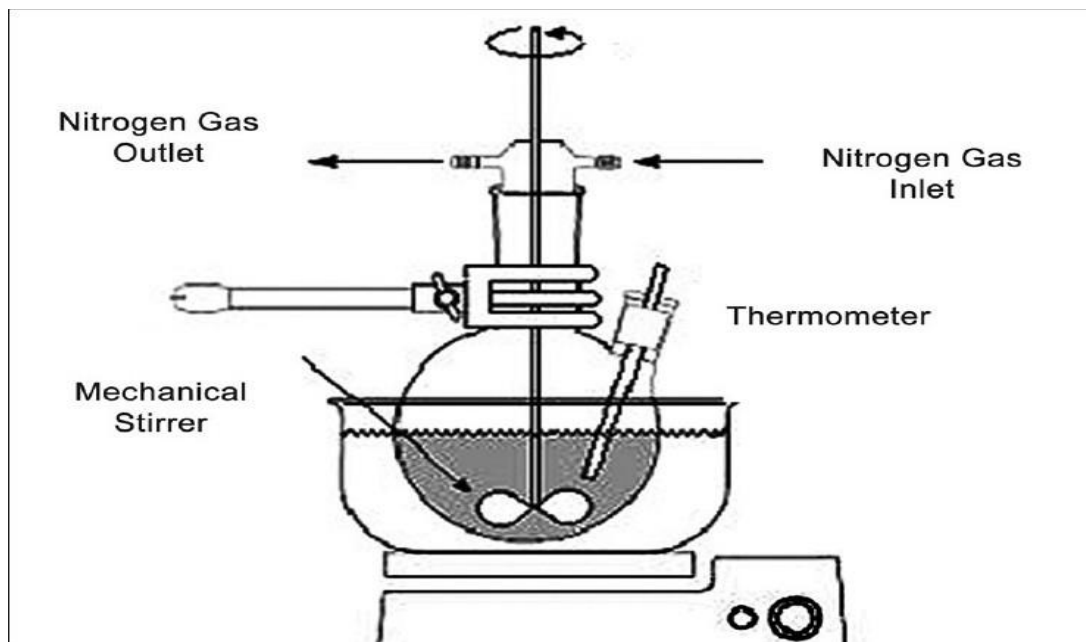


Fig. no. 2 Formation of Suspension for Preparation of Liquid-Liquid Suspension Polymerization.

2. Quasi-emulsion solvent diffusion

When the drug is sensitive to the polymerization conditions, the two-step process is used. In general, an active substance with a different drug: polymer ratios were dissolved in the organic solvent (inner phase). Then, the obtained solution was poured into a polyvinyl alcohol solution (external phase) with continuous stirring in order to evaporate the solvent, then the mixture is filtered to separate the micro sponges. The obtained microsponges are dried and stored in desiccators to ensure the complete removal of residual content.

3. Water in oil in water emulsion solvent diffusion

In this method, the internal aqueous phase containing the emulsifier is dispersed in an organic polymer solution. This water-in-oil emulsion is again dispersed in an external aqueous phase containing PVA to form a double emulsion. In this method, water-soluble and water-insoluble drugs can be trapped.

