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Nanosponges: A recent technology for Nanomedicine

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Abstract
Recent advances in nanotechnology paved path for design of new biomaterials based on nanoscale with many potential applications in the field of nanomedicine. Effective drug delivery at a targeted site had given the possibility to perform the precise function to control the release rates and have a better compliance on the health care system but the chemistry possessing complex form had made conditions complicated. But the invention of nanosponges has given a significant approach toward solving this problem. Nanosponges play an important role in targeting drug delivery in a controlled manner. A wide variety of drugs, both the lipophilic as well as hydrophilic can be loaded into nanosponge for targeting drug delivery and ultimately improve solubility and bioavailability of the same drug. Nanosponge can circulate around the whole body until they interact with the specific target site and stick on the surface and begin to release the drug in a controlled manner. This review attempts to elaborate the interesting features of nanosponges, recent updates of nanosponges in drug delivery and formulation development and evaluation of nanosponges for colon targeting.

Keywords: nanosponges, colon targeting, nanomedicine, drug delivery

Introduction
Nanosponges are a new class of materials and made of microscopic particles with few nano meters wide cavities in which a large variety of substances can be encapsulated [1]. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecule [1]. Nanosponges are tiny mesh like structures. The nanosponge is about the size of a virus with a backbone of naturally degradable polyester. The long strength polyester strands are mixed in solution with small molecules called cross linkers that have an affinity for certain portions of the polyesters. They cross link segments of the polyester to form a spherical shape that has many pockets / cavities where drug can be stored. The nanoscale materials are small enough to be effective in attaching to or passing through cell membranes. The nanosponge can be engineered to be of specific size and to release drugs over time- not just in the "burst" mode common with other delivery methods [2]. The engineering capacity of nanosponge is due to the relatively simple chemistry of its polyesters and linking material (peptides). Compared to many other nanoscale drug delivery systems, nanosponge should be able to scale (e.g. ramp up to commercial production levels) without requiring unusual equipment or procedures. The polyster is predictably biodegradable, which means that when it breaks up in the body, the drug can be released on a known schedule [3]. Nanosponge was originally developed for topical delivery of drugs. Nanosponges are tiny sponges with a size of about a virus with an average diameter below 1µm [4]. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and began to release the drug in a controlled and predictable manner. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more effective for a particular given dosage [5]. Nanosponges are capable of providing solutions for several formulation related problems. Owing to their small size and porous nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability. They can be crafted for targeting drugs to specific sites, prevent drug and protein degradation and prolong drug release in a controlled manner [6].
Nanosponges are obtained by suitable cross linking process and also by different organic and inorganic materials. Nanosponges can encapsulate various types of molecules by forming inclusion and non inclusion complexes. The active ingredient is added to vehicles in the entrapped from since the nanospong particles have an open structure (they do not have continues membrane surrounding them) the active substance is free to move in or out from the

particles into the vehicle until the equilibrium is reached when the vehicle become saturated. Once product is applied to skin, the active substance that already in vehicle will become unsaturated, therefore distributing the equilibrium. This will start flow of active from nanosponges particles into vehicle from it, to skin until vehicle is either dried or absorbed. Even after that nanospones particles retained on the surface of the stratum corneum will continue to gradually release active to skin providing prolong release over time [4]. Furthermore, nanosponges show a remarkable advantage in comparison with the common nanoparticles: indeed, they can be easily regenerated by different treatments, such as washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating, or changing pH or ionic strength. For all these characteristics, nanosponges have been already employed in different applied fields, such as cosmetic and pharmaceutical sectors.

Nanosponge based drug delivery systems

The nanosponges are encapsulated nanoparticles which encapsulates the drug molecules within its core. Depending on the method of associating with drugs, the nanoparticles can be classified into 3 types.

1. Encapsulating nanoparticles: This type is represented by nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are spongelike nanoparticles containing many holes that carry the drug molecules. Nanocapsules such as poly (isobutyl cyanoacrylate) (IBCA) are also encapsulating nanoparticles. They can entrap drug molecules in their aqueous core.
2. Complexing nanoparticles: This category includes complexing nanoparticle, which attracts the molecules by electrostatic charges.
3. Conjugating nanoparticles: These conjugating nanoparticles link to drugs through covalent bonds.

