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NANOSPONGES - NOVEL EMERGING DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT: The advent of nanotechnology lead to invention of many dosage forms. Effective targeted drug delivery systems have been a dream for a long time, due to several major drawbacks, a practical approach has been developed for the formation of discrete functionalized particles, which have been termed as 'Nanosponge'. The development of new colloidal carrier called Nanosponges has the potential to solve these problems. Nanosponge is a novel and emerging technology it can precisely control the release rates of controlled drug delivery for topical use. The invention of Nanosponges has become a significant step toward overcoming these problems. Nanosponges are tiny 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. Another important character of these sponges is their aqueous solubility; this allows the use of these systems effectively for drugs with poor solubility.

INTRODUCTION: The drug delivery technology has certainly a new interest for drugs by providing them new life through their therapeutic targets. Nowadays, targeting drug delivery is the major problem which is being faced by the researchers. Target oriented drug administration with improvements in therapeutic efficacy, reduction in side effects and optimized dosing regimen, shall be the leading trends in the area of therapeutics.

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Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at preidentified (preselected) target in therapeutic concentration, while restricting its access to non-target normal cellular linings and thus minimizing toxic effects and maximizing therapeutic index of the drug [1].

An ideal drug therapy achieves effective concentration of drug at the target site for a specified period of time in order to minimize general and local side effects. To obtain a desirable therapeutic response, the correct amount of drug should be transported and delivered to the site of action with subsequent control of drug input rate. The distribution of drug to other tissues therefore seems unnecessary, wasteful and a potential cause

of toxicity. Targeted drug delivery is the delivery of drug to receptor, organ or any part of the body to which one wishes to deliver the drug exclusively [2].

Effective targeted drug delivery systems have been a dream for long time, now but it has been largely frustrated by the complex chemistry that is involved in the development of new systems. Targeting drug delivery has long been a problem for medical researchers i.e., how to get them to the right place in the body and how to control the release of the drug to prevent overdoses. The development of new and complex molecule called Nanosponges has the potential to solve this problem.

Nanosponges are a new class of tiny sponges that are about the size of a virus, filling them with a drug and attaching- special chemical "linkers" that bond preferentially to a feature found only on the surface of tumour cells and then injecting them into the body. These tiny sponges circulate around the body until they encounter the surface of a tumour cell where they stick on the surface (or are sucked into the cell) and begin releasing their potent drug and begin releasing their potent drug in a controllable and predictable fashion [3].

Nanosponges are like a Three-dimensional net work or scaffold," Whose backbone is long-length polyester. It is mixed in solution with small molecules called cross-linkers that act like tiny grappling hooks to fasten different parts of the polymer together. The net effect is to form spherically shaped particles filled with cavities where drug molecules can be stored. The polyester is biodegradable, so it breaks down gradually in the body. The size of nanosponge particles can also possible to control by varying the proportion of cross-linkers to polymer, the nanosponge particles can be made larger are smaller (Based on the structure of Nanosponges **Fig 1** and **Fig 2**). The research has shown that drug delivery system they are smaller than 100 nm, the nanosponge particles used in the current study were 50 nm in size [2].

Nanosponges are tiny mesh-like structures that may revolutionize the treatment of many diseases and this technology is five times more effective at delivering drugs for breast cancer than conventional methods [2].