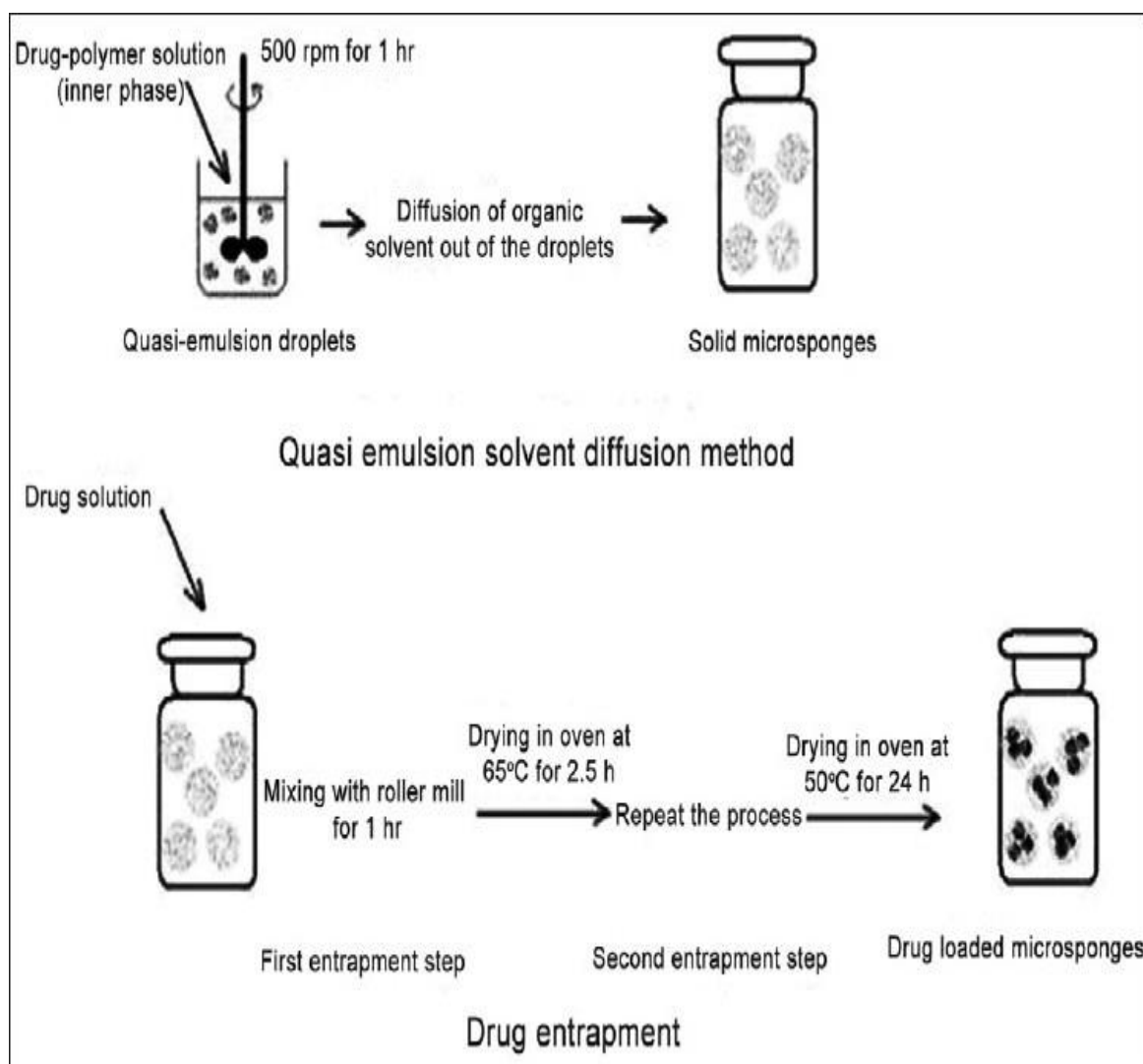


Fig. no. 3 Preparation of microsponges by the quasi-emulsion solvent diffusion method

4. Oil in oil emulsion solvent diffusion

According to this method, the emulsion was prepared as the internal phase consisting of volatile organic liquid. In most of the preparation, dichloromethane is used as the volatile solvent. And the polymer used in this is polyactide glycolic acid, span 85 as an external phase. The internal phase was added to the dispersion medium dropwise with continuous stirring to get the microsponge.

5. Addition of porogen

For this, the internal phase includes porogen such as hydrogen peroxide or sodium bicarbonate. The porogen was dispersed in the polymer solution to form a homogeneous dispersion and the substance was redispersed in the aqueous phase containing the PVA. The effect of adding hydrogen peroxide leads to the formation of interconnected pores with a diameter of 5 to 20 μm .

6. Lyophilisation In this method,

Microspheres are converted into porous microspheres by rapid solvent removal, resulting in porous microspheres. This is done using a solution of chitosan hydrochloride. The microspheres were incubated in this solution and then lyophilized. Cracks and shrinkage of the microparticles may occur due to the rapid removal of the solvent.

