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NANOSPONGE APPROACHES FOR ORAL DOSAGE FORM: A REVIEW

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ABSTRACT

Targeted and regulated drug delivery for both topical and oral application is made possible by an inventive and evolving technology known as a nanosponge. In the pursuit of directing the drug to the required site of action, nanoparticle-based drug delivery systems, such as nanosponge delivery, are essential. The oral route is seen to be the most convenient for administering medications to patients. A designed product can be made utilizing nanosponges, which are built on nanoscale polymer spheres that can suspend or entrap drug substances. The major developments in the therapeutics area will be target-oriented drug administration advances in therapeutic efficacy. These tiny sponges can travel through the body to their designated target area, where they stick to the surface and begin to release the medication gradually and precisely. Nanosponge formulations involve encapsulation of drugs in a polymeric material and thus provide patient compliance, controlled site-specific drug release, increased formulation efficacy, improved stability and drug dosing. The drugs which have low solubility will be delivered to the site using the nanosponge formulations. With enhanced solubility and increased bioavailability, nanosponge tablets assist cure conditions like cancer, diabetes mellitus, inflammation, and more. This article deals with the general introduction to nanosponge and oral delivery of nanosponges, its formulation, characterization with the different applications of nanosponge tablets.

KEYWORDS: Nanosponges, Oral route, Targeted, Solubility, Bioavailability.

INTRODUCTION

The primary trends in the therapeutics field are the target-oriented medication administration, improvements in therapeutic efficacy, a decrease in adverse effects, and improved dosing regimen. Nanoparticle based drug delivery system like nanosponge delivery plays a major role in targeting the drug to required site of action.[1]

Nanosponges (NSs) are porous polymeric delivery systems that are small spherical particles with large porous surface. NSs are soluble in water and organic solvents. They are porous, nontoxic and stable. NSs have an advantage in comparison with the common nanoparticles. 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.[2] NSs are encapsulating type of nanoparticles which encapsulate the drug molecules within its core. These are fused in solution along with tiny molecules coined as cross-linkers that helps to break different parts of the polymer together. The size of the nanosponge particles can be changed by adjusting the ratio of cross-linker to polymer.[3] NSs have higher drug loading capacities compared to other nanocarriers. Both hydrophilic and hydrophobic medications can be transported by the NSs, which also makes the water compound more soluble.[4]

NSs are three-dimensional scaffolds (backbone) or polyester networks and are naturally able to degrade. It is combined with a solution called cross-linker with small molecules such as tiny grappling hooks to join together various polymers more easily.[5] For administration of drugs to patients, the oral route is considered to be the most convenient among all.[6] NSs can be orally administered in the form of tablets or capsules. To produce tablets for oral delivery, NSs can be easily included into a matrix of excipients, diluents, lubricants, and anti-caking agents. Nanosponge tablets with either immediate release or prolonged release can be formulated, and these will serve as the carrier of NSs for oral delivery.[7]

NSs are classified into four generations.

- The 1st generation comprises urethane, carbonate, ether and ester NSs synthesized by reacting with a crosslinking agent.
- In the 2nd generation polymers are used for preparation with specific properties.
- Stimuli-responsive NSs of the third generation occur, and these NSs vary their behavior in response to environmental changes such pH, temperature gradients, or oxidative/reducing conditions.

- The fourth generation NSs have exceptional selectivity for particular guest molecules and are molecularly imprinted.[8]

Factors affecting NSs formulation

1. Drug substance

The following characteristics should be present in the drug molecules used to create nanosponge complexes:

- Molecular weight should be between 100 and 400 Daltons.
- The average medication molecule contains not more than five condensed rings.
- Water solubility should be less than 10 mg/ml.
- The melting point of the drug should be less than 250˚C.[9]

2. Type of polymer used

The type of polymer used in nanosponge formulation will have an effect on the NSs formation and performance. The polymer used in the formulation determines the size of the nanosponge cavity and drug complexation.

e.g.; Hyper cross-linked Polystyrenes, Ethyl Cellulose and Polyvinyl alcohol.

