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Research Article

MICROSPONGE: A NOVEL DRUG DELIVERY SYSTEM

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Abstract

Conventional topical formulations are intended to work on the surface of the skin. Normally, upon application such formulations release their active ingredients and producing a highly concentrated layer of active ingredient that is quickly absorbed. Microsponge delivery System was originally developed for topical delivery of drugs can also be used for controlled oral delivery of drugs using water soluble and bioerodible polymers. It holds a promising future in various pharmaceutical applications in the coming years like enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical, and chemical stability of product. Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle. The outer surface is typically porous, allowing a sustained flow of substances out of the sphere. Microsponges are porous, polymeric microspheres that are used mostly for topical use and have recently been used for oral administration. Microsponges are designed to deliver pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release.

Key words: *Microsponge, bioerodible,topical formulation ,drug delivery ,controlled.*

INTRODUCTION:

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.

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Microsponges are prepared by several methods utilizing emulsion system or by suspension polymerization in a liquid–liquid system. The most common emulsion system used is oil-in-water (o/w), with the microsponges being produced by the emulsion solvent diffusion (ESD)method [1,2]. It was shown that the drug: polymer ratio, stirring rate, volume of dispersed phase influenced the particle size and drug release behaviour of the formed microsponges and that the presence of emulsifier was essential for microsponge formation [3,4] there has been considerable emphasis given to the development of novel microsponge base drug delivery systems, in order to modify and control the release

behavior of the drugs. By incorporation into a carrier system, it is possible to alter the therapeutic index and duration of the activity of drugs. The ever-increasing interest among consumers with regard to skin care and skin treatment products has been fostered by the widespread use of ingredients like α-hydroxy acids and vitamins in topical products, which can induce perceivable and demonstrable benefits – especially in aging or photo-damaged skin. Although quite useful, in many instances, these ingredients may produce irritancy; such irritancy can be perceived as burning, stinging or redness and particularly occurs in individuals with sensitive skin. Recognizing this problem, the formulators have attempted to deal with this problem in one of the two methods. They have reduced the concentration of such ingredients, but in the process, sacrificed efficacy. They have also modified the vehicle in order to make the product more emollient or skin-compatible.[5] However, this approach, in many cases, also reduces the beneficial effects of the final product. The expanding arena of emerging drugs, increased sensitivity to clinical outcomes, and healthcare costs are driving the need for alternative drug delivery methods and devices. Drug delivery systems that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system. Several predictable and reliable systems been developed for systemic drugs under the heading of transdermal delivery systems (TDS) using the skin as a portal of entry.[6] It has improved the efficacy and safety of many drugs that may be better administered through skin.

Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts, is an area of research that has only recently been addressed with success. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum-corneum and underlying skin layers and not beyond the epidermis 2. Moreover, the application of topical drugs suffers many problems, such as, ointments, which are often aesthetically unappealing, greasiness, stickiness, and so on, that often results into lack of patient compliance. These kinds of formulations require high concentrations of active ingredients for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users.[7]

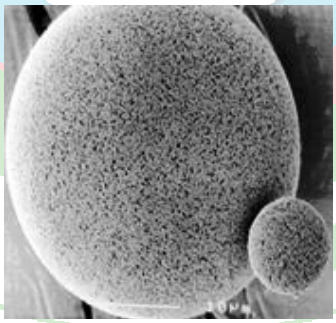

Figure 1.porous nature of microsponges

Potential Advantages of the Microsponge Drug Delivery System

Oil control: it can absorb oil up to 6 times its weight without drying. Extended release up to 12 hours Reduced irritation and better tolerance hence improved patient compliance Improvement of product aesthetics. Microcapsules cannot usually control the release rate of the active pharmaceutical ingredients (API). Once the wall is ruptured the API contained within the microcapsules will be released. Can the Microsponge drug delivery system can do it.

- Micerosponge drug delivery systems have stability over a pH range of 1 – 11.
- Stable up to temperature 130°C.
- Pay load is up to 50 – 60%.
- Free flowing and cost effective.

