ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 16, Issue 4, 2023

Online - 2455-3891
Print - 0974-2441

Review Article

NANOSPONGES - A REVOLUTIONARY TARGETED DRUG DELIVERY NANOCARRIER: A REVIEW

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Received: 26 September 2022, Revised and Accepted: 20 December 2022

ABSTRACT

Effective targeted drug delivery systems have long been a dream, but have been largely hampered by the complex chemistries involved in developing new systems. The creation of novel colloidal carriers known as nanosponges has the potential to resolve these issues. An innovative and developing technology called nanosponge provides regulated medication delivery for topical application. Highly porous nanosponges have a unique capacity to entrap active molecules and have the advantage of programmable release. Nanosponges are small three-dimensional porous structures about the size of nanometer that can contain many different drugs. These tiny sponges can move throughout the body until they meet a specific target site and attach to surfaces and begin to release the drug in a controlled and predictable manner. Because the drug can be delivered to a specific target site instead of circulating throughout the body, it is more effective for a given specific dose. They are easy to make and safe for biological use. Different types of cyclodextrins can be cross-linked using a carbonyl or a dicarboxylate chemical as a cross-linker to create nanosponges. This groundbreaking technology has been extensively investigated for the delivery of medications for oral, topical, and parental administrations. Vaccines, antibodies, proteins, and enzymes can all be effectively transported via Nanosponges. The current review emphasizes the methods, advantages, disadvantages, characterization, and applications of nanosponges.

Keywords: Nanosponges, Targeted drug delivery, Cyclodextrins, Nanocarrier, Enhanced bioavailability.

 DOI: http://dx.doi.org/10.22159/ajpcr.2023v16i4.46453. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

The drug delivery technology has definitely a new interest for medication by providing them new life through their therapeutic targets. Targeted drug administration, also known as smart drug delivery [1], is a method of administering medication to a patient in such a way that the concentration of the medication in certain parts of the body is higher than in others. These nanoparticles would be drug-loaded and directed to specific areas of the body with only diseased tissue, avoiding interactions with healthy tissue. The goal of a targeted drug delivery system is to extend, localize, target, and preselected and has controlled medication contact with the diseased tissue. To enhance regenerative procedures, targeted medication delivery systems have been developed. This system is based on a method that delivers a certain amount of a therapeutic agent to a diseased part of the body for extended length of time. This helps maintain the proper plasma and tissue drug levels in the body, preventing any drug-induced harm to healthy tissue. The drug delivery system is highly integrated, necessitating the collaboration of experts from several disciplines, including as chemists, biologists, and engineers, to optimize it [2]. The conventional drug delivery technique involves drug absorption across a biological membrane, whereas the targeted release system involves drug release in a dose form. Many drug-delivery systems, such as nanoparticles, nanoemulsions, nanosuspensions, nanosponges, and so on, have now been produced employing nanomedicine technology and are associated with several benefits, including enhanced bioavailability [3]. Polysaccharides are frequently utilized in nanomedicine technology because they are non-toxic, hydrophilic, biodegradable, and inexpensive. Starch derivatives, particularly, cyclodextrin-based nanosponges (CD NSs) have recently evolved as a result of their exceptional capabilities due to their unique structure [4]. In fact, CD NSs are characterized by their three-dimensional (3D) network composed of cross-linked cyclodextrin units. In addition, the presence of tunable functional groups and their ability to interact with biological tissues, resulting in bio adhesion which is particularly useful in drug delivery. Nanosponges were first called "cyclodextrin Nanosponges" by Ma and Li in 1998 [5].

Nanosponges are a kind of nanoparticle, is about a size of virus that is usually made from a carbon-containing polymer. These sponges are three dimensional structures formed by hyper-cross-linkage cyclodextrins, either alone or in combinations with significant amounts of linear dextrin cross-linked with an acceptable cross-linking agent [6]. These tiny sponges can circulate throughout the body, where they encounter the exact target spot and attach to the surface, allowing the medicine to be released in a regulated and predictable manner. They can bind poorly-soluble medicines within the matrix and increase their bioavailability because of their small size and porous nature. These have a solid nature and can be made into dosage forms for oral, parenteral, topical, or inhalation use. Nanosponges can be disseminated in a matrix of excipients, diluents, lubricants, and anti-caking agents for oral delivery that is suited for the creation of tablets or capsules. These can easily be combined with sterile water, saline, or other aqueous solutions for parenteral delivery. They can be successfully integrated into topical hydrogel for topical delivery [7-9].

