

Review Article**Multifunctional nanosponges for the treatment of various diseases: A review****Nargish Bano¹, Sudhir Kumar Ray¹, Tripti Shukla^{*1}, Neeraj Upmanyu¹, Ruchi Khare¹, Sharad P. Pandey², Prabhat Jain³**¹School of Pharmacy & Research Peoples University, Bhopal (M.P.) India²Shri Govindram Seksaria Institute of Technology and Science, Indore (M.P.) India³Scan Research Laboratories, Bhopal (M.P.) India

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Abstract

Recent advances in nanotechnology demonstrate the increased attention that is now being turned to the supramolecular assembly of simple components for therapeutic and diagnostic purposes. This review contains detail about materials used in synthesis of nanosponges, different methods of preparation, characterization and applications. Targeted drug delivery to specific sites is the significant problem which is being faced by the medical researchers. The new developed colloidal system called nanosponge has potential to overcome these problems. Nanosponges are novel class of hyper-cross linked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. They enhance stability, reduce side effects and modify drug release. The outer surface is typically porous, allowing sustain release of drug to specific sites, prevent drug and protein degradation. Nanosponges are small sponges with a size of about a virus, which can be filled with a wide variety of drugs. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more effective for a particular given dosage. To varying the portion of cross-linkers and polymers, the nanosponge particles can be made larger or smaller size. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules. It has various applications like enhancing bioavailability of drugs and delivery of drugs into oral, topical as well as parenteral routes.

Keywords: Nanotechnology, targeted drug delivery, nanosponges, bioavailability, controlled release

Introduction

The pharmaceutical and health care industry has been creating and using nano-scale materials for solving many physical, chemical and biological problems associated with the treatment of disease. Nanotechnology is the science and technology of correctly manipulating the structure of matter at the molecular level. It is the use and manoeuvring of matter at a tiny scale. Nanotechnology deals with the formation of useful materials, device and systems and systems through control of matter on the nanometer length scale and exploitation of novel phenomena and properties at that length scale. With advancements in

nanoscience and technology, a large number of materials and improved products may be available with a change in the physical properties when their sizes are shrunk. Nanotechnology-based delivery systems can also protect drugs from degradation. These properties can help reduce the number of doses required, make treatment a better experience and reduce treatment expenses. A number of nano-based systems allow delivery of insoluble drugs, allowing the use of previously rejected drugs or drugs which are difficult to administer e.g. paclitaxel. At present these systems are generally used for existing, fully developed off-patent drugs, the so called low-hanging fruit of nanotechnology-based delivery. Nanotechnology should not be viewed as a single technique that only affects specific areas. It is more of a catch-all term for a science which is benefiting a whole array of areas, from the environment, to healthcare, to hundreds of commercial products (Joseph and

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Moore, 2008; Duncan, 2006).

The area of drug delivery technology is developing rapidly and becoming highly competitive day by day. The developments in the delivery systems are being utilized to optimize the efficacy and the cost effectiveness of therapy. The major challenges faced by drug development industry are: sustained release technology for reducing irritation of a broad range of APIs thereby increasing patient/client compliance and results. Enhanced formulation stability ensuring long term product efficacy and extended shelf life and Also targeting the drug delivery has long been a problem for medical researchers perhaps how to get them to the right place in the body and how to control the release of the drug to prevent overdose (Naseri et al., 2007). The development of new and complex molecules called nanosponges has the potential to solve these problems (Deshmukh and Poddar, 2011).

Nanosponges are novel class of hyper-cross linked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. They enhance stability, reduce side effects and modify drug release. The outer surface is typically porous, allowing sustain release of drug and use for topical drug delivery. Size range of nanosponge is 50nm-100nm with an average diameter below 4 μ m. This technology is being used in cosmetics, over-the counter skin care, sunscreens and prescribed drugs. Conventional formulation of topical drugs accumulates excessively in epidermis and dermis. Nanosponges prevent the accumulation of active ingredient in dermis and epidermis. Nanosponge system reduce the irritation of effective drug without reduce their efficacy (Swaminathan et al., 2013).

Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. Nanosponges are non-irritating, non-mutagenic, non allergenic and non-toxic. Nanosponges are tiny mesh-like structures that used for the treatment of many diseases and this technology is five times more effective at delivering drugs for breast cancer than conventional methods. Nanosponges are more like a three dimensional network or scaffold. The backbone is a long length of polyester which is mixed in solution with small molecules called crosslinkers that act like tiny grappling hooks to fasten different parts of the polymer together (Shinde et al., 2011G). The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms. For oral administration, these may be dispersed in a matrix of excipients, diluents, lubricants and anti-caking agents which is suitable for the preparation of tablets or capsules. For parenteral administrations, these can be simply mixed with sterile water, saline or other aqueous solutions. For topical administration, they can be effectively incorporated into topical hydrogel. Topical nanosponge can be more patient