Properties of the Actives for the Entrapment into Microsponges

Active ingredients that are entrapped in microsponges can then be incorporated into many products such as creams, gels, powders, lotions and soaps. Certain considerations are taken into account while, formulating the vehicle in order to achieve desired product(8) characteristics:

- It should be either fully miscible in a monomer or capable of being made miscible by the addition of a small amount of a water-immiscible solvent.
- It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- It should be stable when in contact with the polymerization catalyst and under conditions of polymerization .
- The spherical structure of the microsponges should not collapse.
- Not more than 10 to 12% w/w microsponges must be incorporated into the vehicle in order to avoid cosmetic problems.
- Payload and polymer design of the microsponges for the active must be optimized for required release rate for given period of time (8)

Methods of Preparation of Microsponges

Liquid-liquid suspension polymerization

Microsponges are prepared by suspension polymerization process in liquid-liquid systems (one-step process). Firstly, the monomers are dissolved along with active ingredients (non-polar drug) in an appropriate solvent solution of monomer, which are then dispersed in the aqueous phase with agitation. Aqueous phase typically consist of additives such as surfactants and dispersants (suspending agents) etc in order to facilitate the formation of suspension. Once the suspension is established with distinct droplets of the preferred size then, polymerization is initiated by the addition of catalyst or by increasing temperature as well as irradiation. The polymerization method leads to the development of a reservoir type of system that opens at the surface through pores. During the polymerization, an inert liquid immiscible with water however completely miscible with monomer is used to form the pore network in some cases. Once the polymerization process is complete, the liquid is removed leaving the microsponges which is permeate within preformed microsponges then, incorporates the variety of active substances like anti fungal, rubefacients, anti acne, anti inflammatory etc and act as a topical carriers. In some cases, solvent can be used for efficient and faster inclusion of the functional substances9. If the drug is susceptible to the condition of polymerization then, two-step process is used and the polymerization is performed by means of alternate porogen and it is replaced by the functional substance under mild conditions.10

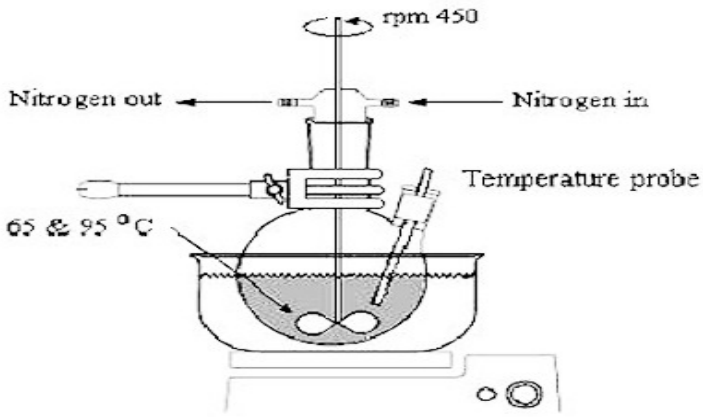

Figure 2: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerisation

The various steps involved in the preparation of microsponges are summarized as follows:

Step 1: Selection of monomer as well as combination of monomers.

Step 2: Formation of chain monomers as polymerization starts.

Step 3: Formations of ladders as a result of cross-linking between chain monomers.

Step 4: Folding of monomer ladder to form spherical particles.

Step 5: Agglomeration of microspheres leads to the production of bunches of microspheres.

Step 6: Binding of bunches to produce microsponges.

Quasi- Emulsion Solvent Diffusion:

To prepare the inner organic phase, Eudragit RS 100 is dissolved in ethyl alcohol. Then, the drug is added to solution and dissolved under ultrasonication at 35° C. The inner phase is poured into the polyvinyl alcohol solution in water (outer phase). Following 60 min of stirring, the mixture is filtered to separate the microsponges. The microsponges are dried in an air-heated oven at 40 °C for 12 h.