Unlike other nanoparticles, nanosponges are porous, non-toxic, insoluble in water and organic solvents, stable at high temperatures up to 3000 c, and non-toxic [7,10,11].

Advantages [12-15]

1. These compositions remain stable between pH values of 1 and 11
2. Higher temperatures do not affect these compositions
3. The majority of vehicles and additives can be used with these compositions
4. Since bacteria cannot pass through their 0.25 mm average pore size, these are self-sterilizing
5. These formulations can be economical and free-flowing
6. This method offers higher stability, increased elegance, and fewer adverse effects, trapping of components, and increased formulation flexibility
7. The properties of nanosponges include not being abrasive, poisonous, mutagenic, allergic, or irritating
8. It is possible to achieve extended release action for up to 12 h
9. Immiscible liquid can be included, which improves material processing because liquid can be turned into powder
10. Straightforward scaling up for commercial production

11. The ratio of cross-linker to polymer can be changed to alter the size of the Nanosponges
12. The medication release characteristics might be fast, medium, or slow depending on the dose requirement
13. Foreseeable release
14. Nanosponges can be regenerated using eco-friendly solvents, light heating, stripping with relatively inert hot gases, mild heating, changing pH, or altering ionic strength
15. Fewer severe adverse effects since the medicine come into contact with healthy tissue less frequently.

Disadvantages

1. Only tiny molecules can be included by nanosponges
2. Nanosponges may be crystalline or Para crystalline in nature
3. The amount of crystallization primarily determines how much a nanosponge can load
4. Different loading capacities can be seen in para crystalline nanosponges.

DETERMINANTS IMPACTING DEVELOPMENT OF NANOSPONGES [16]

The following features of the drug molecules should be present when they are complexes with nanosponges.

Types of polymer

The kind of polymer utilized can have an impact on how successfully nanosponges develop and function. The cavity size of the nanosponge should be appropriate to hold a drug molecule of a specific size for complexation [17].

Type of drugs [18-20]

- The drug's molecular weight should range from 100 to 400 Daltons
- The average drug molecule has four to five condensed rings
- Ideally, solubility in water is <10 mg/mL
- The substance's melting point must be lower than 250°C.

Temperature

Drug/nanosponge complexation may be impacted by temperature fluctuations. In general, when temperature raises, the strength of the drug/nanosponge complex's apparent stability constant falls. This could be because the interaction forces between the drugs and nanosponges, such as Van der Waal and hydrophobic interactions, may weaken over time [13,21].

SYNTHESIS OF NONOSPONGES

It is one of the crucial requirements for the production of the product achieved activity in titanium oxide and cyclodextrin.

Solvent method

The necessary solvent is combined with the polymer primarily in a polar aprotic solvent, such as dimethyl formamide or dimethyl sulfoxide. This mixture is then added in excess amounts to the cross linker, with a desirable molar ratio of 4–16. The reaction is carried out at a solvent reflux temperature for 1–48 h. Dimethyl carbonate and carbonyl di-imidazole are two cross linkers that may be preferred [22-25]. When the reaction is finished, the solution is allowed to cool at room temperature before the product is added to extra bi-distilled water, recovered by filtration under vacuum, and purified at the same time by extended Soxhlet extraction with ethanol. The product is then vacuum-dried and mechanically milled to generate a uniform powder [26,27].

Ultrasound assisted synthesis

In this approach, nanosponges are created by reacting polymers with cross-linkers in the absence of a solvent and sonication is maintained. This technique will produce spherical, uniform-sized Nanosponges [28]. In a flask, combine the cross-linker and the polymer in a certain molar ratio. Heat the flask to 90°C by submerging it in a water-filled ultrasonic bath. For 5 h, sonicate the mixture. When then, break the mixture roughly after it has cooled.

The product should be washed in water to get rid of any non-reacted polymers before being purified using a prolonged ethanol Soxhlet extraction. Store the finished product at 25°C until use by vacuum-drying it [29-31].

Loading of drug into Nanosponges

To maintain a mean particle size of 500 nm or below, nanosponges should be pre-treated. In order to avoid the presence of aggregates and particles, nanosponges were suspended in water and sonicated. The colloidal fraction was then obtained by centrifuging the nanosponges, and the supernatant was then separated and the sample was dried by freezing and drying [32,33].

The next step begins with creating an aqueous suspension of nanosponges. Extra drug is administered to keep the suspension constantly stirred for a set amount of time to allow for complexation. Once complexation is complete, un-dissolved drug (in its uncomplexed condition) is separated from complexed drug using centrifugation. Using freeze drying or solvent evaporation, this procedure aids in the development of solid nanosponge crystals. When compared to crystalline nanosponges, para-crystalline nanosponges demonstrated differing loading capacities, and poorly crystalline nanosponges acted to load drugs as a mechanical mixture rather than an inclusion complex [34-37].

