Nanosponges Overview on Novel Drug Delivery Formulation

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ABSTRACT: Targeting the drug to a particular site to reduce the drug toxicity requires a special drug delivery system. Nanosponges are tiny particles with porous cavities to facilitate drug substances. Nanosponges efficiently transport both hydrophilic and lipophilic drug substances the present manuscript focus method of preparation, mechanism of drug release, evaluation and application of nanosponges.

KEYWORDS: Nanosponges, Targeted release, Controlled release, Hydrophilic, Hydrophobic.

INTRODUCTION

Nanosponges are nanostuctures having a few nanometer-wide cavities, these small cavities can accommodate a variety of drug substances. These tiny particles have the potential to transport both hydrophilic and lipophilic therapeutic substances and can improve the stability of poorly water-soluble pharmacological substances or compounds [1]. Nanosponges are three-dimensional scaffold (backbone) or network of polyester that can degrade spontaneously. To create Nanosponges, these polyesters are combined with a crosslinker in a solution. The polyester in this case is normally biodegradable, thus it breaks down in the body moderately. When the nanosponge scaffold degrades, it releases the drug molecules that were loaded in a negative manner.

Advantages of nanosponges:
1. Increase the aqueous solubility of the medication that is weakly water soluble.
2. Nanosponges can release medicinal molecules in a predictable pattern.
3. Nanosponges operate as a self-sterilizer due to their tiny hole size of 0.25 µm, preventing germs from entering.
4. The nanosponges drug delivery method is non-irritating, non-mutagenic, and non-toxic.
5. Nanosponges serve to eliminate poisonous and venomous substances from the body.
6. The Nanosponges drug delivery mechanism reduces side effects.
7. Increase the formulation's stability and flexibility.

Figure shows: Structure of a nanosponge showing a cavity for drug
8. Reduce the frequency of dose.
10. Nanoparticles complexes are stable throughout a wide pH range (from 1 to 11) and a temperature of 130 °C [2-4].

Disadvantages of nanoparticles:
1. While nanoparticles can encapsulate small molecules, they are not suited for bigger molecules.
2. Sometimes there is dose dumping [5].

Method of preparation:
1. Solvent method:
Nanoparticles are made by combining polar aprotic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) with polymers. A 1:4 cross linker is then added to the mixture. The reaction should be carried out at 10°C to reflux the solvent temperature for 1–48 hours. Once the reaction is complete, the solution is cooled to room temperature and the resulting product is added to bidistilled water. The product is recovered by vacuum filtering, soxhlet extraction with ethanol, and drying.

Table shows: Materials used in the preparation of Nanoparticles.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Copolymer</th>
<th>Cross linker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper cross-linked polystyrenes, Cyclodextrine and its derivatives like Methyl β- cyclodextrine, 2-Hydropropyl β-cyclodextrine.</td>
<td>Ethyl cellulose (EC), Polyvinyl alcohol (PVA)</td>
<td>Di-phenyl carbonate (DPC), di-aryl carbonate, di-isocyanates, pyromelliticanhydride, carbonyl diimidazole, 22-bis(acrylamide)acidic acid and dichloromethane,[6,7]</td>
</tr>
</tbody>
</table>

2. Ultra-sound assisted synthesis:
Polymers are created to react with cross linkers in a flask with no solvent. The flask is placed in an ultrasonic bath that is filled with water and heated up to 90°C. The mixture is sonicated for 5 hours. The combination is then cooled to normal temperature, and the result is roughly broken up. Finally, the non-reacting polymer is removed by washing the product with water, and the nanoparticles are refined using a soxhlet apparatus (ethanol) [8].

Figure shows: Flow diagram for the preparation of Nanoparticles by ultra sound assisted method.
3. Emulsion solvent diffusion method:
To make nanosponges, different amounts of ethyl cellulose and polyvinyl alcohol are used. This method has two phases: dispersed and continuous. The dispersed phase is composed of ethyl cellulose and medicine, which is then dissolved in 20 ml of dichloromethane and combined with polyvinyl alcohol (PVA) in 150 ml of the continuous phase (aqueous). The mixture is then stirred at 1000 rpm for around two hours. The product, namely the nanosponges, is collected via filtration. Next, dry the goods in an oven at 400˚C [9].

4. Loading of drug into nanosponges:
Nanosponges should be pre-treated to produce particles smaller than 500 nm. To get this range, the nanosponges are dissolved or suspended in water. The nanosponges in suspension are sonicated vigorously to prevent buildup. The suspension is centrifuged to yield a colloidal fraction. The supernatant is removed, and the sample is dried with a freeze dryer.