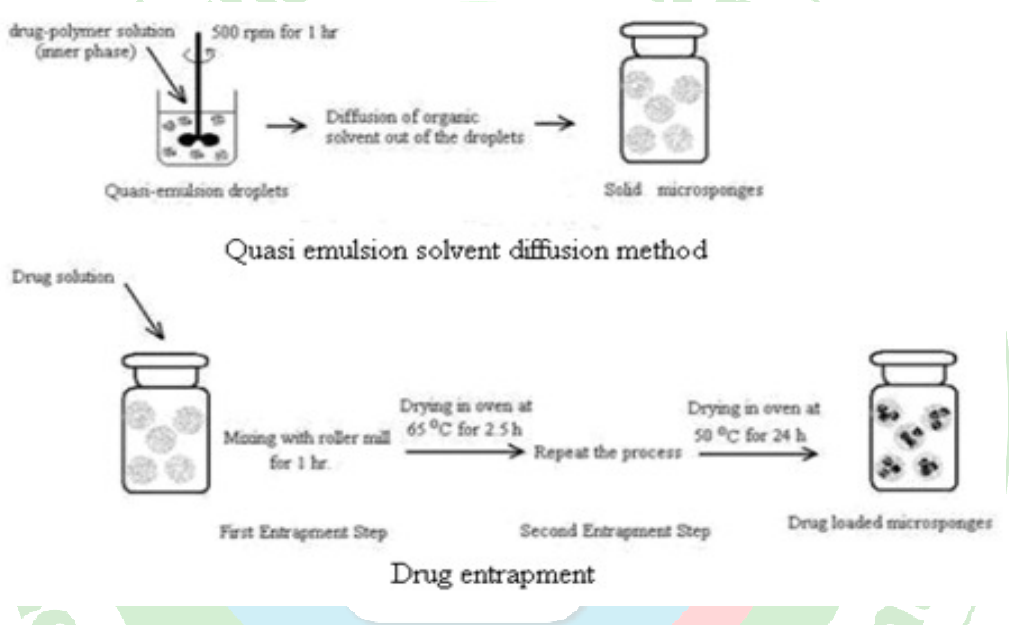

Figure: 3. Scematic representation of Prepration of microsponges by Quasi emulsion solvent diffusion method

Ingredients can be entrapped in microsponge polymers either at the time of synthesis or if too labile to withstand polymerization conditions, they can be post-loaded after the microsphere structure has been pre-formed. In general, the latter process is the preferred mode since many cosmetic ingredients, and most pharmaceutical ones, would decompose at the temperatures employed for polymerization.[11]

Release Mechanism:

Microsponges can be intended to release given amount of active ingredients over time in response to one or morefollowing external triggers i.e. pressure, temperature change and solubility etc which are described as follows:

Temperature change: At room temperature, few entrapped active ingredients can be too viscous to flow suddenly from microsponges onto the skin. With increase in skin temperature, flow rate is also increased and therefore release is also enhanced12

Pressure: Rubbing or pressure applied can release the active ingredient from microsponges onto skin14.

Solubility: Microsponges loaded with water miscible ingredients like antiseptics and anti-perspirants 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 [12]

Evaluation parameters of microsponges:

- Particle size analysis (Microscopy)
- Characterization of pore structure
- Entrapment efficiency and production yield
- Morphology &surface topography of microsponges
- Characterization of pore structure
- Determination of true density
- Polymer/monomer composition
- Compatibility studies Resiliency
- In vitro release study

Particle size analysis:

Particle size determination of loaded as well as blank microsponges can be carried out
by laser light diffractometry or any other appropriate method. Values can be expressed for all the formulations.
in terms of mean size range. It can be studied by plotting cumulative % drug release from microsponges of different particle size against time to study effect of particle size on drug release. Particles having sizes bigger than 30 µm can impart grittiness and thus particles having sizes between 10 and 25 µm are favored to be use in final topical formulation13

Determination of entrapment efficiency and production yield:

The entrapment efficiency (%) of the microsponges can be calculated according to the following equation16:

Entrapment efficiency (%) = [Actual drug content/Theoretical drug content] X 100

The production yield of the microsponges can be obtained by calculating accurately the initial weight of the
raw materials and the last weight of the microsponge obtained.

Production yield= [Practical mass of microsponges/Theoretical mass (polymer + drug)] X 100

Morphology and surface topography of microsponges:

The internal and external morphology and surface topography can be studied by scanning electron microscopy (SEM). Prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then SEM images of microsponges were recorded at the required magnification. SEM of a
fractured microsponge particle can also be taken to illustrate its ultra structure14..

Characterization of pore structure:

Pore volume and pore diameter are critical in controlling the intensity as well as duration of effectiveness of the active ingredient. Pore diameter can also affects the passage of active ingredients from microsponges into the vehicle in which the material is dispersed. The effect of pore diameter as well as volume with rate of drug release from microsponges can be studied by mercury intrusion
porosimetry. Porosity parameters of microsponges such as intrusion–extrusion isotherms, total pore surface area, pore size distribution, average pore diameters, shape and morphology of the pores, bulk and apparent density can also be determined by using mercury intrusion porosimetry14

Determination of true density:

The true density of microsponges was measured by an ultra-pycnometer under helium gas and was calculated from a mean of repeated determinations15.

Polymer/ Monomer composition:

Various factors such as microsphere size, polymer composition and drug loading govern the drug release from microspheres. Polymer composition can also influence the partition coefficient of the entrapped drug between the microsponge system and the vehicle and thus have direct affect on the rate of release of entrapped drug. Drug release from microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time. The choice of monomer is dictated both by the vehicle into which it will be dispersed and characteristics of active ingredient to be

entrapped. Polymers with varying degrees of hydrophobicity or lipophilicity or electrical charges may be prepared to give flexibility in the release of active ingredients. A variety of probable monomer combinations will be screened for their appropriateness with drugs by studying their drug release profile15.

