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IJPBS |Volume 3| Issue 1 |JAN-MAR |2013|214-226

Review Article
Pharmaceutical Sciences

MICROSPONGE: COMPREHENSIVE REVIEW OF APPLICATION

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ABSTRACT

Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. When applied to the skin, the Microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc) Microsponge consists of macroporous beads, typically 5 - 300µm microns in diameter, loaded with active agent. That are used mostly for topical and recently for diagnosis of diseases like Heart diseases, HIV, cancer. Now a days used in RNA silencing, Microsponge delivery system (MDS) can provide increased efficacy for topically active agents with enhanced safety, extended product stability, enhanced formulation flexibility, reduced side effects and improved aesthetic properties in an efficient and novel manner. In addition these are non-irritating, non-mutagenic, non-allergenic, and non-toxic. This technique reaching the goal of controlled and site specific drug delivery system. The present review introduces Microsponge technology along with its Advantage over the other Dosage form and release mechanism of MDS.

KEY WORDS

Microsponge, PBNC, RNA silencing.

INTRODUCTION

The Microsponge technology was developed by Won in 1987 [1]. Microsponges are patented delivery systems composed of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within anon-collapsible structure with a large porous surface. The size of the microsponges ranges from 5 - 300µm (**Figure 1**) in diameter and a typical 25µmsphere can have up to 250000 pores(**Figure 2**) and an internal pore structure equivalent to 10ft in length, providing a total pore volume of about 1ml/g. These microsponges have the capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens and anti-infective, etc. are used as a topical carrier system [2]. Further, these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Release of drug into the skin is initiated by a variety of triggers, including rubbing and higher than ambient skin temperature [3]. Their high degree of cross-linking results in particles that are insoluble, inert and of sufficient strength to stand up to the high shear commonly used in manufacturing of creams, lotions, and powders. Their characteristic feature is the capacity to adsorb or "load" a high degree of active materials into the particle and on to its surface. Its large capacity for entrapment of actives, up to three times its weight, differentiates microsponge products from other types of dermatological delivery

systems. The active payload is protected in the formulation by the microsponge particle; it is delivered to skin through controlled diffusion. This sustained release of actives to skin over time is an extremely valuable tool to extend the efficacy and lessen the irritation. Several probable and reliable systems were developed for systemic drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry. It has improved the efficacy and safety of many drugs that may be better administered through skin. But TDS is not practical for delivery of materials whose final target is skin itself [4, 5].

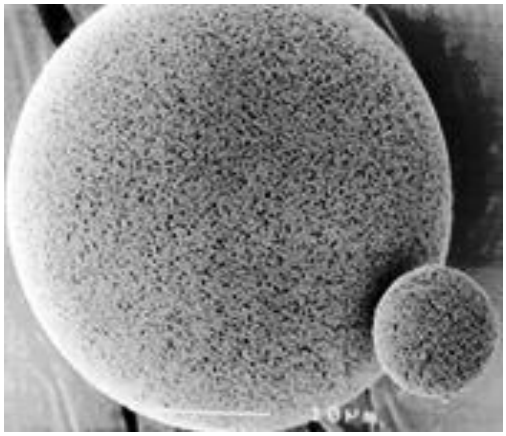

Figure 1: Microspong

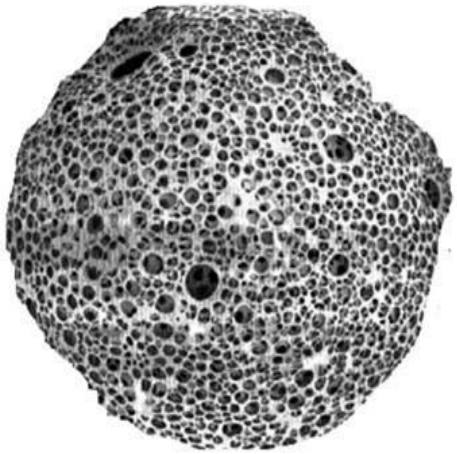

Figure 2: Highly porous nature of Microspong Characteristics Of Materials That is Entrapped in Microsponges.

