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Nanosponges: A Novel Polymeric Nanocarrier System for Controlled and Targeted Drug Delivery

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ABSTRACT

Nanosponges are a kind of nanoparticles, mostly a polymer that contains synthesized carbon. They feature a porous structure with pores that are about 2 nanometers in diameter, allowing for the absorption of a little amount of materials or toxin. Nanosponges are porous polymeric delivery systems that are small spherical particles with large porous surface. These are used for the passive targeting of cosmetic agents to skin, there by achieving major benefits such as reduction of total dose, retention of dosage form on the skin and avoidance of systemic absorption. These nanosponges can be effectively incorporated onto topical systems for prolonged release and skin retention thus reducing the variability in drug absorption, toxicity and improving patient compliance by prolonging dosing intervals. Nanosponges also serve as targeted delivery systems and tactics for detoxification and as a means to avoid harm caused by an injury in medicine. Presence of crosslinking agent and cyclodextrin cavities in the nanosponge structure favours interaction with active molecules. These features permit several substances to be included and get solubilized in the formed cavities. Reduction in drug crystallinity occurs by preparing inclusion complexes or solid dispersions with cyclodextrins which enhances drug solubility or rate of dissolution of poorly water soluble drugs. The hydrophobic functionality of the complex hides in the interior cavity of the cyclodextrin while hydrophilic hydroxyl groups on the external surface remain exposed to the environment, the net effect is that a water soluble complex is formed.

Keyword: nanosponges, zetasizer, cyclodextrin, polymers.

INTRODUCTION:

Nanosponges are a kind of nanoparticles, mostly a polymer that contains synthesized carbon. They feature a porous structure with pores that are about 2 nanometers in diameter, allowing for the absorption of a little amount of materials or toxin. Nanosponges are porous polymeric delivery systems that are small spherical particles with large porous surface. These are used for the passive targeting of cosmetic agents to skin, there by achieving major benefits such as reduction of total dose, retention of dosage form on the skin and avoidance of Systemic absorption. These nanosponges can be effectively incorporated onto topical systems for prolonged release and skin retention thus reducing the variability in drug absorption, toxicity and improving patient compliance by prolonging dosing intervals. Nanosponges also serve as targeted delivery systems and tactics for detoxification and as a means to avoid harm caused by an injury in medicine. They can also be used to clean up the environment through activities such as water purification or metal deposits. Its small size enables fluids like water and blood to travel swiftly. Allowing it to quickly find and target harmful compounds. Nanosponges are frequently made synthetically, but they often contain natural elements that help them work better when injected into the body. Nanosponges are superior to micro sponges, since the smaller scale allows less damage to the device in question, thereby reducing the likelihood of failure or adverse effects. Nanosponges are superior. The "nano" prefix means that objects of that size are measured to a scale of 10 meters (-19 m long).

POLYMER BASED NANOSPONGE :

Nanospongs are porous polymer delivery systems with a tiny spherical particle size (250nm- 1µm), with large porous surfaces. These drugs are used to target cosmetic agents passively on the skin, thus gaining substantial advantages such as reducing the overall dose, maintaining the dosage type on the skin and preventing systemic absorption. These nanosponges can be integrated effectively into topical systems that reduce the risk of drug uptake, the toxicity and the improvement of biodisposability for extended releases and skin retention. Because nanosponge particles (without a continuous membrane around them) the active element can be inserted

or forced into the vehicle from inside or from the particles until a balance is reached on the vehicle. The active component in the vehicle becomes unsaturated and breaks balance once the product is applied to the skin.

Nanosponges were originally developed for topical delivery of drugs. They are colloidal carriers have recently been developed and proposed for drug delivery, since their use can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability and in some case modifying its pharmacokinetics parameters.. The average diameter of a nanosponge is below 1 μm but fractions below 500 nm can be selected, micro sponges are 10-25 microns in diameter. They can also decrease side effect and protect drug from degradation. 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.