compliant and provide sufficient patient benefits by reducing repeated doses and side effects (Targe et al., 2015). Cyclodextrin-based nanosponges (CDNS), which are proposed as a new nanosized delivery system, are innovative cross-linked cyclodextrin polymers nanostructured within a three-dimensional network. This type of cyclodextrin polymer can form porous insoluble nanoparticles with a crystalline or amorphous structure and spherical shape or swelling properties. The polarity and dimension of the polymer mesh can be easily tuned by varying the type of cross-linker and degree of cross-linking (Ansari et al., 2011). Nanosponge functionalization for site-specific targeting can be achieved by conjugating various ligands on their surface. These materials are a safe and biodegradable, share negligible toxicity on cell cultures and are well-tolerated after injection in mice. CDNS can form complexes with different types of lipophilic or hydrophilic molecules. The release of the entrapped molecules can be varied by modifying the structure, in order to modulate the release kinetics. The nanosponges could be used to improve the aqueous solubility of poorly water-soluble molecules, protect degradable substances, obtain sustained delivery systems or design innovative drug carriers for nanomedicine (Cavalli et al., 2010). Nanosponges show a remarkable advantage in comparison with the common nanoparticles. Indeed, they can be easily regenerated by different treatments, such as washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating or changing pH or ionic strength. For all these characteristics, nanosponges have been already employed in different applied fields, such as cosmetic and pharmaceutical sectors (Swaminathan, 2006; Liang et al., 2002). The engineering capacity of nanosponges is due to the relatively simple chemistry of its polyesters and crosslinking peptides, compared to many other nanoscale drug delivery systems. Nanosponges are water soluble but does not breakup chemically in water. They mix with water and use it as a transport fluid. They can be used to mask unpleasant flavors, to convert liquid substances to solids. The chemical linkers enable the nanosponges to bind preferentially to the target site (Salisbury, 2010).

Nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core (Subramanian et al. 2012). As compared to other nanoparticles, nanosponges are insoluble in water and organic solvents, porous, non toxic and stable at high temperatures up to 300°C.

Predictable release is one of the major advantages of this system compared to other nanoparticle delivery systems under development. When they reach their target, many

other nanoparticle delivery systems unload most of their drug in rapid and uncontrollable fashion. This is called the burst effect and makes it difficult to determine effective dosage levels, whereas nanosponges when they reach their target site. Controlled release nanoparticle drug delivery system, which may be an improved delivery method for delivering anticancer therapies, including direct injection into tumour site. These nanoparticles circulate in the body until they encounter the surface of a tumour cell, where they adhere to the surface and start releasing the drug in a controlled and predictable manner (Arnum, 2011).

The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. By the method of associating with drugs, the nanoparticles can be classified into:

Encapsulating nanoparticles: These are represented by nanosponges and nanocapsules. Nanosponges such as alginate nanosponges containing many holes that carry the drug molecules. Nanocapsules such as poly (isobutyl-cyanoacrylate) (IBCA) are also encapsulating nanoparticles. They can entrap drug molecules in their aqueous core.

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

Conjugating nanoparticles: These nanoparticles linked to drug molecules through a strong covalent bond (Trotta et al., 2009).

The main disadvantage of these nanosponges is their ability to include only small molecules. The nanosponges could be either paracrystalline or in crystalline form. The loading capacity of nanosponges depends mainly on degree of crystallization. Paracrystalline nanosponges can show different loading capacities. These nanosponges can be magnetized when they are prepared in the presence of compounds having magnetic properties (Alongi et al., 2011). The tiny shape of enables the pulmonary and venous delivery of nanosponges (Trotta et al., 2007).

Advantages of Nanosponges

- Targeted site specific drug delivery.
- Can be used to mask unpleasant flavours and to convert liquid substances to solids.
- Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
- Nanosponge particles are soluble in water, so the hydrophobic drugs can be encapsulated within the nanosponge, after mixing with a chemical called an adjuvant reagent.
- Particles can be made smaller or larger by varying the proportion of cross-linker to the polymer.
- Production through fairly simple chemistry called click

chemistry

- Easy scale-up for commercial production.
- The drug profiles can be tailored from fast, medium to slow release, preventing over or under-dosing of the therapy
- The material used in this system can provide a protective barrier that shields the drug from premature destruction within the body
- Improved stability, increased elegance and enhanced formulation flexibility.
- Nanosponges systems are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- These are self sterilizing as their average pore size is 0.25µm, where bacteria cannot penetrate
- Extended release - continuous action up to 12 h.
- Biodegradable
- It minimizes the irritation and it gives better tolerance which leads to improved patient compliance.
- These formulations are stable over wide range of PH (1-11) and temperature (up to 130°c) .
- These are free flowing, highly compatible with wide variety of ingredients and cost effective.
- They have better thermal, physical and chemical stability (Patel and Patel, 2008; Khopade et al., 1996; Jain et al., 2013; Vishwakarma et al., 2014).

Disadvantages

1. Nanosponges include only small molecules.
2. Depend only upon loading capacities of drug molecules.

Materials used for the synthesis of nanosponges

Polymers

Polymers used for the synthesis of nanosponges are including: Hyper cross linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxy-carbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly (valerolactone-allylvalerolactone) & Poly (valerolactone-Poly(valerolactone-allylvalerolactoneoxepanedione) and Ethyl Cellulose & Poly vinyl acetate (PVA).

Crosslinkers

Crosslinkers used for the synthesis of nanosponges contain Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromell iticanhydride, Carbonyldiimidazoles, Epichloridrine, Glutaraldehyde, Carboxylic acid dianhydrides, 2,2-is(acrylamido) Acetic acid and

Dichloromethane (Lala et al., 2011).

