



A REVIEW ON NANOSPONGES AND POLYMERS USED IN THEIR PRODUCTION

Pharmaceutics

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ABSTRACT

Nanospoges are a novel targeted drug delivery technology. Nanospoges are cross-linked polymers that are nanostructured within a three-dimensional network. They are mainly used as controlled drug delivery systems for pharmaceutical applications. In cancer applications, these nanospoges complexes are drug-loaded and release targeting peptides that are tightly bound to the radiation-induced cell surface layer of tumour receptors. Upon contact, the nanospoges adhere to the surface of tumour cells and begin to release drug molecules. Nanospoges also have the potential for the treatment of SARS-CoV-2. Such nanospoges are derived from membranes of human cells/tissues that are naturally attacked by SARS-CoV-2. These nanospoges can bind and destroy viruses and induce clinical improvement through cytokine neutralization. Thus nanospoges can successfully protect hosts from any kind of invading cells

KEYWORDS

Nanosponge; Polymers; Co-polymers; Cross-linkers; Polymerisation

INTRODUCTION

The potential for cyclodextrin nanospoges to serve as drug carriers was not recognised until a study by Trotta and colleagues. But it was Min Ma and DeQuan Li who introduced the terminology "Nanosponge" in 1998. Today pharmaceutical delivery technology certainly bestows its current interest in drugs by giving them new life through their therapeutic pretension. Nanosponge is a substitutive approach that eminently delivers controlled drug delivery. Nanosponge is an emerging technology for targeted drug delivery^[1,2]. The manipulation and development of materials on a nanoscale scale is the focus of much of today's research in the fields of nanotechnology and nanomedicine. Innovative cross-linked cyclodextrin polymers that are nanostructured inside a three-dimensional network constitute cyclodextrin-based nanospoges (CD-NS). Highly porous nanoparticles called CD-NS have high surface areas, crystalline or amorphous structures, and swelling tendencies^[3,4]. Cyclodextrin-based nanospoges (CD-NSs) are highly cross-linked, insoluble 3D network polymers used in a variety of scientific and technological fields.

However, the main focus of research is on pharmaceutical applications, where CD-NSs are primarily used as drug delivery systems. In general, four successive generations of CD-NSs can be identified based on their chemical makeup and physical characteristics. The first generation of NSs is simple nanospoges which thus involve several categories based on the chemical make-up of the functional group joining the CD to the cross-linker: urethane, carbonate, ester, and ether NSs. The second generation of NSs has modified nanospoges with unique characteristics including electric charge and fluorescence. The third generation of NSs is represented by stimuli-responsive CD polymers, which are capable of changing their behaviour in response to environmental changes such as pH and temperature gradients, oxidative/reducing conditions, and finally, the fourth generation of NSs, a new family of molecularly imprinted CD polymers (MIPs), exhibiting a high selectivity towards specific molecules^[5].

Materials Used In The Production Of Nanospoges:-

Various chemical substances are currently employed in the production of nanospoges. Some of them include polymers, co-polymers and cross-linkers. These compounds are the most essential components and are for sure included while compounding nanospoges. As depicted in **Table 1** and **Table 2**. Some of the polymers are stated along with their properties in **Table 2**.

Polymers:-

Any member of the family of natural or artificial substances known as polymers is made up of very big molecules, or macromolecules, which are repetitions of simpler chemical building blocks known as monomers. Numerous components of living things as well as substances for living things are all made of polymers^[6]. Sequence-controlled polymers are macromolecules in which monomer units of different chemical natures are arranged in an ordered format^[7].

Examples: Methyl β -cyclodextrin, Hydroxy propyl β -cyclodextrin

(from table 1. For individual properties refer table 2)

Co-polymers:-

Copolymer Typically, the copolymer is made up of replicating units of two different monomers. Block copolymers, graft copolymers, random copolymers, and alternative copolymers are some types of these copolymers. Repeating units are positioned arbitrarily in random copolymers; alternative copolymers have them in an ordered fashion; block copolymers have monomers positioned at terminals, and graft copolymers have the monomer chains positioned at various locations on host polymers. A new family of materials called supramolecular copolymers has seen much of its potential realised in recent years. Noncovalent polymers with many components can be used to combine advantageous traits like dynamicity and novel functionality^[8,9].

