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Review Article

Nanosponges as Potential Carriers in Drug Delivery

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ABSTRACT

Recent advancements in nanotechnology led to the development of components with simple substances such as liposomes, nanocrystals, inorganic nanoparticles, nanosponges etc. These nanoparticulate drug delivery systems are useful in the improvement of the therapeutic purpose of the drugs. This review contains the details about the types of nanosponges, synthesis, characterization and applications of nanosponges and examples of some marketed formulations. Pharmaceutical industries after carrying out certified clinical studies developed nanosponges as effective carriers for the delivery of the active moieties. Nanosponges are three-dimensional network of polyester or scaffold (backbone) with colloidal sizes. Nanosponges have multifunctional applications in cosmetic preparations enhancing the effectiveness and reducing the side effects and accumulation of most of the drugs. Nanosponges having tiny particle size cross various biological barriers into specific intracellular compartments, when attached with the molecular transporter, which are very difficult for several drugs to achieve. These nanoparticles when encounters the tumor cell gets adhere to the surface of the tumor cell and begin releasing the drug in controlled and predictable fashion.

1. Introduction

Treatment of several diseases is associated with the various physical, chemical and biological problems hence the health care professionals and pharmaceutical industries has been creating nano-scale materials.[1] Nanotechnology is the science and technology dealing with the formation of useful materials, devices and systems with the modification of the structure and properties in the nanometer length scale. Nanotechnology-based drug delivery systems can protect drugs from degradation, reduces the number of doses required, and treatment expenses. Insoluble drugs which are difficult to administer such as paclitaxel can be delivered effectively by the nano-based systems. Nanotechnology affects the whole array of areas, from the environment to health care to hundreds of commercial products. The areas of drug delivery are developing rapidly and becoming highly competitive.[2] These developments are utilized to optimize the effectiveness of therapy and efficacy. The major challenges faced in the development of the drug products are, sustained release action of the drug and improving the patience compliance. Enhanced formulation stability and targeting of the drugs to the specific sites and long-term product efficacy has been problem for the medical researchers. The new drug complexes called as the nanosponges has the potential to solve the problem.[3] By definition nanosponges are the three-dimensional network of polyester or scaffold (backbone) that is capable of degrading naturally. Nanosponges consisting of solid nanoparticles with colloidal sizes and nanosized cavities are hyper cross-linked polymer based colloidal structures. They have the size range of 50nm-100nm with average diameter below 4µm.[1] This technology is used in cosmetics, over-the counter skin care, sunscreens and prescribed drugs. Drug accumulation of active ingredients in dermis and epidermis is prevented by using nanosponges. When compared to conventional methods nanosponges because of their tiny mesh like structures show effectiveness in the delivery of drug products for breast cancer.[4] Nanosponges having solid nature can be formulated into different dosage forms such as oral, parenteral, topical and inhalation forms. When simply mixed with sterile water, saline or other aqueous solution can be administered orally, for topical delivery can be formulated as hydrogels. As nanosponges encapsulate the drug molecules into its core they are known as encapsulating nanosponges. They are porous, non-toxic and stable at high temperatures up to 300˚C. [5] Compared to other

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nanoparticle drug development, predictable release is the one of the major advantages of the nanosponges. By the method of associating with the drug molecules the nanosponges are classified as follows:

Encapsulating nanosponges: Nanosponges such as alginate and nano capsules are encapsulating nanosponges which entraps different drug molecules. Nano capsules like poly (isobutyl-cyanoacrylate) entraps the drug molecules in their aqueous core.

Complexing nanosponges: These nanoparticles attract the drug molecule by electrostatic charges.

Conjugating nanoparticles: conjugating nanoparticles links to drug molecules through a strong covalent bond.[6]

Nanosponges involves the highly selective release of the drug substances due to the presence of cavities in the nanomeric size and tunable polarity, these nanosponges can be easily regenerated by using different methods such as washing with eco-compatible solvents, mild heating, stripping with moderately inert hot gases, changing the pH or ionic strength.[7] Nanosponges are often magnetized by preparing with the components having the magnetic properties. The tiny shape enables the pulmonary and venous delivery of nanosponges. Most of the drug delivery systems have the difficulty in scale up as they require complicated chemistry, but the nanosponges can be produced by simple chemistry enabling the technology to scale up easily for the production of the commercial products. The size of nanosponges can be controlled by varying the proportion of the cross-linker to polymer ratio. Due to their novel and versatile nature, they can be used in delivery of the proteins, DNA and the smaller chemical compounds like most drugs. They can be used in vaccination which allows the delivery of new drugs in a direct way.