Microsponges can absorb oil up to 6 times its weight without drying. It provides continuous action up to 12 hours i.e. extended release. Liquids can be converted in to powders improving material processing. It has flexibility to develop novel product forms.MDS can improve bioavailability of the drugs. Microsponge formulations are stable over range of pH1 to 11 and at the temperature up to 130^{o}C. Microsponge formulations are compatible with most vehicles and ingredients and they are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate into them, they can be cost effective [6].

Recent application of Microsponges derived from seaweed may help to diagnose heart disease, cancers, HIV and other diseases quickly and at far lower cost than current clinical

methods. The biomarkers are sequestered in tiny sponges set into an array of inverted pyramid-shaped funnels in the microprocessor heart of the credit card-sized PBNC [7].

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 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 over Conventional Formulations

Conventional formulations of topical drugs are intended to work on outer layers of the skin. Such products release their active ingredients upon application, producing a higher concentrated layer of active ingredient that is rapidly absorbed. When compared to the microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy. For example, by delivering the active ingredient gradually to the skin like MDS. Benzoyl peroxide formulations have excellent efficacy with minimal irritation.

Advantages over Microencapsulation And Liposomes

The MDS has advantages over other technologies like microencapsulation and liposomes. Microencapsules cannot usually control the release rates of actives. Once the wall is ruptured the actives contained within microcapsules will be released. Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability. While microsponge system in contrast to the above systems are stable over range of pH 1 to 11, temperature upto 130°C;compatible with most vehicles and ingredients; self-sterilizing as average pore size is 0.25µm where bacteria cannot penetrate; higher payload (50 to 60%), still free flowing and can be cost effective.

Advantages Over Ointments

Ointments are often aesthetically unappealing, greasiness, stickiness etc. That often results into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting in irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled. Evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles, when microsponge system maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration in to the body [8-11].

Advantages of Microsponge Delivery System:

- Microsponges 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.
- It can also improve efficacy in treatment.
- They have better thermal, physical and chemical stability.
- These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- MDS allows the incorporation of immiscible products.
- They have superior formulation flexibility.
- In contrast to other technologies like microencapsulation and liposomes, MDS has wide range of chemical stability, higher payload and are easy to formulate.
- Liquids can be converted in to powders improving material processing.
- It has flexibility to develop novel product forms.
- MDS can improve bioavailability of the drugs [12].

Release Mechanisms:

By proper manipulation of the aforementioned programmable parameters, microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers.

1. Pressure: Rubbing/ pressure applied can release active ingredient from microsponges onto skin. 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.

2. Temperature change: Some entrapped actives 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.

3. Solubility: Microsponges loaded with water-soluble ingredients like anti-prespirants and antiseptics will release the ingredient in the presence of water. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system.

4. 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 [13].

APPLICATION

Microsponges are used mostly for topical, 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. Microsponge drug delivery system unique, novel and versatile and extremely attractive in cosmetic world. Recent applications of microspong from sea weed were to detect the diseases andalso microspong drugdelivery in RNA silencing. Some applications of MDS are describe in **Table 1** [14].

Applications
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.

Table 1: Application of Microsponge

TOPICAL DRUG DELIVERY USING MICROSPONGE TECHNOLOGY

Conventional formulations of topical drugs are in-tended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. The Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the Microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy. Further these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Microsponges consisting of non-collapsible structures with porous surface through active ingredients are released in a controlled manner. Depending upon the size the total pore length may range up to 10 ft and pore volume up to 1 ml/g [15].

Products under development or in the market place utilize the Topical Microsponge systems in three primary ways:

1. As reservoirs releasing active ingredients over an extended period of time.
2. As receptacles for absorbing undesirable substances, such as excess skin oils.
3. As closed containers holding ingredients away from the skin for superficial action.

Dicyclomine, it's an anticholinergic drug, has direct smooth muscle relaxant action, and it shows antispasmodic action. Dicyclomine causes gastrointestinal (GI) side effects like other antispasmodic drugs. Its plasma half life is 4 - 6 h. The present study was designed to formulate a drug which reduces the (GI) side effects. Dicyclomine loaded, Eudragit based microsponges were prepared using a quasi

emulsion solvent diffusion method. Cumulative release for the microsponges over 8 hours ranged from 59 - 86 %.

Flurbiprofen, Microsponge system containing flurbiprofen was formulated for the colonic delivery of the drug for targeted action.