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 anticaking agents which is suitable for the preparation of tablets or capsules. For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions. For topical administration, they can be effectively incorporated into topical hydrogen.

These nanoparticle 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 manner5. Targeted drug delivery systems of this type have several basic advantages. As the drug is released at the tumor site instead of circulating widely through the body, it should be more effective for a given dosage.

Targeting the delivery of drugs has long been a problem for medical researchers - how to get them to the right place in the body and how to control the release of the drug to prevent overdoses. The developments of new and complex molecules called nanosponges have the potential to solve these problems. Nanosponges are a new class of materials and made 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.

Nanosponges are tiny mesh-like structures that may revolutionise the treatment of many diseases and early trials suggest this technology is up to five times more effective at delivering drugs for breast cancer than conventional methods. The nanosponge is about the size of a virus with a ‘backbone’ (a scaffold structure) of naturally degradable polyester. The long length polyester strands are mixed in solution with small molecules called cross- linkers that have an affinity for certain portions of the polyester. They ‘cross link’ segments of the polyester to form a spherical shape that has many pockets (or cavities) where drugs can be stored. The polyester is predictably biodegradable, which means that when it breaks up in the body, the drug can be released on a known schedule.

A rendering of the nanosponges attracting bloodstream-borne toxins:

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, complexing nanoparticles and conjugating nanoparticles. The first type is represented by nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are spongelike nanoparticles 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. The second category is Complexing nanoparticle, which attracts the molecules by electrostatic charges. The third type is Conjugating nanoparticle, which links to drugs through covalent bonds.These nanosponges represent a novel class of nanoparticles usually obtained by natural derivatives. As compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non toxic and stable at high temperatures up to 300°C.

Nanosponges are used as nanomaterials in the pharmacy, diagnosing and concentrating the correct position in the body and tracking release of the drug and nanotechnology. These smaller nanosponges circulate throughout the body until they reach the precise target location, When they attach themselves to the organ surface and the drug begins to release in a controlled, predictable way. Because the medicine may be delivered to a specific area, it is more effective for a single dose than for systemic circulation in the body.

By reacting polyesters (cyclodextrins) with appropriate crosslinking agents, a novel nanostructured material can be obtained, known as nanosponges.

Formation of Nanosponges:

The cyclodextrin to crosslinker ratio can be varied throughout the preparation period by improving the drug loading capacity and ultimately acquiring a tailored release profile. Highly porous nanomeric nature of nanosponges enables the drug molecules to orient themselves in inclusion as well as interact in a non-inclusion fashion, which offers higher drug loading when compared to their respective parent cyclodextrin molecules.

Nanosponges are solid in nature. They are found to be safe for oral and invasive routes; hence they can serve as an inherent carrier for drug delivery. The tiny shape of nanosponges permits the pulmonary and venous delivery of nanosponges. For oral delivery, the complex may be dispersed in a matrix of excipients (diluents, lubricants and anti-caking agents). For parenteral delivery, the complex may be simply carried in sterile water, saline or other aqueous solutions. For topical delivery they can be effectively integrated into topical hydrogel.

Characteristic Features of Nanosponges :

Nanosponges provide a range of dimensions (1 μm or less) with tunable polarity of the cavities.

- They exhibit paracrystalline or crystalline forms, depending on the process conditions. Crystal structure of nanosponges plays a crucial role during complexation with drugs.

- Drug loading capacity depends on the degree of crystallization.

- Various drug loading capacities can be shown by paracrystalline nanosponges. 6. They are nontoxic, porous particles, insoluble in most organic solvents and stable up to 300 °C.

- They are stable at the pH range of 1-11.

- They form clear and opalescent suspension in water.

- They can be reproduced by simple thermal desorption, extraction with solvents, by using microwaves and ultrasounds.

- Their three-dimensional structure allows capture, trans- portation and selective release of a variety of substances.