Preparation of Nanosponges

Nanosponges are prepared by means of following methods:

Emulsion solvent diffusion method

Nanosponges can be prepared by using different proportions of ethyl cellulose and polyvinyl alcohol. 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 2 hrs. The nanosponges formed were collected by filtration and dried in an oven at 40°C for 24 hrs. The dried nanosponges were stored in vacuum desiccators to ensure the removal of residual solvent (Sharma et al., 2011).

Solvent method

Mix the polymer with a suitable solvent, in particular in a polar aprotic solvent such as dimethylformamide (DMF), dimethylsulfoxide (DMSO). Then add this mixture to excess quantity of the cross-linker, preferably in crosslinker/polymer molar ratio of 4 to 16. Carry out the reaction at temperature ranging from 10°C to the reflux temperature of the solvent, for time ranging from 1 to 48 hrs. Preferred cross linkers are carbonyl compounds (dimethyl carbonate and carbonyl diimidazole) (Alongi et al., 2011). After completion of the reaction, allow the solution to cool at room temperature, then add the product to large excess of distilled water and recover the product by filtration under vacuum and subsequently purify by prolonged Soxhlet extraction with ethanol. Dry the product under vacuum and grind in a mechanical mill to obtain homogeneous powder (Lala et al., 2011).

Ultrasound-assisted synthesis

In this method nanosponges can be obtained by reacting polymers with cross-linkers in the absence of solvent and under sonication. The obtained nanosponges will be spherical, uniform in size and smaller than 5 microns. In this method di-phenyl carbonate (or) pyromelitic anhydride is used as cross-linker. Here, mix the polymer and cross-linker in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90°C and sonicate for 5 hours. Then, the solid was ground in a mortar and Soxhlet extraction with ethanol to remove either impurities (or) unreacted polymer. After Purification nanosponges were stored at 25°C (Trotta et al., 2007; Swaminathan et al., 2010).

From hypercross-linked β -cyclodextrins

Nanosponges can be obtained by cross linking with different types of cyclodextrins (CD's) with a carbonyl or a dicarboxylate compound as a cross linker (Trotta and Cavalli, 2009). The ratio of CD's can be varied during preparation to improve the drug loading and to obtain a tailored release profile β -cyclodextrin

nanosponges were prepared as 100 ml of Dimethyl Formamide (DMF) was placed in a round bottomed flask and 17.42g of anhydrous β -CD was added to achieve complete dissolution. Then 9.96 g of carbonyl di-imidazole (61.42mmol) was added and the solution was allowed react for 4 hrs at 100°C. Once condensation polymerization was completed, the transparent block of hyper cross linked cyclodextrin was roughly ground and an excess of de-ionised water added to remove DMF. Finally residual by-products or unreacted reagents were completely removed by Soxhlet extraction with ethanol. The white powder thus obtained was dried overnight in an oven at 60°C and subsequently grinded in a mortar. The fine powder obtained was dispersed in water. The colloidal part that remained suspended in water was recovered and lyophilised. The obtained nanosponges are sub-micron in dimension and with a spherical shape (Setijadi et al., 2009; Swaminathan et al., 2007; Cavalli et al., 2006; Vavia et al., 2006).

Loading of Drug into Nanosponges

To obtain the particle size less than 500 nm, nanosponges should be pre-treated. To obtain this range, the nanosponges are dissolved or suspended in water. The suspended nanosponges 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 nanosponges is prepared. 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 uncomplexed drug is separated from the complexed drug by using centrifugation. The solid crystals of the nanosponges are obtained by using a freeze dryer or by evaporating the solvent. This Solid Crystal structure of nanosponges has a crucial rule in complexation of the drug. The drug loading capacities of paracrystalline nanosponges is lesser when compared to crystalline nanosponges. The drug loading takes place as a mechanical mixture in weakly crystalline nanosponges (Indira et al., 2012).

Factors influencing to the formulation of nanosponges

Nature of polymer

The polymer used in the preparation of nanosponges can influence its formation and can also affect the pre-formulation. The size of the cavity of a nanosponge should be big enough to entrap a drug molecule of a particular size into it for complexation (Bezawada et al., 2014).

Nature of drugs

To be complex with nanosponges, the drug molecules should have some specific characteristics as mentioned below:

- The MW of the drug molecule should be in range ranging from 100-400 daltons.
- Structure of drug molecule should not consist of more than 5 condensed ring.
- The solubility of the drug in water should be <10 mg/ml.
- The melting point of the drug should be <250°C.

Temperature

Changes in the temperature can affect the complexation of drug or nanosponges. Increasing the temperature generally decreases the extent of the stability constant of the drug or the nanosponge complex which may be due to the reduction of interaction forces such as hydrophobic forces and Van der Waal forces of drug/nanosponges with an increase in the temperature (Challa et al., 2005).

Degree of substitution

The number, position, and type of the substituent of the parent molecule can affect the ability of complexation of the nanosponges to a greater extent.

Method of preparation

The method of drug loading into the nanosponges can cause a change in the complexation of drug and the nanosponges. Although, the success of a method mainly depends on the nature or the characteristics of the drug and polymer; in some cases, freeze drying has also been known to affect the drug and nanosponge complexation.