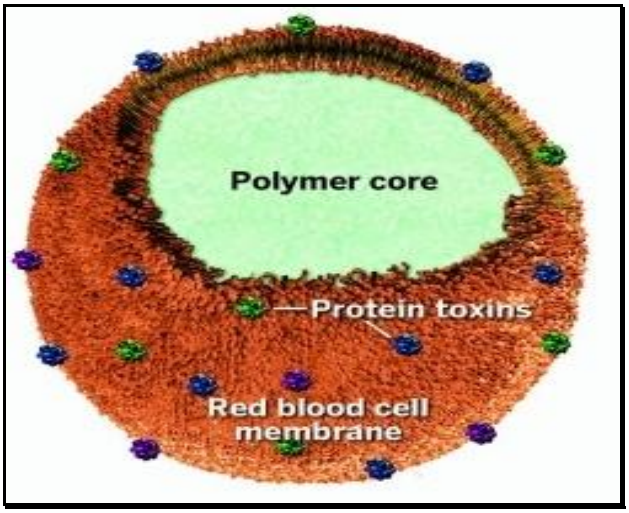

FIG 1: POLYMER BASED NANOSPONGE

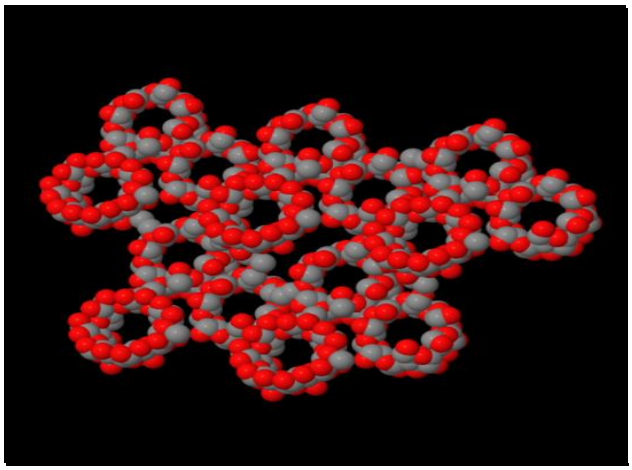

FIG 2: CYCLODEXTRIN BASED NANOSPONGE

Nanosponges are made up of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules [4]. Nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core [5]. As compared to other nanoparticles, nanosponges are insoluble in water and organic solvents, porous, non toxic and stable at high temperatures up to 300^0c [5].

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 [6].

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 [7].

Nanosponges represent a novel class of nanoparticles usually obtained by natural derivatives. As compared to the other nanoparticles, they are soluble both in water and organic solvents, porous, non-toxic and stable at high temperature up to 300^{o}c. Due to its 3D structure containing cavities of nanomeric size, tunable polarity and high selectively release a wide variety of substances.

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 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 [8].

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 [9]. The tiny shape of enables the pulmonary and venous delivery of nanosponges [4].

The list of polymers and cross linking agents used for the synthesis of Nanosponge is presented in **Table 1**.

TABLE: 1 CHEMICALS USED FOR THE SYNTHESIS OF NANOSPONGES [10]

Polymers	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-oxepanedione) and Ethyl Cellulose & Poly vinyl acetate(PVA).
Cross linkers	DiphenylCarbonate,Di-arylcarbonates, Di-Isocyanates, Pyromellitic anhydride,Carbonyldi-imidazoles, Epi-chloridrine, Glutraldehyde, Carboxylic acid di-anhydrides, 2, 2- bis (acrylamidos), Acetic acid and Dichloromethane

ADVANTAGES OF NANOSPONGES [11-14]

- Targeted site specific drug delivery.
- This Technology offers entrapment of wide variety of ingredients and reduced side effects.
- Improved Stability, increased elegance and enhanced formulation flexibility.
- Nanosponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- A Nanosponge provides continuous action up to 12 hours i.e. extended release.
- It minimizes the irritation and it gives better tolerance which leads to improved patient compliance.
- Allows incorporation of immiscible liquids which improves material processing. Liquid can be converted to powders.

- These formulations are stable over wide range of PH (1-11) and temperature (up to 130°c).
- These are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- These are free flowing, highly compatible with wide variety of ingredients and cost effective.
- They have better thermal, physical and chemical stability.
- Nanosponge particles are soluble in water, so encapsulation can be done within the nanosponge, by the Addition of chemical called an adjuvant reagent.

PREPARATION METHODS OF NANOSPONGES

Emulsion Solvent Diffusion Method [15]

Nanosponges can be prepared by using different proportions of ethyl cellulose (EC) and polyvinyl alcohol (PVA).The dispersed phase containing Ethyl cellulose and drug was dissolved in 20ml dichloromethane and slowly added to a definite amount of polyvinyl alcohol in 150ml of aqueous continuous phase. The reaction mixture was stirred at 1000 rpm for 2hrs. The Nanosponges formed were collected by filtration and dried in oven at 40^{0}c for 24hrs. The dried Nanosponges were stored in vaccum desiccators to ensure the removal of residual solvents. Flow diagram for the preparation of Nanosponges is shown in **(Figure 3)**.