7. Vibration-hole aerosol generation method

Vibration-hole aerosol generation method mainly aims to prepare silica particles in suspension form with the lipid bilayer. Core beads were prepared with reflux-heated tetraethyl orthosilicate, ethanol, water, and hydrochloric acid to prepare the stock solution. And this solution is diluted with solvent-containing surfactant and further stirred to obtain single dispersed droplets. The microspheres formed are enclosed in liposomes.

Here are some reported methods for preparing microsponges. All of the above methods have their own preparation modes. Since then, most microsponges are prepared by quasi-emulsion solvent diffusion. Compared with other methods, solvent diffusion in a semi-emulsion has the least disadvantages for the product to be prepared.

1.3.1 Drugs explored in the microsponge delivery system

Paracetamol
Miconazole
Benzoyl peroxide
Curcumin
Ketoprofen
Tretinoin
Fluconazole
Hydroquinone
Acyclovir sodium
Ibuprofen
Retinol Prednisolone
Erythromycin
Indomethacin
Mupirocin

1.3.2 Polymers used for the preparation of microsponges

Eudragit RS 100
and RL 100
Ethylcellulose
Polystyrene
Acrylic polymer
PHEMA
Carbopol 934

1.4 Mechanism of drug release from microsponges

Drug release from the microsponge occurs over time in response to one or more external agents such as (temperature, pressure, pH and solubility)

1. Pressure Friction or pressure can release the micro-sponge's active ingredients onto the skin.
2. Temperature The production of active ingredients from microsponges is affected by changes in temperature. As the skin temperature increases, the flow also increases and thus the release process also increases.
3. pH Triggered release of active ingredients based on pH can occur by changing the coating on micro-sponges.
4. Solubility Micro-sponges contain hydrophilic active ingredients such as disinfectants and antiperspirants that are released in the presence of water. The release can also be accomplished by diffusion but taking into account the division coefficient of the component between the micro sponges and the external system.

1.4.Characterization of Microsponges

In addition, evaluation studies were also conducted on prepared microsponges to determine:

- Particle size
- Product yield
- Effective payload
- Surface topography
- In vitro release study The particle size of the microsponges was assessed by optical or electron microscopy. Particle size affects formulation performance. The factors affecting drug particle size are polymer ratio as well as emulsifier concentration. As the drug-to-polymer ratio increases, the particle size decreases, and the emulsifier concentration increases leading to larger particle sizes. Particle size was determined by optical microscopy using calibrated eyepieces and stage micrometers. **A small amount of microsponges is spread on a clean slide with a drop of liquid paraffin and a cover sheet is placed on top.** The average grain size was calculated by measuring 100 seeds from each batch.

Production yield

The ratio of drug to polymer also affects the production yield, the drug increases:polymer ratio also leads to increased production yield Production productivity can be calculated as

$$\text{production capacity} = \text{Actual quantity} / \text{Theoretical amount} \times 100$$
Feeding efficiency The loading of drugs into the microsponge depends on the physicochemical properties of the drug. There are two ways of loading drugs, active and passive. Passive charging is the most efficient. Increased drug: polymer ratio leads to increased drug loading efficiency 7.Charging efficiency is measured in

$$\text{Load efficiency} = \text{Actual potion load} / \text{Theoretical potion load} \times 100$$
Surface TerrainDifferent techniques have been used in surface topography, namely scanning electron microscopy (SEM), transmission electron microscopy (TEM), etc. SEM is widely used for

microsponges preparation. Research released in vitro It was performed using a USP XXIII solubilizer equipped with an innovative basket consisting of a 5 µm stainless steel mesh. The dissolution rate was measured at 370°C at 150 rpm. The dissolution medium is selected according to the solubility of the active principles. Samples were taken from the dissolution medium and analyzed using an appropriate analytical method.

In vitro release studies

It is carried out using dissolution apparatus USP XXIII equipped with a modified basket consisted of 5µm stainless steel mesh. Dissolution rates were measured at 370 C under 150 rpm speed. The medium for dissolution is selected according to the solubility of active ingredients. Samples were withdrawn from the dissolution medium and analysed by the suitable analytical method.