Compatibility studies:

Fourier Transform Infra-red spectroscopy (FT-IR) and thin layer chromatography (TLC) was performed to study the compatibility of drug with reaction adjuncts. Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential scanning colorimetry (DSC). For DSC, approximately 5mg samples can be weighed accurately into aluminum pans, then sealed and can be run at a heating rate of 15°C/min over a temperature range 25–430°C in atmosphere of nitrogen16

Resiliency: Viscoelastic properties (resiliency) of microsponges can be tailored to create beadlets which is softer or firmer according to the requirements of the final formulation. Increased crosslinking tends to slow down the release rate. Therefore, resiliency of microsponges will be performed and optimized as per the prerequisite by considering release as a function of crosslinking with time16.

***In-vitro* release studies:**

In-vitro release studies have been carried out using dissolution apparatus USP XXIII equipped with a modified basket consisted of 5µm stainless steel mesh. Dissolution rates were measured at 37°C under 150 rpm rotor speed. The dissolution medium is selected while considering solubility of active ingredients to ensure sink conditions. Sample aliquots were withdrawn from the dissolution medium and analyzed by suitable analytical method (UV spectrophotometer) at regular intervals of time17

SAFETY CONSIDERATION(18,19)

Safety studies of microsponges can be established by:

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

Applications:

Microsponges are used mostly for topical and recently for oral administration as well as biopharmaceutical delivery. It offers the formulator a range of alternatives to develop drug and cosmetic products. These are developed to deliver an active ingredient efficiently at the low dose and also to enhance stability, reduce side effects and modify drug release 20 (Various applications are shown in **table 1**).

Table: No-1(21)

Sr No.	Actives	Applications
1	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
2	Anti-acne e.g. Benzoyl Peroxide	Maintained efficacy with decreased skin irritation and sensitization.
3	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses
4	Anti-fungals	Sustained release of actives
5	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odour with lowered irritation with extended safety and efficacy.
6	Antipruritics	Extended and improved activity.
7	Skin depigmenting Agents	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
8	Rubefacients	Prolonged activity with reduced irritancy greasiness and odour

The Microsponge for Oral Delivery:

A Microsponge system offers the potential to hold active ingredients in a protected environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract, where it will be released upon exposure to specific enzymes in the colon. This approach if successful should open up entirely new opportunities for MDS. In oral applications, the Microsponge system has been shown to increase the rate of solubilization of poorly watersoluble drugs by entrapping such drugs in the Microsponge system's pores. Because these pores are very small, the drug is in effect reduced to microscopic particles and the significantly increased surface area thus greatly increases the rate of solubilization. An added benefit is that the time it takes the Microsponge system to traverse the small and large intestine is significantly increased thus maximizing the amount of drug that is absorbed [22]

Microsponge for topical delivery

Microspongic Delivery Of Fluconazole For Benzoyl peroxide (BPO) is mainly used in the treatment of mild to moderate acne and athlete's foot and the most common side effect associated with BPO is skin irritation and it has been shown that controlled release of BPO from a delivery system to the skin could lessen the side effect while reducing percutaneous absorption. Topical delivery system with reduced irritancy was successfully developed23.

Nokhodchi *et al*25 studied factors affecting the morphology of benzoyl peroxide (BPO) microsponges. It has been revealed that encapsulation and controlled release of BPO can lessen the side effect while, when administered to the skin it also reduces percutaneous absorption. The goal of the study was to design and formulate a suitable encapsulated form of BPO using microsponge technology and investigate the parameters affecting the morphology and other characteristics of the resulting products with the help of scanning electron microscopy (SEM). Benzoyl peroxide particles were prepared by an emulsion solvent diffusion method by including an organic internal phase containing benzoyl peroxide, dichloromethane and ethyl cellulose into a stirred aqueous phase containing polyvinyl alcohol (PVA). Different concentrations of BPO microsponges were incorporated in lotion formulations and the drug release from these formulations were studied. The SEM micrographs of the BPO microsponges used for the measurement of their size and showed that they were porous and spherical. Results showed that the morphology and particle size of microsponges were affected by drug: polymer ratio, amount of emulsifier used and stirring rate. The results obtained also showed that with increase in the ratio of drug: polymer resulted in a reduction in the rate of release of BPO from the microsponges. The release data showed that the highest and the lowest release rates were obtained from lotions containing plain BPO particles and BPO microsponges with the drug: polymer ratio (13:1) respectively. Kinetics studies showed that the release data followed peppas model but diffusion was the main mechanism of drug release from BPO microsponges.