Advantages of Nanosponges: [7-11]

1. Aqueous solubility of the poorly water-soluble drug is increased.
2. Because of the tiny pore size (0.25 µm), they release the drug molecule in a predictable fashion and act as a self-sterilizer thus preventing the entry of bacteria in disinfectant solutions.
3. These are non-irritating, non-mutagenic and non-toxic.
4. Help to get rid of the toxic and venom substance from the body, minimize side effects.
5. Increase formulation stability and enhance the pliability of the formulation.
6. Reduce dosing frequency and increase patient compliance.
7. Nanosponges complexes are stable over wide selection of pH (i.e 1-11) and a temperature of 130°C.

Disadvantages of Nanosponges:[12]

1. Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.
2. Dose dumping may occur at times.

2. Materials Used in the Preparation of Nanosponges[13,14]

Materials that are used in the preparation of nanosponges are polymer, copolymer and cross-linker.

Polymer: Polymer used in the preparation of the nanosponges influences the formulation hence selection depends up on character and purpose of the drug encapsulated. Example of the Polymers used for preparation of the nanosponges include polyvinyl alcohol (PVA), ethyl cellulose, polymethylmethacrylate, hyper connected polystyrenes, cyclodextrins and their derivatives like methyl beta cyclodextrins, alkyloxy carbonyl cyclodextrins.

Co-polymer: Co-polymer used in the preparation of the nanosponges depends upon the active moiety to be incorporated and structure of the polymer. Three-dimensional nano porous products can be obtained effectively by using co-polymer which transforms the molecular nanocavities and possess the ability to entrap the targeted moieties by forming the hydrophobic and hydrophilic matrix these are obtained by varying the degree of cross-linker. Hydrophilic nanosponges are often developed by taking epichlorohydrin as a cross-linker, which may modify the amount of active moiety release, increase the absorption of active moiety through biological barriers and act as a possible system for immediate release formulations.

Cross-linking agents: like pyromellitic anhydride, diisocyanates, diphenyl carbonate diary carbonates, glutaraldehyde, carbonyldiimidazoles, 2,2bis(acrylamido) ethanoic acid and acid dianhydrides end in hydrophobic nanosponge.

3. Types of Nanosponges: [15]

Nanosponges are of two types they are Metal and Polymeric Nanosponges. Type of nanosponges is given in the **Figure 1.**

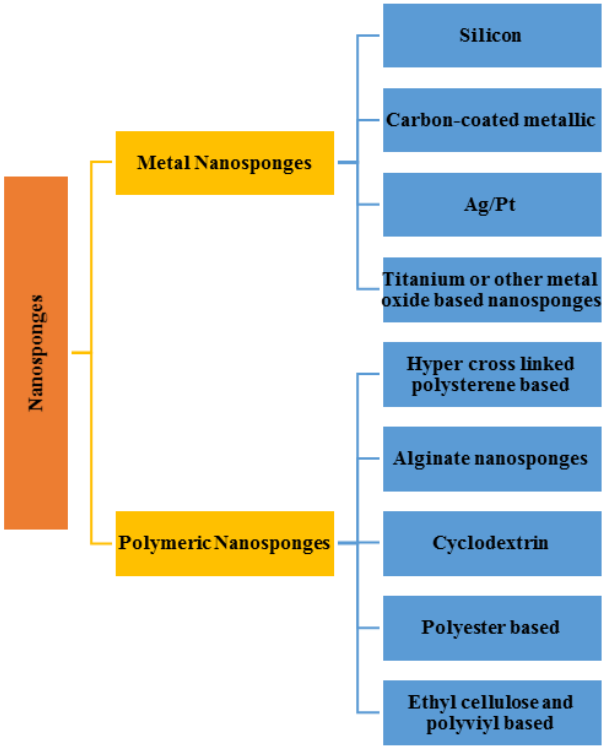

Figure-1: Types of Nanosponges

Metal Nanosponges

The metal nanosponges includes carbon-coated metallic nanosponges, silicon nanosponge particles, Ag/Pt nanosponges, metal-oxide or titanium nanosponges are having little importance in the drug delivery.