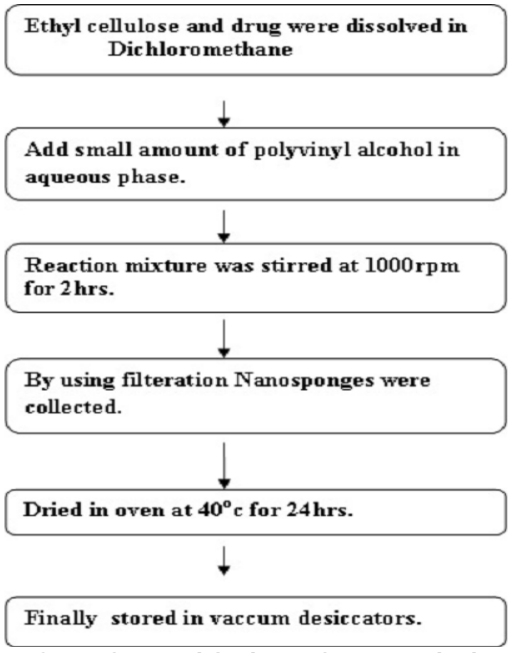

FIGURE 3: FLOW DIAGRAM FOR PREPARATION OF NANOSPONGES

Nanosponges prepared from Hyper Cross Linked _ β Cyclodextrins [16 - 19]

Nanosponge has been recently developed hyper cross linked cyclodextrin polymers nano structured to form 3-dimensional networks; a roughly spherical structure, about the size of a protein, with channels and pores inside. They are obtained by reacting cyclodextrin with a cross-linker such as di isocianates, diaryl carbonates, Dimethyl carbonate, diphenyl carbonate, and carbonyl di-imidazoles, carboxylic acid dianhydrides and 2, 2-Bis (acrylamido) acetic acid. The surface charge density, porosity and pore sizes of sponges can be controlled to attach different molecules. Nanosponge with low cross linking gives a fast drug release.

β-cyclodextrin nanosponges were prepared as 100ml of dimethyl Formaamide (DMF) was placed in a round bottomed flask and 17.42g of anhydrous β-CD was added to achieve complete dissolution. Then 9.96g of carbonyl di-imidazole (61.42m mol) was added and the solution allowed reacting for 4hrs at 100^{0}c. Once condensation polymerization was complete, the transparent block of hyper cross linked cyclodextrin was roughly ground and an excess of deionised 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^{0}c and in a mortar. The fine powder upto spherical shape. The fine powder obtained was dispersed in water. The colloidal part that remained suspended in water was recovered and lyophilized. The obtained nanosponges are sub-micron in dimension and with a spherical shape.

Solvent method: [4, 20]

Mix the polymer with a suitable solvent, mainly in a polar aprotic solvent such as dimethylformamide (DMF), dimethylsulfoxide (DMSO). Then add this mixture to cross linker in a exceed quantity, the ratio for cross linker/ molar ratio is preferred as 1:4. The reaction carried out at temperature ranging from 10^{0}c to the reflux temperature of the solvent, for time ranging from 1 to 48 hr. The cross linkers which may preferred are dimethyl carbonate and carbonyl diimidazole. The

reaction is completed and solution is allow to cool at room temperature then product is added to large excess of bi-distilled water and product is recovered by filtration under vaccum and subsequently purify by prolonged soxhlet extraction with ethanol. Finally product is dried under vaccum and grinded in a mechanical mill to obtain homogeneous powder.

Ultrasound- Assisted Synthesis [4, 20]

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^{o}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^{o}c.

Loading Of Drug into Nanosponges [18, 20, 21]

Nanosponges for drug delivery should be pretreated to obtain a mean particle size below 500nm. Suspend the nanosponges in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to obtain the colloidal fraction. Separate the supernatant and dry the sample by freeze drying.

Prepare the aqueous suspension of Nanosponge and disperse the excess amount of the drug and maintain the suspension under constant stirring for specific time required for complexation. After complexation, separate the uncomplexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or by freeze drying.

Crystal structure of nanosponge plays a very important role in complexation with 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. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than inclusion complex.

FACTORS INFLUENCE NANOSPONGE FORMATION

Type of polymer [22]

Type of polymer used can influence the formation as well as the performance of Nanosponges. For complexation, the cavity size of nanosponge should be suitable to accommodate a drug molecule of particular size.

Type of drugs [22]

Drug molecules to be complexed with nanosponges should have certain characteristics mentioned below.

- Molecular weight of drug should be in between 100 to 400 Daltons.
- Drug molecule consists of less than five condensed rings.
- Solubility in water should be less than 10mg/ml.
- Melting point of the substance should be less than 250°C.

Temperature [23]

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 possible reduction of drug/nanosponge interaction forces, such as van-der Waal forces and hydrophobic forces with rise of temperature.

Method of preparation [23]

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.

CHARACTERIZATION OF NANOSPONGES

Inclusion complexes formed between the drug and nanosponges can be characterized by following methods.

Loading efficiency [24]

The loading efficiency of nanosponge complexes is to be dissolved in suitable solvent, sonicated to break the complex, diluted suitably and then analyzed by UV spectrophotometer & HPLC methods.