Amrutiya *et al*26 developed microsponge based topical delivery system of mupirocin by an emulsion solvent diffusion method and evaluated for sustained release and enhanced drug deposition in the skin. The effect of formulation and process variables like stirring speed and internal phase volume on the physical characteristics of microsponges was analyzed on optimized drug/polymer ratio by 32 factorial design. The optimized microsponges were incorporated into an emulgel base. Several parameters were studied i.e. *in-vitro* drug release, *ex-vivo* drug deposition and *in-vivo* antibacterial activity of mupirocin-loaded formulations. Prepared microsponges were spherical and porous and found no interaction between drug and polymer molecules. Emulgels containing microsponges were showed preferred physical properties. Diffusion-controlled release pattern were . showed by drug release through cellulose dialysis membrane and drug deposition studies using rat abdominal skin has been exhibited significant retention of actives in skin from microsponge based formulations by 24 h. Draize patch test demonstrated that the optimized formulations were stable and nonirritant to skin.

Microsponges based emulgel formulations showed extended efficacy in mouse surgical wound modeinfected with S. aureus. Mupirocin was stable in topical emulgel formulations and showed enhanced retention in the skin demonstrating superior potential of the delivery system for the treatment of primary and secondary skin infections i.e. eczema, impetigo and atopic dermatitis.

Microsponge for oral delivery:

A Microsponge system offers the potential for active ingredients to remain within a protected environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract, where it will be released upon exposure to specific enzymes in the colon. If this approach is successful then it should open up entirely new opportunities for MDS. It has been shown that microsponge system enhances the solubilization of drugs which are poorly soluble by entrapping these drugs in their pores. As these pores are very small, the drug is in effect reduced to microscopic particles and drastically increased surface area consequently, increases the rate of solubilization. Additionally, the time it takes the microsponge system to pass through the small and large intestine is considerably increased as a result maximizing the amount of drug that is absorbed.

Jain *et al*27 prepared paracetamol loaded eudragit RS 100 based microsponges by quasi-emulsion solvent diffusion method. The compatibility of the drug with different formulation components was demonstrated. In order to optimize the formulation process parameters were analyzed. Surface morphology and shape of the microsponges were analyzed using scanning electron microscopy (SEM). Compression coating of microsponges with pectin: HPMC mixture followed by tabletting was used to prepare colon specific formulations. The *in-vitro* drug release studies were done on all the formulations and the results were evaluated kinetically and stastically. The study concluded that the release data followed Higuchi matrix but diffusion was the main mechanism of drug release from microsponges. *In-vitro* studies showed that compression coated colon specific tablet formulations started the release of drug at the 6th hour resultant to the arrival time to proximal colon.

Gonul *et al*28; studied the effects of pressure and direct compression on tabletting of microsponges. In the study, ketoprofen was used as a model drug for systemic drug delivery of microsponges. ketoprofen microsponges were prepared by quasi-emulsion solvent diffusion method with eudragit RS 100 and tablets of microsponges were prepared by direct compression method. In order to determine the optimum pressure value for the compression of the tablets, different pressure values were applied to the tablet powder mass. Results of the study indicated that microsponge compressibility was much better over the physical mixture of the drug and polymer and due to the plastic deformation of sponge like structure; microsponges can produce mechanically strong tablets

Microsponge based Delivery System for Bio-Pharmaceuticals:

The MDS is used for the delivery of biopharmaceuticals and in tissue engineering also. Newton D.W. has overviewed tissue targeted biopharmaceuticals delivery through microsponges [29]. Bone-substitute compounds were obtained by mixing pre-polymerized powders of polymethyl-methacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of a-tri calcium phosphate (a-TCP) grains and calcium-deficient hydroxyapatite (CDHA) powders. The final composites appeared to be porous and acted as microsponges 30,31. The fibroblast growth factor (bFGF) incorporated in a collagen sponge sheet was sustained release in the mouse subcutis according to the biodegradation of the sponge matrix, and exhibited local angiogenic activity in a dose dependent manner. Intra muscular 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 collagen reservoir of bFGF 32. A

biodegradable graft material containing the collagen microsponge was developed for cardiovascular tissue grafting, as it would permit the regeneration of the autologous vessel tissue 33. A thin biodegradable hybrid mesh synthetic poly (DL-lactic-co-glycolic acid) (PLGA) and naturally derived collagen was for a three-dimensional culture of human skin fibroblasts. The hybrid mesh was constructed by forming web like collagen microsponges in the openings of a PLGA-knitted mesh 34. A tissue engineered patch made of our biodegradable polymer and collagen Microsponge provided good in situ regeneration at both the venous and arterial wall, suggesting this patch could be used as a novel surgical material for the repair of the cardiovascular system 35.

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