Silicon Nanosponges [16]

The silicon nanosponges have the particle size ranging from about 1µ to 4µ. These are prepared from metallurgical grade silicon powder having

nanocrystals with disposed pores between the nanocrystals and to the entire nanosponge particle. Preparation method involves treating the silicon powder by jet milling and then separating the silicon particles to isolate particles of size ranging from 1µ to 4µ. And then etching the isolated particles to obtain silicon nanosponge particles. Etching is done by illuminating the isolated silicon particles at a determined time and controlling the wavelength of near infrared, visible, near ultraviolet, far ultraviolet and extreme ultraviolet radiation. Silicon nanosponges are used in the micropatterning of mammalian cells.

Carbon-Coated Metallic Nanosponges [17]

Metallic nanosponges have the disadvantage of undergoing chemical reactions such as oxidization hence protective coating is necessary. Carbon encased metal nanosponges have a metallic core surrounded by a shell of carbon synthesized by metal evaporation technique used in the protection of the polymers.

Ag/Pt Nanosponges [18]

These are prepared by using ascorbic acid. In this nanosponges were deposited on the side walls of sodium dodecyl sulphate micelle-functionalized herring bone graphite nanofibers using electrostatic attraction. These are used for the synthesis and oxygen reduction electrocatalysis.

Titanium or Other Oxide Based Nanosponges

These are synthesized by methods such as dealloying method, sol-gel method, electrochemical deposition method. The porous metal oxide nanosponges are utilized in various fields such as removal of pollutants, used as a biocatalysts and biosensors, supercapacitors and electrodes.[19] Example of such metal oxide nanosponges includes multi stimuli-responsive gold nanosponges used in the treatment of cancer.[20]

Polymeric Nanosponges

Polymeric nanosponges includes hyper-cross-linked polystyrene nanosponges, cyclodextrin-based nanosponges, alginate nanosponges, polyester based nanosponges, ethyl cellulose and polyvinyl alcohol based nanosponges. Polystyrene nanosponges are used for column packing in chromatography. Nanosponges based on the ethyl cellulose and polyvinyl alcohol are used for the topical delivery of the drugs. Cyclodextrin based nanosponges, alginate nanosponges and polyester nanosponges are reported to carry anticancer drugs.

Hyper-cross-linked nanosponges

They have spherical shape and excellent size distribution, but they do not bind to the large quantities of drugs due to their hydrophobic surfaces.

Cyclodextrin-based nanosponges: [12-15]

Cyclodextrin are typical toroidal cone shaped cyclic, non-reducing oligosaccharides. With different types of lipophilic and hydrophilic molecules they form inclusion and non-inclusion complexes and results in the arrangement of atoms in such a way that inside cavity is lipophilic and outside torus is hydrophilic. Solubility of drugs like anti-cancer drugs, steroids and anti-inflammatory having very low aqueous solubility can be enhanced. Cyclodextrin-based nanosponges can be obtained by reacting the cyclodextrin with a suitable cross-linker like diisocyanates, diarylcarbonates and carbonyl diimidazoles, carboxylic acid diianhydrides and 2,2-bis(acrylamido)acetic acid. Among many compounds used as the cross-linking agents' particular results are obtained by using agents like active carbonyl compounds such as carbonyldiimidazole, dimethyl carbonate and diphenyl carbonate. Cyclodextrin nanosponges can be used to prepare oral or injectable formulations. For formulating injectables the complex may be mixed with the suitable vehicle and for oral administration they can be dispersed in a mixture of excipients like diluents, lubricants, and anticaking agents that are suitable for the tablet and capsule preparation. These nanosponges can be magnetised in the presence of the compounds having magnetic properties. Beta-cyclodextrin based nanosponges with the epichlorhydrin as a cross-linker can be used in the column packing for inclusion chromatography, removes unpleasant constituents from grape juice, for the cobalt determination in foods, copper analysis, and also for the decontamination purpose. Cyclodextrin carbonate nanosponges using diphenyl carbonate, carbonyl diimidazole, dimethyl carbonate is used for encapsulating of the drugs such as levodopa, quercetin, curcumin, tamoxifen, paclitaxel etc. Cyclodextrin anhydrin nanosponges using anhydride cross-linkers such as pyromellitic dianhydride, ethylenediaminetetraacetic acid, dianhydride are used for encapsulating drugs such as ibuprofen, doxorubicin, meloxicam, acetylsalicylic acid and creatinine, cilazapril, captopril and enalapril.