Characterization of Nanosponges

The characterization methods for the complexed drug/nanosponges are listed below:

Solubility studies

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of nanosponges on the solubility of drug. Phase solubility diagrams indicate the degree of complexation (Singh et al., 2010). In this method the drug was added to an Erlenmeyer flask containing an aqueous solution of various percentages of nanosponges. The Erlenmeyer flask was stirred on a mechanical shaker at room temperature. When a steady state was reached, the suspension was filtered by centrifugation using a 3000 Dalton molecular filter. The solution obtained was analyzed to determine the drug concentration by HPLC (Cavalli et al., 2009).

Microscopy studies

Scanning electron microscopy and transmission electron microscopy can be used to study the morphology and surface topography of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization

state of the raw materials and the product observed under electron microscope indicates the formation of the inclusion complexes

Particle size and polydispersity

The particle size can be determined by Dynamic Light Scattering Instrument (DLSI) equipped with particle sizing software. From this the mean diameter and Polydispersity Index (PDI) can be determined. PDI is an index of width or spread or variation within the particle size distribution. Monodisperse samples have a lower PDI value, whereas higher value of PDI indicates a wider particle size distribution and the polydisperse nature of the sample. PDI can be calculated by the following equation:

$$PDI = \Delta d / d_{avg}$$

Where, Δd is the width of distribution denoted as SD and d_{avg} is the average particle size denoted as MV (nm) in particle size data sheet. The types of dispersions with PDI values are depicted in table 1 (Wolfgang, 2007).

The particle size can also be determined by Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Atomic Force Microscopy (AFM) and Freeze Fracture Electron Microscopy (FFEM) (Rao et al., 2012).

Table 1. Polydispersity index

| Polydispersity Index | Type of Dispersion |
|----------------------|--------------------------|
| 0-0.05 | monodisperse standard |
| 0.05-0.08 | nearly monodisperse |
| 0.08-0.7 | mid range polydispersity |
| > 0.7 | very polydisperse |

Zeta potential determination

Zeta potential can be defined as the difference of potential between two layers (dispersion medium and immobile layer) of fluid locked up with dispersed particles. Zeta potential is the major key indicator for the stability of the colloidal dispersion. By adding extra electrode on particle size equipment or zeta seizer, the zeta potential can be measured. Higher the value of zeta potential of a colloidal dispersion more is its stability. Also, laser doppler anemometry, zeta potential meter can be used.

Thermoanalytical methods

Thermoanalytical methods determine whether the drug substance undergoes some changes before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition,

oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. The thermogram obtained by differential thermal analysis and differential scanning calorimetry can be 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 of inclusion complexes.

X-ray diffractometry and single crystal x-ray structure analysis

Powder X-ray diffractometry can be used to detect inclusion complexation in the solid state. When the drug molecule is liquid since liquid have no diffraction pattern of their own, then the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponge. This difference of diffraction pattern 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. A diffraction pattern of a physical mixture is often the sum of those of each component, while the diffraction pattern of complexes is apparently different from each constituent and leads to a "new" solid phase with different diffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation. The complex formation of 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 a few new peaks and shifting of certain peaks.

Single crystal X-ray structure analysis

It is used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest molecules can be identified and the precise geometrical relationship can be established.

Thin layer chromatography

In thin layer chromatography, the Rf value of a drug molecule diminishes to considerable extent and this helps in identifying the complex formation between the drug and Nanosponge. Inclusion complexation between guest and host molecules is a reversible process. Consequently, the complex may separate completely in guest and host molecules during the chromatographic process and only the spots of the guest and host molecules are found on the TLC-plate (Aithal et al., 1995).

Infrared spectroscopy

The interaction between nanosponges and the drug in the solid state can be determined by using infrared spectroscopy. Nanosponge bands can slightly change during formation of complexes. Few guest molecules attached in the complexes which are less than 25%, the drug spectrum can be easily masked

by the spectrum of nanosponges. The technique is not appropriate to identify the inclusion complex over the other methods (Farooq et al., 2013).

In-vitro drug release

Drug release from the nanosponges can be measured across the dialysis membrane using Franz Diffusion cell. The dialysis membrane soaked in receptor medium for 8 hrs is used as a barrier between the donor and receptor compartment. A one gram nanosponge is placed on the membrane surface in the donor compartment that is sealed from the atmosphere with aluminium foil. The receptor compartment is filled with specific volume of phosphate buffer of suitable pH (6.8 skin pH). During the experiment, the solution of receptor side compartment is kept at $37 \pm 0.5^\circ\text{C}$ and stirred at 100 rpm with Teflon-coated magnetic stirring bars. Aliquots are collected from the receptor compartment at designated time intervals and replaced by the same volume of fresh receptor solution to maintain sink condition and constant volume. The sample is analysed using UV spectrophotometer. Even, USP type II dissolution apparatus can be used in many cases depending upon the formulation.

Drug release kinetics

To investigate the mechanism of drug release from nanosponge the release data could be analysed using Zero order, First order, Higuchi, Peppas, Hixon-Crowell, Kopcha and Makoid-Banakar etc. models. The data can be analysed using graph pad prism software. The software estimates the parameters of a non-linear function that provides the closest fit between experimental observations and non-linear function (Reddy et al., 2004). The mathematical expressions that describe the dissolution curves are summarized in table 2.

