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SYSTEMATIC REVIEW ON MICROSPONGES: A NOVEL TECHNIQUE OF DRUG DELIVERY

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ABSTRACT

The Microsponges delivery system are novel technique for controlled release and target specific drug delivery system. Microsponges are porous microspheres composed of microscopic size patented polymeric delivery systems of extremely small, inert, and even tinier particles of indestructible clusters. They are tiny, sponge like spherical particles with large porous surface. Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle. These polymer based microspheres can suspend or subjected to 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 rather porous, subterranean outflow of substances from a sustained flow. Microsponges are designed to deliver a pharmaceutically viable ingredient efficiently to the minimum dose and also enhance stability, reduce side effects, and modify drug release.

KEYWORDS: Microsponge, Topical drug delivery, Polymer.

INTRODUCTION

Micrsponges are porous, polymeric microspheres that can penetrate a wide range of active ingredients such as emollients, fragrances, essential oil, and anti-infective, anti-fungal, and anti-inflammatory agents. Like a true sponge, each microsphere consist of a Myriads of interconnecting voids within a non-collapsible structure, with a large porous surface. A larger number of variations of this technique can be applied to pharmaceutical products. Many variations of the technique and applied those to the cosmetic as well as over-the-counter (OTC) and prescription pharmaceutical products, at present this technology is also used in

topical preparations.[1] Microsponge based delivery system gives assurance on drug localization of skin. They also offer an advantage of programmable release and are biologically safe.[2] The size of microsponge can be ranged usually from 5-300m, each sphere can have up to 25,000 spores and have an internal pore structure up to 10 meters in length and this result in a large reservoir system within each microsponge.[3,4] Many conventional systems require high concentration of active ingredients since they are not efficient as delivery systems. Thus, the present investigation is present in the context of an active ingredient, either on the skin surface or in the epidermis which minimizing its penetration into the body. The microsponge based polymeric microspores uniquely fill such requirements.[5] The microsponges are prepared by several methods using polymerization in a liquid-liquid system. The most common emulsion system is oil in the water system, with microsponges being produced by solvent diffusion method.[6]

There has been a concern about the topical dosage of these drugs such as the use of oral contraceptives, creams and other medications from the skin and poor release of drugs from the base. In- hydrophilic ointments are oleaginous, greasy and non-convenient to patients and also medicated powders for topical application.[7] However, the Topical drug delivery system is not practical for the delivery of drugs into circulation, is means of controlling side effects. No efficient vehicles have been developed for drug delivery in stratum Corneum and underlying skin layers and beyond the epidermis. Often aesthetically appealing, greasiness, stickiness, and so on, in topical drug delivery will result in a lack of patient compliance. These vehicles require a high concentration of active ingredients for effective therapy because of their low delivery rate, resulting in irritation and allergic reaction in the larger population.[8-10]

The microsponge particles are too large to be absorbed into the skin and this adds a means of safety to these microsponge materials. So they are collected on tiny nooks and crannies of skin and slowly release the entrapped drug as the skin needs it. They are designed to deliver an effective and efficient approach to drug delivery. These microscopic spheres are capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Microsponges are Spherical particles composed of clusters of even tinier spheres are capable of holding four times their weight in skin secretions. These products typically presented to the consumer in conventional forms like creams, gels or lotions and they contain a relatively high concentration of active ingredients[11] (figure 1)

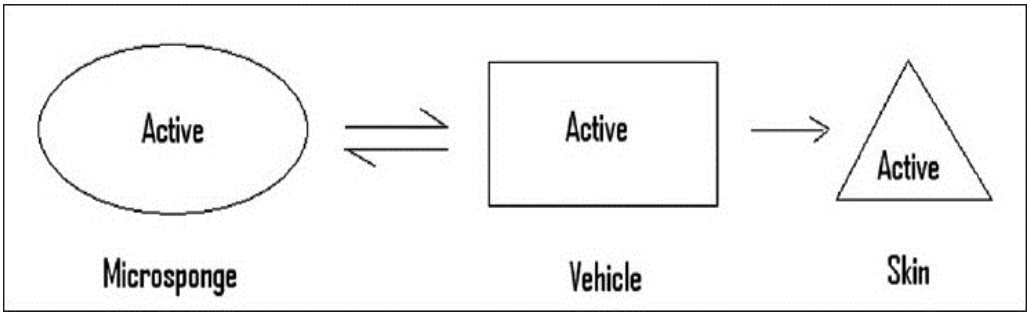


Figure 1: schematic representation of distribution of loaded material on skin.