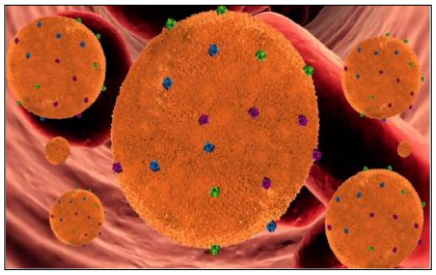

Fig 1: Structure of nanosponge

Nanosponges may be made of many different organic or inorganic materials; their structure presents a nanometric dimension or smaller. Well-known examples are titanium or other metal-oxide based nanosponges, silicon nanosponge particles, carbon coated metallic nanosponges, hyper-cross-linked polystyrene nanosponges and also cyclodextrin based nanosponges. The common characteristic of these materials is the presence of nano-scale pores that give them particular properties [7]. Cyclodextrin nanosponge based drug delivery systems (CDNS) are hyper-cross-linked cyclodextrins that can be obtained with α, β and γ cyclodextrins, either alone or as mixtures containing relevant amounts of linear dextrin, cross-linked with a suitable cross-linking agent [8]. Nanosponge (NS) looks like a three dimensional scaffold possessing a long length polymer backbone. The polymer in solution form is combined with small molecules called crosslinkers that act like tiny grappling hooks to fasten different parts of the polymer together [9]. Interesting results have already been obtained as drug carriers by using an active carbonyl compound, e.g., carbonyldimiidazole, triphosgene, diphenyl carbonate, or organic dianhydrides. The net effect is formation of spherical particles with hydrophobic cavities and hydrophilic channels where drug molecules can be entrapped [10]. A single nanosponge system consists of a myriad of interconnecting voids within a non-collapsible structure capable of holding a wide variety of substances [11].

The list of polymers and crosslinking agents [12] used for the synthesis of nanosponges are presented in Table-1.

Table 1: Polymers and crosslinking agents used for the synthesis of nanosponges

Polymers	Crosslinkers
Hyper cross-linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly (valerolactone-allyl valerolactone) & Poly(valerolactone allyl valerolactone oxepanedione) and Ethyl Cellulose & PVA	Diphenyl Carbonate, Diaryl carbonates, Diisocyanates, Pyromellitic anhydride, Carbonyl diimidazoles, Epichloridrine, Glutaraldehyde, Carboxylic acid dianhydrides, 2,2-bis(acrylamido) Acetic acid and Dichloromethane

Work done on nanosponge based drug delivery system is presented in Table-2.

Table 2: Nanosponge base drug delivery system

Drug	Nanosponge vehicle	Indication	Study	*In-vitro*/ *In-vivo*/ Mathematical Model	Reference
Clotrimazole	β-cyclodextrin	Fungal infections	Antifungal	Diffusion study	[13]
Tamoxifen	β-cyclodextrin	Breast cancer	Cytotoxicity	MCF-7 cell line	[14]
Dexamethasone	β-cyclodextrin	Brain tumours	Drug release Experiment	Dialysis bag technique in-vitro	[15]
Econazole nitrate	Ethyl cellulose Polyvinyl alcohol	Fungal infections	Irritation study	Rat	[16]
Itraconazole	β-Cyclodextrin and copolyvidonum	Fungal infections	Saturation solubility Study	Higuchi Model	[17]
Paclitaxel	β-cyclodextrin	Cancer	Cytotoxicity Bioavailability	MCF-7 cell line Sprague Dawley rats	[18, 19]
Camptothecin	β-cyclodextrin	Cancer	Haemolytic activity Cytotoxicity	Diluted blood HT-29 cell line	[20, 18]
Resveratrol	β-cyclodextrin	Inflammation,	Cytotoxicity	Pig skin	[21]