APPLICATION OF MICROSPONGE

It offers a formulator range of alternatives to develop drug and cosmetic products. Over-the-counter products that incorporate microsponge drug delivery systems include numerous moisturizers, specialized rejuvenated products, and sunscreens.

1.Topical drug delivery using microsponge technology

(A) Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athlete's foot. Controlled release of BPO of the microsponge delivery system to the skin could reduce the side effect.

(B) A Microsponge based topical formulation of mupirocin, used as an antibiotic for skin infection, to achieve sustained drug release. The increased absorption of mupirocin in the skin from the microsponge delivery system suggests the delivery system to be an efficient system for the treatment of primary and secondary skin infections as compared to conventional mupirocinemulgel and marketed mupirocin ointment.

The Microsponge system provides the controlled delivery of oral medications to the lower gastrointestinal tract, where upon exposure to specific enzymes it will be released in the colon. It has been shown that the microsponge system enhances the solubilization of poorly soluble drugs by entrapping these drugs in their pores. Controlled oral delivery of ketoprofen prepared with Eudragit RS100 by quasi emulsion solvent diffusion method and subsequently tablet of microsponge was prepared by the direct compression method results show that compressibility was much improved in the physical mixture of the drug and the polymer due to the plastic deformation of sponge-like microsphere structure.

Microsponge used for bone and tissue engineering

Bone-like compounds are obtained by mixing a pre-prepared polymethyl methacrylate monomer powder with two water-dispersible forms of calcium-deficient tricalcium phosphate and hydroxyapatite particles. The final compound appears porous and grows like a micro-sponge.

1.5 Key Features of Microsponge Delivery System

- Micro sponges are stable at pH 1-11. They are heat stable up to 1300 C.
- It has self-sterilizing properties due to an average pore diameter of 0.25 μ m that bacteria cannot penetrate, so the formulation does not require the addition of preservatives. Microsponges are cost-effective compared to other drug delivery systems.
- They are compatible with most additives and media.
- The micro-sponge has a high load-carrying capacity (50-60% weight), but is still a super-fine, free-flowing powder.
- Good oil control, as it can absorb up to 6 times its weight. Flexible development of new product types.
- Improved thermal, physical, and chemical stability.

Advantages over Traditional Formula

Topical Topologies in that their traditional formulation is designed to act on the outer layers of the skin. Upon application, these products release their active ingredients, forming a dense layer of rapidly absorbed active ingredients. Unlike the microsponge system, it avoids excessive accumulation of ingredients in the epidermis and dermis. Microsponge technology can significantly reduce the irritation of effective drugs while maintaining their potency.

Advantages over ointments

Ointments are typically cosmetically unpleasant due to greasiness, stickiness, and other factors, and patients are less likely to comply. Due to its ineffective distribution technique which causes discomfort and allergic reactions in a significant number of users, these vehicles require a high concentration of active drugs for effective therapy. When a microsponges system maximizes the duration of active substances on the skin surface within the epidermis while decreasing its transdermal penetration into the body, another disadvantage of topical formulations is uncontrolled evaporation of active ingredients, unpleasant odor, and potential incompatibility of drugs with the vehicle.

1.4 Microsponges drug delivery system

A microsponge delivery system (MDS) is a highly cross-linked, porous polymer system consisting of porous microspheres that can retain a wide range of active ingredients such as perfumes, sunscreens, emollients, antifungals, anti-infectives, and anti-inflammatory drugs. , etc. They are mainly used to prolong the duration of topical drug use. Microsponges are small spherical sponge-like particles consisting of numerous interlinked voids in a non-foldable structure having a large porous surface, and the size of this microsponge can vary, usually in diameter. from 5 to 300 μ m depending on the candy level. In addition, they can improve stability, reduce side effects, and favorably alter drug release as well as control drug release rates, making them suitable for topical use. Therefore, by optimizing formulation parameters such as drug: polymer ratio and stirring/stirring speed, an optimized micro-sponge can be made. Microsponges have many advantages that make them a versatile drug delivery system. Microsponges can suspend or trap a variety of substances that can be formulated as gels, creams, liquids, or powders for topical use. When the formula is applied to the skin, MSD releases the active ingredients promptly and in response to other stimuli (friction, temperature, pH). Recently, it has been studied that microsponge is also used for oral drug delivery systems. The microsponge system has been shown to increase the dissolution rate of poorly water-soluble drugs by trapping drugs in the pores of the microsponge system.