Potential charecterastics of microsponges[11-15]

- The microsponges show stability over pH ranging from 1 to 11 and at high temperatures up to 130°C
- They are compatible with most vehicles and ingredients.
- Bacteria cannot penetrate since their pore size is 0.25µ.
- It has a higher payload (50 to 60%)
- They are free-flowing and can be cost-effective.
- Without drying, Microsponges absorb oil up to 6 times their weight.
- These particles are easy to absorb into the skin
- It provides an extended-release. i.e., it provides continuous action up to 12hours
- They have superior formulation flexibility.

Charecterastics of material trapped inside microsponges[16,17]

Microsponges contain active ingredients that can be incorporated into many products such as creams, gels, powders, lotions, and soaps. While taking into account the desired product characteristics such as:

- It should be capable of being miscible by the addition of a small amount of a water-immiscible solvent.
- Must be water-immiscible or only slightly soluble
- It should be inert to monomers.
- The solubility of actives in the vehicle must be limited to avoid cosmetic problems; not more than 10 to 12% w/w
- microsponges must be incorporated into the vehicle. Otherwise, the vehicle will deplete the microsponges before the application.
- The spherical structure of microsponges should not collapse.

- Polymer design and payload of the microsponges for the action must be optimized for required release time, even for a given period.
- It must be stable in interaction with polymerization catalyst and the atmosphere of polymerization.

Benefits of microsponges[18, 19]

- They are biologically safe and shows novel strategies of controlled release.
- They can absorb oil up to 6 times its weight without drying.
- They entrap numerous ingredients and provide improved product daintiness and flexibility.
- Absorb skin secretions.
- Advanced thermal, physical and chemical stability
- Improves material processing e.g. liquid can be converted to powder
- They can provide uninterrupted action up to 12 hours
- Reduced irritation, better tolerance and good consumer acceptance.

Over conventional dossage forms

The conventional dosage forms show their effects on the outer layers of the skin. Such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is highly absorbed. The microsponge system can prevent excess accumulation of substances within the epidermis and dermis. Potentially the microsponge system can reduce the effectiveness of demanding effective drugs without irritation. For example, by delivering the active ingredient gradually to the skin like MDS-Benzoyl peroxide formulations have excellent efficacy with minimal irritation

Over oinments

Ointments are often aesthetically unappealing, greasy and sticky that often results in patient compliance. These vehicles require effective treatments for high concentrations of active ingredients because of their low efficiency of the delivery system, significant users inconsequential and allergic reactions. Other drawbacks of topical formulations include uncontrolled evaporation of active ingredient, unpleasant odor and potential incompatibility with drugs when the system maximizes the amount of time the active ingredient is present on the skin surface or within the epidermis while minimizing its transdermal penetration into the body.

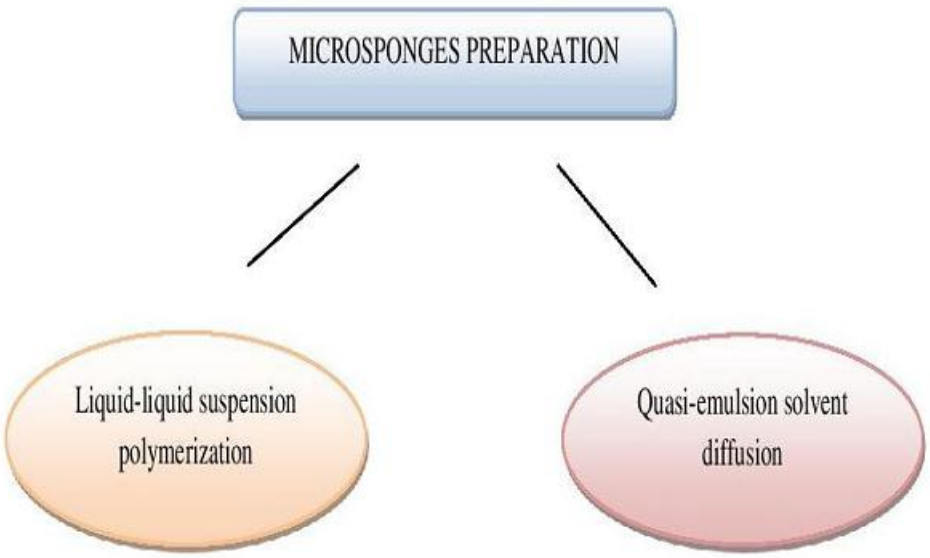
Over microencapsulation and liposomes

Microcapsules cannot normally control the release rate of actives. Once the wall is destroyed, the microcapsules within the actives contained in the liposomes suffer from lower payload, difficult formulation, limited chemical stability, and microbial instability. While the microsponge drug delivery system has a number of advantages over this.