An aqueous suspension of nanosponges is made. To allow for complexation, an excess amount of drug is added to the suspension and stirred continuously for a set period of time. After the complexation has occurred, the uncomplexed drug is separated from the complexed drug by centrifugation. The nanosponges' solid crystals are formed by freeze drying or evaporating the solvent. The solid crystal structure of nanosponges plays an important role in drug complexation. Para-crystalline nanosponges have lower drug loading capabilities than crystalline nanosponges. The drug loading occurs as a mechanical mixing in weakly crystalline nanosponges. [10]

Mechanism of drug release from nanosponges:
Since the nanosponges have an open structure (in the surrounding of nanosponges they do not have any continuous membrane), the active substance is added to the vehicle in an encapsulated form. The encapsulated active substance is able to move freely from the particles into the vehicle until the vehicle gets saturated and the equilibrium is obtained. As soon as the product is applied on to the skin, the vehicle containing the active ingredient gets unsaturated causing a disturbance in the equilibrium. Thus, the flow of active chemicals from nanosponge particles into vehicles begins at the epidermis and continues until the vehicle is absorbed or dried. Even after the nanosponge particles are retained on the skin's surface, known as the stratum corneum, active material is released into the skin for an extended length of time.

Factors influencing in the formulation of nanosponges
Nature of polymer:
The polymer used to make nanosponges can influence their development as well as the pre-formulation. The chamber of a nanosponge should be large enough to contain a drug molecule of a specific size for complexation [11].

Drug:
To interact with nanosponges, medication molecules must have special qualities, as listed below:

• The molecular weight of the medication molecule should range between 100 and 400 Daltons.
• The structure of a medicine molecule should not have more than five condensed rings.
• The drug's solubility in water should be under 10 mg/ml.
• The drug's melting point should be below 250˚C.

Temperature:
Temperature variations can have an effect on medication or nanosponge complexation. Increasing the temperature often reduces the extent of the stability constant of the drug or nanosponge complex, which could be related to a reduction in contact forces such as hydrophobic and Vander Waal forces of drug/nanosponges [12].

Degree of substitution:
The number, position, and type of the parent molecule's substituent can have a significant impact on the nanosponges complexation capacity [13].

Method of preparation:
The mechanism used to load drugs into nanosponges can alter the drug-nanosponge complexation. Although the efficacy of a treatment is mostly determined by the nature or features of the drug and polymer, freeze drying has been shown in some situations to alter drug and nanosponge complexation.
Table Shows: List of drug molecules encapsulated with nanosponges.

<table>
<thead>
<tr>
<th>Category</th>
<th>Nanosponges vehicle</th>
<th>Drugs</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticancer</td>
<td>β- cyclodextrine</td>
<td>Paclitaxel, camptothecin</td>
<td>14</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>β- cyclodextrine</td>
<td>Tamoxifen</td>
<td>14</td>
</tr>
<tr>
<td>Inflammation</td>
<td>β- cyclodextrine</td>
<td>Resveratrol</td>
<td>14</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>Poly(valerolactoneallylvalerolactone) and poly(valerolactoneallylvalerolactone-oxepanedione) Ethyl cellulose polyvinyl</td>
<td>Temozolamide</td>
<td>15</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Ethyl cellulose polyvinyl alcohol β- cyclodextrine</td>
<td>Econazole nitrate, Itraconazole</td>
<td>15</td>
</tr>
<tr>
<td>Cancer therapy</td>
<td>Sodium alginate</td>
<td>Antisense</td>
<td>16</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>β- cyclodextrine</td>
<td>Dexamethasone</td>
<td>16</td>
</tr>
<tr>
<td>Oligonucleotides</td>
<td>Poly L-lysine</td>
<td>Viral infection Pathologic disorder</td>
<td>16</td>
</tr>
<tr>
<td>Cancer therapy</td>
<td>Sodium alginate</td>
<td>Antisense oligonucleotides</td>
<td>17</td>
</tr>
<tr>
<td>Viral infection</td>
<td>Poly L-lysine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathologic disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>β- cyclodextrin</td>
<td>Camptothecin</td>
<td>18,19</td>
</tr>
<tr>
<td>Brain tumors</td>
<td>β-cyclodextrin</td>
<td>Dexamethasone</td>
<td>20</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Ethyl cellulose Polyvinyl alcohol β- cyclodextrine</td>
<td>Econazole nitrate</td>
<td>21,22</td>
</tr>
<tr>
<td>Antifungal</td>
<td>β- cyclodextrin Copolyvidonum</td>
<td>Itraconazole</td>
<td>23</td>
</tr>
<tr>
<td>Cancer</td>
<td>β- cyclodextrin</td>
<td>Paclitaxel</td>
<td>24,25</td>
</tr>
<tr>
<td>Inflammation</td>
<td>β- cyclodextrin</td>
<td>Resveratrol</td>
<td>26</td>
</tr>
<tr>
<td>Cardiovascular diseases, Dermatitis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gonorrhea</td>
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<td>Fever</td>
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<tr>
<td>Hyperlipidemia</td>
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<td></td>
<td></td>
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<tr>
<td>Breast cancer</td>
<td>β- cyclodextrin</td>
<td>Tamoxifen</td>
<td>27</td>
</tr>
<tr>
<td>Brain tumors</td>
<td>Poly(vaerolactone Allylvalerolactone) Poly(Valerolactone-Allylvalerolactone-Oxepanedione)</td>
<td>Temozolamide</td>
<td>2</td>
</tr>
</tbody>
</table>