Benzylperoxide, Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes' foot. Normal ointments produce Skin irritation it's a common side effect. Therefore, the ethylcellulose Microsponge system was formulated containing BPO which were able to control the release of BPO to the skin. And 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.

Fluocinolone acetonide, (FA) is a corticosteroid primarily used in dermatology to reduce skin inflammation and relieve itching. FA entrapped microporous microparticles (microsponges) were formulated to control the release of drug to the skin, which reduces the skin irritation and produce controlled release of active medicament.

Tretinoin photo-damage treatment, icrosponge product used for photo damage, premature aging of skin and skin cancer [16].

Hydroquinone (HQ) Disorders of hyper pigmentation such as melisma and post inflammatory hyper pigmentation (PIH) are common, particularly among people with darker skin types. Bleaching creams are considered the gold standard for treating hyper pigmentation. Recently, a new formulation of HQ 4% with retinol 0.15% entrapped in microsponge reservoirs was developed for the treatment of melasma and PIH. Microsponges were used to release HQ gradually to prolong exposure to treatment and to minimize skin irritation [17].Hydroquinone prevents the overproduction of melanin, while lightening the brown spots on the skin [18, 19].

Aceclofenac is a NSAID having excellent anti-inflammatory and analgesic activity but NSAID produces GIT ulceration, liver and kidney trouble especially in case of oral administration. In view, of adverse drug reaction associated with oral formulations, aceclofenac is increasingly administered by topical route. Aceclofenac loaded microsponge are prepared by using quasi-emulsion solvent diffusion method. It is incorporated in gel base and various parameters are studied [20].

Microsponge Technology in Cosmetics

An interesting application of the microsponge technology could be in oral cosmetics, such as tosustain the release of volatile ingredients, thus increasing the duration of the 'fresh feel'.Microsponges of such volatile ingredients may be easily incorporated in tooth pastes or mouthwashes. Colours entrapped in microsponges may be used in a variety of coloured cosmetic products such asrouge or lipsticks to make them long lasting. As stated above, microsponges help in uniform spreading and improving covering power. Thus, coloured cosmetics formulated with microsponges would be highly elegant [21].

Marketed formulation using the MDS includes Dermatological products which can absorb large amounts of excess of skin oil, while retaining an elegant feel on the skin's surface. Among these productsare skin cleansers, conditioners, oil control lotions, moisturizers, deodorants, razors, lipstick, makeup, powders, and eye shadows; which offers several advantages, including improved physical and chemical stability, greater available concentrations, controlled release of the active ingredients, reduced skin irritation and sensitization, and unique tactile qualities [22].Retinol is a highly pure form ofvitamin A which has demonstrated a remarkable ability for

maintaining the skin's youthful appearance. However, it becomes unstable when mixed with other ingredients. Stabilized retinol in a formulation which is cosmetically elegent and which has a low potential for skin irritation is successfully developed and marketed [23].

Oral Drug Delivery System Using Microsponge Technology

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.

Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, Eudragit RS, by changing their intraparticle density.

The release of ketoprofen incorporated into modified release ketoprofen microsponge 200 mg tablets and Profenid Retard 200 mg was studied in vitro and in vivo. The formulation containing ketoprofen microsponges yielded good modified release tablets. An in vivo study was designed to evaluate the pharmacokinetic parameters and to compare them with the commercially available ketoprofen retard tablets containing the same amount of the active drug. Commercial ketoprofen retard tablets showed a more rapid absorption rate than modified release tablets and peak levels were reached within almost 3.6 h after administration. However, the new modified release tablets showed a slower absorption rate and peak levels were reached 8 h after administration [24].

Paracetamol loaded Eudragit based microsponges were prepared using quasiemulsion solvent diffusion method, then the colon specific tablets were prepared by compressing the microsponges followed by coating with pectin: hydroxyl propyl methyl cellulose (HPMC) mixture [25].

