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A Review: Novel Method for Microsponges Drug Delivery System

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Abstract: *Microsponges drug delivery(MDS), because of their benefits,have been leading researchers around the globe to investigate them as drug carrier. MDS are reliable delivery systems that encapsulate both water insoluble and water sparing agents to improve their effectiveness with great potential attributes to their unique characteristics. Many applications are also recommended for the production of drug and or cosmetic products with improved safety and effectiveness. Various marketed formulations are also available carac, retinol cream, ultra Guard. Major challenge of the formulation is to achieve the desired concentration in the blood of the medication. This microsponges (MSPs) are multifunctional as they are non-irritating, non-mutagenic, non-allergenic and non-toxic. One of the best feature of this technology is that it own self-sterilizing. The review elaborate mirosponges technology along with its preparation method, characterization, method of evaluation and future prospects.*

Keywords: *Microsponges, quasi-emulsion solvent diffusion method, preparation, liquid-liquid suspension method, drug delivery.*

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I. Introduction

Differential system for systemic drug under the transdermal delivery systems class were developed using the skin as the entry portal. The greatest challenge for the scientists now is to controlling rate of delivery to predetermined site of active pharmaceutical ingredients. Researcher focused on the development of the precise controlled release drug delivery system to improve safety and patient adherence[1,2]. Microsponges a polymeric drug delivery systems composed of porous microsphere[3].

Microsponges are non-collapsible structures. The length of the pore may be up to 10 ft and the volume of the pore may be upto 1 ml/g depending upon the size[4].

In 1987, the microponges technology developed, and advanced polymer system, Inc, authorized the original patents. Microsponges with a variety of inter connected volume ranging from 5-150 µm of particle voids. The average pore size of human skin is 5 micron, particles larger than 10 µm remain on the surface of the skin, microsponges with 10-40 micron will yield the best result and give a smooth touch feel. Microsponges are capable of absorbing skin secretion and then reducing skin oils and shine. The particle however, are extremely minute inert imperishable sphere that cannot pass through the skin pores and release the trapped drug into the skin slowly[5-7].

Thus, the need exists for delivery system in recent study is to achieve the desired concentration of the drug in the blood in MDS (microsponges drug delivery system) that is longer term therapeutically more active and non-toxic. The use of TDS is primarily microsponge[8,9].

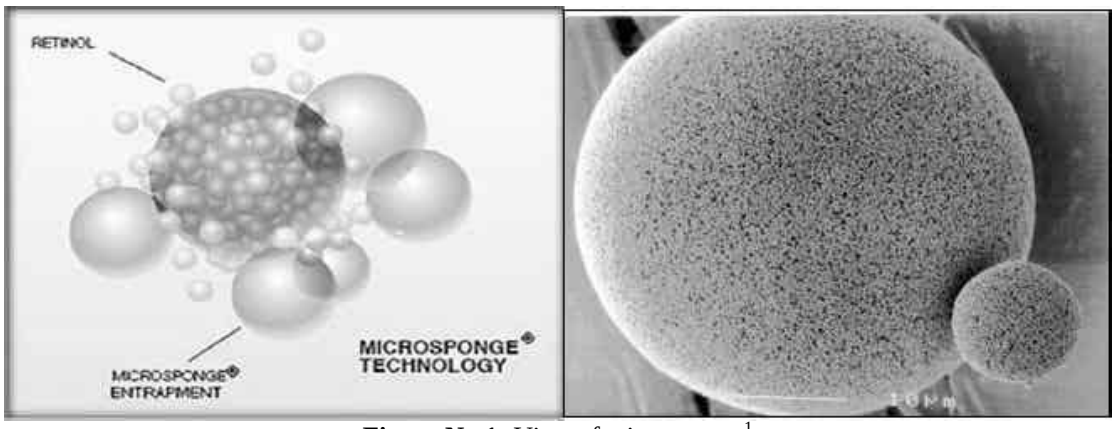

Figure No.1: View of microsponge[1]

Advantages over conventional formulations

Conventional topical formulation are intended for local effects. Due to their rapid absorption into the skin these type of product contain a high concentration of API and a productive lower result. Through preventing excessive accumulation of ingredients within the epidermis and dermis, microsponges comparatively need the much smaller amount of API to provide the necessary therapeutic action than traditional formulation. In addition they are also significantly reduce the side effects due to the accumulation of API on skin surface providing safety and increasing patient compliance because of uncontrolled API evaporation[10,11].