Microscopy studies [19, 25]

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the drug, nanosponges and the product (drug/nanosponge complex).

The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes, even if there is a clear difference in crystallization state of the raw material and the product obtained by co-precipitation.

Particle size and polydispersity [19, 26]

The particle size can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software. From this the mean diameter and polydispersity index can be determined.

The polydispersity index (PDI) can also be measured from dynamic light scattering instruments. 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.

Zeta potential [19]

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

Fourier Transform Infrared (FTIR) Analysis

Fourier transform infrared analysis was conducted to verify the possibility of interaction of chemical bonds between drug and polymer. Samples were scanned in the range from 400-4000 cm^{-1} and carbon black reference. The detector was purged carefully by clean dry helium gas to increase the signal level and reduces moisture.

Thin Layer Chromatography [25, 27]

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.

Infra-Red spectroscopy [25]

Infra-Red spectroscopy is used to estimate the interaction between Nanosponge and the drug molecules in the solid state. Nanosponge bands often change only slightly upon complex formation and if the fraction of the guest molecules encapsulated in the complex is less than 25%, bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of nanosponges. The technique is not generally suitable to detect the inclusion complexes and is less clarifying than other methods.

The application of the Infra-red spectroscopy is limited to the drugs having some characteristic bands, such as carbonyl or sulfonyl groups. Infrared spectral studies give information regarding the involvement of hydrogen in various functional groups. This generally shifts the absorbance bands to the lower frequency, increases the intensity and widens the band caused by stretching vibration of the group involved in the formation of the hydrogen bonds. Hydrogen bond at the hydroxyl group causes the largest shift of the stretching vibration band.

Thermo-analytical methods [28, 25]

Thermo-analytical 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 the 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 the weight loss also can provide supporting evidence for the formation of inclusion complexes.

X-ray diffractiometry and single crystal X-ray structure analysis [25]

Powder X-ray diffractiometry 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 are apparently different from each constituent and lead 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 [25, 29]

This method used to determine the detailed 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. This information obtained during the analysis lead to know about the formation of inclusion complexes.

***In-Vitro* drug release study** [30]

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

Drug release kinetics [30]

To investigate the mechanism of drug release from the Nanosponge the release data was analysed using Zero order, First order, Higuchi, Korsemeyer-Peppas, Hixon Crowell, Kopcha and Makoid-Banakar 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.

APPLICATIONS OF NANOSPONGES

Nanosponges for drug delivery

Because of their nanoporous structure, nanosponges can advantageously carry water insoluble drugs (Biopharmaceutical Classification System 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. β-Cyclodextrin based nanosponges are reported to deliver the drug to the target site three to five times more effectively than direct injection[2].Drugs which are particularly critical for formulation in terms of their solubility can be successfully delivered by loading into the nanosponges.

List of some BCS Class II dugs which can be developed as nanosponges are given in **Table 2**.

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 [9]. For the parenteral administration the complex may be simply carried in sterile water, saline or other aqueous solutions [9]. For topical administration they can be effectively incorporated into topical hydrogel [30, 31]. The nanosponges used in the formulation of some drugs are provided in the **Table 3**.

TABLE 2: BIOPHARMACEUTICAL CLASSIFICATION SYSTEM CLASS II DRUGS [32]

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

TABLE 3: EXAMPLES OF NANOSPONGES

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	34
Camptothecin	β-cyclodextrin	Cancer	Haemolytic activity	Diluted blood HT-29 cell line	20,35
Paclitaxel	β-cyclodextrin	Cancer	Bioavailability Cytotoxicity	Sprague dawley rats MCF7 cell line	36,37
Tamoxifen	β-cyclodextrin	Breast cancer	Cytotoxicity	MCF7 cell line	9
Dexamethasone	β-cyclodextrin	Brain tumors	Drug release experiment	Dialysis bag technique *In-vitro*	10
Temozolamide	Poly (valerolactoneallyl valerolactone) and poly (valerolactoneallyl valerolactoe-Oxepanedione)	Brain tumors	Drug release study	*In-vitro* and *In-vivo* studies.	38
Econazole nitrate	Ethyl cellulose Polyvinyl alcohol	Antifungal	Irritation study	Rat	31,32
Itraconazole	β-cyclodextrin and copolyvidonum	Antifungal	Saturation solubility study	Higuchi model	39
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	40
Bovine serum albumin	Cyclodextrin based Poly (amidoamine)	Protein supplement	Drug release study Stability study	*In-vitro* release modulation and stability.	41
Voriconazole	Ethyle cellulose(EC), Polymethyl methacrylate (PMMA), PVA	Antifungal	Drug release Experiment	Rat	42

Nanosponges as a carrier for biocatalysts [10, 22]

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 high reaction speed, and are highly specific. They have a beneficial effect on the 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.

