A REVIEW: RETINOL-INFUSED PRODUCTS BY MICROSPONGE TECHNOLOGY

[1]MISS. MAYURI PRALHAD PANDIT, [2]PROF. RUTUJA AHER

[1]STUDENT [2]TEACHER PES MODERN COLLEGE OF PHARMACY (FOR LADIES) MOSHI, PUNE, INDIA

Abstract

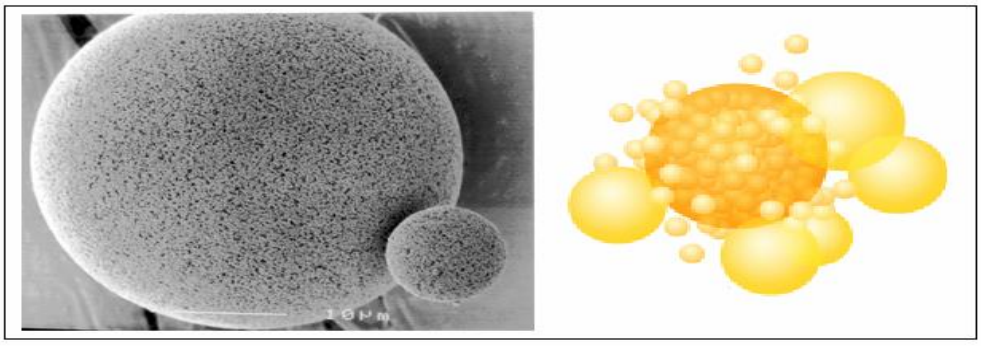
Microsponges are at the leading edge of the rapidly developing novel drug delivery technology field. The microsponge-based drug delivery system is a unique technology for a controlled release system and enhanced drug deposition within the skin while minimizing transdermal penetration of topically active agents. Drug-loaded microsponge consists of microporous beads, typically 10-25 µm in diameter. When applied to the skin, the microsponge releases its active ingredient on a time mode and also in response to other stimuli like rubbing, pressure, temperature, pH, etc. Microsponge technology offers entrapment of active ingredients and is believed to contribute to reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. additionally, it's non-irritating, non-allergenic, non-mutagenic, and non-toxic. This technology is being employed currently in cosmetics, over-the-counter skincare, sunscreen, and prescription products [12]. Vitamin A is the most multifunctional vitamin within the anatomy and constitutes a gaggle of organic lipid-soluble compounds comprising retinol and its derivatives, mainly the retinol esters, retinyl palmitate, and retinyl acetate. Retinol is deeply involved in growth and maintenance thanks to its cellular contribution to cell proliferation and differentiation from early embryogenesis to adulthood. Topical retinoids are used for the clinical treatment of psoriasis, hyperkeratosis, acne, early aging, and photodamage. However, its high instability hence oil and water-soluble microsponge delivery of the retinol has been developed [16].

Keywords: Microsponges ,Controlled release, transdermal delivery, Biopharmaceutical delivery, Cosmeceuticals, Skin care.

Introduction

Several predictable and reliable systems are developed for systemic drugs under the heading of the transdermal delivery system using the skin as a portal of entry. It has improved the efficacy and safety of the many drugs that will be better administered through the skin. But TDS isn't practical for the delivery of materials whose final target is the skin itself. Controlled release of medication onto the epidermis with the reassurance that the drug remains primarily localized and doesn't enter the circulation in significant amounts, is a section of research that has only recently been addressed successfully. In recent years, there has been considerable emphasis given to the event of microsponge-based novel drug delivery systems, to switch and control the discharge behavior of the drugs. By incorporation into a carrier system, it's possible to change the therapeutic index and duration of the activity of the medication [9].

Microsponges are porous microspheres, biologically inert particles that are made of synthetic polymers, and also the particles serve to shield the entrapped drug compound from physical and environmental degradation. It consists of porous microspheres, each microsphere consisting of a myriad of interconnecting voids within a non-collapsible structure with an oversized porous surface. The porous sphere polymers vary in diameter from 5 to 300 microns. Their characteristic feature is the capacity to adsorb or "load" a high degree of active materials into the particle and onto its surface and it is delivered to the skin via controlled diffusion. Spherical particles composed of clusters of even tinier spheres are capable of holding fourfold their weight in skin secretions. Microsponge particles are extremely small, inert, indestructible spheres that do not undergo the skin. Rather, they collect within the small nooks and crannies of the skin and slowly release the entrapped drug, because the skin needs it. Although the microsponge size may vary, a typical 25 µm sphere can have up to 250000 pores and an enclosed pore structure like 10 ft long. These microscopic spheres are capable of absorbing skin secretions, therefore reducing the oiliness and shine of the skin. The microsponge system can prevent excessive accumulation of ingredients within the epidermis and also the dermis. Potentially, the microsponge system can significantly reduce the irritation of effective drugs without reducing their efficacy [9,18].