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 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. Entrapment efficiency of microsponges is 50%-60%. whereas that of liposomes is about 30%. Liposomes are therefore difficult to manufacture, are highly costly, have no microbial, stability, have less Chemical stability and have lower payload than microsponge.[12]

Advantages over ointments

Ointments require a high concentration of API due to their low permeation efficiency to require effective therapeutic action. It leads to side effects such as allergic reactions and irritation due to high concentration and is often unattractive, sticky, leading to lack of patient compliance. They also have an unpleasant odor and an uncontrolled evaporation of the active ingredient. In compatibility between drugs and vehicles may arise in these formulations compared to ointments, the microsponges drug delivery system has improved permeation with minimal trandermal penetration into the body, which increase the drug retention time within the skins surface layer.[13]

BENEFITS OF MICROSPONGES[14]

When applying microsponges on the skin, its release of drug can be controlled by diffusion. Microsponges release the active ingredient on the target skin site in a programmable manner, benefiting from increased drug effectiveness, reducing pain associated with potent therapeutic agents such as BPO.
Several benefits of MDS are pictorially represented in (fig.2).

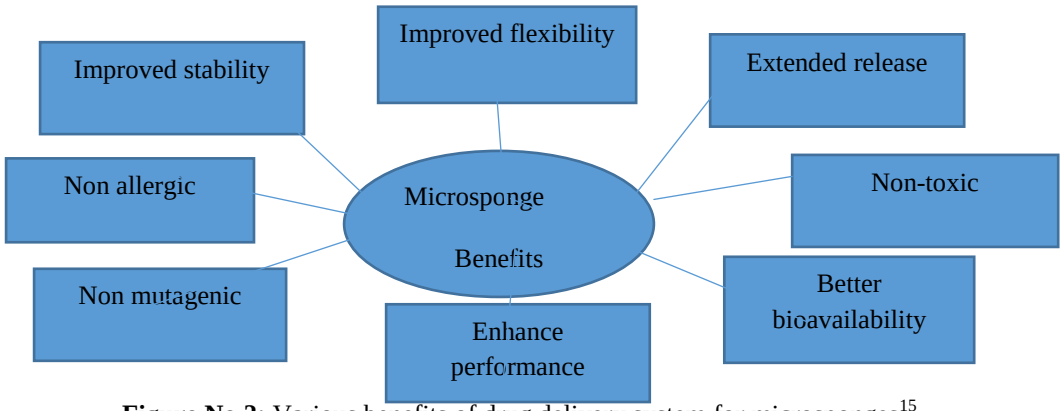

Figure No.2: Various benefits of drug delivery system for microsponges[15].

The features of MDS[16-18]

- Microsponges has pH range stability ranging from 1-11.
- MDS can withstand up to high temperature(130C).
- They have high efficiency of trapping up to 50%-60%.
- MDS act as good skin absorbent.
- MDS withstand moisture attack.
- MDS has a comparatively longer half-life.
- They are non-mutagenic, non-irritating, and non - allergenic and non-toxic.

Properties of drug for loading into microsponge[19]

- It should be fully miscible in monomers or capable of being made miscible by addition of small amount of water immiscible solvent.
- It should be inert in terms of monomer.

- The spherical structure of the microsponges should not collapse.
- No more than 10-12%w/w microsponges must be included in the vehicle to avoid cosmetic problems.
- In contact with the polymerization catalyst , it should be stable.