Table 2. Mathematical expressions of dissolution curves

| Model | Equation |
|------------------------|-----------------------------|
| Zero order | $Q_t = Q_0 + K_0 t$ |
| Higuchi model | $Q_t = Q_0 + K_H t^{1/2}$ |
| Korsemeyerpeppas model | $Q_t = K K P t^n$ |
| Kopcha model | $Q_t = A t^{1/2} + B t$ |
| Makoid-banakar model | $Q_t = K M B t^n e^{-(et)}$ |

Loading efficiency

The loading efficiency of a nanosponge particle can be determined by the estimation of drug loaded into the nanosponge using UV spectrophotometer and high-performance liquid chromatography method for the

nanosponges. The loading efficiency of nanosponges can be calculated by using the following equation.

Loading efficiency = Actual drug content in nanosponge / Theoretical drug content × 100

Resiliency

Resiliency (viscoelastic properties) of sponges can be modified to produce beadlets that are softer or firmer according to the need of final formulation. Increased crosslinking tends to slow down the rate of release. Hence resiliency of sponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time (D'souza, 2008).

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 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 i.e. the stratum corneum, the release of active substance continues to skin for a long period of time (Mandava and Thavva, 2012).

Application of Nanosponges

Nanosponges have a wide range of application in the pharmaceutical field, because of its biocompatibility and versatility. In the pharmaceutical industry, nanosponges can be used as an excipient for the formulation of tablets, capsules, granules, pellets, suspensions, solid dispersions and topical dosage forms. Nanosponges can accommodate both lipophilic and hydrophilic drug molecules, basically, those drugs substances which belong to the biopharmaceutical classification system (BCS-class II) as well as the poorly water-soluble drug (Trotta et al., 2014).

Nanosponges for drug delivery

Nanosponges can carry the water-insoluble drug because of their tiny porous structure. To increase the dissolution rate, solubility and permeability of drug nanosponges complexes play a major role. This is reported that β -cyclodextrine based nanosponges are three or five times more effective to deliver the drug to the targeted site. Nanosponges are generally solid in nature and can be prepared for oral, parental, topical and inhalation dosage form. For the preparation of tablet, capsule i.e. oral administration the nanosponges complexes are dissolved in a suitable excipient like lubricants, diluents and anti-cracking

agent. Nanosponges have several properties that boost the product performance and elegance, controlled release, sustained release, decrease skin irritation, improve solubility and increase product flexibility. List of some BCS Class II drugs which can be developed as nanosponges are given in table 3. The nanosponge technology used in formulation of some drugs is mentioned in the table 4.

Nanosponges as biocatalysts carrier

Nanosponges act as carriers in the delivery of enzymes, proteins, vaccines and antibodies. Many industrial processes involving chemical transformation are associated with operational disadvantages. Non-specific reactions lead to low yields and the frequent need to operate at high temperatures and pressures requires consumption of large amounts of energy and very large amounts of cooling water in the down-stream process. All these drawbacks can be eliminated or significantly reduced by using enzymes as biocatalysts. These enzymes operate under mild reaction conditions, have higher action speed and are highly specific. They have a beneficial effect on environment because they reduce energy consumption and reduce production of pollutants. Developments in genetic engineering have increased the stability, economy, specificity of enzymes and number of their industrial applications is continually increasing day by day. Examples of industrially useful enzymes include alpha amylase, trypsin, cellulose and pectinase for fruit juice clarification processes, ligninase to breakdown lignin, lipase in the detergent industry and biodiesel production etc. The catalytic activity of enzymes depends mainly on the correct orientation of the active site (Vyas et al., 2008). Proteins, peptides, enzymes and derivatives thereof also can be used in the biomedical and therapeutic field. Proteolytic enzymes can be used to treat cancer or type I mucopolysaccharidosis, while DNA and oligonucleotides are used in gene therapy. The administration of these molecules presents various problems and limitations. Most protein drugs are poorly absorbed through the biological membranes due to the some factors such as large molecular size, hydrophilic nature, degree of ionization, high surface charge, chemical and enzymatic instability and low permeability through mucous membranes. Following intravenous administration, protein molecules may be rapidly cleared from blood, bind to plasma proteins, and sensitive towards proteolytic enzymes. With oral administration bioavailability is the problem. Various approaches exist for therapeutic use, such as increasing the dose or using absorption promoters, which can cause toxicity problems (Vyas et al., 2008; Swaminathan et al., 2010). A number of systems for carrying enzymes and proteins have been developed, such as nano and microparticles, liposomes

Table 3. Biopharmaceutical classification system class II drugs

| Category/Class | Examples |
|--|---|
| Antihypertensive drugs | Felodipine, Nicardipine, Nifedipine, Nisoldipine |
| Antiarrhythmic agents | Amiodarone hydrochloride |
| Antibiotics | Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethoxazole |
| Anticonvulsants | Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone |
| Antifungal agents | Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole, Lansoprazole, Vericonazole |
| Antineoplastic agents | Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan, Paclitaxel, Raloxifene, Tamoxifen, Temozolamide, Topotecan |
| Antipsychotic drugs | Chlorpromazine Hydrochloride |
| Antiretrovirals | Indinavir, Nelfinavir, Ritonavir, Saquinavir |
| NSAIDs | Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin, Piroxicam, |
| Antidiabetic and Antihyperlipidemic drugs | Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone |
| Antiulcer drugs | Lansoprazole, Omeprazole |
| Anthelmintics | Albendazole, Mebendazole, Praziquantel |
| Antiepileptic drugs | Phenytoin |
| Cardiac drugs | Carvedilol, Digoxin, Talinolol |
| Diuretics | Chlorthalidone, Spironolactone |
| Gastroprokinetic agent | Cisapride |
| Immunosuppressants | Cyclosporine, Sirolimus, Tacrolimus |
| Anticoagulant | Warfarin |
| Antihistamines | Terfenadine |
| Antioxidants | Resveratrol |
| Steroids | Danazol, Dexamethazone, |
| Antianxiety drugs | Lorazepam |
| Miscellaneous | Atovaquone, Melarsoprol, Phenazopyridine, Ziprasidone, |

