Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2014; 6(4): 385-390

ISSN- 0975 1556

Research Article

Microsponge: A Drug Delivery System

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Available Online: 1st Oct, 2014

ABSTRACT
Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. The Microsponge Delivery System (MDS) is a unique technology for the controlled release of topical agents and consist of macro porous beads, typically 10-25 microns in a diameter, loaded with active agent. When applied to the skin, the Microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, pH, etc.). MDS technology is being used currently in cosmetics, over the counter (OTC) skin care, sunscreens and prescription products. Conventional preparations have some disadvantages like unpleasant odour, greasiness and skin irritation. These problems are overcome by microsponge delivery system. Microsponge based drug delivery system produces controlled released action. It also produces site specific and target organ action produced. Microsponge (MDS) mainly developed in topical drug delivery as well as oral controlled delivery system. It also used in cosmetic formulations.

Key words- Microsponges, drug delivery, preparation, characterization, topical, oral.

INTRODUCTION

A Microsponge drug delivery system (MDDS) is a patented, highly cross-linked, porous, polymeric microspheres polymeric system (10-25 µ) consisting of porous microspheres particles consisting of a myriad of inter connecting voids within non-collapsible structures with a large porous surface that can entrap wide range of actives (cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products) and then release them onto the skin over a time and in response to trigger. A typical 25µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10ft in length providing a total pore volume of about 1ml/g. Microsponge do not pass through the skin.[1, 6]

Characteristics of Microsponge [4]

- Microsponges formulations are stable over range of pH 1-11;
- Microsponge formulations are stable at temperature up to 130°C;
- Microsponge formulations are self-sterilizing as their average pore size o.25 µm where bacteria cannot penetrate;
- Microsponge formulation have higher payload (50-60%), still free flowing and can be cost effective.

Characteristics of Materials that is Entrapped in Microsponges[1]

Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microsponges must meet following requirements,

- It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers.
- 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

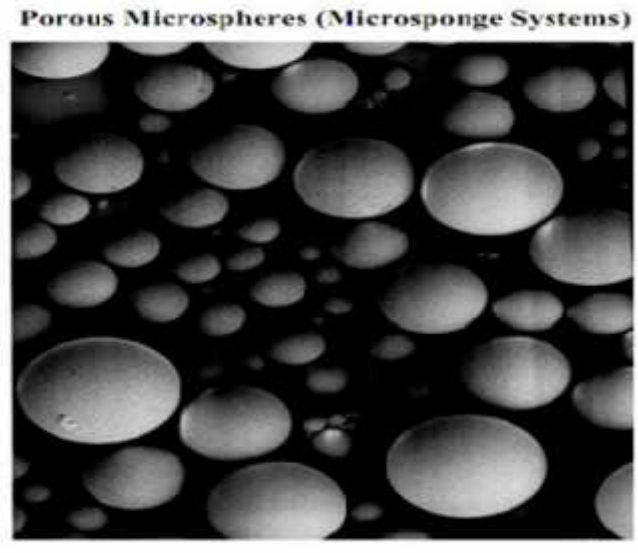

Fig. 1: Porous Microsponge

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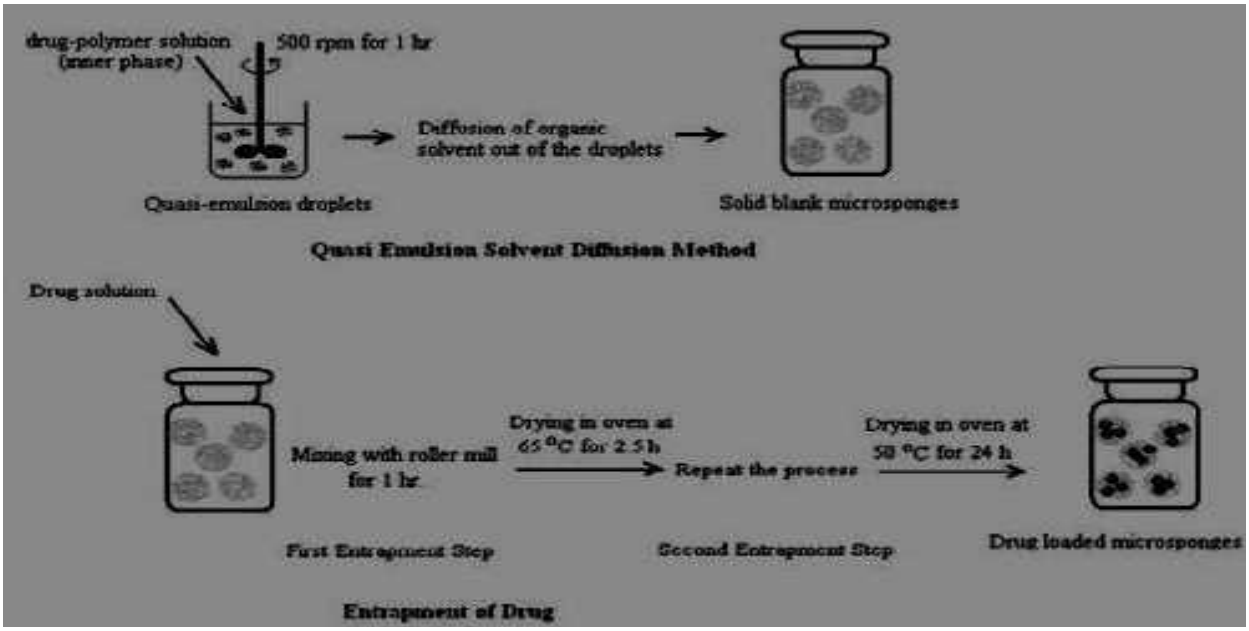