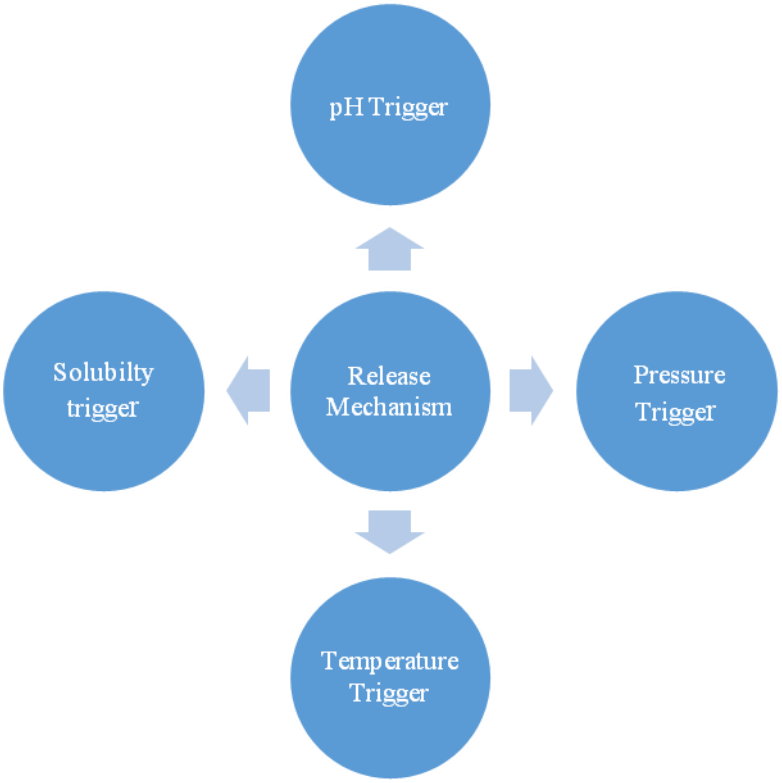

Figure No.3 : Release mechanism from microsponges.

Release Mechanism[10]

The given programmable parameters can be controlled effectively in response to one or more external stimuli to design MDS for releasing functional substance over a period of time. This system release mechanism is mainly:

A.Sustain or time release[10]

Specific physical and chemical properties of the entrapped active substance including viscosity, volatility and solubility will be studied in the development of a sustained release microsponge while the polymeric microspopnge pore diameter, volume, and resilience of the polymeric microsponge will be evaluated to give necessary sustained release effect.

Release on command

Micosponges can be designed in response to one or more external stimuli to release the specified amount of active ingredients over time:

Pressure change

when pressurized or rubbed,the MDS release the entrapped material. The amount release may also depend on the sponge release and the microsponge's resilience.[20]

Temperature change

It is possible to activate the release of active ingredients from microsponges by temperature many entrapped active ingredients at room temperature may be too viscous to immediately stream from microsponges to the skin. Increasing the skin temperature also increase the flow rate and thus also increase the release.[21]

pH change

The activity's pH based release can be activated by changing the microsponge coating. This has a lot of drug delivery applications.[20]

Solubility change

Microsponges loaded with water will release miscible ingredients such as antiseptics and antiperspirants. The release can also be triggered through diffusion but the partition coefficient of the active between the microsponge and the external system may be considered.[22]

PREPARATION OF MICROSPONGES[23-27]

Drug loading in Msps may take place in two processes, i.e liquid suspension polymerization and quasi-emulsion solvent diffusion techniques, based on the physicochemical properties of the drug to be loaded.

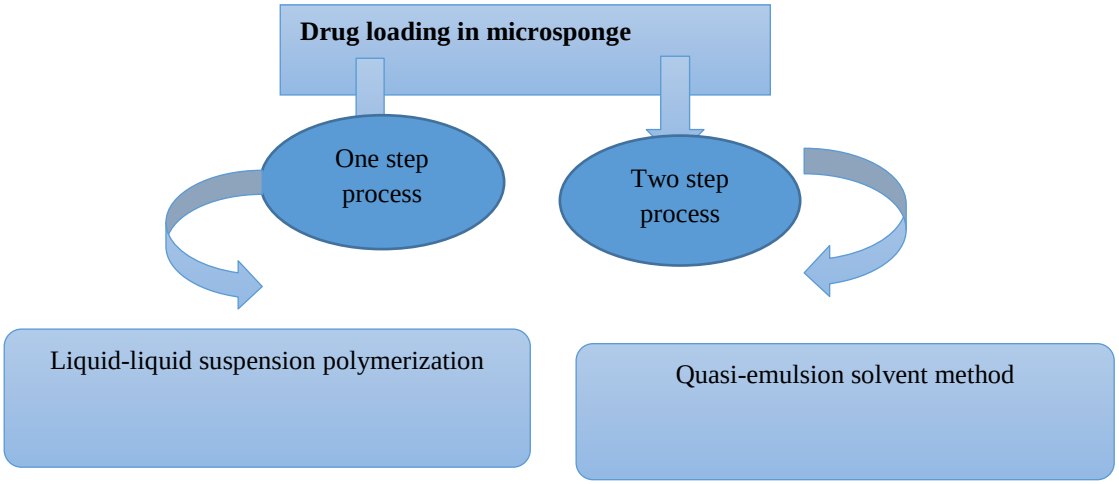

Figure No.4 : Prepration of microsponge.