3. Temperature

The drug and nanosponge complexation can be affected by temperature changes. The persistent increase in temperature of the Drug and Nanosponge complex may be attributed to the potential reduction of drug or Nanosponge interaction forces as temperature rises.[10]

Mechanism of drug release from NSs

The NSs have an open structure since the active ingredient is given to the vehicle in an encapsulated form. In oral administration tablets or capsules will release the NSs at the absorption site. These microscopic sponges can move through the body until they reach the intended target region, where they attach to the surface and begin dispensing the medicine in a steady and controlled manner.[11] From the particles into the vehicle, the encapsulated active ingredient can travel freely until the vehicle becomes saturated and equilibrium is reached. As that of the skin, 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. The flow of active substances from nanosponge particles into vehicles starts to epidermis until the vehicle is either absorbed or dried. Even after the retention of the nanosponge particles on the surface of skin, the release of active substance continues to skin for a long period of time.[12]

Advantages of NSs

1. Nanosponge as a drug delivery can be used as a controlled as well as targeted drug delivery systems.
2. The major advantage of this delivery when compared to other nanoparticles delivery systems is that it offers predictable release of drug.
3. Improved stability, increased elegance, and enhanced formulation flexibility.
4. The solubility of poorly water-soluble drugs can be increased.
5. Side effects related to higher dose is reduced by this novel approach.[13]

Disadvantages of NSs

1. Nanosponge formulations have potential to incorporate just small molecules, not large molecules.
2. Dose dumping may happen.
3. The loading ability of NSs rests on degree of crystallization.[14]

Preparation of Nanosponges

Solvent method

NSs are prepared by mixing polar aprotic solvents like Dimethyl sulfoxide (DMSO), Dimethylformamide (DMF) with the polymer. The resultant mixture follows by receiving a crosslinker. The above solvent is reflexed at 10˚C for the time ranging from 1 to 48 h. Once the reaction has completed, the solution is cooled down at room temperature and then obtained product is added to distilled water. The product is recovered by filtering the product under vacuum and refining by Soxhlet extraction with ethanol followed by drying.[15]

Emulsion solvent diffusion method

The different proportion or amount of ethyl cellulose and polyvinyl alcohol are used to prepare NSs. This approach employs both dispersed and continuous phases. The dispersed phase consists of ethyl cellulose and the drug, which is then dissolved in 20 ml of dichloromethane and some amount of polyvinyl alcohol (PVA) is added to 150 ml of the continuous phase (aqueous). Then, the mixture is stirred at the speed of 1000 rpm for about 2 hours. By filtering, the product is collected. Then product is dried in an oven at a temperature of 40˚C for 12 hours.[16]

Loading of drug into NSs

To obtain the particle size less than 500 nm, NSs should be pre-treated. The NSs are dissolved or suspended in water and the suspended NSs are sonicated vigorously to prevent the accumulation. The suspension is centrifuged to produce a colloidal fraction. The supernatant is separated and the sample is dried using a freeze dryer. An aqueous suspension of NSs is prepared and an excess amount of drug is added to the suspension and continuously stirred for the certain period of time for the complexation to occur. After the complexation has taken place, the un-complexed drug is separated from the complexed drug by using centrifugation. The solid crystals of the NSs are obtained by using a freeze dryer or by evaporating the solvent.[17]

Preparation of Nanosponge tablets

Nanosponge tablets can be prepared by direct compression method. The prepared nanosponges and Excipients such as Glidants, Polymers, Lubricants were

accurately weighed and sieved. Tablet compression is carried out using tablet punching machine.

Evaluation of NSs

Particle size determination: The size of particles is maintained during polymerization for the formation of free-flowing powders having fine aesthetic attributes. Particle size analysis of loaded and unloaded NSs performed by laser light diffractometry or malvern zeta sizer. Particle size less than 500nm is best for the delivery.

Entrapment efficiency: UV Spectrophotometric method was used to determine entrapment efficiency of drug loaded NSs. The amount of the drug in the suspension was analyzed by centrifugation at 1000 rpm for 30 minutes and the concentration of drug in the supernatant layer is measured. UV spectrophotometric analysis was used to determine the drug's quantity.[18]

Scanning & Transmission Electron Microscopy: NSs were subjected to scanning & transmission electron microscopy (SEM & TEM) studies. Images were recorded at the required magnification at an acceleration voltage of 20 kV using a scanning electron microscope.

X-Ray Diffraction Studies: XRD studies of drug and NSs were recorded using X-ray diffractometer, which is operated at the current and voltage of 40 kV and 40 mA respectively. These studies are useful to investigate the changes in the crystallinity of drugs and NSs. The samples were smeared over a low background sample holder, and XRD patterns were recorded in the 2θ geometry and step 0.020 size at the speed of 5°C/min.[19]

Evaluation of Nanosponge Tablets

Weight Variation: Twenty tablets were selected randomly from each formulation, weighed individually, and the average weight and % variation of tablet weight was calculated.