CHARACTERIZATION OF NANOSPONGE

Particle size determination

By regulating the size of the particles during polymerization, it will be feasible to produce free-flowing powders with fine aesthetic qualities. Both loaded and unloaded nanosponges will have their particle sizes analyzed using Malvern Zetasizer or laser light diffractometry. Particles between 10 and 25 m in size are preferred for use in the final topical formulation because particles bigger than 30 m can cause a gritty feeling [38].

Assessing loading effectiveness and production yield

Subtracting the un-entrapped drug from the total drug amount yields the prepared nanosponge loading efficiency. By isolating un-entrapped drug that has been evaluated by any applicable method of analysis, the effectiveness of the drug entrapment will be ascertained [19,20,39,40]. Gel filtration, dialysis, and ultra-centrifugation are the techniques used to separate un-entrapped drug [41].

$$Loading\ \ Efficiency = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} \times 100$$

$$Production\ yield\left(PY\right) = \frac{Practical\ mass\ of\ NS}{Theoretical\ mass\left(polymer + Drug\right)} \times 100$$

Porosity

To determine the extent of produced nano channels and nano cavities, a porosity analysis is conducted. A helium pycnometer is used to measure the porosity of nanosponges since helium gas may pass through both inter- and intra-specific channels in materials. The helium displacement method establishes the material's actual volume. Because they are porous, nanosponges have greater porosity than the parent polymer utilized to create the system [24,25].

$$\%\ Porosity = \frac{Bulk\ Volume - True\ Volume}{Bulk\ Volume} \times 100$$

Swelling and water uptake

By soaking the produced nanosponges in aqueous solvent, water absorption for swellable polymers such as polyamidoamine nanosponges can be assessed. Equations can be used to calculate swelling and water absorption [42].

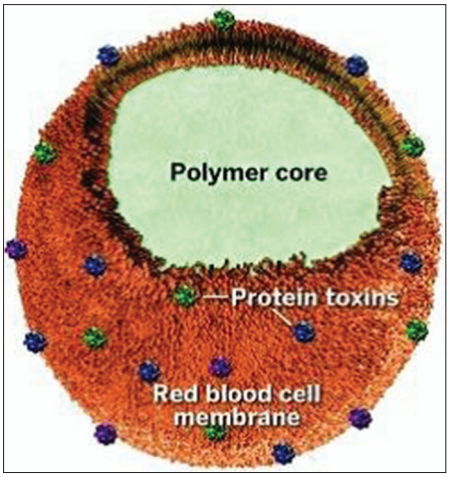

Fig. 1: Polymer based nanosponge

$$\% \ Swelling = \frac{Making\ of\ cylinder\ at\ a\ specified\ time\ point}{Initial\ marking\ before\ \ soaking} \times 100$$

$$\% \ Water\ uptake = \frac{Mass\ \ of\ hydrogel\ after\ 72\ hours}{Initial\ mass\ of\ dry\ polymer} \times 100$$

Resiliency (Viscoelastic properties)

Depending on the requirements of the final formulation, the resilience of sponges can be altered to yield beadlets that are either softer or stiffer. The rate of release is typically slowed down by increased crosslinking. To study and improve sponge resilience, the release as a function of cross-linking over time will be taken into account [43-45].

Zeta potential

Surface charge can be calculated using zeta potential. Zetasizer can be used to assess the surface charge of nanosponges [46-49].

***In vitro* release studies**

Using the dissolution apparatus USP XXIII with a modified basket made of 5 m stainless steel mesh, the dissolving profile of nanosponge can be examined. The rotational speed is 150 rpm. To achieve sink conditions, the dissolution medium is chosen while taking the solubility of the actives into account. A suitable analytical technique can be used to examine samples from the dissolving medium. Utilizing a modified basket made of 5 m of stainless steel mesh, the dissolution apparatus USP xxiii was used to conduct the study. The rotational speed is 150 rpm. To achieve sink conditions, the dissolution medium is chosen while taking the solubility of the actives into account. A suitable analytical technique can be used to examine samples from the dissolving medium [7,9,10,50].

Permeation studies

To investigate how a produced nanosponge dissolves and releases through a cellophane membrane, diffusion studies of the nanosponge can be conducted in a Franz diffusion cell. At 37°C and using 250 mL of phosphate buffer (pH 7.4) as the dissolution media, diffusion tests on a nanosponge sample (0.5 g) were conducted. Each sample will be replaced with an equal volume of new dissolution media every time 5 mL of each sample is withdrawn at intervals of 1, 2, 3, 4, 5, 6, 7, and 8 h [51,52].