Beta-cyclodextrin nanosponges includes the following:

Beta-cyclodextrin based carbamate nanosponges: [11] These nanosponges are prepared by treating beta-cyclodextrin with diisocyanates such as toluene-2,4-diisocyanate and hexamethylene diisocyanates in dimethylformamide at 70˚C for 16-24h by rigorous washing with organic solvents like ethanol, acetone etc. The residual solvent is removed and the solid cross-linked polymer is obtained. Unreacted reagents are completely removed by using the Soxhlet extraction with ethanol or acetone. These nanosponges are used for purification of water as they have the highest binding ability with the organic molecules. Compounds like 2-methylisoborneol and geosmin are eliminated by using the beta-cyclodextrin carbamate based nanosponges. Ex: effects like gastric ulceration are overcome by Naproxen loaded toluene disocyanate cross-linked beta-cyclodextrin nanosponges.

Beta-cyclodextrin carbonate based nanosponges: Solvent evaporation technique or melt method is employed for the preparation of this kind of nanosponges. Drugs such as dexamethasone, doxorubicin, flurbiprofen etc.

Beta-cyclodextrin based ester nanosponges: These nanosponges are prepared by dissolving beta-cyclodextrin and pyromellitic anhydride (PMDA) in dimethyl sulfoxide. Triethylamine or pyridines which are organic bases acts as a catalyst for reaction. Polar carboxylate anion helps ester nanosponges to individually host the apolar organic molecules and cations. Ionic component of nanosponges-PMDA can be complexed at different pH values, with the number of heavy metal cations such as aluminium, nickel, cobalt, copper etc.

Polyamido amine nanosponges: Beta-cyclodextrin polymerizes with the acetic acid after 94 h at room temperature. Sodium dodecyl sulphate-polyacrylamide gel electrophoresis technique showed the confirmational stability of the formulation and the protein.

Modified nanosponges: These nanosponges are prepared by modifying the classical carbonate-based nanosponges. By treating cyclodextrin nanosponges with fluorescein isothiocyanate in dimethyl sulfoxide at 90˚C for 1-2 h. Fluorescent nanosponges are formed which are widely used in the cancer therapy.

Polyester nanosponges: [21,22]

Degradable aliphatic polyesters like Poly glycolic acid and poly carboxylic acid and their polymers have received considerable importance within

the pharmaceutical and medical field. They're used as implant materials and diagnostic systems. To alleviate, the deficiencies of conventional nanoparticles compositions, a discrete functionalized polyester nanoparticle are reported.

Alginate nanosponges: [21-24]

Alginate nanosponges are sponge like nanoparticles which consists of many holes that carry the oligonucleotides. Alginate nanosponges have advantages over nanoparticles as they are prepared in the aqueous medium without any organic solvent thus loading of the drug is easy. The drug remains intact during the preparation and it can be protected. The drug is localized in the core instead of association on the surface of a particle. Nanosponges protects oligonucleotides from proteins and enzymes through electrostatic force. The preparation method of the alginate nanosponges involves two steps. First step involves the gelation of the sodium alginate; this involves addition of the calcium chloride under magnetic stirring to obtain calcium alginate pregel. Second step involves, the poly-L-lysine (PLL) was added to form a polyelectrolyte complex with free remaining negative charges of the Pregel, leading to a colloidal nanosponges.

Ethyl cellulose and poly vinyl based nanosponges

Ethyl cellulose and polyvinyl based nanosponges are used for the preparation of the drugs for the topical delivery. This method involves the use of the ethyl cellulose which is dissolved in the aprotic solvents such as dichloromethane. Required amount of polyvinyl alcohol is dissolved in sufficient amount of water. Then the dispersed phase containing drug and ethyl cellulose is added slowly to the continuous phase and stirred with magnetic stirrer for about 1000RPM for 2 hours. Then the nanosponges formed are collected by filtration and filtered material is dried in oven at 40˚C for 24 hours.

4. Method of Preparation of Nanosponges[25]

The various methods employed for the preparation of nanosponges involves the following.

Melt method

In melt method cross-linking agent together with the cyclodextrin and other components are mixed and heated to 100˚C for five hours on a magnetic stirrer. Then the above matrix is allowed to cool. Unreacted components and by-products are eliminated by frequent bathing.