1) Liquid-liquid suspension polymerization[28-30]

The microsponges based on porous microsphere are prepared using liquid-liquid suspension polymerization.Firstly, the monomers are dissolved in an effective solvent with active ingredients wich are then dispersed in the aqueous phases, consist of additives(dispersants or surfactants). Polymerization is then initiated by activating monomers either by increasing temperature or irradiation, polymerization continue leads to formation of spherical structure. Once the polymerization process is completed the liquid will be removed, leaving the microsponges.

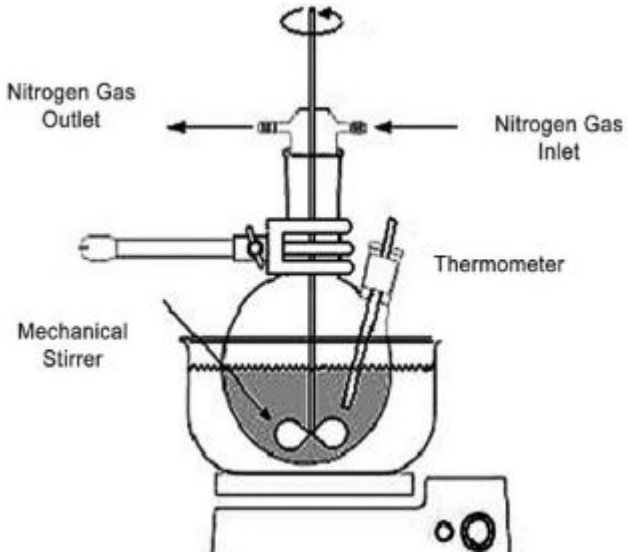

Figure No.5: Prepration of liquid-liquid suspension polymerization using reaction vessel.

2) **Quasi-emulsion solvent diffusion**[31-33]

The method of quasi-emulsion solvent porous microsphere (microsponges) using internal phase containing eudragit dissolve in ethyl alcohol. Then drug can be then added slowly to the polymer solution,then dissolved under ultrasonication at 35℃ temperature and plasticizer such as triethylcitrate (TEC) is added to aid

the plasticity. The internal phase is then poured into an external phase that contain polyvinyl alcohol and distilled water with continuous stirring for 60 mins. The product is then filtered to isolate the microsponges and

then washed and dried by vacuum oven at 40℃ for 12h.

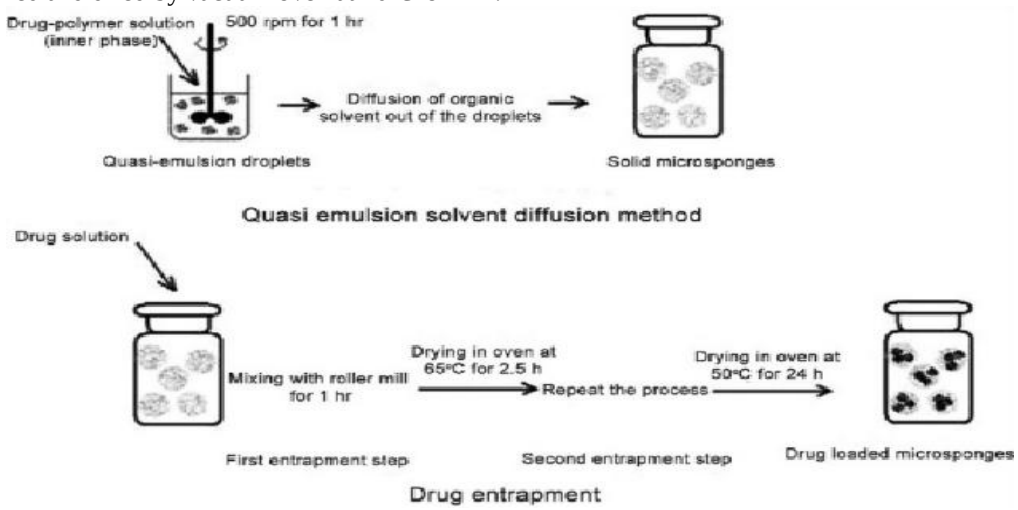

Figure No.6: Quasi-Emulsion solvent Diffusion Method.