APPLICATIONS OF NANOSPONGES

Drug delivery employing nanosponges

Nanosponges are advantageous for carrying drugs that are not soluble in water because of their nonporous nature (Biopharmaceutical Classification System [BCS] Class-II drugs).The BCS Class II drugs listed in Table 2 have a very low solubility, making them the most suitable candidates for nanosponges. These complexes can be used to hide disagreeable odors, turn liquid substances into solids, and boost the pace, solubility, and stability of drugs [53-56].

Table 1: Chemical ingredients used in the fabrication of nanosponges

Polymers	Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives such as Methyl β-Cyclodextrin, AlkyloxycarbonylCyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins, and Copolymers like Poly (valerolactone-allylvalerolactone) and Poly (valerolactone-allylvalerolactoneoxepanedione) and Ethyl Cellulose and PVA
Crosslinkers	Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles, Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, 2, 2-bis (acrylamido) Acetic acid, and Dichloromethane
Apolar solvents	Ethanol, Dimethylacetamide, Dimethyl formamide

PVA: Poly valerolactone-allylvalerolactoneoxepanedione

Table 2: BCS class II drugs [87-95]

Classification of drugs	Name of the drug
Antioxidants	Resveratrol
Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan, Paclitaxel, Raloxifene, Tamoxifen, Temozolamide
Immunosupressants	Cyclosporine, Sirolimus, Tacrolimus
Antidiabetic and Antihyperlipidemic	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone
Cardiac drugs	Carvedilol, Digoxin, Talinolol
Anticoagulant	Warfarin
Antihypertensive	Felodipine, Nicardipine, Nifedipine, Nisoldipine
Antiarrhythmic agents	Amiodarone hydrochloride
Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin
Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole
NSAIDs	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, buprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin, Piroxicam
Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone
Antipsychotic drugs	Chlorpromazine Hydrochloride
	AntiretroviralsIndinavir, Nelfinavir, Ritonavir, Saquinavir
Antianxiety drugs	Lorazepam
Steroids	Dexamethazone
Antiulcer drugs	Lansoprazole, Omeprazole
Diuretics	Chlorthalidone, Spironolactone
Miscellaneous	Atovaquone, Melarsoprol, Phenazopyridine, Ziprasidone

BCS: Biopharmaceutical classification system

Chemical sensors incorporating nanosponges

Titania-based nanosponges, a subclass of "metal oxides," serve as chemical sensors for the highly sensitive detection of hydrogen. Since there is initially no point of contact, electron transport is less impeded and there are more titania nanosponges with higher 3D interconnects, which are sensitive to H_2 gas [40,57].

Use of a nanosponge for oral administration

When taken orally, it creates a system of pores called a nanosponge that speeds up the process by which medications with low water solubility

Table 3: Examples of nanosponges

Drug	Nanosponge vehicle	Indication	Study	*In vitro/in vivo* mathematical model	Ref
Paclitaxel	β-cyclodextrin	Cancer	Bioavailability	Sprague dawley rats	[30]
Camptothecin	β-cyclodextrin	Cancer	Haemolytic activity	MCF7 cell line	[19,24]
Tamoxifen	β-cyclodextrin	Breast cancer	Cytotoxicity	MCF7 cell line	[25]
Itraconazole	β-cyclodextrin and copolyvidonum	Antifungal	Saturation solubility study	Higuchi model	[14]
Voriconazole	EC, PMMA, PVA		Antifungal	Drug release Experiment	[30]
Econazole nitrate	EC	Antifungal	Irritation study	Rat	[13]
Temozolamide	Poly valerolactoneallylvalerolactone) andpoly (valerolactoneallylvalerolactoe-Oxepanedione)	Brain tumors	Drug release study	*In vitro* and *in vivo* studies	[31]
Dexamethasone	β-cyclodextrin	Brain tumors	Drug release experiment	Dialysis bag technique *in vitro*	[17]
Bovine serum albumin	Cyclodextrin based Poly (amidoamine)	Protein supplement	Drug release study Stability study	*In vitro* release modulation and stability	[31]
Resveratrol	β-cyclodextrin	Inflammation, Cardiovascular disease, Dermatitis, Gonorrhea, fever and hyperlipidemia Cytotoxicity	Accumulation of drug in the buccal mucosa of rabbit *ex vivo* study Permeation study	HCPC-I cell line Rabbit buccal mucosa Pig skin	[32]

