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A MINI REVIEW: RECENT TRENDS ON NANOSPONGE

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ABSTRACT
Efficient targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complex chemistry that is involved in the development of new systems. The invention of nanosponges has become a significant step toward overcoming these problems. Nanosponges have emerged as one of the most promising fields of science because of their perceived application in controlled drug delivery. Effective drug delivery at a targeted site had given the possibility to perform the precise function to control the release rates and have a better compliance on the health care system but the chemistry possessing complex form had made conditions complicated But the invention of nanosponges has given a significant approach toward solving this problem. Nanosponges are tiny sponges having size of about a virus and can be filled with variety of drugs.

Keywords: Nanosponges, Solvent Method, Ultrasound-assisted synthesis

INTRODUCTION

Nanosponges are diminutive mesh-like structures (Figure A) in which a bulky variety of substances can be encapsulated[1,2].They have spherical colloidal nature and extremely high solubilization capacity for poorly soluble drugs by their inclusion and non-inclusion behavior[3]. Lately, nanosponges have been developed and proposed for drug delivery. Nanosponges can solubilize poorly water soluble drug and provide longer release as well as enhancing drugs bioavailability[4]. Nanasponges are able to load both polar and non-polar drug molecules due to their inner hydrophobic cavities and external hydrophilic branching, thus providing unparalleled flexibility[5]. Nanosponges are tend to have threedimensional network or scaffold. Cross linker is named when a long length of polyester,backbone which is mixed in solution with small molecules to fasten different parts of the polymer together[6].

Nanosponges can be synthesized as neutral or acid and can be swellable according to the agent used as crosslinker[10]. The result is to form spherically shaped particles filled with drug molecules in cavities [11]. During preparation, the cross-linking-to-cyclodextrin ratio can be differentto enhance the drug loading and to gain a tailored release profile[12-14]. Their highly porous nanomericnature allows drug molecules to orient themselves in nanosponge's inclusion as well as interact ina non-inclusion fashion, which gives higher drug loading related with the parent cyclodextrinmolecules[12].

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Nanosponges show a remarkable merit in comparisonwith the common nanoparticles. They can be easily regenerated by varying treatments. For instanceswashing with co-compatible solvents, stripping with moderately inner hot gases, mild heating or changing pH or ionic strength.

The capacity of nanosponges is because of the simple chemistry of its polyesters and crosslinking peptides, compared to many other nanoscale drug delivery systems[16]. Although nanosponges are water soluble but they do not breakup chemically in water. They mix with water and act as a transport fluid. They can beused to mask undesired flavors, converting liquid substances to solids. The chemical linkers allow the nanosponges to bind specifically to the target site [16].

The nanosponges are solid in nature [17]. They are harmless for oral and invasive routes, and thus they could serve as a potential carrier for drug delivery [14,15]. The tiny shape of nanosponges allows the pulmonary and venous delivery of nanosponges[18]. 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 oral route.The complex may be simply carried in sterile water, saline or other aqueous solutions for parenteral administration. For topical administration

they can be effectively incorporated into topical hydrogel[19,20]

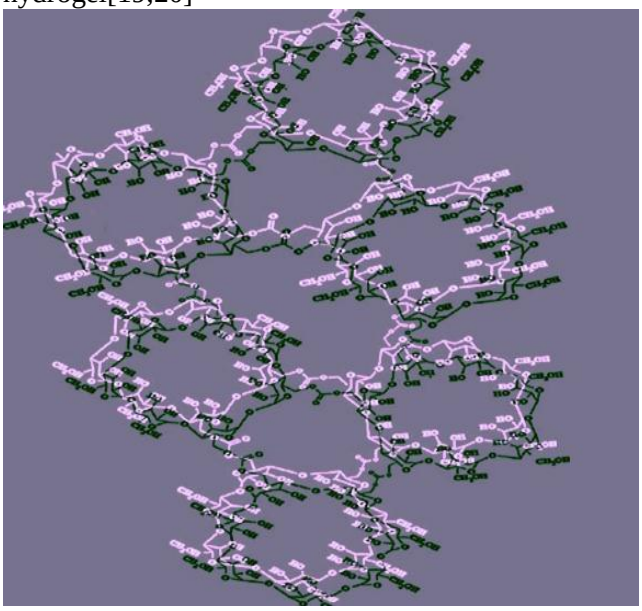

Figure-A: Molecular structure of cyclodextrin carbonates nanosponges. [7-9].

FORMULATION TECHNIQUES OF NANOSPONGE

Solvent method:

In this method, suitable solvent was mixed with the polymer, in particular in a polar aprotic solvent such as dimethylformamide, dimethylsulfoxide. This mixture was added to excess amount of the crosslinker, especially in crosslinker/polymer molar ratio of 4 to 16. The reaction was carried out at temperature ranging from 10 °C to the reflux temperature of the solvent, for time ranging from 1 to 48 h. Carbonyl compounds are the preferable cross linker (dimethylcarbonate and carbonyl diimidazole)[18].After the reaction is completed, the solution was allowedto cool at room temperature. After that, the product was added tolarge excess of bidistilled water and the product was recovered by filtration under vacuum and subsequently purified byprolonged Soxhlet extraction with ethanol. The product wasdried under vacuum and grinded in a mechanical mill toget homogeneous powder[22].

