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REVIEW ARTICLE

Nanosponge: A review of advantages and application as promising drug carrier

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ABSTRACT

Specific site drug is the major problem faced among researchers due to drug poor solubility in water and pharmacokinetic issues. These poorly-water soluble drugs show many problems in formulating them in conventional dosage forms and the critical problem associated is its very low bioavailability. The development of new colloidal carrier called nanosponges has the potential to solve these problems. Nanosponges are a part of nanotechnology. Nanosponges are tiny sponges with a size of about a virus, which can be filled with a wide variety of drugs. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. In this review article, advantages and application of nanosponges have been discussed.

KEY WORDS: Cross-linking agent, Drug delivery, Nanosponge, Targeted delivery

INTRODUCTION

Nanosponges are tiny mesh-like structures, in which a large variety of substances can be encapsulated.[1] They have a proven spherical colloidal nature, reported to have a very high solubilization capacity for poorly soluble drugs by their inclusion and non-inclusion behavior.[2] Nanosponges have recently been developed and proposed for drug delivery. Nanosponges can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability.[3] Nanosponges are able to load both hydrophilic and hydrophobic drug molecules due to their inner hydrophobic cavities and external hydrophilic branching, thereby offering unparalleled flexibility.[4] Nanosponges are more such as a three-dimensional network or scaffold. The backbone is a long length of polyester which is mixed in solution with small molecules called cross-linkers that act like tiny grappling hooks to fasten different parts of the polymer together.[5] It has been reported that, by reacting cyclodextrins (cyclic oligosaccharides) with suitable cross-linking reagents, a novel nanostructured material consisting of hyper-cross-linked cyclodextrins can be obtained, known as nanosponges. Nanosponges can be synthesized as neutral or acid and can be swellable according to the agent used as cross-linker.[6] The net effect is to form spherically shaped particles filled with cavities, where drug molecules can be stored.[7] The cross-linking-to-cyclodextrin ratio can be varied during preparation to improve the drug loading and to obtain a tailored release profile.[8] Their highly porous nanomeric nature enables drug molecules to orient themselves in nanosponge's inclusion as well as interact in a non-inclusion fashion, which offers higher drug loading compared with the parent cyclodextrin molecules. 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

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been already employed in different applied fields, such as cosmetic and pharmaceutical sectors.[9] The engineering capacity of nanosponges is due to the relatively simple chemistry of its polyesters and crosslinking peptides, compared to many other nanoscale drug delivery systems. Nanosponges are water soluble but does not breakup chemically in water. They mix with water and use it as a transport fluid. They can be used to mask unpleasant flavors, to convert liquid substances to solids. The chemical linkers enable the nanosponges to bind preferentially to the target site.[10] The nanosponges are solid in nature. They have been found to be safe for oral and invasive routes, and thus, they could serve as a potential carrier for drug delivery.[11] The tiny shape of nanosponges enables the pulmonary and venous delivery of nanosponges. For oral administration, the complexes may be dispersed in a matrix of excipients, diluents, lubricants, and anti-caking agents suitable for the preparation of capsules or tablets. For parenteral administration, the complex may be simply carried in sterile water, saline, or other aqueous solutions. For topical administration, they can be effectively incorporated into topical hydrogel.[12] Nanosponges are encapsulating type of nanoparticles which encapsulate the drug molecules within its core.[13]

ADVANTAGES OF NANOSPONGES

The current research into novel nanomaterials aims at improving properties of existing materials such as having greater control over the size, homogeneity, high drug loading, and predictable/controlled drug release.[14,15] NS is envisioned as materials having great potential due to the attractive features summarized below.

1. Being amphiphilic in nature, NS, can simultaneously carry both hydrophobic molecules in the hydrophobic cyclodextrin cavity and hydrophilic molecules in the spaces between the single cyclodextrin moieties. Hydrophobic drugs can be loaded into the NS structure to consequently increase their solubility.
2. An attractive feature is the simplicity of chemistry of particles. CD can be cross-linked to form nanopores which serve as sites for drug loading.
3. The superior properties of NS have been attributed to "tunability," that is the ability to control the structure of particles and control the nature and size of aperture. By varying the proportion of cross-linker to polymer, the degree of cross-linking can be modulated, which ultimately affects drug loading and release.
4. One of the major advantages of this system is the ability to produce predictable/controlled drug release.
5. NS can be tagged with specific linkers to target diseased cells hence achieving greater efficacy while reducing side-effects, decreasing dose, and dosing frequency and in turn increasing patient compliance.

APPLICATIONS OF NANOSPONGES

NS prepared using CD has been reported in a number of environmental,[16] enzymological,[17] and pharmaceutical applications. The pharmaceutical applications of NS are summarized below:

Improved dissolution

Poorly-soluble drugs can be incorporated into NS to increase their aqueous solubility by forming inclusion complexes. The poor solubility of NS protects the entrapped drug from precipitation and agglomeration by preventing super saturation in the surrounding media. The drug is incorporated in such a way that the hydrophobic functionalities of the drug occupy the hydrophobic interior cavities of CD units within the NS, while the hydrophilic groups present in the drug associate themselves with the hydrophilic external surface which remains exposed to the environment. XRPD analysis of drug loaded NS shows decrease in the drugs crystallinity, having higher thermodynamic energy. The net effect is enhancement in drug dissolution and consequent increase in drug bioavailability. Vavia *et al*. successfully enhanced solubility of itraconazole by incorporating the drug into NS. They carried out phase solubility studies with a rationale of comparing the solubilization efficiency of NS, copolyvidonum, and a combination thereof. The solubility of itraconazole was enhanced by about 20 folds in NS and more than 50 folds with a ternary solid dispersion system due to enhancement of the amorphous property of the drug.[18] Besides, other drugs in which this technique has been successfully demonstrated include flurbiprofen, doxorubicin,[8] dexamethasone,[19] tamoxifen,[20] and paclitaxel.[21]