. Figure 1: Porous microsphere [10]

Characteristics of Microsponges

1. Stable over a pH range of 1 to 11
2. Stable up to 130o C temperature
3. Compatible with the many the vehicles and active ingredients
4. Self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate
5. Higher payload (50 to 60%)
6. Free-flowing and cost-effective

Advantages

1. Oil-control roll: it can absorb oil up to 6 times its weight without drying.
2. Extended-release up to 12 hours
3. Reduced irritation and better tolerance hence improved patient compliance
4. Improvement of product aesthetics
5. Improved thermal, physical, and chemical stability
6. Incorporation of immiscible products
7. Flexibility to develop novel product forms
8. Improves material processing e.g., Liquid can be converted into powders
9. Improves efficacy within the treatment
10. Increased bioavailability

Advantages over microencapsulation and liposomes

Microcapsules are used by monitoring the release rate of the API to reduce the dosing frequency. when the walls ruptured, the entire API in it is released, these are the potential disadvantage to microsponges. Liposomes are spherical vesicles with phospholipid bilayer which is used as a carrier for various drugs, peptides, and nucleic acids. The entrapment efficiency of microsponges is 50%-60%. whereas that of liposomes is about 30%. Therefore, liposomes are difficult to manufacture, are highly costly, have no microbial, stability, have less Chemical stability, and have a lower payload than microsponge.[11]

Characteristics of Active Ingredients

Active ingredients that can be entrapped in microsponges must meet the following requirements

1. It should be miscible in monomer
2. Miscible by the addition of a small amount of a water-immiscible solvent.
3. It should be water-immiscible or at most only slightly soluble.
4. It should be inert to monomers.
5. It should be stable in contact with the polymerization catalyst and conditions of polymerization.

Preparation of Microsponges

Drugs entrapped in microsponges can take place in two ways, based on the physicochemical properties of the drug.

One-step process and two-step process with respective liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques. If the drug is typically an inert non-polar material, it will create the porous structure called porogen.

A. Liquid-Liquid Suspension Polymerization
   It is also referred to as the Bottom-up approach (starting with the monomer). In general, a solution is made comprising of monomers and the active ingredients (nonpolar). This phase is then suspended with agitation in an aqueous phase containing additives such as surfactants and dispersing agents. Once the suspension is established with discrete droplets of the desired size, polymerization is affected by activating the monomers either by catalysis, increased temperature, or irradiation.
   The various steps summarized
   1. Selection of monomer or combination of monomers
   2. Formation of chain monomers as polymerization begins
   3. Formation of ladders as a result of crosses linking between chain monomers
   4. Folding of monomer ladder to form spherical particles
   5. Agglomeration of microspheres, which gives rise to the formation, of bunches of microspheres
   6. Binding of bunches to form microsponges.

The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. Impregnating them within preformed microsponges then incorporates the functional substances. Sometimes solvent may be used for faster and more efficient incorporation of the active substances. Once the polymerization is complete, the solid resulting from the process is recovered from the suspension. The particles are then washed and processed until they are substantially ready for use. The microsponge product can be made using styrene, divinylbenzene, methyl methacrylate, and ethylene glycol dimethacrylate as starting materials [12].

Optimum values for microsponge formulation [32]

Specification	Optimum values
Drug: polymer ratio	3:1, 4:1 and 5:1
Amount of drug (gm)	2
PVA (mg)	30-70
Inner phase solvent	Ethyl alcohol
Amount of inner phase solvent(ml)	10 ml
Amount of water in the outer phase (ml)	200 ml
Temp in inner phase (°C)	37
Stirrer type	Three-blade
Stirring rate (rpm)	500

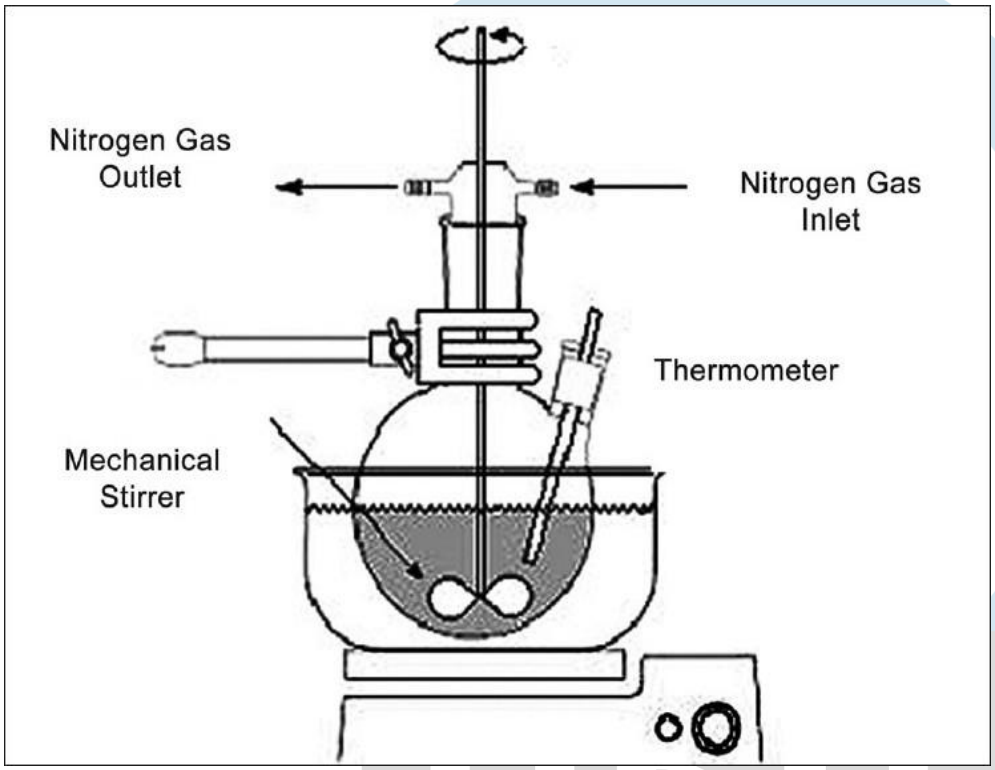


Figure 2: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization [13]

B. Quasi-Emulsion Solvent Diffusion

The microsponges can also be prepared by a quasi-emulsion solvent diffusion method by a two-step process (Top-down approach: starting with preformed polymer) using an external phase containing 200 ml distilled water and 40 mg polyvinyl alcohol (PVA) 72 000. The internal phase consisted of the drug, ethyl alcohol, polymer, and triethyl citrate (TEC), which was added at an amount of 20% of the polymer 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 microsponges. The product was washed and dried in a vacuum oven at 40°C for 24 hours [12].

