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Nanosponges: An Attractive Strategy for Enhanced Therapeutic Profile

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Abstract:

Oral route of drug administration is the most preferred route as its ease of administration and painless approach. Poor bioavailability by the oral route is noticeable with the majority of new active pharmaceutical ingredients due to its dissolution rate limited absorption. Failure to accomplish proposed therapeutic effects of the poorly water soluble drugs by this route directed the development of a new drug delivery system which will accomplish therapeutic. Although various formulation approaches like complexion, pH modification, solid dispersions, cocrystals formation, lipid based drug delivery systems increased appliance with the noticeable enhancement of drug absorption. Targeted delivery of drug and bioavailability enhancement of poorly water soluble drugs by development of an efficient drug delivery system has been a vision for a long time. Designing of efficient drug delivery system by the means of nanotechnology has gained significance in recent times. Nanosponge formulation is one of such efficient delivery system of the drug which overcomes the problems of poor bioavailability and drug toxicity. Nanosponges are innovative carriers, which are about a size of a virus with a 3-dimensional network and a nanometric cavity size. These can act as the carriers for lipophilic drugs which have poor water solubility. The backbone is a long length of polyester which is mixed in solution with small molecules called cross-linkers that work like tiny grappling hooks to tie up different parts of the polymer together. The net consequence is to form small spherical particles containing cavities where drug molecules can be stored. The present review provides comprehensive information on the methods of preparation, characterization, applications, recent advances in the field.

Keywords: Drug delivery system, Hydrophilic and lipophilic drugs, Nanosponges, Pharmaceutical applications

INTRODUCTION:

Advances in *in vitro* screening process of newly synthesized chemical moiety lead to the emergence of many challenging chemical components with noticeable therapeutic activity. However, about 40% of them are poorly water soluble drugs which have low oral bioavailability as their absorption is dissolution rate limited.[1] Apart from this, major drawbacks of oral drug delivery of these drugs suffer from rapid metabolism, lack of steady state blood/plasma concentration of the drug, and inter individual variability.[2] The intrinsic properties of chemical moieties can be tailored by means like salt formation and reduction in particle size of the drug to improve the bioavailability deprived of any formulation approach though it is not possible at all times with all drug moieties. Oral delivery of poorly water soluble drugs in the form of nanosponge is a new and recent approach to overcome the aforementioned problems. Nanosponges contains microscopic particles of few nanometers wide cavities, in which a large variety of drug substances can be encapsulated. These microscopic particles are capable of carrying both hydrophilic and lipophilic substances and of enhancing the solubility of poorly water soluble molecules.[3] Nanosponges are minute mesh-like structures that may update the treatment of many diseases and as per early trials this technology is up to five times more efficient drug delivery in breast cancer than conventional methods.[4] Nanosponges are made of a scaffold structure of naturally degradable polyester. The long chain polyester strands are mixed with small cross-linking molecules which have an affinity for certain portions of the polyester there by polyester segments cross-link to form a spherical shape which contain many cavities where drugs can be stored. This polyester molecule are predictably biodegradable so, when it breaks up in the body, the drug can be released on an identified schedule.[5] Site specific drug delivery in the body can be achieved by congugating various ligands on nanospong surface there by minimize the adverse effects and increase the effectiveness of the drug. The nanosponge can be engineered to be of a particular size by varying the proportion of polymer to cross-linker ratio and to release drugs over a predetermined time as not in the split open mode which is common with other drug delivery methods.[6] The engineering capability of nanosponge is due to the relatively straightforward chemistry of its cross-linking peptides and polyesters, contrast to many other nanoscale drug delivery systems. The nanosponges can be magnetized when they are prepared in the presence of compounds having magnetic properties. Nanosponge shows a potential future in the coming years due to its variety of pharmaceutical applications like extended release, better product performance and elegance, improved physical, thermal and chemical stability of product, reduced irritation.[7]

The list of polymers and crosslinking agents used for the synthesis of nanosponges are presented in Table 1.

Table 1: Polymers and crosslinking agents used for the synthesis of nanosponges

Polymers	Hyper cross-linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly (valerolactone-allylvalerolactone) Poly (valerolactone-allylvalerolactone-oxepanedione) and Ethyl Cellulose & PVA
Crosslinking agents	Diphenyl Carbonate, Diaryl carbonates, Diisocyanates, Pyromellitic anhydride, Carbonyl diimidazoles, Epichloridrine, Glutaraldehyde, Carboxylic acid dianhydrides, 2,2-bis(acrylamido) Acetic acid and Dichloromethane

Figure 1: The structure of nanosponges containing cavity for drug encapsulation

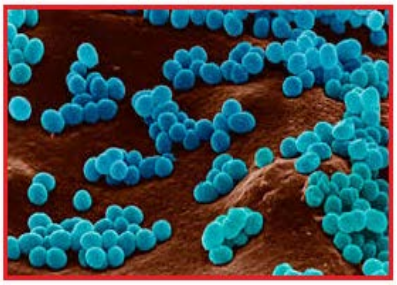


Figure 2: Spherical shape nanosponges

Depending on the method of association of nanoparticles with a drug, the nanoparticles can be classified into 3 types[8]

Encapsulating nanoparticles:

This type of nanoparticles are represented by nanocapsules and nanosponges.