Fig 2: Quasi-Emulsion Solvent diffusion

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 active must be optimized for required release rate for given time period.
- It should be stable in contact with polymerization catalyst and conditions of polymerization.

Advantages of MDS

- Micro sponges can absorb oil up to 6 times its weight without drying.
- It provides continuous action up to 12 hours i.e. extended release.
- Improved product elegancy.
- Lessen the irritation and better tolerance leads to improved patient compliance.
- They have better thermal, physical and chemical stability
- These are non-irritating, non-mutagenic, nonallergenic and non-toxic.
- MDS allows the incorporation of immiscible products.
- They have superior formulation flexibility

Preparation Of Microsponges: Micro sponges drug delivery system can be prepared in two ways, one-step process or by two-step process that is liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques based that is based on physicochemical properties of drug to be loaded

Quasi-Emulsion Solvent Diffusion: To prepare the inner organic phase, Eudragit RS 100 is dissolved in ethyl alcohol. The drug is added to solution and dissolved under ultrasonication at 35º C the inner phase is poured into the polyvinyl alcohol solution in water. Following stirring for 60 min, then mixture is filtered to separate the microsponge. The Microsponges are dried in an air-heated oven at 40º C for 12 hr. ingredients can be entrapped in microsponge polymers at the time of synthesis. They can be post-loaded after the microsphere structure has been pre-formed. The letter process is the preferred mode since many pharmaceuticals and cosmetic ingredients would decompose at the temperatures used for polymerization.

Liquid-liquid Suspension Polymerization[5]: The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In this method the monomers which are immiscible are first dissolved along with active ingredients in a suitable solvent monomer and are then dispersed in the aqueous phase, which consist of additives like surfactant, suspending agents to facilitate formation of suspension. The polymerization is then activated by increasing temperature or irradiation or by addition of catalyst. The polymerization process continues the formation of a reservoir type of system with spherical structure. After the polymerization process the solvent is removed leaving the spherical structured porous microspheres, i.e., microsponges.

Hypothetical Mechanism of Microsponge[1]: The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (i.e., they do not have a continuous membrane surrounding them), the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the microsponge particle into the vehicle, and from it to the skin, until the vehicle is either dried or absorbed. Even after that the microsponge particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with microsponge entrapments.