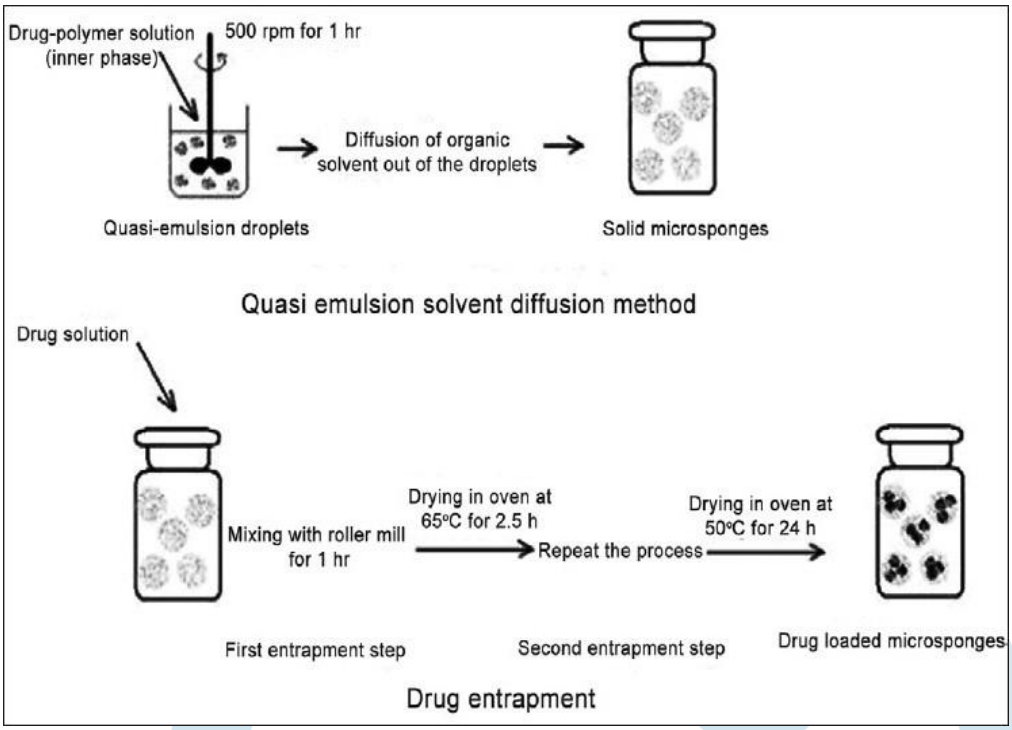


Figure 3: Preparation of microsponges by the quasi-emulsion solvent diffusion method [14].

Limitations [12]

Both the methods usually use organic solvents as porogens, which pose an environmental hazard, as some are also highly inflammable, posing a security hazard. Moreover, within the case of the Bottom-Up approach traces of residual monomers are observed, which can be toxic and dangerous to health. While the limitations seem serious, they can be easily overcome by using proper quality control measures and washing post-manufacture in addition to good standardization of the various processes.

Formulation considerations [15]

Actives entrapped in MDS can then be incorporated into many products such as creams, gels, lotions, powders, and soaps or can be compressed into tablets. When formulating the vehicle, certain considerations are taken into account 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 action must be optimized for the required release rate for the given period.

Hypothetical mechanism of action

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (they do not have a continuous membrane surrounding them), the action 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 activity 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 action 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 activity 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 action 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 action 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 [15].

Release mechanisms [15]

The mentioned programmable parameters can be effectively manipulated to design a Microsponge delivery system for the release of functional substance over some time in response to one or more external stimuli. The release mechanism of this system is mainly

A. Sustained or Time

Release In the development of a sustained-release Microsponge, different physical and chemical parameters of the entrapped active substance such as volatility, viscosity and solubility will be studied while in the case of polymeric microsponge pore diameter, volume, and resiliency of the polymeric microsponge are evaluated to give necessary sustained release effects.

B. Release on Command

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

Figure 4: Release mechanism of active ingredient from microsponges[31]

1. Pressure Release
   The Microsponge system releases fluid or active ingredient when it is pressed or squeezed, thereby replenishing the level of entrapped active ingredient onto the skin. The amount released may also depend upon the release of the sponge and the resiliency of the Microsponges.
2. Temperature Release
   The release of active ingredients from microsponges can be activated by temperature. At room temperature, few entrapped active ingredients can be too viscous to flow suddenly from microsponges onto the skin. With the increase in skin temperature, the flow rate is also increased, and therefore release is also enhanced.
3. pH
   Triggering the pH-based release of the action can be achieved by modifying the coating on the microsponge. This has many applications in drug delivery.
4. Solubility
   Microsponges loaded with water-miscible ingredients like antiseptics and antiperspirants will release the ingredient in the presence of water. The release can also be activated by diffusion but taking into consideration, the partition coefficient of the ingredient between the microsponges and the external system.