**EVALUATION OF NANOSPONGES**

The evaluation of prepared nanosponges is done for the following parameters.

1. **Particle size Determination:**

   The particle size of Nanospone is a critical factor in the optimization process. Laser light diffractometry or the Zeta sizer can be used to determine particle size. The cumulative percentage drug release from nanosponges of varying particle size can be plotted against time to investigate the effect of particle size on drug release. Particles bigger than 30 nm can have a gritty feel, whereas particles between 10 and 25 nm are preferable for topical medication administration. [29,30]

2. **Zeta Potential:**

   The potential difference between two fluid layers (dispersion medium and immobile layer) that are locked up with dispersed particles is known as the zeta potential. The zeta potential is a strong predictor of colloidal dispersion stability. The zeta potential can be calculated by adding an additional electrode to particle size equipment or a zeta seizer. A colloidal dispersion is more stable as its zeta potential increases.
3. Polydispersity:
Dynamic light scattering (DLS) is a technique used to determine the size distribution of nano-size particles. Finally, the particle diameter and poly-dispersity index (PDI) can be determined.

4. Compatibility Studies:
The drug should be compatible with the polymers used in nanaosponges. Drug and adjuvant compatibility can be determined using Fourier Transform Infrared Spectroscopy (FT-IR), Powder X-ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC) are two techniques for analyzing crystalline properties. [31,32]

5. Microscopy Studies:
SEM (Scanning Electron Microscopy) can be used to study the microscopic characteristics of nanospheres. [33,34] SEM analysis can be used to determine the shape of nanospheres. [35]

6. Loading Efficiency:
The loading efficiency of a nanosponge particle can be determined by measuring the amount of drug loaded into the nanosponge using a UV spectrophotometer and high-performance liquid chromatography for nanospheres. The loading efficiency of nanospheres can be calculated using the equation below.

\[
\text{Loading efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100
\]

7. Production Yield:
The production yield (PY) can be determined by calculating the initial weight of raw materials and final weight of nanospheres. [36]

\[
\text{Production yield} = \frac{\text{Practical mass of Nanosponge}}{\text{Theoretical mass (polymer+drug)}} \times 100
\]

Application of nanospheres:
Nanospheres offer a wide range of applications in the pharmaceutical industry due to their biocompatibility and adaptability. Nanospheres can be utilized as an excipient in pharmaceutical formulations such as tablets, capsules, granules, pellets, suspensions, solid dispersions, and topical dosage forms. Nanospheres can accommodate both lipophilic and hydrophilic drug molecules, i.e. chemicals classified as biopharmaceutical (BCS-class II) and weakly water-soluble medicines [37].

1. Nanospheres for drug delivery:
Nanospheres due to their microscopic porosity structure, can transport water-insoluble drugs. Drug nanosphere complexes are three times as efficient than direct injections in reducing tumor growth. The nanosphere binds to a medication and exposes a targeting peptide that forms a tight bond with a radiation-induced cell top layer on the tumor receptor. When nanospheres come into contact with a tumor cell, they stick to its surface and begin to release medication molecules. The advantage of targeted drug administration is that it produces a more effective therapeutic impact at the same dose while minimizing side effects [38].

2. Nanospheres for cancer therapy:
Delivering anticancer drugs is one of the most difficult tasks in the pharmaceutical industry today due to their low solubility. According to one article, nanosphere complexes are three times as efficient than direct injections in reducing tumor growth. The nanosphere binds to a medication and exposes a targeting peptide that forms a tight bond with a radiation-induced cell top layer on the tumor receptor. When nanospheres come into contact with a tumor cell, they stick to its surface and begin to release medication molecules. The advantage of targeted drug administration is that it produces a more effective therapeutic impact at the same dose while minimizing side effects [38].