Solvent evaporation technique

In solvent evaporation method, the fusion step is avoided and solvents like dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) are used to solubilize the cross-linking agent. Polymer is dissolved in solvent and the mixture obtained is put in solution of cross-linker and refluxed for 1–48hrs. Filtration is done to recover the final product and is purified using Soxhlet extraction for prolonged periods. The product achieved is spherical and solid nanostructures with high water solubility. The size of nanosponges is often reduced by high homogenization where water suspension of prepared nanosponges is homogenized at constant speed for 10 min. The flow chart for the preparation of nanosponges by solvent evaporation method is given in the **Figure 2.**

Emulsion Solvent Diffusion Method

In this method different proportions of ethyl cellulose and poly vinyl alcohol is used for the preparation of nanosponges. The dispersed phase containing Ethyl cellulose and drug was dissolved in 20ml dichloromethane and slowly added to a definite amount of polyvinyl alcohol in 150ml of aqueous continuous phase. The reaction mixture was stirred at 1000 rpm for 2hrs. The Nanosponges formed were collected by filtration and dried in oven at 40˚c for 24hrs. The dried Nanosponges were stored in vacuum desiccators to ensure the removal of residual solvents. The flow chart for the preparation of nanosponges by emulsion solvent diffusion method is given in the **figure 3.**

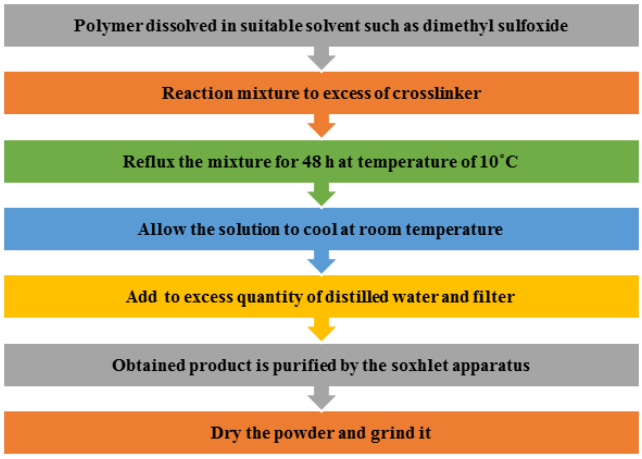

Figure-2: Flow Chart for Preparation of Nanosponges By Solvent Evaporation Method

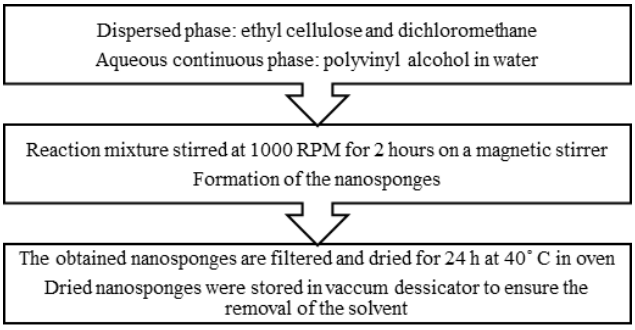

Figure-3: Flowchart for The Preparation of Nanosponges By Emulsion Solvent Diffusion Method

Ultra-sound assisted synthesis

In this method polymer is mixed with the crosslinkers in a flask without the solvent, then the flask is placed in an ultrasound bath containing water and heated up to 90˚C and the mixture is sonicated for 5h, Mixture is cooled down and the product is broken down into rough pieces. At last, non-reacting polymer is removed by washing with water and refining is done using Soxhlet apparatus to get nanosponges.

Microwave assisted synthesis

Microwave irradiation is the simplest method used for the synthesis of cyclodextrin nanosponges which reduces the reaction rate up to four times when compared with the common melt method leading to the formation of nanosponges with high degree of crystallization and homogenous particle distribution.

Loading of Drug Into Nanosponges: [15]

Nanosponges are pre-treated by dissolving or suspending in water so as to obtain the particle size of less than 500nm. The suspended nanosponges are sonicated vigorously to stop the build-up and therefore the suspension is centrifuged to supply a colloidal fraction. The supernatant is separated and the sample is dried using a freeze dryer.