Reconstruction Of Vascular Wall Using Microsponge Technology

The tissue-engineered patch was fabricated by compounding a collagen microsponge with a biodegradable polymeric scaffold composed of polyglycolic acid knitted mesh, reinforced on the outside with woven polylactic acid. Tissue-engineered patches without precellularization were grafted into the porcine descending aorta (n = 5), the porcine pulmonary arterial trunk (n = 8), or the canine right ventricular outflow tract (as the large graft model; n = 4). Histological and biochemical assessments were performed 1, 2, and 6 months after the implantation.There wasno thrombus formation in any animal. Two months after grafting, all the grafts showed good in situ cellularization by hematoxylin/eosin and immune staining [26].The quantification of the cell population by polymerase chain reaction showed a large number of endothelial and smooth muscle cells 2 months after implantation. In the large graft model, the architecture of the patch was similar to that of native tissue 6 months after implantation and this patch can be used as a novel surgical material for the repair of the cardiovascular system [27].

CardiovascularEngineering Using Microsponge Technology

A biodegradable material with autologous cellseeding requires a complicated and invasive procedure that carries the risk of infection. To avoid these problems, a biodegradable graft material containing collagen microsponge that would permit the regeneration of autologous vessel tissue has developed. The ability of this material to accelerate in situ cellularization with autologous endothelial and smooth muscle cells was tested with and without precellularization. Poly (lactic-co-glycolic acid) as a biodegradable scaffold was compounded with collagen microsponge to form a vascular patch material. These poly (lacticco-glycolic acid)-collagen patches with (n =10) or without (n = 10) autologous vessel cellularization were used to patch the canine pulmonary artery trunk. Histologicand biochemical assessments were performed 2 and 6 months after the implantation. There was no thrombus formation in either group, and the poly (lactic-co-glycolic acid) scaffold was almost completely absorbed in both groups. Histologic results showed the formation of an endothelial cell monolayer, a parallel alignment of smooth muscle cells, and reconstructed vessel wall with elastin and collagen fibers. The cellular and extracellular components in the patch hadincreased to levels similar to those innative tissues at 6 months. This patch shows promise as a bioengineered material for promoting in situ cellularization and the regeneration of autologous tissue in cardiovascular surgery [28].

Microsponge Based Delivery System For Bone Substitute

Compounds were obtained by mixing pre-polymerized powders of poly methyl methacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of a-tricalcium phosphate (a-TCP) grains and calcium deficient hydroxyapatite (CDHA) powders. The finalcomposites appeared to be porous. Osteo conductivity and osteo inductivity of the final composites were tested in vivo by implantation in rabbits. Formation of new trabecular bone was observed inside the pores where the inorganic powders had been placed. The material produced shows a good level of biocompatibility, good osteo integration rate and osteogenetic properties [29].

Microsponges for Biopharmaceuticals Delivery

The microsponge delivery system (MDS) is employed for both in the delivery of biopharmaceuticals as well as in tissue engineering. Dai 2010et al. developed 3D scaffolds hybrid structures that have advantages of natural type I collagen and synthetic PLGA knitted mesh. The collagen microsponges facilitated cell seeding and tissue formation and mechanically. Strong PLGA mesh served as a skeleton. The scaffolds were divided into three groups:

a) Thin: collagen microsponge formed in interstices of PLGA mesh;
b) Semi: collagen microsponge formed on one side of PLGA mesh
c) Sandwich: collagen sponge formed on both sides of PLGA mesh.

In the scaffolds Bovine chondrocytes were cultured and transplanted subcutaneously into nude mice for 2, 4, and 8 weeks. All transplants showed natural chondrocyte morphology, homogeneous cell distribution, and abundant cartilaginous ECM deposition. Production of GAGs per DNA and the expression of type II collagen and aggre can mRNA were much higher in the Semi and Sandwich groups than in the Thin group. Young's modulus showed 54.8, 49.3%mechanical strength of the engineered