- They can be sited to different target sites because of their capacity to link with different functional groups.

- Chemical linkers permit nanosponges to bind preferably to the target site.

- By complexing with different drugs nanosponges can form inclusion and non-inclusion complexes.

- By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges.

- Nanosponges are porous particles having high aqueous solubility, used mainly to encapsulate the poor soluble drugs.

- These Nanosponges are capable of carrying both lipophilic and hydrophilic drugs.

- They protect the drug from physicochemical degradation.

- They are able to remove the organic impurities from water.

ADVANTAGES OF NANOSPONGES :

- This technology offers entrapment of ingredients and reduces side effects.

- Improved stability, increased elegance and enhanced formulation flexibility.

- These formulations are stable over range of pH 1 to 11.

- These formulations are stable at the temperature up to 1300C.
- These are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- These formulations are free flowing and can be cost effective.
- These modify the release of drug.
- They increase the solubility of poorly soluble drug.
- They increase the bioavailability of drug..
- Nanosponges can be significantly reducing the irritation of drugs without reducing their efficacy.
- To improving patient compliance by prolonging dosing intervals.
- Biodegradable.
- Easy scale up for commerical production.
- Disadvantages
- Nanosponges have ability to include only small molecules.
- 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.

Type of Nanosponges:

1.CD-based carbamate nanosponges:

CDs are reacted with suitable diisocyanates such as hexamethylene diisocyanate and toluene- 2, 4-diisocyanate in the presence of DMF solution at 70°C for 16 to 24 hours under a nitrogen atmosphere. Residual DMF is removed by thorough washing with acetone and powder of the crosslinked polymer is obtained. These nanosponges have an ability to bind to organic molecules and used for water purification. The loading capacity for organic molecules ranges from 20 to 40 mg per cm^3.

2.CD-based carbonate nanosponges:

The main crosslinkers used for preparation of this type of nanosponges are active carbonyl compounds such as CDI, DPC and trifosgene. The resulting CD nanosponges exhibit carbonate bonds between two CD monomers. The reaction can be carried out at room temperature or at 80 to 100°C in the presence or absence of a solvent, i.e., employing either the solvent technique or melt technique. Some of the important characteristics of carbonate-CD- based nanosponges are adjustable polarity and changeable dimensions of their cavities. They can be obtained in different forms, like amorphous or semi-crystalline, by carrying out the reaction under different conditions. Carbonate-CD-based nanosponges have been used to encapsulate many drugs such as paclitaxel, camptothecin, dexamethasone, flurbiprofen, doxorubicin hydrochloride, itraconazole, 5-fluorouracil, cilostazol, progesterone, oxcarbamazepine, nelfinavir mesylate, resveratrol and tamoxifen. Carbonate nanosponges do not significantly affect the surface tension of water.. A unique feature of CD-based carbonate nanosponges is that their ability of solubility enhancement depends significantly on their degree of crystallinity.

3.CD-based ester nanosponges:

A suitable dianhydride such as pyromellitic anhydride is used as a crosslinking agent for fabrication of these nanosponges. The exothermic crosslinking reaction is very fast (completed within a few minutes) and is carried out at room temperature, dissolving the CD and the dianhydride in DMSO in the presence of an organic base such as pyridine or triethylamine (to accelerate the reaction

in a forward direction). This type of nanosponges can host both apolar organic molecules and cations simultaneously since it contains a polar free carboxylic acid group.

4.Polyamidoamine Nanosponges:

These types of nanosponges are prepared by carrying out the reaction in water. β- CD polymerizes with acetic acid 2, 20-bis (acrylamide) after long standing (i.e., 94 h at room temperature). They swell in water (pH dependent behavior) and have both acid and basic residues. The polymer forms a translucent gel instantly on contact with water. Time-dependent swelling studies in bio relevant media confirmed the stability of the gel for up to 72 h. The studies were carried out using albumin as a model protein exhibiting very high encapsulation efficiency, around 90%. In vitro drug release studies showed that protein release can be modulated up to 24 h. Sodium dodecyl sulphate (SDS PAGE) technique was used to investigate the stability of the product. Conformational stability of the protein, examined using the SDS PAGE technique, showed that the formulation was stable for as long as several months.