Limitations

This method usually includes poisonous organic solvent such as porogen, which cause environmental hazard as some may be highly inflammable posing a safety liazard. In some cases, the monomer of the traces has been observed, which may be toxic and hazardous to health.

Formulation of microsponges[20-22]

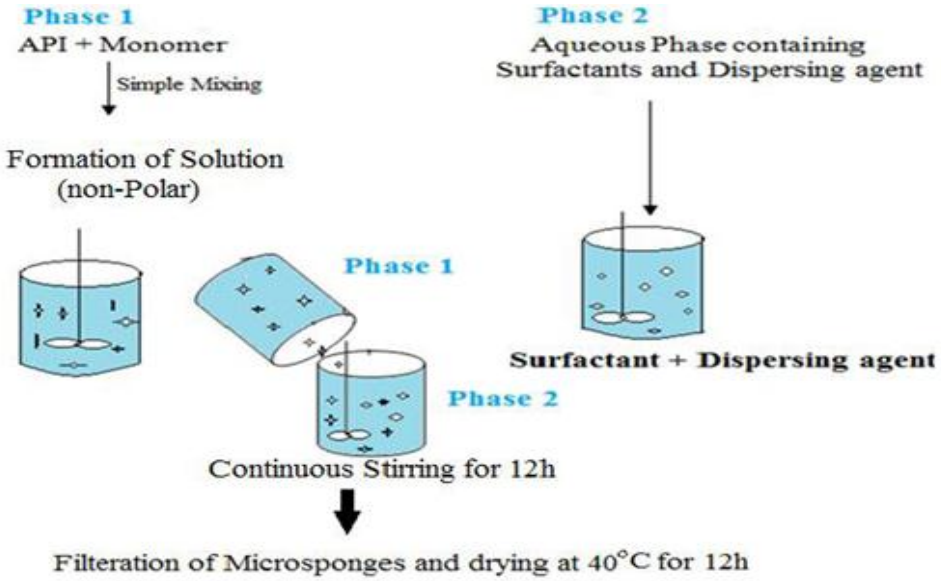


Liquid liquid suspension polymerisation

The microsponges are prepared by suspension polymerization in liquid-liquid polymerization. The monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and then dispersed into an aqueous phase containing suspending agents such as surfactants and dispersants to facilitate the formation of suspension. Polymerization is initiated by adding a catalyst or by increasing temperature, ultimately solvent is removed leaving spherical structure porous. After polymerization, the solvent is removed leaving microsponges. Once the droplet of discrete size is formed, then incorporates the variety of active substances like anti-fungal, rubefacients, anti-acne, anti-inflammatory, etc and act as a topical carriers.

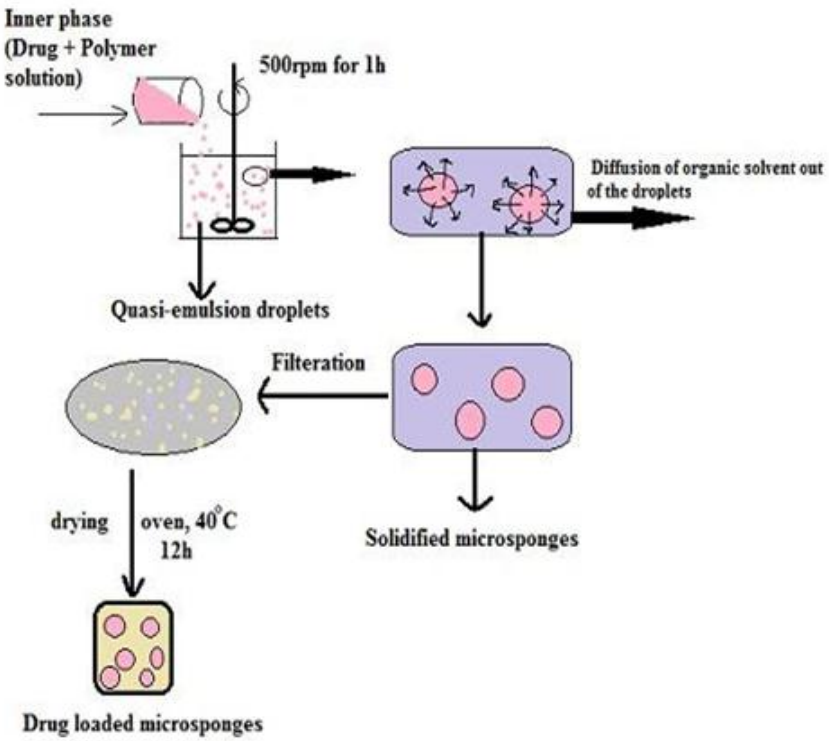
The various steps in the preparation of microsponges are summarized as