Ultrasound-assisted synthesis:

According to this method, nanosponges were gained by reactingpolymers with crosslinkers in the absence of solvent andunder sonication. Spherical and uniform size of the nanosponges will be obtained by this method[17]. The polymer wasmixed and the crosslinker in aexact molar ratio in a flask. The flask which put in an ultrasound bath filled withwater will be heated to 90 °C. The mixture was sonicated for5 h. Then the mixture was allowed to cool and the productwas broken roughly. After that, the product was washed with water toremove the non reacted polymer and subsequently purifiedby prolonged Soxhlet extraction with ethanol. Theproduct was dried under vacuum and stored at 25 °C [17,22].

Loading of drug into nanosponges:

Nanosponges for drug delivery should have a mean particle size below 500 nm. The nanosponges were suspended in water and sonicated to prevent the presence of aggregates and then centrifuged the suspension to get the colloidal fraction. The supernatant was separated and dried the sample by freeze drying[22]. The aqueous suspension of nanosponges was dispersed the excess amount of the drug and the suspension was maintained under constant stirring for specific period of time required for complexation. The uncomplexed (undissolved) drug was separated from complexed drug by centrifugation after complexation. Then solvent evaporation or freeze drying is carried out to get the solid crystals of nanosponges[18,22]. Crystal structure of nanospongeis very important in complexation with drug. A study showed that paracrystallinenanosponges revealed different loading capacities when compared to crystalline nanosponges. The drug loading is better in crystalline nanosponges than paracrystalline one.

CHARACTERIZATION OF NANOSPONGES

Particle size:

A scanning electron microscope (Zeiss, Germany)was used to scan the surface morphology of nanosponges. The samples weremounted on aluminum stub with adhesive tape and coated withplatinum/palladium alloy under vacuum.). The difference in crystallization state of the raw materials and the product observed under electron microscope indicates the formation of the inclusion complexes[23,24].

Particle size analysis

Particle size of the nanosponge formula-tions was measured by a laser light scattering particle size analyzer [25]. Samples were added in water and such suspensions stirred when the particle size analysis. Triplicate measurement was done.

Zeta potential analysis

Zetasizer was used to measured the zeta potential of nanosponges(Malvern instruments, UK) at 25◦C. Before the measurement, nanosponge formulations

werediluted with deionized water. Each measurement was carried out in triplicate [26]

Moisture uptake studies

Three nanosponge formulations were open to three differenthumidity conditions at 23◦C. Various saturated salt solutionslike calcium carbonate in 31% RH desiccator, potassium nitrate in45% RH desiccator, and ammonium chloride in 79.3% RH desiccator were used to construct the controlled humidity in desiccators . Formulations were subjected to these various humidity for 30 days [27].

Encapsulation efficiency

The calcium content of nanosponge formulations (F1, F2 andF3) was assayed by Atomic Absorption Spectrophotometer [25]. Formulations of nanosponges equivalent to 250 mgof calcium carbonate were dissolved in few millilitre of 6 M HCIthen diluted with deionized water. The concentrations of calciumin these formulations were calculated.

In vitro release study

In vitro, dissolution test apparatus (Electrolab, USA) USP apparatus II was used to perform the releasing of calcium from nanosponges formulations at 50 rpm at 37◦C. A 100 mg of formulation was placed 500 ml of simulated gastric fluid (pH 1.2) for first2 h and then it was transferred in 500 ml phosphate buffer (pH 7.0) and aliquot samples were withdrawn.at specific time interval. Atomic absorptionspectrophotometer was used to determine the calcium content in the sample.

Accelerated stability study

The accelerated stability study was carried out according to ICHguidelines [28]. Sealed vial of freshly prepared formulation (F3) were placed in stability chamber maintained at 25◦C,60% RH. The formulations subjected to stability tests were analyzedfor 3 months period for its physical appearance, size and nature ofdrug with a frequency of 1 month sampling.

X-ray diffractiometry and single crystal X-ray structure

Inclusion complexation in the solid state can be detected by Analysis Powder X-Ray diffractiometry. Since the drug molecule is liquid have no diffraction pattern, then the diffraction pattern of a newly formed substance clearly differs from that of uncomplexednanosponge. The complex formation is indicated by the difference of diffraction pattern., A comparison has to be made between the diffractogram of the assumed complex and that of the mechanical mixture of the drug and polymer molecules when the drug compound is in solid state[29].

A diffraction pattern of a physical mixture is frequently the total of those of each component, while the diffraction pattern of complexes is apparently vary from each constituent and leads to a "new" solid phase with various diffractograms. Diffraction peaks for a mixture of compounds are responsible for the chemical decomposition and complex formation[29]. The diffraction patterns and the crystalline nature of the drug are altered by the complex formation of drug with nanosponges. The complex formation leads to the improving of the existing peaks, appearance of a few new peaks and changing of certain peaks[29].