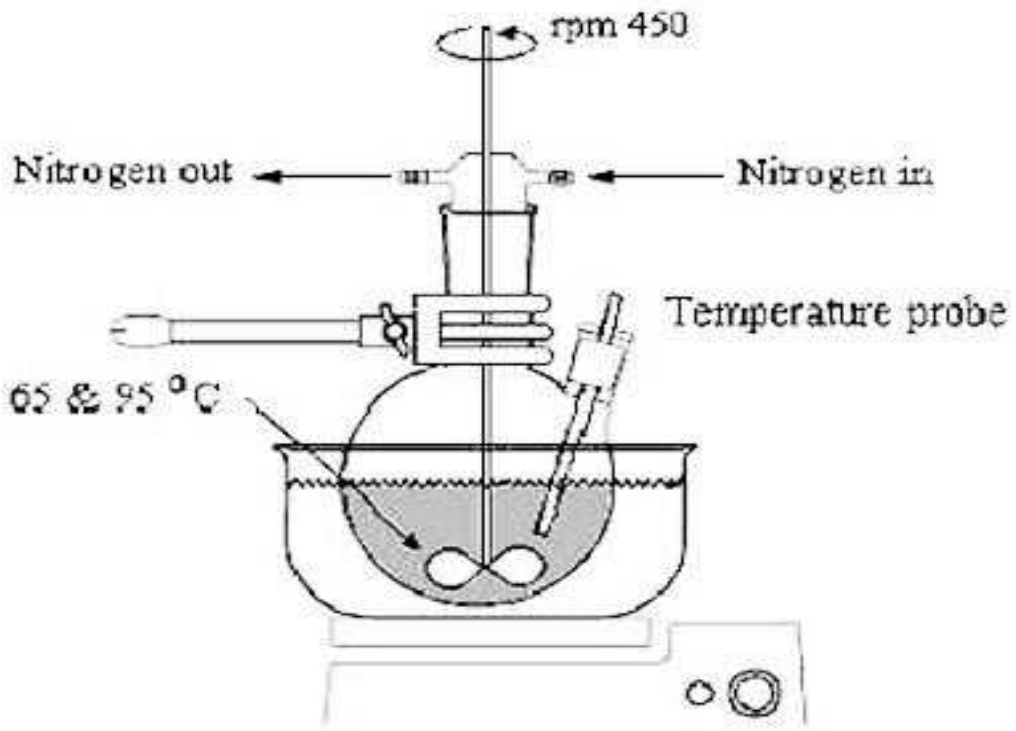

Fig. 3. Liquid-liquid Suspension Polymerization

Table 1: Market Formulation Using A MDS [1]

Sr.no	Product	Advantage	Manufacturer
[1]	Retinol cream	The retinol molecule is kept in the microspongesystem to protect the potency of the vitamin A. This helps to maximize retinol dosage while reducing the possibility of irritation. Retinol is a topical vitamin A deriva-tive which helps maintain healthy skin, hair and mucous membranes	Biomedic
[2]	Salicylic Peel 20	Deep BHA peeling agent for (professional use only): Salicylic acid 20%, Microsponge Technology, Excellent exfoliation and stimulation of the skin for more resistant skin types or for faster results. Will dramatically improve fine lines, pigmentation, and acne concerns.	Biophora
[3]	Dermalogica Oil Control Lotion	Exclusive skin response complex soothes and purifies, provides effective skin hydration, without adding excess oil; eliminate shine for hours with Dermalogica Oil Control Lotion. Oil Control Lotion is a feather-light lo-tion, formulated with oil absorbing Microsponge technology and hydrat-ing botanicals.	John and Ginger Dermalogica Skin Care Products

Programmed Drug Release [1]

Pressure triggered systems: Microsponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon various characteristics of the sponge. By varying the type of material and different process variables, the microsponge best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect. The duration of emolliency was also much more for the microsponge systems.

Temperature triggered systems: Some entrapped active ingredients can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an increased flow rate and hence release. So it is possible to modulate the release of substances from the microsponge by modulation of temperature. For example, viscous sunscreens were found to show a higher release from microsponges when exposed to higher temperatures; thus a sunscreen would be released from a microsponge only upon exposure to the heat from the sun.

pH triggered systems: Triggering the pH-based release of the active can be achieved by modifying the coating on the microsponge. This has many applications in drug delivery.

Solubility triggered system: Microsponges loaded with water-soluble ingredients like anti-prespirants and antiseptics will release the ingredient in the presence of water. Presence of an aqueous medium such as perspiration can trigger the release rate of active ingredients. Thus release may be achieved based on the ability of the external medium to dissolve the active, the concentration gradient or the ability to swell the microspore network.

Characterization of microsponges [7, 11]

Measurement of particle size: Various formulation and process variables can greatly affect the particle size of

microsponge formulations. Measurement of particle size of loaded and unloaded microsponges can be performed using laser light diffractometry or any other suitable method. Results can be expressed in terms of mean size range. Cumulative (%) drug release from microsponges of different particle sizes should be plotted against time to study the effect of particle size on drug release. Particles larger than 30 µm can impart grittiness and hence particles of sizes between 10 and 25 µm are preferred to be used in topical formulations.

Morphology and Surface topography: The surface structure of microsponges can be examined using scanning electron microscopy (SEM) technique. The prepared microsponges are coated with gold palladium under an argon atmosphere at room temperature, and then SEM images are recorded at the required magnification. SEM images may also be recorded for a fractured microsponge to study its ultrastructure.

Production yield and entrapment efficiency

Percentage yield can be calculated using the equation

Production Yield (PY)= Practical mass of microsponge / Therotical mass (Polymer+drug)×100

The entrapment efficiency of the microsponges can be computed using the equation:

Loading Efficiency = (Actual drug content in micorsponge / Therotical drug content)×100

Determination of true density: True density can be measured by an ultra-pycnometer using helium gas, and calculated as a mean of repeated determinations.