Nanosponges which are sponge like nanoparticles, containing many holes that carry the drug molecules such as alginate nanosponge. Nanocapsules are encapsulating nanoparticles. They can entrap drug molecules in their aqueous core such as poly isobutyl cyanoacrylate nanosponges.

Complexing nanoparticles:

This type are representaed by complexing nanoparticle, which attracts the molecules by electrostatic charges.

Conjugating nanoparticles:

This type are representaed by conjugating nanoparticle, which link to drugs through covalent bonds.

Significance of Nanosponges:

- Biodegradable, non-toxic and non - irritating.
- Size of the nanosponges can be varied by changing the ratio of polymer to cross-linker.
- Used to increase aqueous solubility of poorly water solubility.
- Capable of carrying both hydrophilic as well as lipophilic drugs.
- Possible predictable release. Provides extended release up to 12hrs.
- Protects the active ingredient from degradation.
- Improved stability, elegance and formulation flexibility, the drug release profiles can be varied from fast, medium to slow release.
- As nanocarriers for biomedical applications.
- Mask unpleasant flavors and to change liquid substances into soilds.

The nanosponges are usually obtained by natural derivatives. As compared to the other nanoparticles, they are insoluble both in water and organic solvents. They mix with water and use as a transport fluid. The chemical linkers enable the nanosponges to bind preferentially to the target site and stable at high temperatures up to 300^0C. They are able to capture, transport and selectively release a huge variety of substances because of their 3D structure containing cavities of a nanometric size and tunable polarity. Furthermore, 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 gasses, mild heating, or changing pH or ionic strength.[9]

Nanosponges can be used as a vessel for pharmaceutical principles to improve aqueous solubility of lipophilic drugs, to protect degradable molecules and to formulate drug delivery systems for various administration routes besides the oral one. The simple chemistry of polymers and crosslinkers does not pose many problems in the preparation and this technology can be easily ramp up to commercial production levels. They can be used to mask unpleasant flavors, to convert liquid substances to solids.[7]

Advantages

1. These formulations are stable over range of pH 1 to11.
2. These formulations are stable at higher temperatures.
3. These formulations are compatible with most vehicles and ingredients.
4. These are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
5. These formulations are free flowing and can be cost effective.
6. This technology offers entrapment of ingredients and reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility.
7. Nanosponges are non-irritating, non-mutagenic, non-allergenic, and non-toxic.
8. Extended release action up to 12 hrs can be attained.
9. Nanosponges allows incorporation of immiscible liquid, Improves material processing as liquid can be converted to powders.[10-12]

Disadvantages

1. Nanosponges have ability to include only small molecules.
2. Nanosponges could be either paracrystalline or in crystalline form.
3. The loading capacity of nanosponges depends mainly on degree of crystallization.
4. Paracrystalline nanosponges can show different loading capacities.[12]

MECHANISM OF DRUG RELEASE FROM NANOSPONGES

As the nanosponges have an open structure with pores on its surface i.e in the surrounding of nanosponges they do not have any uninterrupted 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 attained. When the product is applied on to the skin, the vehicle containing the active ingredient

gets unsaturated causing a disturbance in the equilibrium. This will start a flow of the active from the sponge particle into the vehicle and from it to the skin until the vehicle is either dried or absorbed. Even after the withholding 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. [13]

FACTORS INFLUENCING IN THE FORMULATION OF NANOSPONGES[14,15]

Nature of polymer

The polymer used in the preparation of nanosponges can influence in the formation and pre-formulation. The cavity size present in the nanosponge should be huge enough to entrap a particular size drug molecule into it for complexation.

Drug

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

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

Temperature

Temperature changes can affect Drug/Nanosponge complexation. In general, increasing in the temperature decreases the magnitude of the apparent stability constant of the drug/Nanosponge complex may be due to a result of the possible reduction of drug/nanosponge interaction forces, such as van der Waal forces and hydrophobic forces with rising of temperature.

Method of preparation

The method of loading the drug into the nanosponge can affect Drug/Nanosponge complexation. However, the effectiveness of a method depends on the nature of the drug and polymer, in many cases freeze-drying was found to be most effective for drug complexation.

Degree of substitution

The complexation ability of the nanosponge may be greatly affected by type, number, and position of the substituent on the parent molecule.

PREPARATION OF NANOSPONGES

Nanosponges possess a three-dimensional network or scaffold phenomenon. These are prepared by reacting polyesters with appropriate crosslinking agents, a novel nanostructured material can be obtained, known as nanosponges.

Methods used for the preparation of Nanosponges:

1. Melt Method
2. Solvent diffusion method
a. Emulsion solvent diffusion method.
b. Quasi-emulsion solvent diffusion.
3. Solvent method
4. Ultra Sound Assisted Method.