cartilage and in stiffness 68.8, 62.7%, respectively, in Semi and Sandwich when compared to native articular cartilage. These scaffolds could be used for the tissue engineering of articular cartilage with adjustable thickness. Developed a biodegradable graft material containing collagen microsponge that would allow the regeneration of autologous vessel tissue in order to avoid these problems. Poly (lactic-co-glycolic acid) has been used as a biodegradable scaffold which was compounded with collagen microsponge to form a vascular patch material. The poly (lactic-co-glycolic acid) collagen patches with or without autologous vessel cellularization were used to patch the canine pulmonary artery trunk. Biochemical and histologic assessments were performed 2nd and 6th months after the implantation. Resulting, there was no thrombus formation in either group but the poly (lactic-co-glycolic acid) scaffold was approximately completely absorbed in both groups. Histologic results showed the formation of an endothelial cell monolayer, a parallel alignment of smooth musclecells, and reconstructed vessel wall with elastin and collagen fibers. The cellular and extra-cellular components in the patch had enlarged to levels analogous to those in native tissue at 6 months. This patch also shows promise as a bioengineered material for promoting in-situ cellularization and the regeneration of autologous tissue in cardiovascular surgery [30]. Tateishi et al., has also been studied developed biodegradable porous scaffolds for tissue engineering. 3D biodegradable porous scaffolds play a vital role in tissue engineering. A novel method were used for preparing porous scaffolds which consists of synthetic biodegradable polymers and developed by combining porogen leaching and freeze-drying techniques utilizing pre-prepared ice particulates as the porogen material. Biodegradable hybrid porous sponges of synthetic polymer and collagen have been prepared by hybridizing synthetic polymer sponges with collagen microsponges. The collagen microsponges were produced in the pores of synthetic polymer sponges. Hybrid sponges of synthetic polymer, collagen and inorganic hydroxyapatite were prepared by depositing hydroxyapatite particulates on the surfaces of the collagen microsponges in the synthetic polymer-collagen sponges. The synthetic polymer sponge were used as a mechanical skeleton to aid the formation of these hybrid sponges into desired shapesand contributed good mechanical strength and handling whereas the collagen and hydroxyapatite are used to promote cell interaction and facilitate cell seeding[31].

Microspong From Seaweed Use In Diagnose The Diseases.

Microsponges derived from seaweed may help diagnose heart disease, cancers, HIV and other diseases quickly and at far lower cost than current clinical methods. The microsponges are an essential component of Rice University's Programmable Bio-Nano-Chip (PBNC) (**Figure 3**) and the focus of a new paper in the journal Small PBNCs capture biomarkers molecules that offer information about a person's health found in blood, saliva and other bodyfluids. The biomarkers are sequestered in tiny sponges set into an array of inverted pyramid-shaped funnels in the microprocessor heart of the credit card-sized PBNC. When a fluid sample is put into the disposable device, micro fluidic channels direct it to the sponges, which are infused with antibodies that detect and capture specific biomarkers. Once captured, they can be analyzed within minutes with a sophisticated microscope and computer built into a portable, toaster-sized reader.

The biomarker capture process is the subject of the Small paper. The microsponges are 280-micrometer beads of agarose, a cheap, common, lab-friendly material derived from seaweed and often used as a matrix for growing live cells or capturing proteins. The beauty of agarose is its ability to capture a wide range of targets from relatively huge protein biomarkers to tiny drug metabolites. In the lab, agarose starts as a powder, like Jell-O. When mixed with hot water, it can be formed into gels or solids of any size. The size of the pores and channels in agarose can be tuned down to the nano scale. The team found that agarose beads with a diameter of about 280 micrometers are ideal for real-world applications and can be mass-produced in a cost-effective way. These agarose beads retain their efficiency at capturing biomarkers, are easy to handle and don't require specialized optics to see. The agarose beads serve the dual role of analyte capture and signal generation and reagent capture is observed both on the bead exterior and interior [32]. Employing 3D "nanonets" composed of agarose strands supported within beads and a fluorescent signal output from nanoparticles (nano), the PBNC immobilizes and quantitates medically relevant species (bio) from complex samples within an enclosed miniature flow chamber (chip). This chemical processing unit uses an etched silicon or stainless-steel chip populated with sensitized beads to quantify proteins, oligonucleotides, small molecules, and ions [33, 34, 35, 36].

Figure 3: ProgramableBio-nano Cheap.

Various gold-standard systems, such as enzyme-linked immune sorbent assay (ELISA), the PBNC has assay times measured in minutes rather than hours, limits of detection two or more orders of magnitude lower, and a multiplex capacity of 6 or more concurrent analytes with internal controls. Like ELISA, the PBNC utilizes a sandwich immunoassay; however, the immune complexes are present throughout the 3D bead matrix, rather than deposited on a 2D flat surface. These initial observations provide some information about the nature of molecular transport within the beads. However, they also catalyze the emergence of additional questions related to the exact mode of transport and the influence the agarose density/pore size has on the time course of reagent capture [37].