Pore structure: Porosity parameters of microsponges are essential in monitoring the intensity and the duration of active ingredient effect. Average pore diameters, shape and morphology of he pores can be determined by using mercury intrusion porosimetry technique. The effect of pore diameter and volume on the rate of drug release from microsponges can also be studied using the same technique . Pore volume and diameter are vital in controlling the intensity and duration of 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. Porosity parameters of microsponges such as intrusion– extrusion isotherms, pore size distribution, total pore surface area, average pore diameters, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry. Incremental intrusion volumes can be plotted against pore diameters that represented pore size distributions. The pore diameter of microsponges can be calculated by using Washburn equation

$D= -4\gamma\cos\theta/P$

Where D is the pore diameter (m); the surface tension of mercury (485 dyn cm−1); the contact angle (130o); and P is the

$$A_{tot} = \frac{1}{\gamma \cos \theta} \int_0^{V_{tot}} P.dV$$

pressure (psia). Total pore area (Atot) was calculated by using equation, Where P is the pressure (psia); V the intrusion volume (mLg−1); Vtot is the total specific intrusion volume (mL g−1). The average pore diameter (Dm) was calculated by using equation,

$D_m= 4V_{tot}/A_{tot}$

Envelope (bulk) density of the microsponges was calculated by using equation,

$\rho= W_s/V_p-V_{Hg}$

Where W_s is the weight of the microsponge sample (g); V_p the empty penetrometer (mL); V_{Hg} is the volume of mercury (mL).

Viscoelastic properties: Microsponges with varying viscoelastic properties can be produced according to the needs of the final formulation.The degree of cross-linking affects the drug release from the prepared microsponges, where increased crosslinking tends to decrease the release rate. Hence, viscosity measurements should be done so that the viscoelastic properties of microsponges can be modified and adjusted to obtain the desired release properties

Physicochemical characterization [8]

Thermoanalytical methods*:* Thermal analysis using differential scanning calorimetry (DSC) is carried out for the pure drug, polymer and the drug-polymer physical mixture to confirm compatibility. DSC is also performed for the microsponge formulations to ensure that the formulation process does not change the nature of the drug. Samples (approximately 2 mg) are placed in aluminum pans, sealed and operated at a heating rate of 20°C/min over a temperature range 40 to 430°C. The thermograms obtained by DSC for the physical mixtures, as well as microsponges, should be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. The peak corresponding to the melting of the drug should be preserved in all thermograms.

Fourier transform infrared spectroscopy (FTIR): Fourier transform infrared spectroscopy (FTIR) is carriedout for the pure drug, polymer and the drug-polymer physical mixture and microsponge formulations. The samples are incorporated in potassium bromide discs and evaluated using FTIR spectrometer. The peaks corresponding to the characteristics bands of the drug should be preserved in the spectra of the microsponges to indicate that no chemical interaction or changes took place during the preparation of the formulations.

Powder X-ray diffraction (XRD): Powder X-ray diffraction (XRD) can be performed for both pure drug, polymer and microsponge formulation to investigate the effect of polymerization on crystallinity of the drug. The disappearance of the characteristic peaks of the drug in the formulation could indicate that the drug is dispersed at a molecular level in the polymer matrix.

In vitro release studies, release kinetics and mechanism*:* *In vitro* release studies can be performed using United States Pharmacopeial (USP) dissolution apparatus equipped with a modified basket consisted of 5 µm stainless steel mesh at 37°C. The release medium is selected according to the type of formulation that is,

topical or oral, while considering solubility of active ingredients to ensure sink conditions. Sample aliquots are withdrawn from the medium and analyzed by suitable analytical method at regular intervals of time. The drug release from topical preparations (for example, creams, lotions and emul gels containing microsponges can be carried out using Franz diffusion cells. Dialysis membrane is fitted into place between the two chambers of the cell. A predetermined amount of formulation is mounted on the donor side of Franz cell. The receptor medium is continuously stirred at and thermostated with a circulating jacket. Samples are withdrawn at different time intervals and analyzed using suitable method of assay. To determine the drug release kinetics and investigate its mechanism from microsponges, the release data are fitted to different kinetic models. The kinetic models used are; first order, zero order, Higuchi and Korsmeyer-Peppas models. The goodness off it was evaluated using the determination coefficient (R2) values.