1. Melt Method

Nanosponges are prepared by reacting cyclodextrin with a crosslinker like dimethyl carbonate, diphenyl carbonate, diisocyanates, diaryl carbonates, carbonyl diimidazole, carboxylic acid anhydrides and 2, 2-bis (acrylamide) acetic acid. All the ingredients are finely homogenized, placed in a 250 ml flask and heated at 100˚ C. Carry out the reaction for about 5hrs by using magnetic stirrer. Allowed the mixture to cool and break down the product. Then wash the obtained product with a suitable solvent to remove extra unreacted excipients and by products. The porosity, pore sizes and surface charge density of nanosponges can be controlled to attach different molecules.[16]

2. Solvent diffusion method

a. Emulsion solvent diffusion method

Nanosponges prepared by using a different proportion of ethyl cellulose and polyvinyl alcohol. Dissolve the dispersed phase containing ethyl cellulose and drug in 20ml dichloromethane and slowly added to a definite amount of polyvinyl alcohol in 150 ml of the aqueous continuous phase. Stir the reaction mixture at 1000 rpm for 2 hrs. Collect the formed nanosponges by filtration and dried in an oven at 400C for 24 hrs. The dried nanosponges were stored in vacuum desiccators to ensure the removal of residual solvent.[17]

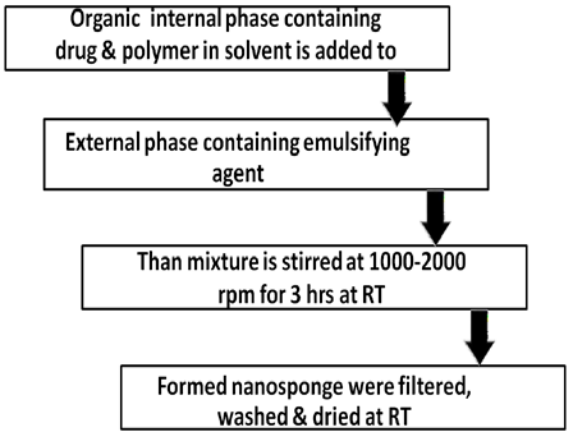


Figure 3: Flow diagram for the preparation of nanosponges by Emulsion solvent diffusion method

b. Quasi-emulsion solvent diffusion

The nanosponges can also be prepared by a quasi-emulsion solvent diffusion method using the different proportion of polymer. To the inner phase can be prepared by dissolving eudragitRS100 in a suitable solvent. Then, the drug can be added to the solution and dissolved under ultrasonication at 350c. Pour the inner phase into the PVA solution in water (outer phase) and allowed for stirring for 1hr, then filter the mixture to separate the nanosponges. The nanosponges are dried in an air-heated oven at 40˚c for 12 hrs.[16]

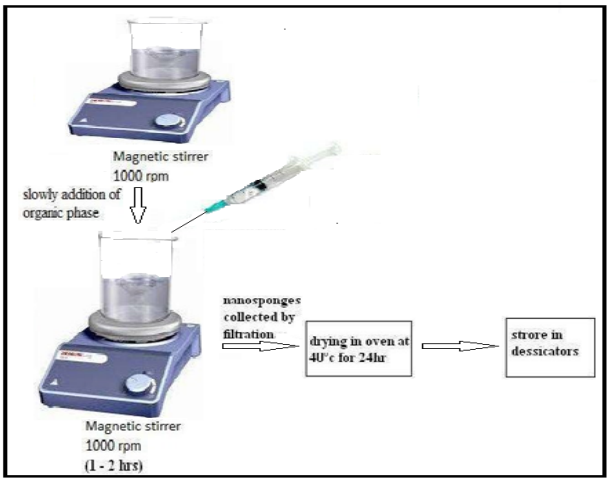


Figure 4: Flow diagram for the preparation of nanosponges by Quasi-emulsion solvent diffusion

3. Solvent method

Mix the polymer with a suitable solvent, in a polar aprotic solvent such as dimethyl formamide, dimethyl sulfoxide. The preferred crosslinkers are carbonyl compounds (Dimethyl carbonate & Carbonyldi imidazole). After completion of the reaction, allow the solution to cool at room temperature and recover the product by filtration under vacuum and subsequently purify by prolongedsoxhlet.[18]

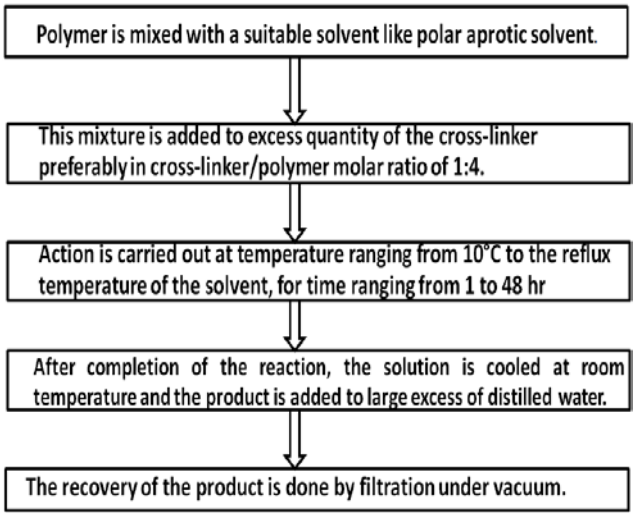


Figure 5: Flow diagram for the preparation of nanosponges by the Solvent method

4. Ultrasound-Assisted synthesis

In this method, nanosponge can be obtained by reacting polymers with cross-linkers in the absence of solvent and under sonication. The nanosponges obtained by this method will be spherical and uniform in size. Wash the product with water to remove the non-reacted polymer and subsequently purify by prolonged soxhlet extraction with ethanol followed by drying under vacuum and store at 250C until further use.[18,19]