and hydrogels. Carriage in a particular system can protect proteins from breakdown, modify their pharmacokinetics and improve their stability *in-vivo*. Now, it has been found that cyclodextrin based nanosponges are particularly suitable carrier to adsorb proteins, enzymes, antibodies and macromolecules. In particular when enzymes are used, it is possible to maintain their activity, efficiency, prolong their operation and extends the pH and temperature range of activity and allows the conduct of continuous flow processes. Moreover, proteins and other macromolecules can be carried by adsorbing or encapsulating

them in cyclodextrin nanosponges (Vyas et al., 2008).

Solubility enhancement

Nanosponges have been also used for improving the solubility and dissolution rate of poorly soluble drugs as well as providing controlled release profile. Swaminathan et al. studied a formulation of itraconazole in Nanosponges. Itraconazole has a dissolution rate limited poor bioavailability. Nanosponges improved the solubility of the drug more than 27-fold. When copolyvidonum was added as a supporting component of the nanosponge formulation,

Table 4 Examples of nanosponges

| Drug | Nanosponge vehicle | Indication | Study | In vitro / in vivo / Mathematical model |
|----------------------------|---|---|--|---|
| Paclitaxel | β -cyclodextrin | Cancer | Bio-availability Cytotoxicity | Sprague Dawley rats MCF7 cell line |
| Camptothecin | β -Cyclodextrin | Cancer | Haemolytic activity, Cytotoxicity | Diluted blood HT-29 cell line |
| Tamoxifen | β -Cyclodextrin | Breast cancer | Cytotoxicity | MCF-7 cell line |
| Resveratrol | β -Cyclodextrin | Inflammation, Cardiovascular diseases, Dermatitis, Gonorrhoea, Fever and Hyperlipidemia | Cytotoxicity Accumulation of drug in the buccal mucosa of rabbit, Ex-Vivo Study Permeation study | HCPC-I cell line, Rabbit buccal mucosa, Pig skin |
| Temozolamide | Temozolamide Poly (valerolactoneallylvalerolactone) and poly (valerolactoneallylvalerolactone-oxepanedione) | Brain tumors | Drug release study | In vitro and in vivo studies |
| Econazole nitrate | Ethyl cellulose Polyvinyl alcohol | Antifungal | Irritation study | Rat |
| Itraconazole | β -Cyclodextrin&copolyvidonum | Antifungal | Saturation solubility study | Higuchi Model |
| Dexamethasone | β -Cyclodextrin | Brain tumors | Drug release experiment | Dialysis bag technique in vitro |
| Antisense oligonucleotides | Sodium alginate Poly L-lysine | Cancer therapy Viral infections Pathologic disorders | Pharmacokinetic studies | Mice |
| Bovine serum albumin | Cyclodextrin based Poly (amidoamine) | Protein supplement | Drug release study Stability study | <i>In-vitro</i> release modulation and stability. |
| Voriconazole | Ethylecellulose (EC), Polymethyl methacrylate (PMMA), PVA | Antifungal | Drug release Experiment | Rat |

this exceeded to 55-fold. Nanosponges solubilize drug by possibly masking the hydrophobic groups of itraconazole, by increasing the wetting of the drug, and/or by decreasing the crystallinity of the drug.

For protein delivery

Bovine serum albumin (BSA) protein in solution is not stable; hence it is stored in lyophilized state. However proteins can reversibly denatured on lyophilisation and adopts conformation markedly different from native structure. Major drawback in protein formulation and development is to maintain its native structure during processing and long term storage. In the nanosponges based approach proteins like BSA are encapsulated in swellable cyclodextrin based poly (amidoamine) nanosponges to increase the stability of proteins (Swaminathan et al., 2010).

Nanosponges as a sustained delivery system

Acyclovir is a widely used antiviral agent due to its efficacy in the treatment of herpes simplex virus infections (O'Brien et al., 1989). However, neither the parenteral nor the oral administration of the currently available formulations of acyclovir is able to result in suitable concentrations of the agent reaching at target sites. Acyclovir's absorption in the

gastrointestinal tract is slow and incomplete, what's more, its pharmacokinetics following oral medication is highly variable. The in vitro release profiles of acyclovir from the two types of nanosponges showed a sustained release of the drug from the two types of nanosponges indicating the encapsulation of acyclovir within the nanostructures. The percentages of acyclovir released from Carb-nanosponges and nanosponges after 3 h in vitro were approximately 22% and 70%, respectively. No initial burst effect was observed for either formulation, proved that the drug was not weakly adsorbed onto the nanosponges surfaces (Lemboa et al., 2013). The earlier work done on Nanosponges is also studied (Table 5).