Marketed formulation of retinol-infused products by using a microsponge drug delivery system [12]

1. Retin-A-Micro
   It is a novel formulation containing either 0.1% w/w or 0.04% w/w tretinoin by weight for the topical treatment of acne vulgaris.
   Compositions –
   This formulation uses patented methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (MICROSPONGE System) to enable the inclusion of the active ingredient, tretinoin, in an aqueous gel, without the use of oils or organic solvents like ethanol or acetone, which themselves can contribute to irritation. It is a member of the retinoid family of compounds and an endogenous metabolite of Vitamin A. Other components of this formulation are Purified Water, Carbomer 934P in the 0.1% w/w strength and Carbomer 974P in the 0.04% w/w strength, Glycerin, Disodium EDTA, Propylene Glycol, Propylene Glycol Dicaprylate/Dicaprate, Sorbic Acid, PPG-20 Methyl Glucose Ether Distearate, Cyclomethicone and Dimethicone Copolyol, Benzyl Alcohol, Trolamine, and Butylated Hydroxytoluene.

   Mechanism of action -
   Tretinoin is a member of the retinoid family of compounds, and an endogenous metabolite of Vitamin A. Tretinoin is highly effective in the treatment of acne, although the exact mode of action of tretinoin is unknown. Current evidence suggests that this efficacy is due primarily to the ability of tretinoin to modify abnormal follicular keratinization. Comedones form in follicles due to abnormal keratinization and intercellular cohesiveness, with an excess of keratin retained in the follicle. Tretinoin promotes the detachment of cornified cells and the enhanced shedding of corneocytes from the follicle. By increasing the mitotic activity of follicular epithelia, tretinoin also increases the turnover rates of thin, loosely adherent corneocytes. Through these actions, the comedo contents are extruded and the formation of the microcomedo, the precursor lesion of acne vulgaris, is reduced.
   Additionally, tretinoin acts by modulating the proliferation and differentiation of epidermal cells. These effects are mediated by tretinoin's interaction with a family of nuclear retinoic acid receptors. Activation of these nuclear receptors causes changes in gene expression. The exact mechanisms whereby tretinoin-induced changes in gene expression regulate skin function are not understood.

Dosage ad administration-
RETIN-A MICRO tretinoin gel (microsphere) should be applied once a day, to acne-prone skin areas, after washing with mild, non-medicated soap and dry skin gently. The gel may be applied at any time during the day or at bedtime. Use only a sufficient quantity of medication to cover the entire affected area lightly. Application of excessive amounts of gel may result in "caking" of the gel and will not provide incremental efficacy. Therapeutic results may be noticed after two weeks, but more than four weeks of therapy are required before consistent beneficial effects are observed. Patients in clinical trials were treated for 12 weeks.

Manufactured by the company-
Ortho-McNeil Pharmaceutical, Inc.

Figure 5:Marketed formulation of Retin-A-Micro [35]

2. Retinol 15-night cream
Nighttime treatment cream with a Microsponge system. The formula contains pure retinol. Continuous use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles, and improve skin discolorations.

Compositions-

Ingredient name	Its use
Water (Aqua)	solvent
Petrolatum	emollient
Cetearyl Alcohol	emollient, viscosity controlling, emulsifying, surfactant/cleansing
Glycerin	skin-identical ingredient, moisturizer/humectant
Glyceryl Stearate	emollient, emulsifying
Retinyl Palmitate	cell-communicating ingredient
Triethanolamine	buffering
PEG-40 Stearate	emulsifying, surfactant/cleansing
Propylene Glycol	moisturizer/humectant, solvent, viscosity controlling
PEG-8 Stearate	emulsifying, moisturizer/humectant, surfactant/cleansing

Stearic Acid	emollient, viscosity controlling

Manufactured by the company- Biomedic,sothys

3. 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.

   Manufactured by the company- Biomedic

4. Line eliminator dual retinol facial treatment
   Lightweight cream with retinol (Vitamin A) in MDS, delivers both immediate and time-released wrinkle-fighting action.

   Manufactured by the company- Avon

5. EpiQuin micro
   The Microspong system entraps hydroquinone and retinol. The microsponges release these ingredients into the skin gradually throughout the day, which may minimize skin irritation
   Manufactured by the company- Skin Medica Inc

Other marketed formulations by using a microsponge drug delivery system[12,10]

1. Carac cream, 0.5%
   Carac cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge) composed of methyl methacrylate/glycol dimethacrylate cross polymer and dimethicone.

   Manufactured by the company- Dermik Laboratories, Inc.Berwyn, PA19312 USA

2. Aramis fragrances
   24-Hour high-performance antiperspirant spray sustained the release of fragrance in the microsponge. The microsponge comes in the form of an ultra-light powder, and because it is micro in size, it can absorb fragrant oil easily, while maintaining a free-flowing powder characteristic where release is controlled due to moisture and temperature.

   Manufactured by the company- Aramis Inc

3. Oil-free matte block SPF 20
   This sunscreen provides a shield for the skin from damaging UV rays and controls oil production. Microsponge technology absorbs the oil, maintaining an all-day matte finish. The oil-free formula contains soothing Green Tea to help calm inflammation caused by breakouts. Cornstarch and Vinyl Dimethicone / Methicone Silsesquioxane Cross-polymer act as microsponges to absorb excess surface oil on the skin.