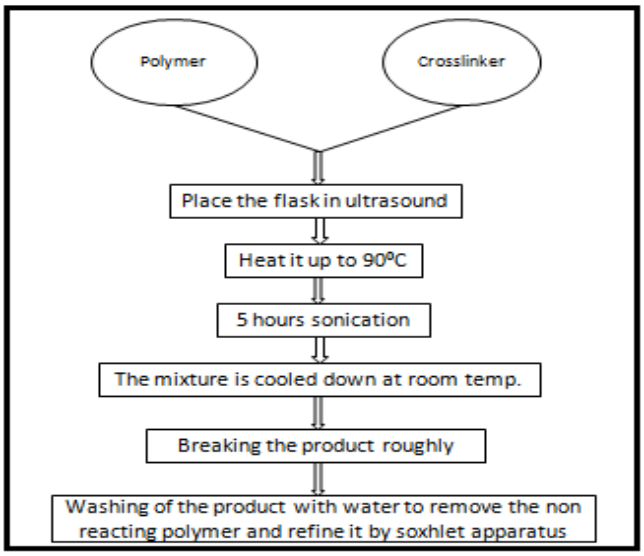
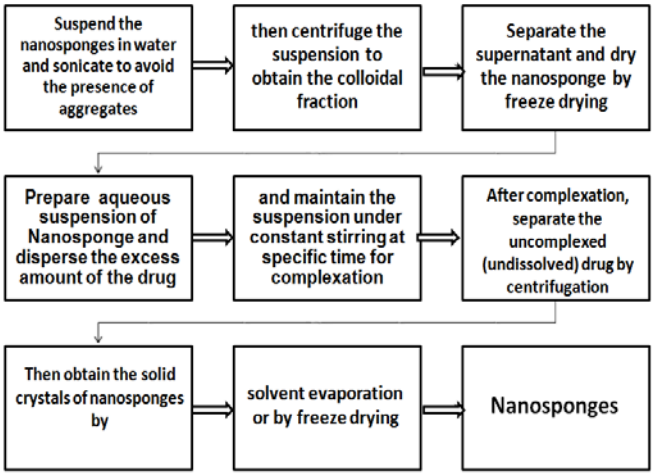


Figure 6: Flow diagram for the preparation of nanosponges by the ultrasound-assisted method

LOADING OF THE DRUG INTO NANOSPONGES



Crystal structure of nanosponge plays a very important role in complexation with the drug. A study revealed that paracrystalline nanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than paracrystalline one.[17]

EVALUATION OF NANOSPONGES

1. Solubility studies

The phase solubility approach is most widely used to study inclusion complexation, which examines the effect of nanosponges on the solubility of the drug. In this method, the drug was placed into an Erlenmeyer flask. This flask contains an aqueous solution of various percentages of nanosponges. The solution thus obtained was analyzed to determine the concentration of drug by HPLC/ UV. [20]

2. Microscopy studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the morphology and surface topography of the drug, nanosponges and the product (drug/nanosponge complex) by coating with gold–palladium under an argon atmosphere at room temperature. The difference in crystallization state

of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes. [21]

3. Determination of zeta potential

Zeta potential is a measure of surface charge. It can be measured by using an additional electrode in the particle size equipment. [17]

4. Loading efficiency and production yield

Loading efficiency: Dissolve the weighed amount of nanosponges in distilled water and kept overnight. The loading efficiency (%) of nanosponges can be calculated by using the below equations,

$$\text{Loading efficiency (\%)} = \frac{\text{Actual drug content in nanosponges } (M_{actual})}{\text{Theoretical drug content } (M_{theoretical})}$$

Production yield: The production yields of nanosponges can be calculated by using following equation after determining the weight of final product after drying with respect to the initial total weight of the raw material used for the preparation of nanosponges.[17]

$$\text{Production yield} = \frac{\text{Practical mass (nanosponges)}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

6. Infrared spectroscopy

For estimation of the interaction between drug, polymer &nanosponges in the solid state, infrared spectroscopy is used. The peaks obtained are characteristic of the functional groups present in the sample. This technique is not suitable to find the inclusion complexes and also is less clarifying than other methods. [21]

7. X-ray diffractometry

For detecting inclusion complexation in the solid state, powder x-ray diffractometry is used. The complex formation of the drug in 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, the appearance of a few new peaks and shifting of certain peaks. This difference in 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 mechanical mixture of the drug and polymer.[18]