Encapsulation of gases

Cyclodextrin based carbonate Nanosponge was used to form inclusion complexes with three different gases, i.e. 1-methylcyclopropene, oxygen and carbon dioxide. The complexation of oxygen or carbon dioxide could be useful for many biomedical applications. In particular, the oxygen-filled Nanosponge could supply oxygen to the hypoxic tissues which are present in various diseases. Because of its super porous nature; the Nanosponge also has been explored

Table 5. Earlier work done on nanosponges (Pawar et al., 2016)

| | |
|------------------------|--|
| Moura and Lago, (2009) | Studied catalytic growth of carbon nanotubes and nanofibers on vermiculite to produce floatable hydrophobic “nanosponges” for oil spill remediation |
| Alongi et al. (2011) | Reported novel flame retardants containing cyclodextrin nanosponges and phosphorous compounds to enhance ethyl vinyl acetate copolymer combustion properties |
| Wong et al. (2009) | Reported that three-dimensional nanosponges play an important role in the fractionalization of peptides for proteomic applications |
| Lee et al. (2011) | Synthesized graphite-nanofiber-supported porous Pt-Ag nanosponges and mesoporous platinum nanosponges as electrocatalysts for the oxygen reduction reaction. The precise control of chiral photoreactions or photochirogenesis is one of the most challenging topics in current photochemistry. A supramolecular approach to photochirogenesis provides a convenient and also promising tool to facilitate excited-state chirality transfer from chiral host to prochiral substrate. |
| Arkas et al. (2006) | Reported that nanosponges have the property of encapsulating organic pollutants from water. Ceramic porous filters can be impregnated with these nanosponges resulting in hybrid organic/inorganic filter modules. These hybrid filter modules were tested for the effective purification of water, employing a variety of water pollutants. It has been established that polycyclic aromatic hydrocarbons can be removed very efficiently (more than 95%). Representatives of the pollutant group of trihalogenmethanes, monoaromatic hydrocarbons, and pesticides (simazine) can also be removed (>80%) |
| Liang et al. (2002) | Developed the pyromellitate-linked cyclodextrin nanosponges, employed for the first time as supramolecular reaction media for sensitizing the enantio differentiating photoisomerization of (Z)-cyclooctene and (Z, Z)-1,3-cyclooctadiene exhibited unique photochirogenesis behaviour significantly different from the conventional sensitizer-modified cyclodextrins |
| Alongi et al. (2011) | Studied the interaction between β -cyclodextrin nanosponges and two different ultraviolet stabilizers (namely, 2-hydroxy-4(octyloxy)-benzophenone and triphenyl phosphate) in the photooxidation of polypropylene exposed to UV light have been investigated. A significant decrease of the oxidation induction time has been observed in the presence of β -CD nanosponges |
| Yang et al. (2012) | Developed noncytotoxic scaffolds with a nanometer resolution through using silicon substrates as the backbone. This method was merged an optics-based approach with chemical restructuring to modify the surface properties of an IC-compatible material, switching from hydrophilicity to hydrophobicity. Through this nanofabrication-based approach, they synthesized hydrophobic oxidized silicon nanosponges. This study had demonstrated the potential application of using these silicon-based nanopatterns such as influencing cellular behaviours at desired locations with a micro-/nanometer level. |

as an effective gas carrier. Nanosponge formulation shows the ability to store and release oxygen in a controlled manner. In future, they could be one useful tool for the delivery of some vital gases (Trotta et al., 2013; Trotta et al., 2011).

Nanosponges as protective agent from light or degradation

Gamma-oryzanol is a ferulic acid ester mixture, has recently attracted a great interest as natural antioxidant and usually employed to stabilize food and pharmaceutical raw materials, moreover as a sunscreen in the cosmetics industry. Its

application is limited by its high instability and photodegradation. Gamma-oryzanol was encapsulated in nanosponges, showing a good protection from photodegradation. A gel and an O/W emulsion were formulated with the gamma-oryzanol-loaded nanosponges (Sapino et al., 2013).

Nanosponges for cancer therapy

Most challenging works nowadays in the pharmaceutical field is the delivery of anticancer drug because of their low

Table 6. Examples of patent report on β -cyclodextrin nanosponges

| S. No | Patent/ App No/ year of issue | Applicant | Title |
|-------|-------------------------------|------------------------------|---|
| 1 | W02003041095A1 (2003) | Alberto Bocanegra Diaz | Process of composites preparation between particulate materials and cyclodextrin and/or their derivatives |
| 2 | W02003085002A1. (2003) | Sea Marconi Technologies Diw | Cross-linked polymers based on cyclodextrin for removing polluting agents. |
| 3 | DE10008508A1 (2001) | Bayer AG | Cyclodextrin-enthaltende Polycarbonate |
| 4 | EP0502194A1 (1992) | Toppan printing Co Ltd | Cyclodextrin polymer and cyclodextrin film formed there from. |

solubility. Researcher at Vanderbilt University have developed nanosponges which can be used as delivery system for anticancer drugs to tumours. They claim that the method is three to five times more effective at reducing tumour growth than direct injection of the drugs. The tiny nanosponges are filled with a drug load and expose at targeting peptide that binds to radiation-induced cell surface receptors on the tumour. When the sponges encounter tumour cells they stick to the surface and are triggered to release their cargo. Benefits of targeted drug delivery include more effective treatment at the same dose and fewer side-effects.

Antiviral application

Nanosponges can be useful in 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 RTI 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).