   Manufactured by the company -Dermalogica

4. 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.

   Manufactured by the company- John and Ginger Dermalogica skincare products

5. 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.

   Manufactured by the company -Biomedic

6. 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.

Manufactured by the company -Andover, NJ, S.A. 07821

7. Ultra guard
Microsponge system that contains dimethicone to help protect a baby's skin from diaper rash The new wipe contains a skin protectant that helps keep wetness and irritants from the baby's
skin. The solution is alcohol-free, hypoallergenic, and contains
dimethicone, an ingredient found in baby creams, lotions, and skin protectants

Manufactured by the company- Scott Paper[10].

Evaluation Parameters of Microsponges

1. Particle size and size distribution
Particle size and size distribution are evaluated using either an optical microscope or an electron microscope. This is an extremely crucial step, as the size of the particles greatly affects the texture of the formulation and its stability. Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded Microsponges can be performed by laser light diffractometry or any other suitable method. The values (d50) can be expressed for all formulations as a mean size range. Cumulative percentage drug release from Microsponges of different particle sizes will be plotted against time to study the effect of particle size on drug release[15].

2. Morphology and Surface topography of SPM
For morphology and surface topography, various techniques have been used like photon correlation spectroscopy (PCS), Scanning electron microscopy (SEM), transmission electron microscopy (TEM), etc. SEM is used widely for which prepared Microsponges are coated with gold-palladium under an argon atmosphere at room temperature and then the surface morphology of the Microsponges is studied[15].

3. Determination of loading efficiency and production yield
The loading efficiency (%) of the Microsponges can be calculated according to the following equation:

$$\%\text{loading efficiency} = \frac{\text{actual drug content in microsponges}}{\text{theoretical drug content}} \times 100$$

The production yield of the microparticles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the SPM obtained.

$$\%\text{Production yield} = \frac{\text{Production yield}}{\text{theoretical mass (polymer + drug)}} \times 100$$

4. Determination of true density
The true density of Microsponges can be measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.

5. Characterization of pore structure
Pore volume and diameter are vital in controlling the intensity and duration of the 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 the effect of pore diameter and volume on the rate of drug release from Microsponges. Porosity parameters of Microsponges include intrusion– extrusion isotherms. Pore size distribution, total pore surface area, average pore diameters, shape and morphology of the pores, and bulk and apparent density can be determined by using mercury intrusion porosimetry. An incremental intrusion volume scan is plotted against pore diameters that represented pore size distributions.

- The pore diameter of Microsponges can be calculated by using the Washburn equation:

$$D = \frac{-4\gamma\cos\Theta}{P}$$

Where
D is the pore diameter (μm);
γ the surface tension of mercury (485 dyn cm−1);
θ contact angle (130 degrees);
and P is the pressure (psi).

- the % porosity of the sample was found from the equation,

$$\text{Porosity } \% = \left(1 - \frac{Pse}{}\right) \times 100$$

Psa

- The average pore diameter (Dm) was calculated by using the equation,

$$Dm = \frac{4Vtot}{Atot}$$

6. Compatibility studies

The drug-excipients compatibility studies are carried out to ensure that there is no inadvertent reaction between the two when formulated into a dosage form. The compatibility of drugs with reaction adjuncts can be studied by thin-layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). The effect of polymerization on the crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC). For DSC approximately 5 mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15o C/min over a temperature range of 25–430^{0}C an in an atmosphere of nitrogen[15].

7. Polymer/ Monomer composition

Factors such as particle size, drug loading, and polymer composition govern the drug release from Microsponges. The polymer composition of the Microsponges Drug Delivery system can affect the partition coefficient of the entrapped drug between the vehicle and the Microsponges system and hence have a direct influence on the release rate of the entrapped drug.

The release of drugs from Microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time. The release rate and total amount of drug released from the system composed of methyl methacrylate/ ethylene glycol dimethacrylate are slower than the styrene/divinylbenzene system. Selection of monomer is dictated both by characteristics of active ingredient ultimately to be entrapped and by the vehicle into which it will be dispersed. Polymers with varying electrical charges or degrees of hydrophobicity or lipophilicity may be prepared to provide flexibility in the release of active ingredients. Various monomer combinations will be screened for their suitability with the drugs by studying their drug release profile[15].

8. Resiliency

Resiliency (viscoelastic properties) of Microsponges can be modified to produce beadlets that are softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release. Hence resiliency of Microsponges is studied and optimized as per the requirement by considering release as a function of cross-linking with time.

9. Dissolution Tests

The dissolution profile of microsponges can be studied by the use of dissolution apparatus USP XXIII with a modified basket consisting of 5µm stainless steel mesh at 37^0 C under 150 rpm. The dissolution medium is selected while considering the solubility of the drug to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical methods at various intervals[12].

10. Drug Release from the Semi-Solid Dosage Forms and Drug Deposition Studies

Drug release from the semi-solid dosage forms is performed by the Franz- type static diffusion cells. This epidermal side of the skin was exposed to ambient conditions. While the dermal side was kept facing the receptor solution. The receptor compartment containing 20mL phosphate buffer pH 5.8 was thermostated at 32±0.5°C and stirred at 600 pm. The skin was saturated with a diffusion medium for 1 h before the application of the sample. A 200-mg sample was applied to the donor compartment. For determination of the drug deposited in the skin, the diffusion cell was dismantled after a period of 4, 8, 16, and 24 h. The skin was carefully removed, and the drug present on the skin surface was cleaned with distilled water[12].