Friability: The tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 revolutions, the tablets were dedusted and weighed again. The % weight loss of the tablets was used to calculate their friability.

% Friability = (Initial weight - Final weight) * 100 / Initial weight

Hardness and Thickness: Hardness was measured using the Monsanto hardness tester. The thickness of the tablets was measured by using vernier caliper by picking the tablets randomly.[20]

Drug Content: To calculate drug content, accurately weighed quantity of crushed nanosponge tablet and 5 ml of solvent in a volumetric flask was shaken for 1 min using a vortex mixer. The volume was made up to be 10ml. After filtering and diluting the produced solution, UV spectroscopy was used to determine the nanosponge concentration.[20]

Drug content = Actual Drug Content NSs / Theoretical Drug Content × 100

Wetting Time: Five circular tissue papers of 10 cm diameter were placed into a petridish containing 0.2% w/v solution of volatile liquid. One tablet was placed on the surface of the tissue. The time required to develop the colour on the side of the tablets was noted as a wetting time.

Water Absorption Ratio: A petridish containing 6 ml of water was filled with a little piece of tissue that had been folded twice. A tablet was placed on the paper before the initial weight of the tablet is noted. After that, the wet tablet was weighed.[21]

***In-vitro* Disintegration:** *In-vitro* Disintegration test was carried out with the help of disintegration apparatus. Tablet was placed in every tube of the basket containing 900 ml of solvent, the temperature of immersion fluid was maintained at 37±0.5°C. Apparatus was operated till no residue of the unit under test remains on the screen of apparatus.[22]

***In-vitro* Dissolution Study:** *In-vitro* release studies were performed using the USP Paddle method at 100 rpm and 37 ± 0.5 °C in 900 ml of solvent. Samples were taken at appropriate time intervals of 5 min for required period of time. The filtered samples were analyzed in UV-spectroscopy.

Stability Studies: Stability studies of prepared tablets were performed as per the standard method. The accelerated stability studies at 40 °C ± 2 °C/75% RH ± 5% RH for a period of 1-6 months and at room temperature for 12 months were carried out. Samples were analyzed for (%) drug content and (%) *in-vitro* drug release.[23]

Applications

Cubosomal nanosponge tablet for colon targeting

Raj AR *et al.*, formulated the cubosomal nanosponge tablets. 5-Flurouracil (5-FU) loaded cubosomal dispersion was prepared by the bottom-up technique and formulation was characterized. From this, 5-FU cubosomal NSs were prepared by the emulsion solvent diffusion method using various pH dependent polymers and evaluated. Nanosponge tablet was prepared by direct compression method and also performed the coating of the tablet with Eudragit solution. Evaluation of 5-FU cubosomal NSs predicted better particle size, zeta potential, and better drug entrapment efficiency. Encapsulation of this formulation into a tablet by direct compression method predicted better drug content and *in vitro* release profile of the drug shows that the formulation is mainly targeted to the colon with 85% of the drug release at the colonic pH. The formulated cubosomal nanosponges for targeting into the colon with

the help of pH dependent polymers mainly resulted in the targeted release of the drug. Cubosomal nanosponge tablet have the improved stability, penetrability, improved patient compliance, and enhanced formulation flexibility.[24]

Nanosponge tablets for treatment of diabetes mellitus

Gedam *et al.*, has formulated and evaluated the nanosponge tablets of gliclazide for treatment of diabetes mellitus. This study was undertaken to prepare polymeric NSs of an oral anti-hyperglycemic drug Gliclazide to achieve improved solubility. Nanosponges using ethyl cellulose as a polymer and glutarldehyde as a cross-linker was prepared by the emulsion solvent diffusion method. Drug polymer compatibility study is performed by FTIR and DSC. To obtain optimized batch, 32 factorial designs is performed. Particle size for the optimized batch was 398 nm. The spongy and spherical nature of formulations were changed into tablets to provide immediate release drug delivery for oral route, as seen by a SEM and TEM image of the optimized batch. Cross povidone was used in the preparation of these pills. According to *in-vitro* dissolution experiments, zero-order kinetics governs the percent cumulative drug release. The medication may be present throughout the nanosponges rather than only on their surface, according to a SEM photograph. The Gliclazide loaded nanosponge tablets showed the enhanced solubility and bioavailability.[25]