As absorbent in treating poison in blood

Nanosponges can remove the dangerous poisonous substance from our blood by absorbing the poison. Instead of using antidotes, if we incorporate nanosponges by injection into blood nanosponges can soak up the toxins. In the bloodstream, the nanosponge looks like a red blood cell, tricks toxins into attacking it, and then absorbs it. The number of toxin molecules each nanosponge can absorb depends on the toxin (Hu et al., 2013).

Other Applications of Nanosponges

Nanosponges have many other applications in various fields (Riyaz et al., 2014): Patent report on β -cyclodextrin Nanosponges in (Table 6).

- Biomedical Applications
- In Anti-mycotic Therapy
- Analytical Applications

- For Hydrogen Storage
- In Agriculture
- In Floriculture
- In Food Industry
- For Water Purification
- For Oil Cleaning
- As Chemical Sensors
- As Novel Flame Retardants
- Against Pore Forming Toxins and Superbug Infections
- Micropatterning of Mammalian Cell

Conclusion

From the study it was concluded that the Nanosponges have the ability to incorporate either lipophilic or hydrophilic drug and to release the drug in a controlled and predictable manner to the targeted site. Due to their small particle size and spherical shape these can be developed as different dosage forms like oral, parenteral and topical preparations. Nanosponge technology offers entrapment of ingredients and thus reduced side effects, improved stability, increases elegance and enhanced formulation flexibility. Nanosponge can be effectively incorporated into a topical drug delivery system for retention of dosage form on skin and also use for oral delivery of drugs using bioerodible polymers, especially for colon specific delivery and controlled-release drug delivery system. Thus Nanosponge technology provides site specific drug delivery and prolongs dosage intervals and thus improving patient compliance. Nanosponge formulation could be the best solution for solving various nano related issues in the pharmaceutical industry.

Future Prospects and Challenges

Nanotechnology and nano formulation has revolutionized medical research by shrinking technology to the nano-scale. NP is nanoporous particles which can improve the pharmacokinetic and pharmacodynamic properties of drugs apart from solving formulation related problems such as improving solubility and stability. Achieving superior

therapeutic effects through targeted and controlled drug release would also decrease drug toxicity. This review has focused on NS, since their role is indispensable in nano-technological developments. The future may see adoption of NP as a routine water purifier. However, it would be challenging to bring down the cost by exploring more polymers and cross-linkers and newer methods of production. Owing to their special structure, their role in down stream processing requires in- depth research. Some applications that could be explored include but are not limited to removal of toxic substances from industrial wastes and organic solvent vapours from air. NP could be adopted for entrapping bitter constituents from food and drug products. Tremendous prospects also lie in exploring the effects of method of synthesis, particle size, crystallinity porosity and degree of crosslinking on drug loading and release. So far, the synthetic methods reported include the conventional approach and ultrasound-assisted synthesis. Further research is encouraged to develop a high yielding, economical, reproducible method which can be adapted for mass production in short time. NP may be simple to prepare as exemplified earlier, but a major drawback of any synthetic process lies in residual remains of solvents or reaction by-products in the formulation, which is a major cause of toxic effects on administration. Therefore, elaborate research is required to understand any undesirable effects on health and environment. Moreover, it would be exciting to explore techniques utilizing principles of green chemistry which may not require solvents at all. Biodegradable and bioabsorbable carriers can be developed so that they would break down inside the body without producing any toxic products. Elaborate studies are required to establish the efficacy and fate of these nano-carriers. Furthermore, the pharmaceutical and health care industry might use NP for solving many physical, chemical and biological problems associated with the treatment of disease. It would be interesting to explore NS as diagnostic agents, such as in cancer imaging. NP could stabilize cancer biomarkers which would otherwise undergo enzymatic degradation prior to detection. One of the greatest challenges in bioactive targeting is to optimize safe and efficient delivery of these compounds to the eukaryotic cytosol. Loading bioactive into NP coupled with specific linkers will ensure controlled drug release, in contrast to the burst effect shown by other nanoparticles. The “flexibility” and tunability of these nano-carriers triggers interest in exploring the many routes through which controlled drug delivery could be achieved while ensuring drug stability and minimizing toxic effects. Targeting drugs to the brain for treating cancer is an issue which needs to be addressed. Such drugs could be loaded into NP; however they would require molecular transporters which would help in pulling the drug-loaded NP into the targeted brain tumor cells.

The future is also likely to see vaccines delivered through nanosponge compositions. Nanofoams comprising of drug-loaded NP are interesting developments which can be explored. Magnetic nanoparticles have been used to successfully overcome physiological barriers and deliver the agent to its site of action at therapeutically relevant concentrations for a time sufficient to allow therapeutic action, without undergoing de-stabilization or elimination. On the same lines, drug-loaded magnetic NP could be developed, where a localized magnetic field gradient could be applied to attract particles to the site of action and hold them in place, in the required therapeutic concentration, until therapeutic activity completes. In conclusion, the available literature provides evidence of a number of potential applications of NP in the field of medicine, agriculture, biomedical sciences and engineering technology. Nanosponge technology has gained popularity due to the rationale and simplicity of approach. We suggest that NP can further be explored for targeting drugs to diseased cells, where magnetic NP are one of NDDS which have an important role to play. Finally, new technologies could be developed for preparing and stabilizing NP. The technique should be reproducible, economical, eco-friendly and applicable for scale up in short time.

Conflicts of interest

The authors declare no conflict of interest.

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