11. In-vitro Diffusion Studies

The in-vitro diffusion studies of prepared microsponge gel were carried out in a Keshary-Chien diffusion cell using a cellophane membrane. 100 ml of phosphate buffer was used as the receptor compartment, and then 500 mg of gel containing 10 mg of drug was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.50. The solution on the receptor side was stirred by externally driven Teflon coated magnetic bars at predetermined time intervals, pipette out 5ml of solution from the receptor compartment, and immediately replaced with the fresh 5ml phosphate buffer. The drug concentration on the receptor fluid was determined spectro-photometrically against the appropriate blank. The experiment was carried out in triplicate[12].

Viscosity Measuring

The consistency of the various gel formulation was firm employing a Brookfield viscometer. Brookfield viscometer consists of a cup, that is stationary and a spindle that is rotating totally different sized rotating spindles square measure used and mmersed within the check material. For liquids with low consistency, giant size spindles (large diameter and surface square easure) the square measure is used whereas for higher consistency liquid little spindles (small diameter and surface area) are used.

Rotate the spindle within the microsponge gel until we tend to get a continuing dial reading on the show of the viscometer. This procedure is continual 3 times for duplicable results[19].

Stability Test:
Stability studies of microsponge were studied out of varied formulations at totally different temperatures and ratio. Non-teroidal anti-inflammatory drug gel as per ICH pointers, on keeping at 40ºC with RH 45% for the amount of 90 days[19].
Skin Irritation Test: Skin irritation check of optimized loaded microsponge gel Was compared with the marketed and placebo gel. The microsponge is simply too giant to submit to the horny layer and it might be expected to stay on the skin surface, bit by bit cathartic its contents over time. This reduces the upper exposure to the skin and makes contact with the amount. This was useful to scale back the irritation and toxicity of the drug[19].

Spreadability Studies: One of the standards for a gel to fulfill the best qualities is that It ought to possess sensible spreadability. It's the term expressed to denote the extent of the world to that gel apace spread on application to the skin or affected half. The medical specialty effectualness of a formulation conjointly depends upon its spreadability worth. Spreadability is expressed in terms of your time in seconds taken by two slides to slide aloof from a gel placed in between the slides beneath the direction of sure load. The lesser the time is taken for the separation of two slides the, higher the spreadability. Spreadability is determined by glass slides and an engraving, that was provided by an easy machine at one end. By this method, spreadability was measured on the premise of slip and drag characteristics of gels. A ground glass slide was fixed on this block. Associate way more than gel (about 1gm) of varied formulations was placed on the very cheap slide. The gel was then sandwiched between this slide and another glass slide having the dimension of the fixed ground slide. Way more taken for separation of two slides. The very best plate was then subjected to the drug of 20gm, and lesser spreadability was then calculated by the following formula:- $S = M \times L/T$

Where S is that the spreadability,
M is the burden among the pan (tied to the upper slide),
L is that the length tormented by the glass slide,
T represents the time taken to separate the slide absolutely from each other[19].

12. Safety Considerations
Safety studies of microsponges can be confirmed by;
- Allergenicity in guinea pigs
- Eye irritation studies in rabbits
- Mutagenicity in bacteria
- Oral toxicity studies in rats
- Skin irritation studies in rabbits[15].

Patents Filed Related to Microsponges approaches [15]:

Patent no	Inventors	Publication Date
US4690825	Won, Richard	1987
US4863856	Dean RC Jr et al.	1989
US5292512	Schaefer et al	1989
US5135740	Katz et al.	1992
US5679374	Fanchon; Chantal et al	1994
US5316774	Eury, Robert P et al.	1994
US5725869	Lo; Ray J. R.	1996
US6395300	Straub et al.	1999
US6211250	Tomlinson et al	2001
US20030232091	Shefer et al.	2002
US20040247632	Cattaneo, Maurizio	2004

US20050271702	Wright, Steven G et al.	2005

Recent advances in the microsponge drug delivery system [15]

Various advances were made by modifying the methods to form nanosponges, nanoferrosponges, and porous microbeads. β-CD nanosponges were also developed that can be used for hydrophobic as well as hydrophilic drugs, in contrast to polymeric micro or nanosponges. These advanced systems were studied for oral administration of dexamethasone, flurbiprofen, doxorubicin hydrochloride, itraconazole, and serum albumin as model drugs. These nanosponges were developed by cross-linking the β-CD molecule by re-acting the β-CD with diphenyl carbonate.

Some researchers also observed the nanosponges as a good carrier for the delivery of gases. Researchers also observed that incorporating a cytotoxic in a nanosponge carrier system can increase the potency of the drug suggesting that these carriers can be potentially used for targeting the cancerous cells.

Nanoferrosponge, a novel approach constituted the self-performing carriers having better penetration to the targeted site due to the external magnetic trigger which enforces the carriers to penetrate to the deeper tissue and then causes the removal of magnetic material from the particle leaving a porous system.

Due to the improved characteristics of porous microspheres, a process was developed to produce porous microbeads. This method (High internal phase emulsion, HIPE) consisted of the monomer containing a continuous oil phase, cross-linking agent, and aqueous internal phase. They also observed improved stability of RNA and the relatively effective encapsulation process of siRNA. The approach could lead to novel therapeutic routes for siRNA delivery.