Examples: Ethylcellulose, Polyvinyl alcohol

(from table 1. For individual properties refer table 2)

Cross-linkers:-

The substance that is utilised to make a cross-linked fluid system is called a cross-linker. Cross-linked fluid is produced when a 20–30 lb linear gel system is paired with a cross-linker. By joining the various gel polymers together, cross-linkers make gelling agents more viscous. By joining numerous molecules together, a cross-linker greatly raises the molecular weight of the underlying polymer, raising the viscosity of a linear gel^[10].

Examples: Diphenyl carbonate, Diaryl carbonate, Pyromellitic anhydride

(from table 1. For individual properties refer table 2)

Table 1:- Different Classes Of Compounds With Their Examples Employed In Nanosponges Formulation

S.No	Compounds	Examples
1.	Polymers[6,7]	Hyper cross-linked polystyrene and its derivatives (Alkyloxy carbonyl cyclodextrin, Methyl β -cyclodextrin, Hydroxy propyl β -cyclodextrin)
2.	Co-polymers[8,9]	Poly(valerolactone allyl valerolactone), Ethylcellulose, Polyvinyl alcohol
3.	Cross-linkers[10]	Diphenyl carbonate, Diaryl carbonate, Pyromellitic anhydride, Carbonyl imidazole, Epichlorohydrine, Glutaraldehyde, Dichloromethane

Table 2:- Examples Of Individual Classes With Their Physical Properties And Their Use In Nanosponges Production

S.No	Compound	Molecular Formulae	M.P (°C)	B.P (°C)	Aqueous Solubility	Solubility In other solvents	Uses w.r.t Nanosponges
Polymers							
1.	Cyclodextrin ^[11]	C ₄₂ H ₇₀ O ₃₅	290-300	1541.2±60	Sparingly soluble in water; freely soluble in hot water	slightly soluble in ethanol	as a complexing agent, to Increase the aqueous solubility of the active substance
2.	Methyl β -cyclodextrin ^[12,13]	C ₅₄ H ₉₄ O ₃₅	180-182	1206.9±65	Soluble	ethanol, DMSO, and dimethyl formamide, which should be purged with an inert gas	increase the permeability of cells
3.	Hydroxy propyl β -cyclodextrin ^[14,15]	(C ₆ H ₇ O ₃) _x × (C ₃ H ₅ O) _x	278	1521.9±60	Soluble	tetrahydrofuran, dimethyl formamide, acetone, acetonitrile etc.	Enhancement of Tenoxicam solubility, formulation of anticancer nanosponges
S.No	Compound	Molecular Formulae	M.P (°C)	B.P (°C)	Aqueous Solubility	Solubility In other solvents	Uses w.r.t Nanosponges
Co-polymers							
1.	Ethylcellulose ^[16]	C ₂₀ H ₃₈ O ₁₁	240-255	654.2±55	Practically insoluble	ethanol, methanol, toluene, chloroform and ethyl acetate	non-biodegradable, non-toxicity, biocompatible and tolerable with reduced toxicity

2.	Polyvinyl alcohol ^[7,18]	(C ₂ H ₄ O) _x	200	228	Soluble	slightly soluble in ethanol, but insoluble in other organic solvents	Polymer to Optimize Bioavailability for Poorly Water-Soluble Therapeutic Agents
Cross-linkers							
1.	Diphenyl carbonate ^[19,20]	C ₁₃ H ₁₀ O ₃	83	306	Insoluble	Ethanol, Diethyl ether, Acetate, carbon tetrachloride	Improves solubility of poorly water-soluble drugs
2.	Pyromellitic Dianhydride ^[21,22,23]	C ₁₀ H ₂ O ₆	286	400	Hygroscopic	Dimethyl sulfoxide, acetone, chloroform, n-hexane, benzene, ethyl ether	As a drug delivery system for cancer treatment
3.	Carbonyl Diimidazole ^[24]	C ₈ H ₆ N ₄ O ₆	119	394±25	Reacts with water	Moderately soluble in THF, Soluble in ethanol	Enhance the permeation stability and cytotoxic to damaged cells