Controlled release cyclodextrin-based nanosponge tablet

The use of cyclodextrin-based NSs represents another emerging technological approach to increasing drug solubility and stability. Cyclodextrin-based NSs showed superior complexing ability than natural cyclodextrins towards many molecules. The freeze-drying process is used by **Reddy *et al.*,** to prepare tramadol-loaded NSs. Because of the reduced drug particle size, the creation of a high-energy amorphous state, and intermolecular hydrogen bonding, the dissolution of the tramadol NSs was much higher than that of the pure drug. TEM image revealed the spherical structure of drug-loaded NSs. FTIR, DSC and XRD studies confirmed the formation of the inclusion complex of tramadol with NSs showing a highly porous structure losing all its crystallinity. The NSs was formulated in to tablets and evaluated for weight variation, hardness, friability and disintegration studies and obtained satisfactory results. The maximum quantity of the drug is released within 2 hours from the marketed tablet, while the percentage of tramadol released from NSs tablets after 12 hour was 87.48% and stability studies showed no significant changes within 6 months. This study showed that cyclodextrin NSs can be a promising approach for controlled drug delivery of the opioid analgesic tramadol and showed cyclodextrin based NSs have better solubility with enhanced bioavailability.[26]

Nanosponge tablets for combination therapy

The drugs paracetamol, aceclofenac and caffeine had varied solubility profiles, and formulating them into single tablet did not have the desired dissolution profile for drug absorption. **Moin A *et al.*,** prepared the nanosponge tablet for combination therapy. It is prepared by the hot-melt method. The nanosponge characterization studies confirmed the entrapment of the drug within the colloidal three-dimensional structure of β-CD with the formation of an inclusion complex. The entrapped drug properties have been modified from crystalline to amorphous nature, which enhances drug solubility. The optimized nanosponge loaded formulations obtained by computer-based optimization technique is directly compressed into tablets with suitable diluents. The results of *in vitro* dissolution studies of nanosponge tablets indicated rapid dissolution due to changed solubility properties of the drug, compared to pure drug. This study shows that drug with different solubility profile can be loaded into polymeric nanosponge that have optimized dissolution properties for combination therapy.[27]

Nanosponge loaded floating tablets for gastric ulcer

Poornima *et al.*, prepared gastroretentive floating tablets of Lafutidine for treating gastric ulcer. The NSs is prepared by emulsion solvent diffusion method and optimized by using 32 factorial designs. The observed values for particle size, zeta potential and % entrapment efficiency of the optimized nanosponge is found to be within the acceptable limit. The optimized NSs are spherical in shape and porous in nature. The floating tablets of nanosponge loaded with lafutidine were prepared by using effervescent technology using different grades of polymers. The pre and post-compression parameters was found to be within the I.P limit for uncoated tablet. The *in-vitro* drug release studies results showed that there is complete drug release from NSs within 7 hours whereas the floating tablet showed controlled release of the drug up to 24 hours. The maximal medication content in the optimized formulation was 98.7% and when compared to other formulations had shortest buoyancy lag time and the optimized floating tablet showed controlled drug release for prolonged period of time. The optimized tablet remained stable during the entire period of study when stored at different temperatures and humidity conditions. So, it shows that the floating tablet of nanosponge loaded with lafutidine can be an effective drug delivery system for gastric ulcer with controlled drug release.[28]

CONCLUSION

The NSs can be made into oral dosage forms because they are solid by nature. The complexes may be dissolved for oral administration in a matrix of excipients, diluents, lubricants, and anticaking agents appropriate for the production of capsules or tablets. A polymeric substance is used in the nanosponge formulation, which results in regulated site-specific drug release, enhanced stability and dosage, increased

formulation efficacy, and patient compliance. The size of the particles and the rate of release can be adjusted by adjusting the polymer to cross linker ratio and the stirring rate. NSs are spheres made of nanopolymers that can suspend or can entrap both hydrophilic and lipophilic molecules, improving formulation flexibility and stability while reducing negative effects. The drug-loaded NSs can be used to create tablets with immediate and sustained release. The nanosponge tablets can deliver drugs that are both hydrophilic and lipophilic to the target area. The drugs with low solubility can be delivered to the targeted site using the NSs formulations. Thus, nanosponge tablets improves the solubility and are highly effective and show increased bioavailability in the treatment of cancer, diabetes mellitus, and inflammation.

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