1.6 Advantages of microsponge-based delivery systems

1. Shelf-life and product stability can be prolonged without using preservatives since bacteria are too large to enter into the microsponge
2. The highly compartmentalized nature of microsponges results in very high internal surface area hence, they exhibit high payload capacity
3. Undesirable properties like oiliness and tackiness, or undesirable feel or odor of ingredients can be considerably reduced which makes them suitable for topical delivery to skin
4. Liquids can be transformed into free-flowing powder, providing material handling benefits
5. Microsponges help in improving elegance of the formulation ¹¹
6. MDS augment the efficacy of topically active agents and enables their sustained release
7. Microsponges consist of interconnecting voids within a non-collapsible structure, with large porous surface
8. Stable over a wide pH range of 1–11 and up to a temperature of 130 °C
9. Microsponges in pharmaceutical applications: Topical prescription, over-the-counter, and personal care products use microsponges delivery systems to improve their effectiveness, safety, and aesthetic quality. Microsponges have a wide range of applications, it's usually used topically, although it's also been taken orally recently. Due to its high loading capacity and prolonged release capabilities, it has been stated in several patents that it can be utilized as an excipient.
10. Long lasting-coloured cosmetics: Microsponges can entrap the colors in a variety of coloured cosmetics items, such as rouge and lipsticks, to help them to remain for longer period of time. Microsponge, as previously indicated, aids in consistent spreading and improved covering power. Coloured cosmetics created with microsponges would be extremely exquisite as a result.

1.7 Evaluation Methodology of Microsponge

1. Particle size evaluation-

The particle size distribution is evaluated using an optical microscope or electron microscope. Particle size determination of Microsponge can be performed by laser light diffractometry or other suitable method. The values (d_{50}) can be expressed for all formulations as mean size ranges. Particle size greater than 30 μm can give a gritty feeling and hence particles sizes between 10 and 25 μm are used in the final formulation.

2. Morphology and surface topography

In the morphological study of microsponge topography various techniques are used such as the photon correlation spectroscopy (Pcs), Transmission electron spectroscopy (TEM), scanning electron microscopy (SEM).

3. Determination of loading efficiency: The loading efficiency (%) of the microsponges can be calculated as follows:-

$$\text{Loading efficiency} = \frac{\text{Actual Drug content in microsponges}}{\text{Theoretical drug content}} \times 100$$

4. Determination of production yield: The production yield of the microsponges can be determined by:

$$\text{Production yield} = \frac{\text{practical mass of microsponges}}{\text{Therotical mass (polymer+ drug)}} \times 100$$

5. Determination of true density- The true density of the microsponge can be measured using an ultracycnometer in the presence of helium gas and is calculated from a mean of repeated determinations.

6. Compatibility study- It can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on the crystallinity of drug can be studied by powder X-ray diffraction (XRD) and differential scanning calorimetric.

7. Release evaluation: Release of microsponges can be controlled through diffusion or other triggering mechanism such as moisture, pH, friction, temperature. This release mechanism used to enhance product aesthetics.

8. Resiliency: For the production of bullets a particle that is softer or firmer according to the needs of the final formulation viscoelastic properties of the microsponge can be modified. Increased cross-linking tends to decrease the rate of release.

9. Stability study: Gel formulation is subject to stability testing as per ICH norms. Gel fill in clean, lacquered, collapsible aluminium tubes, and various replicates kept at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ relative humidity in a humidity Chamber. Gel assessed for change in appearance, pH and in vitro release profile at an interval of 30, 60 and 90 days.