1. An aqueous suspension of nanosponges is prepared by adding an excess amount of drug to the suspension and continuously stirred for certain period of time for the complexation to occur. After the complexation, the uncomplexed drug is separated from the complexed drug by centrifugation. The solid crystals of the nanosponges are obtained by employing a freeze dryer or by evaporating the solvent.
2. This solid crystal structure of nanosponges features a crucial role of complexation of the drug. The drug loading capacities of Para crystalline nanosponges is lesser in comparison to crystalline nanosponges. The drug loading takes place as a mixture in weakly crystalline nanosponges.

Mechanism of Drug Release From Nanosponges: [15]

Since the nanosponges have an open structure the active substance is added to the vehicle in an encapsulated form. The encapsulated active substance is in a position to maneuver freely from the particles into the vehicle until the vehicle gets saturated and therefore 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 substances from nanosponge particles into vehicles starts, it proceeds to epidermis until the vehicle is either absorbed or dried. Even after the retention of the nanosponge particles on the surface of skin i.e., the stratum corneum, the release of active substance continues into skin for a long period of time.

Factors Influencing the Formulation of Nanosponges

The various factors influencing the formation the nanosponges are types of cross-linkers and polymers, drug, temperature, degree of substitution, method of preparation given in the **Figure 4.**

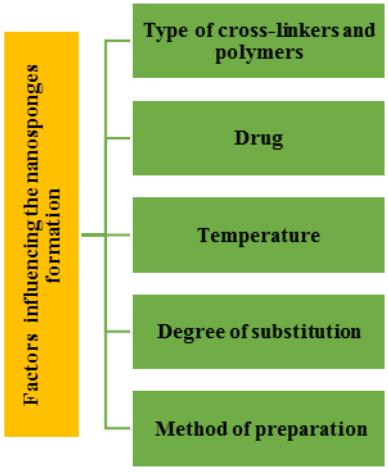

Figure-4: Factors Influencing the Nanosponge Formulation

Type of cross-linkers and polymers: [15]

The polymer utilized, influences the nanosponges formation and also pre-formulation. For complexation the cavity size of nanosponges should be large enough to entrap a drug molecule of specific size. Alteration in the degree of cross-linkers and polymers leads to the formation of hydrophilic and hydrophobic cavities which holds the drug molecule of particular size. Hydrophilic nanosponges: application of epichlorohydrin as a cross-linker leads to the formation of the hydrophilic nanosponges which modulates drug release rate and absorption of drug through biological barriers. Hydrophobic nanosponges: this includes the use of cross-linkers such as pyromellitic dianhydride, diisocyanate, carbonyldiimidazole and diphenyl carbonate. These nanosponges used for the sustained or controlled release profiles including proteins and peptides.

Drug: [26]

The drug molecules should have some specific characteristics to be complexed with the nanosponges as mentioned below:

1. Molecular weight should be in range of 100-400 Daltons.
2. Structure of drug molecule should not consist more than 5 condensed rings.
3. Solubility of drug in water should be <10ml/ml
4. Melting point <250˚C.

Temperature: [27]

Changes with the temperature can affect the complexation of drug or nanosponges. Increasing the temperature generally decreases the extent of the stability constant of the drug and results in the reduction in the interaction forces such as hydrophobic and vanderwaals forces of drug thus affecting the nanosponge complex.

Degree of substitution: [27]

The complexation of the nanosponges greatly suffers from the amount, position, and sort of substituent of the parent molecule.

Method of preparation: [27]

Method of preparation affects the nanosponge complexation and thus successful use of method depends up on the characteristics of the drug and the polymer, in some cases freeze drying can also shown to affect the drug and nanosponge complexation.

Characterization of Nanosponges

The characterization methods for the nanosponges are listed below:

Solubility studies: [1]

Solubility studies are generally an approached technique for analysis of the inclusion complexes as they enhance the solubility and bioavailability. Degree of complexation is often known by the plot of phase solubility. Solubility studies are conducted to access the pH of the drug, solubilization outline and to gauge the factors affecting drug solubility.

Microscopic study: [5]

Microscopic studies of nanosponges/drug are often conducted by using scanning microscope and transmission microscope. Inclusion complex formation is indicated by the difference within the crystallization state and therefore the product seen under a microscope.

Zeta potential determination: [1]

Zeta potential is defined as the difference of potential between two layers (dispersion medium and immobile layer) of fluid locked up with dispersed phase. Zeta potential is an indicator of stability of the colloidal dispersion. By adding extra electrode on particle size equipment or zeta sizer, the zeta potential is often measured. Higher the zeta potential of a colloidal dispersion more is its stability.