3. Nanospheres for delivery of protein:
The encapsulating capacity of β-cyclodextrin-based nanospheres was investigated using bovine serum albumin (BSA) as a model protein. Bovine serum albumin (BSA) protein solution is unstable, hence it is stored lyophilized. Lyophilization can cause proteins to become denatured from their original structure. The fundamental disadvantage of protein formulation and development is the need to retain its native structure and long-term storage both during and after processing. Nanospheres based on cyclodextrine can
improve the stability of proteins such as bovine serum albumin (BSA) during administration. Nanosponges have also been utilized to immobilize enzymes, encapsulate proteins, and provide regulated distribution and stabilization [39].

4. Role of nanosponges for treatment of fungal infections:
Fungal skin infections are one of the most hazardous diseases in the world [40]. Topical therapy is an appealing option for treating coetaneous infections due to a variety of benefits, including drug tailoring to the primary site of infection and a reduction in systemic adverse effects. Econazole nitrate (imidazole) is a topically applied antifungal or pharmaceutical fungicide that treats athlete's foot, ringworm, tinea-pyriasis versicolor, jock itch, and vaginal thrush. Econazole nitrate items available in the market include cream, ointment, lotion, and solution. Adsorption of econazole nitrate is minimal when applied to the skin, and successful therapy requires a high concentration of active drugs to be combined. For this reason, econazole nitrate nanosponges were created using the emulsion solvent process and put into a hydrogel as a topical administration system for prolonged drug release [41,42]. Itraconazole is an antifungal medicine classified as class II in the biopharmaceutical classification system, with a low dissolving rate and poor bioavailability. So the goal of this study was to increase the solubility of itraconazole in order to alleviate the bioavailability problem. Using β-cyclodextrine cross-linked with carbonate bonds in nanosponges and loading it with itraconazole can boost its solubility.

5. As absorbent in treating poison in blood:
Nanosponges can absorb toxic substances and eliminate them from our bloodstream. Instead of employing antidotes, if we put nanosponges into the bloodstream, they can absorb toxins. In the bloodstream, the nanosponge resembles a red blood cell, tricking toxins into fighting it before absorbing it. The quantity of toxin molecules that each nanosponge can absorb varies depending on the toxin [43].

6. Nanosponges in solubility enhancement:
Swaminathan et al. investigated an itraconazole formulation using nanosponges. [44] Itraconazole is a BCS Class II medication with a low dissolution rate and poor bioavailability. Nanosponges increased the drug's solubility more than 27-fold. When copolyvidonum was introduced as a supportive component in the nanosponge formulation, this increased by 55-fold. Nanosponges solubilize drugs via perhaps concealing itraconazole's hydrophobic groups, boosting wetting, and/or lowering crystallinity. [44]

7. Nanosponges in enzyme immobilization:
Enzyme immobilization is particularly significant for lipases since it increases stability and alters properties such as enantio selectivity and reaction rate. [45] As a result, there is an increasing need for new solid supports that are appropriate for this enzyme family. Boscolo et al. discovered that Pseudomonas fluorescens lipase adsorbed on a novel form of cyclodextrine-based nanosponges had an impressive catalytic efficiency. [46]

8. Nanosponges as a carrier for delivery of gases:
Gases have an important function in medicine, both diagnostically and therapeutically. A lack of proper oxygen delivery, known as hypoxia, has been linked to a range of disorders, including inflammation and cancer. In clinical practice, it may be challenging to provide oxygen in the proper form and amount. Cavalli et al. developed nanosponges formulations as topical oxygen delivery devices capable of storing and gradually releasing oxygen over time. [47]

9. Nanosponges as protective agent from light or degradation:
Gamma-oryzanol, a ferulic acid ester, is becoming popular as a natural antioxidant. It is commonly used to stabilize food and pharmaceutical raw materials, as well as a sunscreen in the cosmetics industry. Its uses are limited because to significant instability and photo degradation. Gamma oryzanol was encapsulated in nanosponges to provide adequate light shielding. Nanosponges loaded with gamma-oryzanol were employed to make both a gel and an O/W emulsion. [48]

CONCLUSION
Nanosponges are novel approach for the drug delivery, which deliver both hydrophilic and lipophilic drug effectively in a controlled manner at target site, delivering drug through nanosponges are beneficial over conventional drug delivery system.

REFERENCES