1. Choice of monomer or combination of monomers.
2. Formation of chain monomers as polymerization begins.
3. Formations of ladders as a result of cross-linking between chain monomer
4. Folding of monomer ladder to form spherical particles
5. Agglomeration of microspheres leads to the formation of bunches of microspheres.
6. Binding of bunches to form microsponges.



Quasi emulsion solvent method

The quasi emulsion technique is a solvent diffusion technique. If the drug is sensitive to polymerization, a two-step process is used for the preparation of microspheres, where the formation of two phases i.e., internal phase and external phase take place. In the inner organic phase, Eudragit is dissolved in ethyl alcohol. Then, the drug can be then added to polymer-like tri-ethyl citrate (TEC) to maintain plasticity. They are then dissolved under Ultrasonication at 35°C. The inner phase was poured into the polyvinyl alcohol solution in distilled water and stirring for 60 minutes. Then the mixture is filtered to separate the microsponges. The microsponges are dried in an air heated oven at 40 for 12 hours. On comparing with liquid-liquid polymerization, this method has the advantage of less exposure to ambient conditions, lower solvent residues in the product and the solubility of the solvent in aqueous media or due to its volatile nature, producing matrix-type pores.



Mechanism of action[23, 24]

The active ingredient is added to the vehicle in an entrapped form. Since, 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 vehicle gets depleated. It 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 controlled release over time.

Safety studies

Safety studies of microsponges can be established by:

- Eye irritation studies in rabbits.
- Oral toxicity studies in rats.
- Allergenicity in guinea pigs
- Skin irritation studies in rabbits.
- Mutagenicity in bacteria

Evaluationof microsponges

Paticle size and size distribution[24]

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 formulation and its stability. Free-flowing powders with fine aesthetic attributes are achieved by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded microsponges can be performed using laser light diffractometry or any other suitable method. The values are the mean size range for all the formulation to be expressed. Drug release on the particle size of study results in different particle size of drugs from a cumulative percentage drug release. Particles larger than 30μm can impart grittiness and hence particles of sizes between 10 and 25μm are preferred to be used in topical formulations.

Morphology and surface topogrphy of microsponges[25]

For morphology and surface topography, prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy (SEM).

Charecterisation of pore structure[27]

Pore volume and diameter are the major components of controlling the intensity and duration of active ingredient. Pore diameter also affects the migration of active ingredients from the microsponges into the vehicle which is dispersed. Microsponges from drug release of rate with pore diameter and volume of study effect to mercury intrusion porosimetry can be employed. Microsponges of porosity parameters such as intrusion extrusion isotherms pore size distribution, total pore surface area, average pore diameters, interstitial void volume, percent porosity, and vitality, the percent porosity is filled, the shape and the morphology determined by the possibilities, the bulk and the apparent density can be obtained by using intensity porosimetry.

Polymer\monomer composition[28]

Variable factors such as microsphere size, polymer composition and drug loading regimen from drug release. The polymer composition can also be influenced by the partition coefficients of the entrapped drug between the microsponge system and the vehicle and thus the rate of release of the entrapped drug. Different polymer compositions of microsponge systems from drug release can be studied by plotting cumulative drug release time. The

choice of the monomer is dictated by the vehicle into which it is dispersed and the characteristics of the active ingredient. Active ingredients of varying degrees of hydrophobicity or lipophilicity or electrical charges may be prepared with polymers. A large diversity of monomer combinations will be screened for their drug release profile by drugs in the appropriate manner.