Thin layer chromatography:

The Rf values of a drug molecule diminish to considerable extent and this available to know the complex formation between the drug and nanosponge[29].

APPLICATIONS OF CYCLODEXTRIN NANOSPONGES IN PHARMACEUTICALS

Nanosponges prepared from cyclodextrins are used as drug carriers in pharmaceutical formulations. Molecular encapsulations of the drug and other modifications with suitable cyclodextrin based nanosponges can solve the problems such aspermeability, insolubility, sensitivity, etc., and facilitate safe and efficient delivery of drugs [30]. Nanosponges can carry water insoluble drugs and BCS (Biopharmaceutical Classification System) based class-II and IV drugs and can be also used to enhance the dissolution rate, solubility and stability of such drugs. Nanoporous structures enable entrapment of flavors by adsorption.Therefore,it helps to mask the unpleasant flavors and also changes liquid substances to solids. Nanosponges can adsorb odorous material and hence facilitate its removal from organic materials, water and other products. Nanosponges are solid in nature and can be easily formulated as oral, parenteral, topical or inhalation dosage forms.Some specific applications of CD based nanosponges include the following:

Enhancement of drug stability:

b-CD units are conjugated with a polymer, where a number of b-CD units are bound to the same polymer chain. Several b-CD units improve the stability of the drug complex [31]. Moreover, the polymer may work together with the b-CD moieties in stabilizing the complexes. Such studies have been

carried out for proteins and peptides due to their insufficient stability, costly production, immunogenic, allergic potential and also poor bioavailability and sensitivity towards proteases [32]. Bovine serum albumin (BSA) proteins in solution are unstable, they are stored in lyophilized state. Nonetheless, proteins can get be denatured on lyophilization and get conformation different from the native structure. A major demerit is protein formulation and development is the need to maintain its native structure during processing and long-term storage [33].

Nanosponges as carriers for enzymes, proteins,vaccines and antibodies:

Proteins, peptides, enzymes and derivatives are helpful in the biomedical and therapeutic fields. Proteolytic enzymes are used to treat cancer or type I mucopolysaccharidosis, while DNA and oligonucleotides are used in gene therapy. Administration of these molecules presents different limitations [34]. There are some concerns with enzyme, vaccine and antibody stability. Proteins and other macromolecules can be delivered across a biological barrier, targeting them towards the site by adsorbing or encapsulating them in cyclodextrinnanosponges.

Modifying drug release:

Often administration is the major demerit of most of the commercially available delivery systems. Nevertheless, a drug loaded in the nanosponge structure can be hold and released slowly over time.The rate of drug release of hydrophilic CD NS can be changed, which can be used for enhancement of drug absorption across biological barriers, act as a potent drug carrier in immediate release formulations. It may act as sustained release carriers for water-soluble drugs, including peptide and protein drugs [35].

Anticancer drug therapy:

They may provide protection for the drug during its passage through the stomach. This drug is released slowly at pH 1.1, whereas release is faster if pH is raised to 7.4.

Effective delivery carriers:

For instances, Cyclodextrinnanosponges have been used as antitumor drugs such as paclitaxel, camptothecin and tamoxifen which present bioavailability problems due to their solubility in water is low or non-existent. The drugs were incorporated into nanosponges and investigation of theirantiproliferative effect is carried out . Complexes showed greater effect than that of thedrug alone [36].

Solubility enhancement:

The presence of cross-linking and cyclodextrin cavities in the structure enhances the interaction with active molecules. These characteristics allows different substances to be solubilized in the formed cavities. Inclusion complexation or solid dispersions with CDs can enhance drug solubility or rate of dissolution of poorly water-soluble drugs because of the reduction in drug crystallinity. Most of hydrophobic functionality in the interior cavity of the CD hide by resulting complex while polar hydroxyl groups on the external surface remain exposed to the environment; as a result water soluble complex is formed [37]. Methylated CDs with relatively low molar substitution are the most powerful solubilizers. CD nanosponges can further enhance drug dissolution even when there is no complexation and act as release enhancers [35].

CDs also enhance the permeability of hydrophobic drugs by improving drug solubilityand dissolution. Therefore, it makes them free at the surface of the biological barrier, wherefrom they partition into the membrane without disturbing the lipid layers of the barrier. Comparison of improved aqueous solubility of lipophilic drugs was made with the hydrophilic drug doxorubicin after the drugs were loaded into nanosponges. This action could be ascribed to the larger number of lipophilic sites free for the complexation of lipophilic drugs in comparison with the hydrophilic sites on the cyclodextrin cage [36].

CONCLUSION

The nanospongesare able to release the drug in a controlled manner to the targeted site. They have the ability of carrying both non-polar and polar molecules. Due to their small particle size and spherical shape these can be developed as different dosage forms like oral, parenteral and topical preparations. Nanosponges technology offers variety entrapment of ingredients and as a result lowered side effects, enhanced stability, improved elegance and enhanced formulation flexibility. Hence, nanosponges technology bring site specific drug delivery and prolongs dosage time intervals and thus patient compliance. Nanosponge formulation could be the best solution for solving various nano related issues in the pharmaceutical industry.

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