Future Prospects

Microsponge drug delivery system holds a promising opportunity in various pharmaceutical applications in the upcoming future as it has unique properties like enhanced product performance and elegancy, extended-release, improved drug release profile, reduced irritation, and improved physical, chemical, and thermal stability which makes it flexible to develop novel product forms. The real challenge in the future is the development of the delivery system for oral peptide delivery by varying ratios of polymers. The use of bio-erodible and biodegradable polymers for the drug delivery is enabling it for the safe delivery of the active material. As these porous systems have also been studied for the drug delivery through the pulmonary route which shows that this system can show effective drug release even in the scarce the dissolution fluid thus colon is an effective site for targeting drug release. These carriers are also required to be developed for alternative drug administration routes like the parenteral and pulmonary routes. These particles can also be used as the cell culture media and thus can also be employed for stem cell culture and cellular regeneration in the body. Due to their elegance, these carrier systems have also found their application in cosmetics. These developments enabled researchers to utilize them variably. These novelties in the formulation also open new ways for drug delivery [15].

Conclusion

With demand for innovative and highly efficient Pharmaceutical as well as Cosmetic products, the market holds considerable potential for Microsponge technology and the versatility they offer. As formulators consider new and creative ways to deliver actives, they can realize the full capabilities of these unique materials providing enhanced safety, improved stability, reduced side effects from actives, enhanced multifunctionality, and improved ingredient compatibility. Complemented by novel development approaches and creative formulation techniques, the Microsponge delivery system can be a winning strategy for a new generation of the Pharmaceutical and Cosmetic industry. Microsponges have a distinct advantage over the existing conventional topical dosage forms for the treatment of tropical diseases; it is a unique technology for the controlled release of topical agents also use for oral as well as biopharmaceutical drug delivery. This shows an advantage over other products by nonmutagenic, nontoxic, and nonirritant. So microsponge drug delivery system has got a lot of potential and is a very emerging field which is needed to be explored in the future with most research studies [15].

REFERENCES

1. Panwar, A.S., Yadav, C.S., Yadav, P., Darwhekar, G.N., Jain, D.K., Panwar, M.S. and Agarwal, A., 2011. Microsponge is a novel carrier for cosmetics. *J Global Pharma Technology*, *3*(7), pp.15-24.
2. Mantry, S., Bagchi, A., Das, S., and Das, S., 2015. Microsponge as a novel strategy for drug delivery system. *Universal Journal of Pharmaceutical Sciences and Research*, *1*(1), pp.32-38.
3. Jadhav, N., Patel, V., Mungekar, S., Bhamare, G., Karpe, M. and Kadams, V., 2013. Microsponge delivery system: an updated review, current status and future prospects. *Journal of Scientific and Innovative Research*, *2*(6), pp.1097-1110.
4. Lalitha, S.K., Shankar, M., Likhitha, D., Dastagiri, J. and Babu, M.N., 2016. A current view on microsponge drug delivery system. *Eur J Mol Biol Biochem*, *3*(2), pp.88-95.
5. Thakur, R., Kumar, S. and Gaba, P., 2020. A review: novel method for microsponge drug delivery system. *Journal of Pharmacy and Biological Sciences*, *15*(4), pp.35-44.
6. Aloorkar, N.H., Kulkarni, A.S., Ingale, D.J. and Patil, R.A., 2012. Microsponges as innovative drug delivery systems. *Int J Pharm Sci Nanotechnol*, *5*(1), pp.1597-1606.