Compactability studies[29]

Studies have shown that, Thin-layer chromatography (TLC) and Fourier Transform Infra - red spectroscopy (FT - IR) can be studied by comparing the reaction with the drug of compatibility. The effect of crystallinity on the polymerization of the drug can be studied by powder X - ray diffraction (XRD) and differential scanning colorimetry (DSC). For DSC approximately 5 mg of samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15 ° C / min over a temperature range of 25 - 430 ° C in the atmosphere of nitrogen 22, 23, and 24 volume ml.

Invitro diffusion studies[29]

In - vitro release studies have been carried out using dissolved apparatus USP XXIII equipped with a modified basket of 5um stainless steel mesh. Dissolution rates were measured at 37 ° C under 150 pm color speed. The dissolution medium is the time of regular intervals at the selected analytical method (UV spectrophotometer) to determine the active ingredients of the solubility and the sink conditions, while the sample aliquots were chosen.

Stability studies

In pharmaceutical sense stability is a specific container or closure system that is technically defined as the capacity to remain in its physical, chemical microbiological, therapeutic and toxicological specification. The physical, chemical, microbiological, therapeutic and toxicological specification of a particular formulation remains in the formulation of the capability of a product. Storage of Microsponge cel formulation of Stability is a great concern as it is marketed preparations of major resistance in development. The prepared formulation was tested for stability at 4 4 1 ° C, 25 + 2C and 37 + 5 ° C & RH (Relative Humidity) 75%. After one month and three months they evaluated the following parameters - Appearance, pH, Dog content analysis, Dug release. profiles, Rheological properties etc.

Determination of true density[30]

Ultra-picnometer under helium gas is used for the measurement of ture density and they are calculated by taking mean of repeated directions.

Resiliency[31]

Softer and firmer beadlets are produced according to the needs of the final formulation on the basis resiliency(visco elastic properties).

Applications

Microsponges are designed to deliver the pharmaceutical active ingredient efficiently at minimum dose and also to improve stability, reduce side effects and modify drug release. Microsponge drug delivery systems offer the ingredients of entrapment and are expecte contribute to reduced side effects, improved stability, reduces systemic exposure and minimize local cutaneous reactions, increased elegance, and enhanced formulation flexibility. It is used mostly for topical and recently for oral administration. Have several patents reported that it can be used as excipients due to its high loading capacity and sustainability release ability. Topical Microsponge Systems for Products Under Development or Marketplace Utilization in three primary ways.

1. Extended period of time over active ingredients releasing, as reservoirs
2. aspiration for undesirable substances, such as excess skin oils, or
3. Superficial action for the skin from the ingredients holding as closed containers.

- **Topical drug delivery employing microsponge technology**[32]

The microscopic supply of benzoyl peroxide was developed using an emulsion solvent diffusion method, adding an internal organic phase containing benzoyl peroxide, ethylcellulose, and dichloromethane in a stirred aqueous solution phase containing polyvinyl alcohol, and by suspension polymerization of styrene and divinylbenzene. The prepared microsponges were dispersed in a gel base and microsponges gels were evaluated for antibacterials and skin irritation The trapped system released the drug to as lower speed than the system containing free BPO. The topic delivery system with reduced irritation was successfully developed. A new formulation of hydroquinone (HQ) 4%, with 0.15% retinol, trapped in microsponge deposits, was developed to release HQ gradually, to prolong exposure for treatment and to minimize skin irritation. Security and The efficacy of this product was evaluated in a 12-week open-label study. In this open study, 4% HQ with retinol 0.15% was safe and effective. The microsponges topical administration system of fluconazole

gel was observed. They have the potential to extend the launch. An MDS Retinoic acid system was developed and tested for Drug release and anti-acne efficacy. Statistically significant, greater reductions in inflammatory and non-inflammatory lesions were obtained with tretinoin trapped in the microsponge. Topical, anti-inflammatory and analgesic counter-irritant medications in a microsponge® are used for musculoskeletal system management.