8. Particle size and polydispersity

Particle size diameter is one of the important parameters for evaluating the particle size of nanosponges. PDI is an index of width or spread or variation within the particle size distribution. Monodisperse samples have a lower PDI value; whereas a higher value of PDI indicates a wider particle size distribution and the polydisperse nature of the sample. The particle size and polydispersity index (PDI) can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software or laser light diffractometry or Malvern Zeta sizer. From this, the mean diameter and polydispersity index can be determined.[21]

9. Dissolution test

The dissolution profile of nanosponges can be studied by use of USP dissolution test apparatus II with a modified basket consisted of 5m stainless steel mesh, the speed of the rotation is 150 rpm. The dissolution medium is selected while considering the solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical method.[20]

10. Drug release kinetics

To investigate the mechanism of drug release from the Nanosponge the release data was analyzed using Zero order, First order, Higuchi, Peppas, Hixon Crowell, Kopcha and Makoid-Banker models. The data can be analyzed 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 The mathematical expressions that describe the dissolution curves are summarized in table 2.[22]

Table 2: The mathematical expressions of dissolution curves.

Model	Equation
Zero-order	Qt = Q0 + K0 t
Higuchi model	Qt = Q0 + KH t1/2
Korsemeyer peppas model	Qt = KKPtn
Kopcha model	Qt= At1/2 + Bt
Makoid-banker model	Qt= KMBtn e(-et)

11. Thermoanalytical methods

Thermoanalytical methods determine whether the drug substance undergoes some change 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 complex formation. The thermogram obtained by DTA and DSC can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in weight loss also can provide supporting evidence for the formation of inclusion complexes.[22]

APPLICATIONS

Nanosponges have the capacity to incorporate drugs within their structure, either as inclusion complexes or as non-inclusion complexes. Nanosponges have a wide range of application in the pharmaceutical field, because of its biocompatibility and versatility.

Nanosponges for Drug Delivery

Because of their nanoporous structure, nanosponges can advantageously carry water-insoluble drugs and/or agents (BCS Class-II drugs). These complexes can be used to increase the dissolution rate, solubility, and stability of drugs, to mask unpleasant flavors and to convert liquid substances to solids. B–cyclodextrin-based nanosponges are reported to deliver the drug to the target site three to five times more effective than direct injection. Drugs which are particularly critical for formulation in terms of their solubility can be successfully delivered by loading into the nanosponges. The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalation

dosage forms. For the oral administration, the complexes may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents suitable for the preparation of capsules or tablets. For the parenteral administration, the complex may be simply carried in sterile water, saline or other aqueous solutions. For topical administration, they can be effectively incorporated into the topical hydrogel. [23]

Oral Delivery of Drugs

Oral delivery of drugs using bioerodible polymers, especially for colon-specific delivery and controlled release drug delivery system thus reducing drug toxicity and improving patient compliance by providing site particular drug delivery system and prolonging dosage intervals. Molecular studies include itraconazole, flurbiprofen, dexamethasone, danazol, nelfinavir, and oxycarbamazepine. These are BCS class-II drugs having low solubility and a dissolution rate limited poor bioavailability. However, when formulated with Nanosponge demonstrate enhanced solubilization efficiency, with desired drug release characteristics. [27,28,38]

Topical agents

Nanosponge delivery system is a unique technology for the controlled release of topical agents of prolonged drug release and retention of drug form on the skin. Conventional dermatological and personal care products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short term over medication followed by long term under medication. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, this technology allows an even and sustained rate of release, reducing irritation while maintaining efficiency. A wide variety of substances can be incorporated into a formulated product such as gel, lotion, cream, ointment, liquid, or powder.

Econazole nitrate, an antifungal used topically to relieve the symptoms of superficial candidiasis, dermatophytosis, Versicolor and skin infections available in cream, ointment, lotion, and solution. [37,39]

For Protein Delivery

Bovine serum albumin (BSA) protein in solution is not stable; hence it is stored in lyophilized state. However, proteins can reversibly be denatured on lyophilization and adopt conformation markedly different from native structure. The 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. [36,38]

Table 3: The nanosponges used in the formulation of some drugs.

Drug	Nanosponge Vehicle	Indication	Study	*In-Vitro/In-Vivo* Mathematical Model	Ref
Antisense oligonucleotides	Sodium alginate Poly L-lysine	Cancer therapy Viral infection Pathological-disorders	Pharmacokinetic studies	Mice	24
Camptothecin	β-cyclodextrin	Cancer	Haemolytic activity	Diluted blood HT-29 cell line	25,26
Paclitaxel	β-cyclodextrin	Cancer	Bioavailability Cytotoxicity	Sprague dawley rats MCF7 cell line	27,28
Tamoxifen	β-cyclodextrin	Breast cancer	Cytotoxicity	MCF7 cell line	29
Dexamethasone	β-cyclodextrin	Brain tumors	Drug release experiment	Dialysis bag technique *In-vitro*	30
Temozolamide	Poly (valerolactone allyl valerolactone) and poly (valerolactone allyl valerolactoe-oxepanedione)	Brain tumors	Drug release study	*In-vitro* and *In-vivo* studies.	31
Econazole nitrate	Ethyl cellulose Polyvinyl alcohol	Antifungal	Irritation study	Rat	32,33
Resveratrol	β-cyclodextrin	Inflammation Cardiovascular disease, Dermatitis, Gonorrhea, 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	34
Itraconazole	β-cyclodextrin and copolyvidonum	Antifungal	Saturation solubility study	Higuchi model	35
Bovine serum albumin	Cyclodextrin based Poly (amido amine)	Protein supplement	Drug release study Stability study	*In-vitro* release modulation and stability.	36
Voriconazole	Ethyle cellulose(EC),Polymethyl methacrylate (PMMA), PVA	Antifungal	Drug release Experiment	Rat	37