		Cardiovascular diseases, Dermatitis, Gonorrhoea, Fever and Hyperlipidemia	Accumulation of drug in the buccal mucosa of rabbit Ex-vivo Permeation study		
Temozolamide	Poly (Valerolactone allyl Valerolactone) and poly (Valerolactone allyl Valerolactone -oxepanedione)	Brain tumours	Drug release study	In-vitro and in -vivo studies	[22]
Antisense Oligonucleotides	Sodium alginate Poly L-lysine	Cancer therapy, Viral infections, Pathologic disorders	Pharmacokinetic Studies	Mice	[23]
Acyclovir	β-cyclodextrin	Viral infections	In-vitro release Cellular uptake Cytotoxicity Antiviral activity	Multi compartment rotating cells with dialysis membrane Vero cells HSV-1 MRC	[24]
Voriconazole	Ethyl cellulose Polyvinyl alcohol	Fungal infections	Antifungal activity *In-vitro In-vivo*	Against *Candida albicans* Male Wistar rats	[25]
Bovine serum albumin (BSA)	β-cyclodextrin	Viral, malignant, autoimmune diseases	In-vitro release	Dialysis bag	[26]

Preparation methods of nanosponge

Solvent method

Dissolve the polymer in suitable solvent. Then add this to excess quantity of cross- linker. Reflux the mixture for 48 hours at a temperature of 10 ˚C. Then allow this solution to cool at room temperature. Add this to excess quantity of bi-distilled water and filter the product. Then purify by prolonged soxhlet extraction with ethanol. Dry the product and grind in mechanical mill to get homogenous powder.

Emulsion solvent diffusion method

Nanosponges can be prepared by using ethyl cellulose (EC) and polyvinyl alcohol (PVA). Ethyl cellulose is dissolved in dichloromethane. Add this mixture into aqueous solution of polyvinyl alcohol. Stir the mixture at 1000 rpm for 2 hours in a magnetic stirrer. Then filter the product and dry it in an oven at 400 c for 24 hours.

Ultrasound- Assisted Synthesis In this method, polymers react with cross- linkers in absence of solvent and under sonication. Here, mix the polymer and cross- linker in a flask. Place the flask in an ultrasound bath filled with water and heat it to 900 c and sonicate for 5 hours. Allow it to cool and wash with water to remove the unreacted polymer. Purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and store at 25 ^{0}C. From Hyper Cross- Linked B-Cyclodextrins Here, β- cyclodextrin (β- CD) can be used as carrier for drug delivery. Nanosponges can be obtained by reacting cyclodextrin with a cross- linker. Nanosponges can be synthesized in neutral or acid forms. The average diameter of a Nanosponge is below 1 μm but fractions below 500 nm can be selected.

Loading of drug into nanosponges

Nanosponges for drug delivery should be pretreated to obtain a mean particle size below 500nm. Suspend the nanosponges in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to obtain the colloidal fraction. Separate the supernatant and dry the sample by freeze drying. Prepare the aqueous suspension of Nanosponges disperse the excess amount of the drug and maintain the suspension under constant stirring for specific time required for complexation. After complexation, separate the uncomplexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or by freeze drying Crystal structure of nanosponges plays a very important role in complexation with drug. A study revealed that paracrystalline nanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than paracrystalline one. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than inclusion complex.

Characterization of nanosponges

Particle size determination

The size of particles are maintained during polymerization for the formation of free-following powders having fine aesthetic attributes. Particle size analysis of loaded and unloaded nanosponges performed by laser light diffractometry or malvern zeta sizer. Cumulative graph is maintained or ploted as particle size against time to study effect of particle size on drug release. Particle size larger than 30 m can show gritty feeling and particle size range from 10 –25 m can be preferred for topical drug delivery.

Determination of loading efficiency

The prepared nanosponge loading efficiency is determined by subtracting the un-entrapped drug from the total amount of drug. The drug entrapment efficiency will be determined by separating un-entrapped drug estimated by any suitable method of analysis. The method used for separation of un-entrapped drug by gel filtration, dialysis and ultra centrifugation.

The loading efficiency is calculated as: Loading efficiency = Actual drug content in nanosponge / Theoretical drug × 100.

Porosity

Porosity study is performed to check the extent of nanochannels and nanocavities formed. Porosity of nanosponges is assessed with a helium pycnometer, since

helium gas is able to penetrate inter- and intra-particular channels of materials. The true volume of material is determined by the helium displacement method. Owing to their porous nature, nanosponges exhibit higher porosity compared to the parent polymer used to fabricate the system.
Percent porosity is given by equation: % Porosity = Bulk volume - True volume / Bulk volume × 100
Swelling and water uptake For swellable polymers like polyamidoamine nanosponges, water uptake can be determined by soaking the prepared nanosponges in aqueous solvent.
Swelling and water uptake can be calculated using equations:
% Swelling = Marking of cylinder at a specified time point / Initial marking before soaking × 100.
% Water uptake = Mass of hydrogel after 72 hrs / Initial mass of dry polymer × 100.