- **Oral drug delivery employing microsponge technology**

In oral applications, the microsponge system has shown that the solubilization rate of poorly water soluble drugs is increased by trapping said drugs in the microsponge. system pores Since these pores are very small, the medicine is in reduced effect to microscopic particles and the significant increase in surface area, therefore, increases considerably of solubilization. Controlled oral delivery of ibuprofen Microsponges are achieved with an acrylic polymer, eudragit RS, by changing its intraparticle density.[33] Sustained chloramphenicol maleate release formulation, using Powder coated microsponges, is prepared by dry impact mixing method, for oral administration of medications.[34] Oral controlled supply of ketoprofen prepared with a quasi-emulsion solventbroadcast method with Eudragit RS 100 and later. Microsponge tablets were prepared by the direct compression method, the results indicated that the compressibility it was much better in the physical mixture of the drug andpolymer; due to the plastic deformation of the sponge. Microsponge structure, producing mechanically strong tablet[35] Controlled and specific supply of flurbiprofen colon, was carried out using a commercial Microsponge system. In vitro studies showed that coated compression the specific tablet formulations for the colon began to release the medication at the eighth hour, corresponding to the proximal colon arrival time, due to the addition of the enzyme, after a modified release pattern while drug release from the specific colon formulations prepared by pore plugging the microsponges showed an increase at the eighth hour, when the enzyme addition was made.[36]

- **For bone and tissue engineering using microsponge technology[32]**

Bone substitute compounds were obtained by mixing pre polymerized polymethyl methacrylatepowders and liquid methyl methacrylate monomer with two dispersions of a-tricalciumphosphate grains and calcium-deficient hydroxyapatite powders. The final compounds It seemed to be porous and acted like microsponges. Basic fibroblast growth factor (bFGF) incorporatedinto a collagen sponge sheet remained released in the mouse subcutis according to the spongebiodegradation matrix and exhibited local angiogenic

activity in a dose-dependent manner. Intramuscular Collagen Injection microsponges that incorporate bFGF, induced a significantincrease in blood flow, in the murine ischemic back limb, which could never have been reached by the bolus bFGF injection. These results suggest the importance and therapeutic utility of the collagen as a reservoir of bFGF. A biodegradable graft material containing collagmicrosponge was developed for cardiovascular tissue grafting, as it would allow the regeneration of Autologous vessel tissue. A thin biodegradable synthetic poly hybrid mesh (DL-lactic-co-glycolic acid) (PLGA) and naturally derived collagen was used for the three-dimensional culture of human skin fibroblasts. The hybrid mesh was constructed forming a spider web. Collagenmicrosponges in the openings of a PLGA knitted fabric mesh. A patch designed with fabric madefrom our biodegradable polymer and collagen microsponge provided good regeneration in situ inboth the venous and venous systems arterial wall, suggesting that this patch could be used asnovel surgical material for the repair of the cardiovascular system.

Future aspects

Conventional formulations of topical drugs are intended to work on the epidermis of the skin. Hypothetically, such products release their active ingredients upon application, producing a highly concentrated layer of an active ingredient that is rapidly absorbed, which might lead to toxicity. Thus, the need exists for a system to maximize the amount of time that an active ingredient is present either on the skin surface or within the epidermis. Likewise, the transdermal delivery system requires vehicles at a higher concentration to dissolve the active pharmaceutical ingredient or for effective therapy, it causes irritation and hypersensitivity reactions in significant users. Hence, the need exists for a system to maximize the amount of time that an active ingredient is present either on the skin surface or within the epidermis. Micrsponge drug delivery is the most novel drug delivery system approved; several others are currently under development and clinical study.

Marketed formulation[37]

Salicylic Peel 20 Salicylic acid 20%,	Stimulation of the skin to improve fine lines, pigmentation, and acne concerns and also it has Excellent exfoliation.
EpiQuin Micro	The Microsponge system entraping hydroquinone and retinol release drug to reduce skin irritation.
Sportscream RS and XS	For the management of musculoskeletal conditions these are used as topical analgesic-anti-inflammatory and counterirritant actives in a Microsponge Delivery System.
Line Eliminator Dual Retinol	Lightweight cream with a retinol in MDS delivers both immediate and time released wrinkle-fighting action.
Carac Cream, 0.5%	Carac is a topical prescription product for the treatment of keratosis, which contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge) composed of glycol dimethacrylate cross-polymer and dimethicone.
LactrexTM 12% Moisturizing Cream	Face moisturizer. Soothen skin and also remove excess of oil from our body. Manufactured by: SDR Pharmaceuticals, Inc

CONCLUSION

With increasing demand for innovative and highly efficient pharmaceutical as well as cosmetic products, the microsponge technology holds higher potential. The microsponge drug delivery system is believed to reduce side effects, improve stability, increased elegance, flexibility and also wide entrapment of active ingredients. The microsponge technology has a lot of capability and is an emerging field to be unveiled in the future with more inventories.

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