Examples: Examples of industrially useful enzymes include alpha amylase, trypsin, cellulase and pectinase for fruit juice clarification processes, ligninase to break down lignin, lipase in the detergent industry and biodiesel production, etc. The catalytic activity of enzyme depends mainly on the correct orientation of the active site.

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.

A number of systems for carrying enzymes and proteins have been developed, such as nano and microparticles, liposomes 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.

Cancer Therapy [39]

Nanosponges which can be used as anticancer drug delivery system for tumors. They claim that the method is three to five times more effective at reducing tumor growth than direct injection of the drugs. The tiny nanosponges are filled with a drug load and expose a targeting peptide that binds to radiation-induced cell surface receptors on the tumor. When the sponges encounter tumor 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. Studies so far have been carried out in animals with paclitaxel as the sponge load.

Camptothecin, a plant alkaloid and a potent antitumor agent, has a limited therapeutic utility because of its poor aqueous solubility, lactone ring instability and serious side effects. Cyclodextrin-based nanosponges are a novel class of cross-linked derivatives of cyclodextrin. They have been used to increase the solubility of poorly soluble actives, to protect the labile groups and control the release. This study aimed at formulating complexes of camptothecin with β-cyclodextrin based nanosponges.

Topical agents [42, 15]

Nanosponge delivery system is a unique technology for the controlled release of topical agents of prolonged drug release and retention of drug form on 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 relive the symptoms of superficial candidasis, dermatophytosis, vesicular and skin infections available in cream, ointment, lotion and solution. Adsorption is not significant when econazole nitrate is applied to skin and required high concentration of active agents to be incorporated for effective therapy. Thus, econazole nitrates Nanosponge were fabricated by emulsion solvent diffusion method, and these Nanosponges were loaded in hydrogel as a local depot for sustained drug release.

Solubility enhancement [43, 17]

Nanosponges have been also used for improving the solubility and dissolution rate of poorly soluble drugs as well as providing controlled release profile. However the molecular dimensions and conformation are critical parameters influencing inclusion complexation within nanosponges and thus may not be universally applicable to all molecules. Nanosponges of Cefpodoxime proxetil (CP) have been prepared to improve dissolution rate of Cefpodoxime Proxetil.

Formulation of crosslinked β-cyclodextrins based nanosponges of itraconazole has been reported to enhance the solubility of the poorly soluble drugs. It was found that the solubility of itraconazole was enhanced more than 50-folds with a ternary solid dispersion system. Using copolyvidonum in conjunction with nanosponges helped to increase the solubilization efficiency of nanosponges.

Antiviral application [44]

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 sincytial 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).

Encapsulation of gases [45, 46]

Cyclodextrin based carbonate Nanosponge was used to form inclusion complexes with three different gases, i.e. 1-methylcyclopropene, oxygen and carbondioxide. The complexetion of oxygen or carbondioxide 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 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.

Other applications of Nanosponges [47- 50]

Nanosponges based on cyclodextrins can strongly bind organic molecules and remove them from water even at very low concentrations. The same concept can be useful for elimination of bitter components from grape fruit juice by selective combination of polymer and crosslinker. The microporous hyper cross linked Nanosponges have been used in selective separation of inorganic electrolytes by size exclusion chromatography. The three dimensional Nanosponges will play important role in the fractionalization of peptides for proteomic applications. Nanosponges can be used as carrier for gases like oxygen and carbon dioxide.

These Nanosponges could be useful for many biomedical applications. In particular the oxygen-filled Nanosponges could supply oxygen to the hypoxic tissues which are present in various diseases. Nanosponges can selectively soak up biomarkers for the diagnosis. One study concluded that Nanosponges can harvest rare cancer marker from blood.

Patent report on β-cyclodextrin Nanosponges in **(Table 4)**

TABLE 4: 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	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.
4.	EP0502194A1 (1992)	Toppan Printing co. Ltd.	Cyclodextrin polymer and cyclodextrin film formed.

CONCLUSIONS: The Nanosponges have the ability to release the drug in a controlled manner to the targeted site. They are also capable of carrying both lipophilic and hydrophilic molecules. 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.

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