EC: Ethyl cellulose, PMMA: Polymethyl methacrylate, PVA: Poly valerolactone-allylvalerolactoneoxepanedione

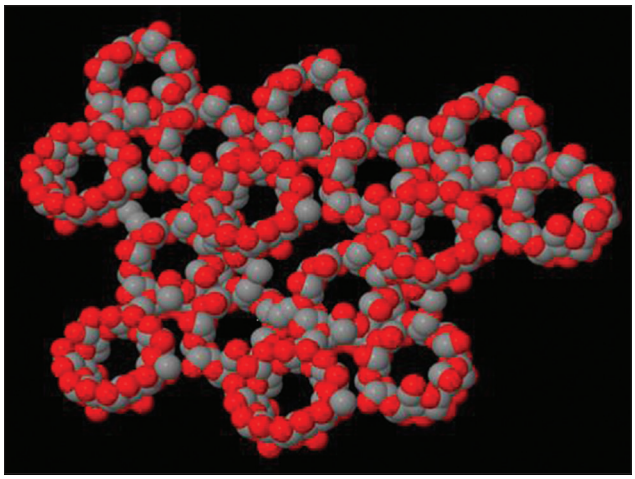

Fig. 2: Cyclodextrin based nanosponge

dissolve after becoming stuck in the pores. Due to nanoscale shape and an increase in solubilization rate, the surface area has increased [58].

Improvement of soluble

The pores in the nanosponge system speed up the solubilization of poorly soluble drugs by trapping them there. Surface area and solubilization rate both dramatically enhanced as a result of nano size [59-62]. Low solubility and low bioavailability are characteristics of BS Class II drugs [63,64]. However, they exhibit improved solubilization efficiency and the desirable drug release characteristics when they are combined with nanosponge [32,65,66].

Use of nanosponges as transporter for biocatalysts and the release of enzymes, proteins, vaccines, and antibodies

It includes the industrial process that is related to operational state. Non-specific reactions result in low yields and call for high temperatures and pressures, which use up a lot of energy and require cooling water in downstream processes. Enzymes can be used as biocatalysts to alleviate these limitations because they operate quickly and under benign conditions [67-70].

Antiviral application

Nanosponges are administered through the nasal and pulmonary routes. To target viruses that may infect RTIs, such as the influenza virus and rhinovirus, it provides specificity for the delivery of antiviral drugs on RNA to the lungs or nasal route by nanocarriers. Zidovudine and saquinavir are two drugs utilized as nanocarriers [71-73].

Cancer

Drug delivery targets a specific spot while evading immune system barriers. With the use of a single injection dose, nanosponges have successfully treated a variety of cancer cells, including breast cancer and fast-acting gliomas [74-76]. Paclitaxel, the main component of the anti-cancer medication Taxol, is one of the significant drugs that have been created as nanosponge [77-80].

Oxygen delivery system

Characterized by the use of cyclodextrins, which are dissolved in water and become saturated with it. With the aid of a nanosponge/hydrogel combination, a silicone membrane can also be used for oxygen permeation [81,82].

Biomedical applications

For contaminated water, a nanosponge can be employed. Water organic contaminants have been removed using nanosponge [83-86].

CONCLUSION

Nanosponge was first created to distribute the drugs topically. They are colloidal carriers that have recently been created and proposed for drug delivery because they can be used to solubilize poorly water soluble drugs, providing delayed release, enhance bioavailability of drugs, and in certain cases change their pharmacokinetics properties.

Nanosponges average diameter is <1 m; however, fractions as small as 500 nm can be chosen.

With the revolutionary method of encapsulating medicine in polymeric materials used in nanosponge technology, regulated site-specific drug release, better formulation efficacy, stability, medication dosing, and patient compliance are all made possible. Particle size and release rate can be adjusted by adjusting the cross-linker to polymer ratio and the rate of stirring. Different dosage forms, including parenteral, aerosol, topical, tablet, and capsule, can be created using nanosponges. In addition to its use in the drug delivery industry, prospective applications include catalysis, biomedicine, agro chemistry, cosmetics, and bioremediation procedures. If clinical trials can establish the safety and efficacy of drugs delivered through nanosponges, the pharmaceutical companies will gain significantly. Nanosponges are hence advantageous for targeted and site-specific drug delivery systems.

AUTHORS CONTRIBUTIONS

All authors contributed significantly to this review article. The manuscript was reviewed by Bhavani B. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors did not have any conflict/competing interests.

AUTHORS FUNDING

No funding was received for this article.

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