5.Modified Nanosponges:

Nanosponges have been modulated by varying the reaction conditions to better fit the application selected. Fluorescent derivative has been obtained by reacting carbonate nanosponges with fluorescein isothiocyanate in DMSO at 90°C for a few hours. Fluorescent nanosponges have found their use in biological studies such as cancer therapy. These nanosponges react with biologically important carriers such as biotin, chitosan, or proteins, possibly providing a promising specific receptor targeting activity for drugs. Powder XRD studies have shown that these nanosponges are amorphous in nature. They are also nonhemolytic and non-cytotoxic. For anti-cancer drugs such as camptothecin, carboxylated nanosponges appear to be promising safe carriers for drug targeting.

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- Drug loading capacity depends on the degree of crystallization.
- Various drug loading capacities can be shown by paracrystalline nanosponges. 6. They are nontoxic, porous particles, insoluble in most organic solvents and stable up to 300 °C.
- They are stable at the pH range of 1-11.
- They form clear and opalescent suspension in water.
- They can be reproduced by simple thermal desorption, extraction with solvents, by using microwaves and ultrasounds.
- Their three-dimensional structure allows capture, trans- portation and selective release of a variety of substances.
- They can be sited to different target sites because of their capacity to link with different functional groups.
- Chemical linkers permit nanosponges to bind preferably to the target site.
- By complexing with different drugs nanosponges can form inclusion and non-inclusion complexes.
- By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges.
- Nanosponges are porous particles having high aqueous solubility, used mainly to encapsulate the poor soluble drugs.
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ADVANTAGES OF NANOSPONGES :

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- Improved stability, increased elegance and enhanced formulation flexibility.
- These formulations are stable over range of pH 1 to 11.
- These formulations are stable at the temperature up to 130^0C.
- These are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- These formulations are free flowing and can be cost effective.
- These modify the release of drug.
- They increase the solubility of poorly soluble drug.
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- Nanosponges can be significantly reducing the irritation of drugs without reducing their efficacy.
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- Biodegradable.
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Disadvantages:

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1.Solubility studies:

Higuchi and Connors have described an approach to study inclusion complexation as the phase solubility method which examines the solubility of drug in nanosponge. Phase solubility diagrams indicate the degree of complexation. In this method Erlenmeyer flask was used. The drug containing an aqueous solution of various percentages of nanosponges is added to the flask. The Erlenmeyer flask was stirred on a mechanical shaker at room temperature till it reaches a steady state, the suspension was filtered by centrifugation using a 3000 Dalton molecular filter (MICRON YN 30, Millipore Corporation, Bedford MA 1730 U.S.A).The solution was analyzed and the drug concentration is determined by high performance liquid chromatography.

2.Microscopy studies:

The morphology and surface topography of the drug, nanosponges and the product (drug/nanosponge complex) can be studied by Scanning electron microscopy and transmission electron microscopy. The difference in crystallization state of the raw materials and the product observed under electron microscope indicates the complex formation.

The loading efficiency (%) of Nanosponge can calculate by using following equation:

$$\text{Loading Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

3.Thermo analytical methods:

Thermo analytical 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.

4. X-ray diffractiometry and single crystal X-ray structure analysis Inclusion complexation in the solid state can be detected by X-ray diffractometry. The liquid drug molecules have no diffraction pattern of their own. The diffraction pattern of the uncomplexed nanosponge differs from the newly formed substance which indaicates complex formation .In case of solid drug substances the diffractogram of the assumed complex and the mechanical mixture of the drug and polymer is compared. A diffraction pattern of a physical mixture is the sum of those of each component, while the diffraction pattern of complexes differs from its constituents and leads to a “new” solid phase with different diffractograms. The chemical decomposition and complex formation is determined from the diffraction peaks. When the complex is formed between the drug and nanosponge there is a change in its diffraction patterns and crystalkline 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.