In Anti-mycotic Therapy

Econazole nitrate, an antifungal agent used topically to relieve the symptoms of superficial candidiasis, dermatophytosis and skin infections available in cream, ointment, lotion, and solution. Adsorption is not significant when econazole nitrate is applied to the skin and required a high concentration of active agents to be incorporated for effective therapy. Thus econazole nitrate nanosponges were fabricated by emulsion solvent diffusion method and these nanosponges were loaded in hydrogel as a local depot for sustained drug release.[40]

In Anti-viral Therapy

Nanosponges can be useful in the ocular, nasal and pulmonary administration routes. The selective delivery of antiviral drugs or small interfering RNA (siRNA) to the nasal epithelia and lungs can be accomplished by nanocarriers in order to target viruses that infect the RTI such as a respiratory sinctial virus, influenza virus, and rhinovirus. They can also be used for Human Immunodeficiency Virus (HIV), Hepatitis-B Virus (HBV) and Herpes Simplex Virus (HSV). The drugs which are formulated in nano delivery systems are zidovudine, saquinavir, interferon-α, acyclovir, nelfinavir, etc. [39]

Solubility enhancement

β-cyclodextrin-based nanosponges of itraconazole have enhanced the solubility of the poorly soluble drug. The solubility increased by 50 folds compared to the ternary dispersion system. Eg. copolyvidonum. [40]

Chemotherapy

Nanosponges have been studied as a potential delivery system for anticancer therapies in which enhancement of bioavailability and activity was seen in molecules such as Paclitaxel and Tamoxifen. Different cancer cells had been treated by nanosponges like breast cancer or fast acting glioma type with the help of a single dose of injections.[25-28]

Nanosponges as a carrier for biocatalysts and release of enzymes, proteins, vaccines, and antibodies

It includes the process applied in the industry which correlate with operational condition. Reactions which are not specific give rise to low yields and require high temperatures and pressures which consume a large amount of energy and cooling water in the downstream process. This is the drawbacks can be removed by using enzymes as biocatalysts as this operate under high reaction speed, mild condition. [36,41]

Nano-carriers for biomedical applications

Nanosponge could be used for contaminated water. Nanosponge has been used for the removal of organic impurities in water. [42]

Analytical Applications

The microporous hyper cross-linked nanosponges have been used in selective preparation of inorganic electrolytes by size exclusion chromatography. The three-dimensional nanosponges will play an important role in the fractionalization of peptides for proteomic applications. [41]

Table 4: Examples of a patent report on nanosponges.

Sr. No.	Patent/App No. Year of Issue	Applicant	Title
1.	WO/2012/147069 (2012)	Trotta, francesco Shende, pravin Biasizzo, Miriam	Method for preparing dextrin nanosponges
2.	PCT/EP2009/004098(2009)	Sea Marconi technologies sas di vandertumiatti	Cyclodextrin nanosponges as a carrier forBiocatalysts, and in the delivery and release of enzymes, proteins, vaccines, and antibodies
3	PCT/EP2008/005290(2008)	Sea Marconi technologies sas di vandertumiatti	Cyclodextrin-based nanosponges as a vehicle for antitumor drug
4	W02003041095A1(2003)	Alberto Bocanegra Diaz	The process of composites preparation between particulate materials and cyclodextrin and/or their derivatives.
5	W02003085002A1(2003)	Sea Marconi Technologies Diw	Cross-linked polymers based on cyclodextrin for removing polluting agents.
6	DE10008508A1(2001)	Bayer Ag	New polycarbonate with cyclodextrin units, used ex: as a chromatographic stationary phase, catalyst, drug delivery system, extractant or moulding material, especially for removing organic compounds from water.
7	EP0502194A1(1992)	Toppan Printing co. Ltd.	Cyclodextrin polymer and cyclodextrin film formed