Stability enhancement

3Drugs

Drug molecules are susceptible to various degradation processes by exposure to (air) oxygen, water, radiation, or heat. To avoid such degradation, the molecule can be entrapped within the NS, which prevents the reactants from diffusing into the cavity and reacting with the protected guest. CAM, an anti-cancer drug, has poor water solubility and a chemically unstable lactone ring. Swaminathan *et al*. characterized, stabilized, and studied cytotoxicity of CAM-NS. They found that the NS structure protected the lactone ring from opening due to its high inclusion abilities, thereby increasing the drug stability along with prolonging release and enhancing the cytotoxic capacity.[22] Nolan *et al*. found that the stability of anti-asthmatic and anti-allergic drug sodium cromoglycate increased on incorporating it into nanoporous nanoparticles/microparticles having sponge like structure. It was also found that NS containing resveratrol, an anti-oxidant, had better stability and

displayed superior permeation characteristics with cytotoxicity against HCPC-I cells.[23]

Oligonucleotides

NS has also been used to prevent degradation of oligonucleotides. Antisense oligonucleotides inhibit gene expression and are therefore generally used for the treatment of viral infections or cancer. However, they have poor stability in biological medium. Another problem associated with them is weak intracellular penetration. Aynie *et al*. prepared alginate NS which led to protection of the oligonucleotide. On intravenous administration of alginate NS, oligonucleotide accumulation in the lungs was ten-fold greater than with poly-isobutylcyanoacrylate which might have been a result of microembolizations in the pulmonary capillary bed or due to specific interactions of the particles with the alveolar macrophages associated with the polysaccharidic nature of these particles.[24]

Proteins

Swaminathan *et al*. prepared swellable cyclodextrin-based poly (amidoamine) NS through water uptake studies that they observed very good swelling capacity of NS which was stable for 72 h at high temperature. Bovine serum albumin was used as the model protein and incorporated into the prepared NS. Enhanced swelling property along with increased stability of protein was observed.[25]

Enzymes

NS has been used for stabilizing enzymes. CD-NS exhibits much higher inclusion constants as compared to CD and has proved to be suitable supports for enzyme immobilization. They are capable of preserving (and sometimes enhancing) the catalytic proficiency and stability of the immobilized enzymes. Enzyme immobilization is necessary for allowing enzyme recycling and facilitates the separation and recovery of products, along with its capacity to increase thermal and operational stability of the biocatalysts. Boscolo *et al*. also studied the high catalytic performances of Pseudomonas fluorescens lipase adsorbed on cyclodextrin-based NS. Lipases are useful for catalyzing the hydrolysis of triacylglycerols and transesterification reactions which are involved in a number of industrial applications.[17]

Nanosponges in drug delivery

Nanosponges are nanomeric in size and have spherical shape; therefore, nanosponges can be prepared in different dosage forms such as topical, parenteral, aerosol, tablets, and capsules. Telmisartan (TEL) is a BCS Class II drug having dissolution rate limited bioavailability. β-CD-based nanosponges were formed by cross-linking β-CD with carbonate bonds. TEL was incorporated into the nanosponges. Saturation solubility and *in vitro* dissolution study of β-CD complex of TEL was compared with plain TEL and nanosponge complexes of TEL. It was found that solubility of TEL was increased by 8.53 folds in distilled water, 3.35 folds in 1 mol HCl, and 4.66 folds in phosphate buffer pH 6.8 by incorporating NaHCO3 in drug-nanosponges complex than TEL. The highest solubility and *in vitro* drug release was observed in inclusion complex prepared from nanosponges and NaHCO3.[26] Paclitaxelis used for cancer chemotherapy having poor water solubility. β-CD-based nanosponges to deliver paclitaxel is an alternative to classical formulation in cremophor EL, because cremophor reduces the paclitaxel tissue penetration. The biological effect of paclitaxel *in vitro* is highly enhanced by nanosponges: Not only its cytotoxicity is greatly increased after 72 h incubation but also even intracellular paclitaxel concentration is significantly enhanced when compared to plain paclitaxel.[12] Econazole nitrate, an antifungal agent used topically to relive the symptoms of superficial candidiasis, dermatophytosis, and skin infections available in cream, ointment, lotion, and solution. Adsorption is not significant when econazole nitrate is applied to skin and required high concentration of active agents to be incorporated for effective therapy. Thus, econazole nitrate nanosponges were fabricated by emulsion solvent diffusion method and these nanosponges were loaded in hydrogel as a local depot for sustained drug release.

CONCLUSION

Nanosponges are versatile drug carrier system as they carry both hydrophilic and hydrophobic drugs by forming inclusion and non-inclusion complexes. They can deliver drugs by various routes such as oral, topical, and parenteral in a predictable manner to the target site. Besides their application in the drug delivery field, potential applications exist for cosmetics, biomedicine, bioremediation processes, agro chemistry, and catalysis, among others. Drugs delivered by nanosponges can be proved safe and effective and the pharmaceutical industries will benefit greatly if clinical studies can prove their potential for human use.

CONFLICTS OF INTEREST STATEMENT

We declare that we have no conflicts of interest.

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