Self-Assembling RNAi Microsponges

Nature Materials describe Microsponges that act as both carrier and cargo for the delivery of gene-silencing RNA (siRNA) into cells. The work reports that, compared with conventional siRNA delivery vehicles, one thousand times lower

concentration of the microsponges achieve the same degree of gene-silencing effect in tumour-carrying mice. siRNA delivery has so far been hampered by carriers that inefficiently encapsulate RNA, and by its degradation prior to cellular uptake. Using RNA-amplification techniques, Paula Hammond and colleagues made very long chains of connected hairpin RNA strands from circular DNA templates. They observed that the chains self-assembled into sponge-like microspheres of pleated crystalline sheets. Because hairpin RNA is cleaved to form siRNA only inside the cell, the hairpin-RNA microsponges function both as a stable cargo and a carrier. To enhance cellular uptake, the authors made the microsponges ten times smaller by coating them with a highly charged polymer. They show that each polymer-coated microsponge delivers over half a million copies of siRNAper cell [38].

Once we generated the microsponges, we did several tests to ensure that we had all RNA sequences. We confirmed that the sponges degrade completely in the presence of RNAse, but not with DNAse, and confirmed the secondary structure of the RNA. We essentially did a basic material analysis of the system, looking at the size distribution and net charge these are very highly charged because of the RNA sequences. Then we wrapped up the microsponge with one adsorbed layer of a polycation. This allowed us to compact the microsponge into a nanostructure. Once we did that, we looked at internalization of the microsponge *in vitro* and saw that cell uptake was quite high in these systems. We actually have hundreds to thousands of copies of the siRNA in each chain that is generated. These chains are extremely long, and they form what appear to be polymeric crystals. The way polymers crystallize is that the repeat sequences begin to fold back on themselves and form a sheet-like structure that can radiate outward from a spherical core, which is what we see with the siRNAs. We believe that we've created a siRNA-polymeric species of a high molecular weight, which is generated in high enough concentrations to form superstructures that are crystalline versions of the polymer. They are self-organized and mono disperses, so all these microsponges are the same size. The construction technique first involved preparing long linear single-stranded DNA encoding complementary sequences of both the antisense and sense sequences of anti-luciferase siRNA. This long strand was then hybridized with short DNA strands containing the T7 promoter sequence, to form circular DNA. The circle was closed using T4 DNA ligase, and the circular DNA then used to produce RNA transcripts by RCT, which encode both antisense and sense sequences of the anti-luciferase siRNA. This effectively generates nanoscale pleated sheets of hairpin RNA that self-assemble into sponge-like microspheres. Critically, once internalized in cells, the RNA is split up into the 21 nucleotide-long RNA component units by activity of the enzyme Dicer, and then converted to active siRNAs by theRNA-induced silencing complex. The authors believe their RNAi-microsponge could represent a more cost-effective and efficient means of delivering high concentrations of siRNAs to target cells for therapeutic applications. The crystalline form of the polymeric RNA protects the RNA itself from degradation during delivery, while the polymerization approach can easily be modified, which means multiple RNA species could be included in the constructs for combination therapy. “The RNAi-microsponge presents a novel materials system in general owing to its unique morphology and nanoscale structure within the polymer particle,” the team concludes, “and provides a promising self-

assembling material that spontaneously generates a dense siRNA carrier for broad clinical applications of RNAi delivery using the intrinsic biology of the cell."[39].

CONCLUSION

The microsponge drug delivery technology is widely applicable to the dermatological drug delivery products. The microsponge delivery technology of controlled release system in which active pharmaceutical ingredients are loaded in the microporous beads and initiates reduction in side effects with improved therapeutic efficacy. The microsponge drug delivery system has properties like improved stability and enhanced flexibility in formulation. MDS is originally developed for topical delivery of drugs like anti-acne, anti-inflammatory, anti-fungal, anti-dandruffs, antipruritics, rubefacientsetc. But MDS also expands its application in oral drug delivery, bone and tissue engineering, in detecting the diseases and inRNAi silencing Hence, the microsponge drug delivery system focus as an important tool for future inventions in controlled drug delivery system.

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