CONCLUSION

Nanosponges are novel drug carriers which encapsulate the insoluble drug moiety in it thereby improve the bioavailability of poorly soluble drugs and prevent drug and protein physiochemical degradation and prolong drug release in a controlled manner. This technology reduced side effects improved stability and increase elegance. They can suspend or entrap a wide variety of substances and can be developed as different dosage forms like parenteral, aerosol, topical, tablets and capsules. Nanosponge is an effective targeted drug delivery system for poorly water-soluble and a variety of drugs such as: hydrophilic and lipophilic. Nanosponge technology involves encapsulation of medicament in a polymeric material in an innovative way and thus provide controlled site-specific drug release, increased formulation efficacy, improved stability, drug dosing, and patient compliance. Thus nanosponge technology is the most promising leading trends in the area of pharmaceutical sciences for drug administration by oral, topical and parenteral route dosage form on skin, and also for oral delivery of drugs using bio-erodible polymers, especially for colon-specific delivery and controlled release drug delivery system thus improving patient compliance by providing site-specific drug delivery system and prolonging dosage intervals. They could be used to deliver two active substances simultaneously for combination therapy, or for simultaneous therapeutic and diagnostic applications. In conclusion, nanosponges can be considered as multifunctional nanoscale systems suitable for the delivery of active molecules in nanomedicine.

Conflicts Of Interest: The authors declare no conflict of interest.

REFERENCES:

1. Dahanand A., Haffman A. Rationalizing the selection of oral liquid based drug delivery systems by an invitro dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs. Journal of controlled release. 2008;129(1):1-10
2. Chakraborty S., Shukla D., Mishra B., Singh S. Lipid an emerging platform for oral delivery of drugs with poor bioavailability. Europian Journal of Pharmaceuitcs and Biopharmaceutics. 2009;73(1):1-15.
3. Subramanian S., Singireddy A., Krishnamoorthy K., Rajappan M. Nanosponges: a novel class of drug delivery system –Review. J Pharm Pharmaceutical Sci. 2012;15(1):103-11.
4. Nanosponge delivers better than injection. Last update 08.06.2010. Accessed on 09.22.2016.
5. David F. Nanosponge drug delivery system more effective than direct injection. 01.06.2010. Available from http://www.physorg.com.
6. Patel E.K., Oswal R.J. Nanosponge and micro sponges: a novel drug delivery system. International journal of research in pharmacy and chemistry. 2012;2(2):237-44.
7. Jenny A., Merima P., Alberto F., Francesco T. Role of β-cyclodextrinnanosponges in polypropylene photooxidation. Carbohydrate Polymers. 2011;86:127-35.
8. Liang L., De-Pei L., Chih-Chuan L. Optimizing the delivery systems of chimeric RNA. DNA oligonucleotides beyond general oligonucleotide transfer. Eur. J. Biochem, 2002; 269:5753-58.
9. Bolmal U.B., Manvi F.V., Rajkumar K., Palla S.S., Paladugu A, Ramamohan K.Recent Advances in Nanosponges as Drug Delivery SystemReddy International Journal of Pharmaceutical Sciences and Nanotechnology. 2013;6(1):219-27
10. Aritomi H., Yamasaki Y., Yamada K., Honda H., Khoshi M. Development of sustained release formulation of chlorpheniramine maleate using powder coated microsponges prepared by dry impact blending method. Journal of PharmaScie and Tech. 1996; 56(1):49-56.
11. Patel G., Patel J. K. Use of a Microsponge in Drug Delivery Systems. Pharmaceutical processing. 2008;12(3);158-63.
12. Khopade A. J., Jain S., Jain N. K. "The Microsponge". Eastern Pharmacist. 1996;13(3): 49-53.
13. Bhowmik H., Nagasamy V. D., Kuila A, Kummari HA. Nanosponges: a review International Journal of Applied Pharmaceutics. 2014:10(4);1-5.
14. Amber V., Shailendra S., Swarnalatha S. Cyclodextrin based novel drug delivery systems **J**. Incl Phenom Macrocycl Chem. 2008;62:23-42.
15. Rajeswari C., Alka A., Javed A., Khar R. K. Cyclodextrins in drug delivery: an update review. AAPS pharm Sci Tech. 2005;6(2):329-57
16. Jyoti P., Tulsi B., Popin K., Chetna B. An Innovative Advancement for Targeted Drug Delivery: Nanosponges. Indo Global Journal of Pharmaceutical Sciences. 2016;6(2):59-64.
17. Carter S. J. Disperse system In: Cooper and Gunn's Tutorial Pharmacy. 6th ed. New Delhi: CBS Publishers and Distributors, 2000, 68-72.
18. Richhariya N., Dr. Prajapati S. K., Dr. Sharma U. K. Nanosponges: an innovative drug delivery system. World Journal of Pharmaceutical Research. 2015;4(7):1747-59.
19. Mark A. M., Przemyslaw R., Greg C., Greg S., Akram S., Jonathan F., et al. In vivo human time exposure study of orally dosed commercial silver nanoparticles. Nanomedicine: Nanotechnology, Biology and Medicine. 2014;10:1-9.
20. Jenny A., Merima P., Alberto F., Francesco T. Role of β-cyclodextrin nanosponges in polypropylene photooxidation. Carbohydrate Polymers. 2011; 86: 127–35.
21. Trotta F., Zanetti M., Cavalli R. Cyclodextrin-based nanosponges as drug carriers. Beilstein J Org Chem.2012;8:2091–9.
22. Renuka S., Roderick B.W., Kamla P. Evaluation of the kinetics and mechanism of drug release from Econazole Nitratenanosponge loaded carbapol hydrogel. Ind **J** Parm Edu Res. 2011;45:25-31.
23. Swaminathan S., Cavalli R., Trotta F., Vavia P. R. Invitro release modulation and conformational stabilization of a model protein using swellable polyamido amine nanosponges of cyclodextrin. J Incl Phemon Macrocycl Chem. 2010:2(1);1-7.
24. Rosalba M., Roberta C., Roberto F., Chiara D., Piergiorgio P., Leigh E., Li S., Roberto P. Antitumor activity of nanosponge-encapsulate Camptotechin in human prostate tumors. Cancer Res. 2011;71(1):4431-39.
25. Shankar S., Linda P., Loredana S., Francesco T., Pradeep V., Dino A., Michele T., Gianpaolo Z., Roberta C. Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization stability and cytotoxicity. Eur J Pharm Biopharm. 2013;74(1):193-201.
26. Torne S. J., Ansari K. A., Vavia P. R., Trotta F., Cavalli R. Enhanced oral Paclitaxel bioavailability after administration of Paclitaxel loaded nanosponges. Drug Delivery, 2010;17(6): 419–25.
27. Ansari K. A., Torne S. J., Vavia P. R., Trotta F., Cavalli R. Paclitaxel loaded nanosponges: in-vitro characterization and cytotoxicity study on MCF-7cell line culture. Curr Drug Deliv, 2011;8(2):194-202
28. William K., Benjamin S., Eva H. Synthesis and Characterization of Nanosponges for Drug Delivery and Cancer Treatment. www.Vanderbilt.edu accessed on 20.12.2011
29. Jenny A., Merima P., Alberto F., Francesco T. Role of ß-CyclodextrinNanosponges in polypropylene photooxidation Carbohydrate Polymers. 2011;86(1):127-35.
30. Lala R., Thorat A., Gargote C. Current trends in ß- cyclodextrin based drug delivery systems. Int J Res Ayur Pharm, 2011;2(5):1520-6.
31. Shankar S., Vavia P. R., Francesco T., Satyen T. Formulation of Betacyclodextrin based nanosponges of Itraconazole. J Incl Phenom Macrocycl Chem, 2007;57:89–94.
32. Renuka S., Roderick B. W., Kamla P. Evaluation of the kinetics and mechanism of drug release from Econazole Nitrate Nanosponge loaded carbapol hydrogel. Ind J ParmEduRes, 2011;45(1):25-31.
33. Benet L. Z. Bioavailability and Bioequivalence, Focus on Physiological Factors and Variability. Department of biopharmaceutical sciences, University of California, San Francisco,