Thermodynamical method: [1]

Thermal degradation of nanosponges, drug molecule or any other particle in the formulation undergoes changes they are often determined by using thermodynamic studies. The changes of drug particles are often melting, evaporation, oxidation and decomposition and polymeric changes. The changes within the drug molecules indicate the formation of an honest complex. The thermogram of DTA and DSC is observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation inclusion complexes.

Swelling studies: [13]

Dried hydrogels were weighed accurately and immersed in 10 ml of phosphate buffer of pH 7.2. Hydrogels were taken carefully at 1, 2, 4, 6, 8,

10, 12 and 24hours intervals. Blotted with filter paper and weighed accurately. Increase in weight was determined as time increases. The percentage swelling was calculated from the equation.

% Swelling = ((wet weight-dry weight) / wet weight) X 100

The swelling studies are important as it is main mechanism for the drug release from gel formulation. Water penetrates to gel and allows the drug to dissolve in water and thus by this mechanism drug is released. Gel upon contact with the buffer, buffer penetrates into the gel and swells thus allows the drug to dissolve and drug gets released. Higher percentage of the swelling indicates the high drug release.

X-ray diffractometry and single crystal: [1]

X-ray structure analysis:

Powder x-ray diffractometry is used to detect inclusion complexation in the solid state. If the drug molecule is in liquid state as the liquid have no diffraction pattern of their own the diffraction of newly formed substance clearly differs from that of uncomplexed nanosponges. The diffraction pattern difference indicates the complex formation. When the drug compound is a solid substance 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. The complex formation of the drug with nanosponges alters the diffraction patterns and also changes the crystalline nature of the drug. The complex formation leads to the sharpening of the existing peaks, appearance of peaks and shifting of peaks.

Single crystal X-ray structure analysis:

The interaction between the host and guest molecule can be identified and the precise geometrical relationship can be established and hence used to determine inclusion structure as well as the mode of interaction.

Particle size and polydispersity: [1]

Particle size can be determined by dynamic light scattering (DLS). It is used to determine the size distribution profile of nanoparticles and poly-dispersity index (PDI).

Infrared spectroscopy: [1]

The interaction between the drug within the solid state and nanosponges are often determined by using infrared spectroscopy. During formation of complexes the nanosponge bands can slightly change.

Loading efficiency: [1,15]

The loading efficiency of a nanosponge particle is often determined by the estimation of drug loaded into the nanosponge using UV spectrophotometer and high-performance liquid chromatography. The loading efficiency of nanosponges is often calculated by using the equation.

Loading efficiency = (Actual drug content/Theoretical drug content) X 100

In-Vitro drug release study: [1,15]

Franz Diffusion cell with a diffusional area of 2.26 cm^2 with dialysis membrane can be used to study the release of drug from the optimized nanosponge formulation. The donor phase consists of drug-loaded nanosponge complex in distilled water. The receptor phase also contains the same medium. The receptor phase is withdrawn completely after fixed time intervals, suitably diluted with distilled water and then analysed by UV spectrophotometer.

5. Applications of Nanosponges

Nanosponges for drug delivery

Nanosponges having nano porous structure can carry water insoluble drugs (BCS class-II drugs). These complexes can be used to increase the dissolution rate, solubility and stability of the drugs, so as to mask the unpleasant flavours and convert liquid substances to solids. Beta-cyclodextrin nanosponges delivers drug to target site 3 to 5 times more effectively than direct injection. Drugs difficult to formulate in terms of their solubility can be effectively delivered as nanosponges. Drugs formulated as nanosponges are given in the **Table-1.**

Table-1: Some Drugs Used in Nanosponge Preparation

Drug	Nanosponges vehicle	Indication
Itraconazole	β-cyclodextrin	Antifungal
Tamoxifen	β-cyclodextrin	Antihypertensive
Terbinafine hydrochloride	PVA and ethyl cellulose	Antifungal
Lemon grass oil leaves	PVA	Antifungal
Resveratrol	Cyclodextrin	Antineoplastic
Griseofulvin	Cyclodextrin	For bitter taste masking
Voriconazole	Ethyl cellulose	Antifungal
Cefalexin	PVA	Antifungal
Paclitaxel	β-cyclodextrin	Antineoplastic

In cancer therapy: [15]

The small nanosponges crammed with a drug load and expose targeting peptide that binds to radiation-induced cell surface receptors on the tumour. When sponges encounter tumour cells they stick with the surface and are triggered to release their cargo.