Methods For Preparation Of Nanosponges:-**a) Solvent Method:-**

Mix a suitable solvent, such as dimethylformamide or dimethyl sulfoxide, in particular with the polymer in question. and after that, add an extra amount of their 4:16 accessible cross-linkers to this mixture. For two days, a temperature of 10°C is maintained for the polymer process. Dimethyl carbonate and carbonyl diimidazole are the most often utilised carbonyl crosslinkers. The product is allowed to cool at room temperature when the reaction is accomplished, and then it is incorporated into the mixture. distilled water is recovered, filtered under an air oven, and purified using a soxhlet apparatus. Ethanol is then added for additional extraction. To obtain a uniform white powder, repeat the drying process under a vacuum and with mechanical power^[25].

b) Emulsion Solvent Method:-

To increase the drug-loading capacity of nanosponges, different ratios of polyvinyl alcohol and ethyl cellulose might be used. Ethyl cellulose and the medicinal substance are dissolved in 20 ccs of dichloromethane to create the dispersion phase. Dissolving polyvinyl alcohol in 150ml of distilled water creates a continuous phase. In the dispersed phase, the continuous phase is dropped in. Then, for about two hours, this mix is allowed to be stirred at 1000 rpm. The obtained nanosponges are collected, dried in ovens for about a day and kept in desiccators^[26].

c) Ultrasound -Assisted Synthesis:-

This approach involves mixing polymers and cross-linkers in a flask, placing the flask in an ultrasound bath filled with water, heating it to 90°C, and then sonicating the mixture for five hours without the use of a solvent. After letting it cool, wash it with water to get rid of the unreacted polymer. Purify via a protracted ethanol-based soxhlet extraction. Store the product at 25°C after vacuum-drying it^[27].

d) Melting Method:-

In this method, crosslinkers and CDs are allowed to melt as all other materials are homogenised for five hours while being stirred magnetically. To eliminate unreacted excipients and reaction byproducts, the aforementioned Solution is allowed to cool and washed repeatedly^[28,29].

e) Loading Of The Drug Into Nanosponges:-

Pre-treating nanosponges are necessary to produce particles smaller than 500 nm. The nanosponges are either dissolved in water or suspended in it to get this range. To stop the buildup, the nanosponges in suspension are sonicated ferociously. To create a portion of colloids, the suspension is centrifuged. Drying the sample with a freeze dryer after separating the supernatant.

Nanosponges are made into an aqueous solution. The drug suspension

overdoses and the complexation process requires stirring the mixture constantly for a predetermined amount of time. Centrifugation is used to distinguish between complexed and uncomplexed drugs once complexation has occurred. Using a freeze dryer or solvent evaporation, the solid crystals of the nanosponges are produced.

A key principle in the complexation of the medication is found in the solid crystal structure of nanosponges. Paracrystalline nanosponges have lower drug-loading capabilities than crystalline nanosponges. In weakly crystalline nanosponges, drug loading occurs as a mechanical mixing^[30].

Polymerisation:-

The monomer is first made into a non-polar drug solution, to which an aqueous phase is then added. This phase typically contains a surfactant and a dispersant to help with suspension. Following the establishment of a suspension with discrete droplets of the desired size, polymerization is accomplished by catalysing the reaction or raising the temperature to activate the monomers. A reservoir-like system that opens through holes at the surface is created as a result of the polymerization process^[28].

Advantages Of Nanosponges

- Hydrophobic drugs can be enclosed inside nanosponge particles because they are soluble in water.
- Site-specific medication delivery that is targeted.
- Less negative side effects
- A 3.62-fold increase in loading capacity, a sustained release pattern, and up to an 8.3-fold increase in the ability of the compound to inhibit the proliferation of MCF-7 cancer cells.
- These compositions remain stable between pH values of 1 and 11.
- These compositions maintain their stability up to 130 °C.
- It can be used to make liquid substances solid and to cover up disagreeable flavours.
- They can be quickly biodegraded.
- These are self-sterilizing because bacteria cannot pass through their 0.25-micron average pore size.
- Augmented compositional flexibility, improved elegance, and long-term stability.

Disadvantages Of Nanosponges

- Large-sized molecules cannot be delivered with drugs because only small-sized molecules, notably those with a mass less than 500 Dalton (Da), can be entrapped.
- They could take the crystalline or paracrystalline form.
- The degree of crystallisation has a major impact on the loading capacity of Nss.
- Paracrystalline NSs can exhibit a variety of loading capabilities^[31,32,33].