Table 1: List of marketed products based on microsponges

Product Name	Pharmaceutical Uses	Manufacturer
Glycolic Acid Moisturizer w/SPF 15	Anti-Wrinkles, soothing	AMCOL Health & Beauty Solution
Retin A Micro	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc
Line Eliminator Dual Retinol Facial Treatment	Anti-wrinkle	Avon
Retinol 15 Night cream	Anti-wrinkles	Sothys
Retinol cream	Helps maintain healthy skin	Biomedic
EpiQuin Micro	Hyper pigmentation	SkinMedicaInc
Sports cream RS and XS	Anti-inflammatory	Embil Pharmaceutical Co. Ltd.
Salicylic Peel 20	Excellent exfoliation	Biophora
Oil free matte block SPF 20	Sunscreen	Dermalogica
Lactrex™12%	Moisturizing Cream	SDR Pharmaceuticals, Inc
Ultra Guard	Protects baby's skin	Scott Paper Company

10. Drug release mechanism from microsponges

One or more external stimuli or triggers can release the active component enclosed in microsponges gradually.

1. Temperature triggered release

In this process, the active substance is released into the system when the temperature changes. At room temperature some medications are too viscous to flow without interacting with the porous system. When applied to the skin, however, an increase in skin temperature causes an increase in flow rate and hence a continuous release of the medicine.

2. Pressure triggered release

In this technique, the entrapped medicine is released by microsponges when the dosage form is brushed across the skin.

The amount of medicine released is determined by a variety of microsponges features, including process factors, robustness, and the type of material utilized.

3. Solubility triggered release

Porous systems containing a water-soluble excipient release the medicine when exposed to water. Diffusion mechanisms, which involve the partition coefficient between the drug and external system, can sometimes cause release.

4. PH triggered release

A change in pH initiates medication release in this method, which is achieved by changing the coating on microsponges for pH-based activities.

4. Hypothetical drug release mechanism ²²

The Drug is encapsulated and added to the vehicle. Drug can freely flow in and out of the microsponge system as well as the vehicle due to the open structure until equilibrium is reached. This results in drug saturation of the vehicle. When a formulation is applied to the skin it results in unsaturation of the vehicle and a loss of equilibrium. To re-establish this balance, the medicine will flow from the vehicle to the skin, until the vehicle has dried or absorbed. The active medicine is then progressively released over time via microsponge particles retained on the stratum corneum surface. Vehicles play an important role in the formulation of microsponges because they allow for the slow and continuous release of active ingredients. As a result, vehicle should be chosen such that the active ingredients solubilizing power is minimal. To avoid early drug leaching from the polymer, the dosage form can contain both free and entrapped drug moieties.

1.8 Factors affecting drug release from microsponges:

1. Physicochemical characteristics of entrapped API.
2. Physical parameters of microsponges such as pore diameter, volume, particle size, resiliency.
3. Characteristics of vehicle that is used for dispersing microsponges.
4. Factors like pore characteristics, monomer composition.

FUTURE EXPECTANCY

Microsponge is novel technology, which is the mostly developed for the topical delivery system and recently for oral administration. It provides various kinds of advantages.

Microsponges are carefully designed pharmaceutical active ingredient that deliver the drug effectively at the target site with the minimum dose and also to enhance stability, reduce side effects and control drug release. The real face off in the future is the development of the delivery system for the oral peptide delivery by altering the ratio of polymers.

Microsponges will be an excellent drug delivery system. Microsponges drug delivery system that can accurately control the release rates to the specific sites of the body will be sought in great detail in the years to come that have an immense on the health care system and Some microsponge related products are already approved; several products are currently under development and clinical assessment.

CONCLUSION

The microsponge delivery system is a novel technology for the controlled release of macroporous beads, loaded with an active agent, offering a potential reduction in side effects and maintaining their therapeutic efficacy. The microsponge drug delivery system is believed to reduce side effects, improved stability, increased elegance, enhanced formulation flexibility, and also offer entrapment of its ingredients. Microsponge systems are, non-mutagenic, non-irritating, non-toxic and non-allergenic. This technology is being used currently in prescription products, cosmetics sciences, (OTC) over-the-counter skin care, and sunscreens. Nowadays the drug delivery technology may lead to a better understanding of the healing of several diseases and disorder.

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