USA, 2007.

34 Khalid A. A., Pradeep R.V., Francesco T., Roberta C. Cyclodextrin-based nanosponges for delivery of Resveratrol: In Vitro characterisation, stability, cytotoxicity and permeation Study. AAPS PharmSci Tech, 2011;12(1):279-86.

35 Mohammad A. M., Mohammad A. R., Talegaonkar S., Zeenat I. In vitro/invivo performance of different complexes of itraconazole used in the treatment of vaginal candidiasis. Brazilian Journal of Pharmaceutical Sciences. 2012;48(4),759-772.

36 Dr. Prathima S., Sreeja K. Formulation and Evaluation of Voriconazole Loaded Nanosponges for Oral and Topical Delivery. Int. J. Drug Dev. & Res., 2013;5(1):55-69.

37 Melanie F., Mura P., Adamo M., Maestrelli F., Gratteri P. and Bonaccini C. New docking CFF91 parameters specific for cyclodextrin inclusion complexes. Chemical Physics Letters. 2003;370(1-2): 280-92.

38 Wong V. N., Fernando G., Wagner A. R., Zhang J., Kinsel G. R, Zauscher S., Dyer D. J., Separation of peptides with polyionic nanosponges for MALDIMS analysis. Langmuir, 2009;25(3):1459-65.

39 Ansari K. A., Torne S., Vavia P. R, Trotta F., Cavalli R., Cyclodextrin- Based Nanosponges for Delivery of Resveratrol: In Vitro Characterization, Stability, Cytotoxicity and Permeation Study, AAPS Pharm Sci Tech. 2011;12(1):279-86.

40 Zuruzi S., MacDonald N. C., Moskovits M., Kolmakov A. Metal oxide "nanosponges" as chemical sensors: Highly sensitive detection of hydrogen using nanosponge titania. Angew and te Chemie, International Edition. 2007;46(23):4298-4301.

41 Sh Arma N., Kumar S. L., Aggarwal HG, Review on nanosponges: A novel drug delivery. World Journal of Pharmacy and pharmaceutical Sciences 2016; 5(5): 406-27.

42 Swaminathan S., Pastero L., Serpe L., Trotta F., Vavia P. Cyclodextrin based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity. Eup J of Pharmaceutics and Biopharmaceutics, 2010;74(2):193-201.