Resiliency (Viscoelastic properties)
Resiliency of sponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased crosslinking tends to slow down the rate of release. Hence resiliency of sponges will be studied and optimized as per the requirement by considering the release as a function of cross- linking with time.
Compatibility Studies the drug should be compatible with the polymers which are used for the preparation of nanosponges. The compatibility of drug with adjuvants can be determined by Thin Layer Chromatography (TLC) and Fourier Transform Infra-red Spectroscopy (FT-IR). Crystalline characteristics can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC).

Zeta potential
Zeta potential is a measure of surface charge. The surface charge of Nanosponge can be determined by using Zeta sizer.

Solubility studies
The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a nanosponge, on the solubility of drug. Phase solubility diagrams indicate the degree of complexation.

Drug release kinetics
To investigate the mechanism of drug release from the Nanosponge the release data was analysed using Zero order, First order, Higuchi, Korsemeyer-Peppas, Hixon Crowell, Kopcha and Makoid-Banakar models. The data can be analysed using graph pad prism software. The software estimates the parameters of a non-linear function that provides the closest fit between experimental observations and non-linear function.

In vitro release studies
In vitro release kinetics experiments are perfomed using a multi compartment rotating cell. An aqueous dispersion of nanosponges (1ml) containing the drug is placed in the doner compartment, while the receptor compartment separated by a hydrophillic dialysis membrane is filled with phosphate buffer at pH 7.4 or pH. 1.2. Each experiment is carried out for 24hr. At fixed times, the receptor buffer is completely withdrawn and replaced with fresh buffer. The amount of drug in the medium is determined by the a suitable analytical method and drug release is calculated to determine the release pattern.

Permeation studies
The diffusion studies of the prepared nanosponge can be carrying out in Franz diffusion cell for studying the dissolution release of nanosponge through a cellophane membrane. Nanosponge sample (0.5g) can taken in cellophane membrane and the diffusion studies were carried out at 37 ± 1° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. 5ml of each sample can with drawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 hrs and each sample will replaced with equal volume of fresh dissolution medium. Then the samples can analyzed for the drug content by using phosphate buffer as blank.

Microscopy studies
Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes.

Characteristic features of nanosponge based drug delivery system
Nanosponges exhibit a range of dimensions (1 μm or less) with tunable polarity of the cavities. Nanosponges of specific size and adjustable polarity can be synthesized by varying the crosslinker to polymer proportion [27]. They could be either para-crystalline or in crystalline form, depending on the process conditions. Crystal structure of nanosponges plays a very important role in their complexation with drugs. The drug loading capacity of nanosponges mainly depends on the degree of crystallization. Paracrystalline nanosponges have shown various drug loading capacities [28]. They are nontoxic, porous particles insoluble in most organic solvents and stable at high temperatures up to 300 °C [7]. Nanosponges as formulations are stable over the pH range of 1 to 11 and temperature up to 130 °C [9]. They form clear and opalescent suspensions in water and can be regenerated by simple thermal desorption, extraction with solvents, by the use of microwaves and ultrasounds [29]. Their 3D structure enables capture, transportation and selective release of a vast variety of substances. They can be targeted to different sites due to their ability to be linked with different functional groups. Chemical linkers enable nanosponges to bind preferentially to the target site. They form inclusion and non-inclusion complexes with different drugs [30]. Magnetic properties can be also imparted to nanosponges (by adding magnetic particles into the reaction mixture).

Colon targeted drug delivery system
Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, least sterility constraints and flexibility in the design of the dosage form. Hydrophilic polymers are becoming very popular in formulating oral controlled release tablets. As the dissolution medium or biological fluid penetrates the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer as well as formulation technology [31]. Several polysaccharides like, pectin, chondroitin sulphate, amylase, guar gum, xanthan gum and chitosan are being investigated as carriers for colon specific