Applications Of Nanosponges

A novel possible medication delivery vehicle into and through the skin has been identified as nanosponges. Which includes the delivery of biologics, including antibodies, enzymes, peptides, proteins, and vaccines, is also receiving more attention lately. have a wide range of uses in pharmaceutical formulations due to their versatility and Biocompatibility. They can be utilised as excipients for creating dosage forms for the skin, such as tablets, capsules, pellets, granules, suspensions, and solid dispersions. Nanosponges can serve as multifunctional carriers for increased product functionality and elegance, prolonged release, decreased irritability and improved thermal, physical and chemical stability of the product. Here are several uses for nanosponges that demonstrate their adaptability.

1. As Solubility enhancers: Molecules with very low water solubility can have their wetting and solubility improved by nanosponges. By molecularly dispersing the medications inside the nanosponge structure before releasing them as molecules, the dissolution process can be skipped. It is possible to boost the drug's apparent solubility as a result. The solubility and dissolving rate of a material can be improved to solve many formulation and bioavailability issues, and nanosponges have the potential to significantly increase medication solubility^[34].

2. As Topical agents: The controlled release of topical agents with delayed drug release and drug form retention on the skin using a nanosponge delivery system is a novel technological advancement. Drugs that can be easily manufactured as topical nanosponges include local anaesthetics, antifungals, and antibiotics. Active substances can

permeate the skin and cause rashes or other more severe negative effects. Contrarily this technique enables a consistent and sustained rate of release, minimising discomfort while preserving effectiveness. A designed product can have a wide range of ingredients, including liquid, gel, cream, lotion, ointment, and powder. The antifungal drug econazole nitrate, which comes in cream, ointment, lotion and solution form, is applied topically to relieve the signs and symptoms of superficial candidiasis, dermatophytosis, Versicolorr and skin infections^[28].

3. Nanosponges As A Sustained Delivery System: Due to its success in treating herpes simplex virus infections, the medication acyclovir is frequently employed as an antiviral agent. This means neither the parenteral nor the oral. Acyclovir medication formulations that are currently on the market can be resulting the drug reaching its target with the appropriate concentration sites. Acyclovir is absorbed in the digestive system is inadequate and sluggish; after oral administration, its pharmacokinetics Medicine is quite varied^[35].

4. Nanosponges in drug delivery: By creating inclusion complexes with numerous medications, these will increase the poorly water-soluble pharmaceuticals' aqueous solubility. These complexes can be employed to generate unpleasant odours, turn liquid compounds into solids, and increase the stability and rate of disintegration of medicinal substances. The polymer-based nanosponges are said to deliver drugs to the target site three to five times more effective than direct injection. They are derived from soil and can be made into dosage forms for oral, parenteral, topical, or inhalation^[36].

5. Nanosponges in enzyme immobilization: Since it increases their stability and affects features like enantio selectivity and reaction speeds, enzyme immobilisation is particularly important for lipases⁵¹. As a result, there is an increasing need for new solid supports that are appropriate for the enzyme family. For this, Boscolo et al. revealed that high catalytic performances of *Pseudomonas fluorescens* lipase adsorbed on a new type of cyclodextrin-based nanosponges^[37].

6. Nanosponges for Cancer therapy: Due to their limited solubility, anticancer medication distribution is currently one of the most difficult tasks in the pharmaceutical industry. When compared to direct injection, the nanosponge complex is three times easier to scale. The complex of the Nanosponge loads a medication and exposes a targeting peptide that firmly adheres to a radiation-induced cell top layer on the tumour receptor. Nanosponges attach to the surface of the tumour cell as they come into contact with it and start releasing medication molecules^[38].

8. Nanosponges as potential Covid-19 treatment:- These nanosponges are created using membranes obtained from human cells that are naturally targeted by SARS-CoV-2. When patients are infected by SARS-CoV-2, as long as the viruses are still in the body such as in the lungs, The nanosponges can bind and destroy viruses and induce clinical promote clinical improvement. SARS-CoV-2 neutralisation is followed by cytokine neutralisation. By competing with the host cells for virus binding, these nanosponges can successfully defend the host cells from SARS-CoV-2 infection^[39].

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Conflict Of Interest

The author(s) declare no conflict of interest

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