Applications: Application Solubility enhancement Site specific action produced on the target organ Increase stability of drug Targeted drug delivery,Colon targated drug delivery,Controlled release drug delivery, Topical drug delivery, Oral drug delivery, Bone tissue engineering, Cardiovascular engineering, Reconstruction of vascular wall.

Sunscreens: Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.

Anti-acne: E.g. Benzoyl peroxide Maintained efficacy with decreased skin irritation and sensitization.

Anti-inflammatory: E.g. hydrocortisone Long lasting activity with reduction of skin allergic response and dermatoses.

Anti-fungals: Sustained release of actives Ingredient.

Anti-dandruffs: E.g. zinc pyrithione, selenium sulfide. Reduced unpleasant odour with lowered irritation with extended safety and efficacy

Antipruritics: Extended and improved activity.

Skin depigmenting: E.g.hydroquinone. Improved stabilization against oxidation with improved efficacy and aesthetic agents appeal.

Rubefacients: Prolonged activity with reduced irritancy greasiness and odour.

Microsponge for topical delivery [5, 11, 12, 13]: The Microsponge systems are based on microscopic, polymer-based microspheres that can bind, suspend or entrap a wide variety of substances and then be incorporated into a formulated product, such as a gel, cream, liquid or powder. A single Microsponge is as tiny as a particle of talcum powder, measuring less than one-thousandth of an inch in diameter. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure that can accept a wide variety of substances. The outer surface is typically porous, allowing the controlled flow of substances into and out of the sphere. Several primary characteristics, or parameters, of the Microsponge system can be defined during the production phase to obtain spheres that are tailored to specific product applications and vehicle compatibility. Microsponge systems are made of biologically inert polymers. Extensive safety studies have demonstrated that the polymers are non-irritating, nonmutagenic, non-allergenic, non-toxic and non-biodegradable. As a result, the human body cannot convert them into other substances or break them down. Although they aremicroscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products. Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne, with skin irritation as a common side effect. It has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, microsponge delivery of Benzoyl peroxide was developed using an emulsion solvent diffusion method by adding an organic internal phase containing benzoyl peroxide, ethyl cellulose and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol and by suspension polymerization of styrene and divinyl benzene .The prepared microsponges were dispersed in gel base and microsponge gels are evaluated for anti-bacterial and skin irritancy. The entrapped system released the drug at slower rate than the system containing free BPO. Topical delivery system with reduced irritancy was successfully developed.

Microsponge for oral delivery [5, 8, 9]: In oral applications, the microsponge system has been shown to increase the rate of solubilization of poorly water-soluble drugs by entrapping such drugs in the Microsponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic. particles and the significant increase in the surface area thus greatly increases the rate of solubilization. Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, Eudragit RS, by changing their intraparticle density. Sustained release formulation of chlorpheniramine maleate, using powder-coated microsponges, is prepared by the dry impact blending method, for oral drug delivery. Controlled oral delivery of Ketoprofen prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterwards tablets of microsponges were prepared by the direct compression method. Results indicated that compressibility was much improved in the physical mixture of the drug and polymer; due to the plastic deformation of the sponge-like microsponge structure, producing mechanically strong tablets. Colon-specific, controlled delivery of flurbiprofen was conducted by using a commercial Microsponge 5640 system. *In vitro* studies exhibited that compression-coated colon-specific tablet formulations started to release the drug at the eighth hour, corresponding to the proximal colon arrival time, due to addition of the enzyme, following a modified release pattern, while the drug release from the colon-specific formulations prepared by pore plugging the microsponges showed an increase at the eighth hour, which was the point of time when the enzyme addition was made.

Microsponge for Bone and Tissue Engineering[3, 5, 10]: Bone-substitute compounds were obtained by mixing pre polymerized powders of polymethylmethacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyl apatite powders. The final composites appeared to be porous and acted as microsponges. Basic fibroblast growth factor (bFGF) incorporated in a collagen sponge sheet was sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix, and exhibited local angiogenic activity in a dose-dependent manner. The injection of collagen Microsponges incorporating bFGF induced a significant increase in the blood flow, in the murine ischemic hind limb, which could never have been attained by the bolus injection of bFGF. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of bFGF.

CONCLUSION

The microsponge delivery system is the best technology for controlled release of macroporous bead loaded with active ingredient and having minimum side effects. This drug delivery system has best therapeutic effect. This system has entrapment of active ingredient which tends have minimum side effect, improved stability , increased elegance ,high formulation flexibility. This system is non-irritating, non mutagenic, non-allergic, non-toxic. This technology is currently used in cosmetics, OTC products. As it is useful in many diseases, it is a valuable drug delivery system.

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