drug delivery. In pharmaceutical formulations, pectin is used as a binder, disintegrant, suspending agent, thickening agent and stabilizing agent [32]. Pectin and guar gum are reported to be potential carriers for colon specific drug delivery[33]. Colon specific drug delivery systems are potential for not only for delivering various drugs to combat the local diseases for colon such as crohn's disease, ulcerative colitis, constipation and colon cancer but also for delivering some drugs for the systematic absorption for treating some diseases such as rheumatoid arthritis, nocturnal asthma, hypertension which possess circadian rhythms in their symptoms [34]. There are several strategies being followed for targeting drugs specifically to the colon. Some of them are, pH dependent, time- controlled, prodrugcontrolled, microbially triggered drug release (enzyme controlled), redox sensitive polymer approach and polysachharide as carrier. The pH approach has been shown to lack site-specificity because of inter/intra subject variation and the similarity of the pH between the small intestine and the colon Some of the natural polysaccharides which have already been studied for their potential as colon specific drug carrier systems are chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, insulin, amylase and bean gum. Approaches being used for new anticonvulsant drugs include the search for agents that block specific cationic channels in neuronal membranes, agents that enhance the activity of the inhibitory neurotransmitter amino butyric acid (GABA), and agents that are capable of inhibiting the activity of the excitatory neurotransmitters glutamic and aspartic acids [35]. The rationale for the development of polysaccharide based delivery system for colon is the presence of large amounts of polysaccharidases in the human colon as the colon us inhabited by a large number and variety of bacteria which secrete many enzymes e.g. D-glucosidase, D-galactosidase, amylase, pectinase, xylanase, D-sylosidase, dextranase, etc [36]. Major approaches utilizing polysaccharides for colon specific delivery are fementable coating of the drug core, embedding of the drug in biodegradable matrix, formulation of drug saccharine conjugate [37]. The potential of pectin as carriers for colonic drug delivery has been demonstrated previously [38]. Pectin is heterogeneous polysaccharides composed mainly of galacturonic acid and its methyl ester[39]. They are refractory to host gastric and intestinal enzymes, but are almost completely degraded by the colonic bacterial enzymes to produce a series of soluble oligogalacturonates. Depending on the plant source and preparation, they contain varying degrees of methyl ester substituent. The degree of methoxylation determines many of their properties, especially solubility and requirements for gelation. High methoxy pectins (HM) are poorly soluble and require a minimum amount of soluble solids [40]. Eudragit S 100 and major drug release in small intestine is avoided by providing pH independent coating of Eudragit polymer [41].

Mechanism of drug release

The sponge particles have an open structure and the active is free to move in and out from the particles and into the vehicle until equilibrium is reached. In case of topical delivery, 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 sponge particle into the vehicle and from it to the skin until the vehicle is either dried or absorbed. Even after that the sponge particles retained on the surface of stratum corneum will continue to gradually release the active to the skin, providing prolonged release overtime.

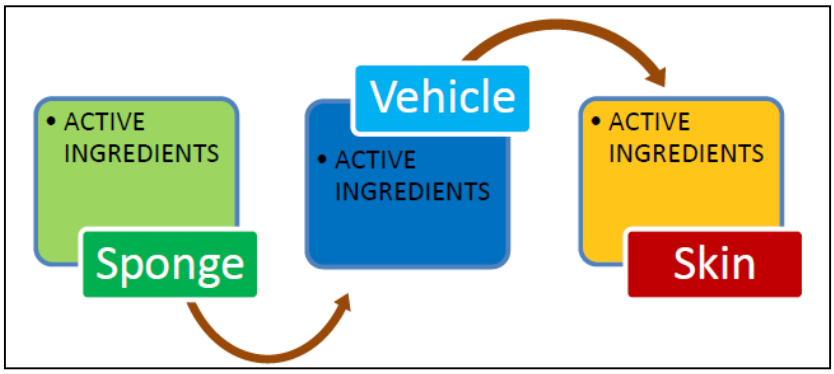

Fig 2: Drug release mechanism

Conclusion

Nanosponge drug delivery system holds a promising opportunity in various pharmaceutical applications in the upcoming future due to its unique characteristics; which makes it supple to design and develop novel product forms. The actual challenge in future is the progression of the delivery systems for oral peptide and other susceptible biomers. The use of bioerodible and biodegradable polymers for drug delivery is enabling it for the safe delivery of the actives via diverse routes. As these porous systems have also been studied for drug delivery through pulmonary route; which depicted that these system has effective drug release even in the scarce of the dissolution fluid, thus colon targeted delivery may be able to expand like such as never before.

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