7. Patil, R.S., Kemkar, V.U. and Patil, S.S., 2012. Microsponge drug delivery system: a novel dosage form. *Am J PharmTech Res*, *2*(4), pp.227-51.
8. Osmani, R.A., Aloorkar, N.H., Kulkarni, A.S., Harkare, B.R. and Bhosale, R.R., 2014. A new cornucopia in topical drug delivery: microsponge technology. *Asian J Pharm Sci Technol*, *4*, pp.48-60.
9. Kaity, S., Maiti, S., Ghosh, A. K., Pal, D., Ghosh, A., & Banerjee, S. (2010). Microsponges: A novel strategy for drug delivery system. *Journal of advanced pharmaceutical technology & research*, *1*(3), 283–290. https://doi.org/10.4103/0110-5558.72416
10. BN, Parikh & GD, Gothi & TD, Patel & Chavda, Hitesh & CN, Patel. (2010). Microsponge as Novel Topical Drug Delivery System. Journal of Global Pharma Technology. 2. 17-29.
11. Iosrjournals.org. 2022. [online] Available at: <https://iosrjournals.org/iosr-jpbs/papers/Vol15-issue4/Series-2/F1504023544.pdf> [Accessed 24 May 2022].
12. Mandava, Shyam Sunder, and Vedavathi Thavva. "Novel approach: microsponge drug delivery system." *International Journal of Pharmaceutical Sciences and Research* 3, no. 4 (2012): 967.
13. Abdul Wahid, Ambekar. (2014). JOURNAL OF DRUG DELIVERY RESEARCH MICROSPONGE:A NOVEL TOPICAL DRUG DELIVERY SYSTEM. JOURNAL OF DRUG DELIVERY RESEARCH. 3. 1.
14. Kaity, Santanu & Maiti, Sabyasachi & Pal, Dilipkumar & Ghosh, Animesh & Banerjee, Subham. (2010). Microsponges: A novel strategy for drug delivery system. Journal of advanced pharmaceutical technology & research. 1. 283-90. 10.4103/0110-5558.72416.
15. Jadhav, N., Patel, V., Mungekar, S., Bhamare, G., Karpe, M. and Kadams, V., 2013. Microsponge delivery system: an updated review, current status and future prospects. *Journal of Scientific and Innovative Research*, *2*(6), pp.1097-1110.
16. Hetland, R.B., Granum, B., Lutzow-Holm, C., Lyche, J.L., Paulsen, J.E., Thrane, V., Alexander, J., Binderup, M.L., Dahl, K.H., Husøy, T. and Sanner, T., 2012. Risk assessment of vitamin A (retinol and retinyl esters) in cosmetics. Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety. *VKM Report*.
17. https://r.search.yahoo.com/_ylt=AwrxzhUhJI9i0CYAuwm7HAx.;_ylu=Y29sbwNzZzMEcG9zAzEEdnRpZAMEc2VjA3Ny/RV=2/RE=1653576866/RO=10/RU=https%3a%2f%2fincidecoder.com%2fproducts%2froc-retinol-correxion-sensitive-night-cream/RK=2/RS=T5ksU7.oWaNFe._VV3vU54pD7Oc-
18. Hussain, H., Juyal, D. and Dhyani, A., 2014. Microsponges: an overview. *International Journal of Drug Delivery Technology*, *4*(4), pp.58-66.
19. Kshatriya, Pravin & Shinde, Jitendra & Chavan, Rajashree. (2020). As Review on Microsponge Gel as Topical Drug Delivery System. Journal of Drug Delivery and Therapeutics. 10. 125-133. 10.22270/jddt.v10i6-s.4455.
20. Bhimavarapu, R., Devi, R.R., Nissankararao, S., Devarapalli, C. and Paparaju, S., 2013. Microsponges as a Novel Imperative for Drug Delivery System. *Research Journal of Pharmacy and Technology*, *6*(8), pp.842-848.
21. Shukla, A., Garg, A. and Garg, S., 2016. Application of microsponge technique in topical drug delivery system. *Asian Journal of Biomaterial Research*, *2*(4), pp.120-126.
22. Tile, M.K. and Pawar, A.Y., 2015. Microsponges: a novel strategy for drug delivery. *International Journal of Pure and Applied Bioscience*, *3*(1), pp.224-235.
23. Pradhan, S.K., 2011. Microsponges as the versatile tool for drug delivery system. *Int J Res Pharm Chem*, *1*(2), pp.243-58.
24. Veer, S.U., Gadhve, M.V. and Khedkar, A.N., 2014. Microsponge: A drug delivery system. *International Journal of Pharmaceutical and Clinical Research*, *6*(4), pp.385-90.
25. Rahman, M., Almalki, W.H., Panda, S.K., Das, A.K., Alghamdi, S., Soni, K., Hafeez, A., Handa, M., Beg, S. and Rahman, Z., 2022. Therapeutic Application of Microsponges-based Drug Delivery Systems. *Current pharmaceutical design*, *28*(8), pp.595-608.
26. Kumar, S., Tyagi, L.K. and Singh, D., 2011. Microsponge delivery system (MDS): A unique technology for delivery of active ingredients. *International Journal of Pharmaceutical Sciences and Research*, *2*(12), pp.3069-3080.
27. Singhvi, G., Manchanda, P., Hans, N., Dubey, S.K. and Gupta, G., 2019. Microsponge: An emerging drug delivery strategy. *Drug development research*, *80*(2), pp.200-208.
28. Bhanse Najuka, D., Shah, C. and Shah, D., 2016. NOVEL AND INNOVATIVE STRATEGY: MICROSPONGES DRUG DELIVERY SYSTEM. *Pharma Science Monitor*, *7*(2).
29. Gandhi, A., Jana, S. and Sen, K.K., 2013. Tailoring effect of microsponge for targeted drug delivery. *Journal of Scientific and Innovative Research*, *2*(6), pp.1073-1082.
30. Darekar, A., Pawar, P. and Saudagar, R.B., 2019. A review on microsponge as emerging drug delivery system. *Journal of Drug Delivery and Therapeutics*, *9*(3-s), pp.793-801
31. Shah, C.N. and Shah, D.P., 2014. Microsponges: A revolutionary path-breaking modified drug delivery of topical drugs. *International Journal of Pharmaceutical Research*, *6*(2), pp.1-13.
32. Babu, A. and Akhtar, M.S., Design and characterization of microsponge drug delivery system: A Review.
33. Kong, R., Cui, Y., Fisher, G.J., Wang, X., Chen, Y., Schneider, L.M. and Majmudar, G., 2016. A comparative study of the effects of retinol and retinoic acid on histological, molecular, and clinical properties of human skin. *Journal of cosmetic dermatology*, *15*(1), pp.49-57.
34. Shaha, V., Jain, H., Krishna, J. and Patel, P., 2010. Microsponge drug delivery: A Review.
35. https://r.search.yahoo.com/_ylt=Awr1ToPgeZBiJso.hprGHAx.;_ylu=c2VjA2ZwLWF0dHJpYgRzbGsDcnVybA--/RV=2/RE=1653664352/RO=11/RU=https%3a%2f%2fayurveda-world.ru%2fkosmetika%2fuhod-za-litsom%2ftretinoin-0-1%2f/RK=2/RS=2FvgotmFJlnnTc08fWVxjzNlHDg-