Topical agents: [28]

Nanosponge delivery system is a unique technology for the controlled release of topical agents, prolonged drug release and retention of drug form on skin. Example includes: Adsorption isn't significant when econazole nitrate is applied to skin and required high concentration of active agents to be incorporated for effective therapy. Thus, econazole Nanosponges were loaded in hydrogel as an area depot for sustained drug release fabricated by emulsion solvent diffusion method.

Antiviral application: [15]

Nanosponges are often useful within the ocular, nasal, pulmonary administration routes. The selective delivery of antiviral drugs or small interfering RNA (siRNA) to the nasal epithelia & lungs can be accomplished by nanocarriers in order to target viruses that infect the respiratory tract infections such as respiratory syncytial virus, influenza virus & rhinovirus. They can also be used for HIV, HBV, and HSV. The drugs which are currently in use as nano delivery system are zidovudine, saquinavir, interferon- α, acyclovir (Eudragit based).

Reduction in volatility of essential oil and material handling benefits: [25]

Nanosponges protect volatile oils against lost by evaporation. These nanosponges resulted in long lasting effect due to slow release of chief volatile components of oils. Further, volatile oil liquids (at room temperature) needed to be formulated into stable solid formulations as they are difficult to handle. Nanosponges helps to convert these volatile oil liquids into amorphous or microcrystalline powders which are convenient to handle.

Cellular Nanosponges Inhibit SARS-CoV-2 Infectivity: [29]

Plasma membranes derived from human lung epithelial type II cells or human macrophages are two types of cellular nanosponges. Both identified and unidentified protein receptors required by SARS-CoV-2 for cellular entry is displayed by the nanosponges. SARS-CoV-2 is neutralized and unable to infect cells when incubated with the nanosponges and hence able to neutralize the virus as long as the target of the virus remains identified host cell.

As absorbent treating of poison in blood: [1]

Dangerous poisonous substances can be removed from the blood by using the nanosponges as they absorb the poison. Instead of using the antidotes nanosponges can be injected into the blood as they soak up the toxins. Each nanosponges can absorb the toxin molecules and absorbing capacity depends upon the number of toxin molecules.

Other applications

Nanosponges have many other applications such as in anti-mycotic therapy, analytical applications, biomedical applications, in floriculture, for water purification, for hydrogen storage, for oil cleaning etc.

Marketed Preparations: [15]

Various marketed preparations of nanosponges are:

1. Prostavastin having composition of prostaglandin E1 and alpha-cyclodextrin given in the form of injection for treatment of chronic arterial occlusive disease, controls hypotension. Marketed in the Japan, Europe, USA.
2. Glymesason consisting of dexamethasone and beta-cyclodextrin given in the tablet form for dermal as an analgesic and anti-inflammatory. Marketed in Japan.
3. Brexin consisting of piroxicam and beta-cyclodextrin for oral delivery given in the form of capsule for analgesic and antiphlogistic. Marketed in the Europe.
4. Prostarmon E consisting of prostaglandin E2 and beta-cyclodextrin tablet form for induction of labor marketed in Japan.

6. Conclusion

The Nanosponges release the drug to the targeted site in a controlled manner. They have the capability of carrying both lipophilic and hydrophilic molecules. These can be developed as different dosage forms like oral, parenteral and topical preparations due to their small particle size and spherical shape. Nanosponge technology involves the entrapment of the drug substances and successful incorporation into topical drug delivery for retention of dosage form on skin, and for oral delivery using bio erodible polymers, especially for colon specific delivery and controlled release of the drug thus increasing the formulation flexibility, enhanced stability, reducing the side effects. Thus, Nanosponge technology prolongs dosage intervals and provides site specific drug delivery thus improving patient compliance. Nanosponge formulation can be the best solution for solving various nano related issues in the pharmaceutical industry. The future challenges of nanosponges involves the delivery of the peptides through oral route and other bio-erodible, and liable biomers. The novelty in development of nanosponge formulation can be potent for new generation of the cosmetics, medicine and high molecular weight protein, gas carriers and water filters.

Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

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