FORMULATION CONSIDERATION[34,35,53]

Theactiveingredientscontainedin microsponges drug delivery system can then be formulated into different products such as (creams, gels , lotions , soaps and powder or compressed into tablets) for the purpose of obtaining desirable product characteristic, other factors are taken into account when formulating the vehicle-

- The solubility of the vehicle's active must be limited otherwise the vehicle would deplete the microsponges during formulation.
- To avoid problems with cosmetics, not more than 10 to 12% w/w microsponges must be incorporated into the vehicle.
- Polymer designed and payload of the active micosponges must be optimized for the required release rate for a specified period of time.

MECHANISM OF ACTION[36,37]

In a entrapped form, the active ingredient is inserted into the vehicle .

Ingredient is free to move in and out of the particles and into the vehicle as they contain an open structure as they do not have continues membrane surrounding them and the vehicle is saturated at equilibrium state.

The active will be absorbed into the skin once the product is applied to the skin, depleting the vehicle, which becomes unsaturated, thereby disturbing the equilibrium.

Particle flow from microsponge to the vehicle and from vehicle to the skin until either the vehicle has been absorbed or dried.Then, the microsponge particle held on the stratum corneum surface will continue to release the active in the skin slowly.

EVALUATION METHODOLOGY OF MICROSPONGE[38-42]

Particle size determination

The distribution of the particle size is evaluated using polarizing or optical microscope and electron microscope.laser light diffractometry or other suitable method can be used to determined the particle size of microsponge.

Morphology and surface topography of microsponges

For morphology and topography, different methods such as the photon correlation spectroscopy (PCS), Transmission electron spectroscopy (TEM), scanning electron microscopy(SEM) etc are used in the morphological study of microsponge topography.

Characterization of pore structure

Pore volume and diameter are important for monitoring the active ingredient's intensity and duration efficacy. Pore diameter also effect the migration of active ingredients from microsponges into the vehicle which disperse the material. Mercury porosimetry intrusion can be used to study the effect of pore diameter and volume. Microsponges porosity parameters include intrusion-isotherms of extrusion. By using mercury intrusion porosimetry the distribution of pore size, average pore size diameters, shape and morphology of the pores, bulk, and apparent density can be determined.

Polymer/Monomer composition

The composition of polymer has a major influence on partition coefficient of the entrapped drug between the microsponges system and the vehicle, thereby influencing the release rate of the entrapped drug. Drug release from microsponges system with various compositions of polymers can be analyzed by plotting against time cumulative percent release of drugs. As the polymer concentration increase,the release rate become sustained. Therefore, one can achieve continuous release of the drug by altering the concentration of polymer.

Determination of the loading efficiency and entrapment efficiency

The Loading efficiency (%) and entrapment efficiency of the microsponges can be calculated on the basis of following equations:-

$$Loading\,efficiency = \frac{actual\,drug\,amount\,in\,microsponge}{initial\,drug\,amount} \times 100$$

$$entrapment\,efficiency = \frac{Amount\,of\ drug\,entrapped\,in\,the\,microsponge}{Total\,amount\,of\ drug\,used} \times 100$$

Release Study

Microsponge release can be regulated by diffusion or other triggering mechanism such as (friction, temperature, pH , moisture). This release approach has been used to improve product aesthetics.

Compatibility studies

Drug compatibility studies by thin layer chromatography(TLC), Fourier transform infra- red spectroscopy(FT-IR), Differential scanning colorimetry (DSC) and effect of polymerization on crystallinity.

Resiliency

Resiliency of microsponges may be altered to produce of bullets a particles which are firmer or softer as required by the final formulation viscoelastic properties of the microsponges can be modified increase in cross linkage tend to lower the rate of release.

Stability studies

The composition of the gel is susceptible to ICH stability studies. Gel fills in safe ,vanished, collapsible aluminium tubes as well as various replicates maintained in the humidity compartment at 40 ±2℃ and 75 ±5 relative humidity . Gel measured at 30.60 and 90 days through change in behavior, pH and in vivo release profile.

Determination of true density

The true density can be measured in the presence of helium gas using ultra-pycnometer and is calculated on the basis of a means of repeated determination.

APPLICATIONS OF MICROSPONGES SYSTEM

Microsponges : as oral delivery system

MSPs has shown to improve the solubilization of drugs that are poorly soluble by capturing these drug in their pores[43]. To give an example, on acrylic polymer, eudragit RS, guided oral delivery of ibuprofen microsponges is accomplished by changing their intraparticle density[44]. controlled oral delivery of ketoprofen produced by quasi-emulsion method eudragit RS 100 was used subsequently microsponges tablets is prepared using the direct compression method.

Results showed that compressibility in drug and polymer mixture was significantly improved because of sponge plastic deformation such as structure of the microsponge[45].

Topical drug delivery using microsponge technology

MDS of Retinoic acid, retinol containing water soluble mds was developed because various cosmetic formulations having limitations like high instability.[46] Controlled release if BPO is delivered from the microsponge to the skin. BPO is widely used in topical formulations to treat acne foot athletesn may reduce the side effects[47]

.

Microsponge used for bone and tissue engineering

By combining polymethylmethacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and hydroxyapatite powder with calcium deficiency bone like compound were obtained. The final compound appeared and formed as microsponge [48].

Drugs explored in the delivery system of the microsponge

Drug	Therapeutic category
Mupirocin	Anti-bacterial
ketoprofen	NSAIDS
Retinol	Vitamin A
Acyclovir sodium	Antiviral
Erthromycin	Antibiotic
Curcumin	Anti-inflammatory
Ibuprofen	NSAID
Paracetamol	NSAID
Tioconazole	Antifungal
Fluconazole	Antifungal

Polymers used for microsponges

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

RECENT ADVANCES IN MICROSPONGES DRUD DELIVERY SYSTEM

In addition to polymeric micro or nanosponges, β-CD nanosponges, have also been developed that can be used for both hydrophobic and hydrophilic drugs. These advanced systems have been studied for dexametasone, fluriprofen, itraconazole, doxorubicin hydrochloride and serum oral administration.through the reaction of the β-CD with diphenyl carbonate, these nanosponges were formed by cross-linking the β-CD molecule[35].

The nanosponges were also observed by some researcher as a strong carrier for gas delivery. Researcher also noted that incorporating a cytotoxic in a nanosponges carrier device may increase the drug's potency, indicating that these carriers may theoretically be used to target cancer cell[54].

Nanoferrosponge, a novel approach consisted of self-performing carrier with improved penetration of target site due to an external magnetic trigger that allows carriers to penetrate deeper tissue and then cause the particle to be removed from the magnetic material leaving a porous system[55].

The method has been designed to produce the porous micro beads because of the improved characteristics of porous microspheres.High internal phase emulsion (HIPE) method comprising of a monomer comprising continuous oil phase,cross linking agent and inner aqueous phase[56]. They also observed an improved RNA stability and the SiRNA encapsulation process that is relatively effective[57].

LIST OF MARKETED PRODUCTS USING MICROSPONGES DRUG DELIVERY SYSTEM[58 -61]

Product Name	Pharmaceutical Uses	Manufacturer
Ultra Guard	protects baby's skin	Scott paper company
Retinol cream	Maintain healthy skin	Biomedic
Carac cream	Anti-Wrinkles	Avon
Lactrex™12%	Moisturizing cream	SDR pharmaceuticals, Inc
Salicylic peel 20	Excellent exfoliation	Biophora
EpiQuin Micro	Hyper pigmentation	skinMedica, Inc
Salicylic peel 20 and 30	pigmentation	Biophora
Retinol 15 nightcream	Enhance skin smoothness	Sothys

MARKETED DOSAGE FORM AVAILABLE[62]

Delivery systems	Drugs
Gels	Acyclovir, Fluconazole,Mupirocin
Lotions	Benzoyl peroxide
Creams	Retinol, Hydroquinone
Tablets	Paracetamol,Dicyclomine,Indomethacin,meloxicam

FUTURE PROSPECTS

Microsponge is the latest innovative technology mainly built for the topical delivery system and oral administration system. Microsponge drug delivery system offers promising opportunities in the near future in various pharmaceutical applications as it has unique properties such as enhanced product performance and elegance, extended release, improved drug release profile, reduced irritation, improved physical, chemical, and thermal stability, making it flexible to develop new product forms . A use in cosmetics has been found in future microsponge carrier systems. The versatility in the formulation makes use of these in different areas and also opens the new path for the drug delivery system.

II. Conclusion

The microsponge delivery system offer various advantages, properties and applications.MDS have many advantages over other products by non-toxic, non-irritant,non-mutagenic. Microsponges delivery system may lead to a better understanding of multiple disease healing. Currently, MDS is being used in cosmetic industry, sunscreens, over-the-counter skin care, and prescription products. MDS is versatile has lot of potential they are used in colon specific delivery and in tissue engineering.

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