5.Single crystal X-ray structure analysis:

The detailed inclusion structure and mode of interaction can be determined from this analysis. The interaction between the host and guest molecules and the precise geometrical relationship can be studied.

6.Infra-red spectroscopy:

The interaction between nanosponges and the drug molecules in the solid state can be detected by Infra-Red spectroscopy. Upon complex formation the nanosponges bands changes. 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. Infra-red spectroscopy is applicable to the drugs having some characteristic bands such as carbonyl or sulfonyl groups. This spectral study reveals 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.

7.Thin layer chromatography:

In thin layer chromatography, the Rf values of a drug molecule is determined. By diminishing the Rf value to considerable extent helps in identifying the complex formation between the drug and nanosponge.

8.Loading efficiency:

The loading efficiency of nanosponges can be determined by the quantitative estimation of drug loaded into nanosponges by UV spectrophotometer and high performance liquid chromatography methods. The loading efficiency (%) of nanosponges can be calculated according to the following equation.

9.Particle size and Polydispersity Index:

With the help of dynamic light scattering using 90 plus particle size reequipped with MAS OPTION particle sizing software the particle size and mean diameter and polydispersity index can be determined. The measurements were made at a fixed angle of 90° for all samples. The samples were suitably diluted with Milli Q water for every measurement.

10. Zeta potential:

Zeta potential is used for the measurement of surface charge by using additional electrode in particle size equipment. In this process nanosponges containing samples were taken and diluted with 0.1mol/l Kcl and placed in electrophoretic cell for an application of 15V/cm of electric field. From this the mean hydrodynamic diameter and poly dispersity index were determined after averaging of the total measurement.

Preparation of Nanosponges:

1.Solvent method:

Mix the polymer with a suitable solvent, in particular in a polar aprotic solvent such as dimethylformamide, dimethyl sulfoxide. Then add this mixture to excess quantity of the crosslinker, preferably in crosslinker / polymer molar ratio of 4 to 16. Carry out the reaction at temperature ranging from 100C to the reflux temperature of the solvent, for time ranging from 1 to 48 hrs. Preferred crosslinkers are carbonyl compounds (Dimethyl carbonate & Carbonyldi imidazole). After completion of the reaction, allow the solution to cool at room temperature, then add the product to large excess of bidistilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet.

2.Emulsion solvent diffusion method:

Nanosponges can be prepared by using different concentration of ethyl cellulose and polyvinyl alcohol. The various ratio of drug to polymer are used to improve the drug loading and to obtain a tailored release. The dispersed phase containing drug and polymer dissolved in 20 ml of dichloromethane was added slowly to definite amount of polyvinyl alcohol in 100ml of aqueous external phase with 1000-1500 rpm stirring speed using magnetic or mechanical stirrer for 3-5 hrs. The formed nanosponges were collected by filtration and dried in oven for 40°C for 24hrs and packed in a container.

3.Emulsion solvent diffusion method:

In this method, polymers react with cross- linkers in absence of solvent and under sonication. Here, mix the polymer and cross-linker in a flask. Place the flask in an ultrasound bath filled with water and heat it to 900c and sonicate for 5 hours. Allow it to cool and wash with water to remove the unreacted polymer. Purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and store at 25^0C.

4:Quasi-emulsion solvent diffusion:

The nanosponges can also be prepared by quasi-emulsion solvent diffusion method using the different polymer mounts. To prepare the inner phase, eudragit RS100 was dissolved in suitable solvent. Then, drug can be added to the solution and dissolved under ultrasonication at 350c. The inner phase was poured into the PVA solution in water (outer phase) and allowed for stirring for 1 hr, then the mixture is filtered to separate the nanosponges. The nanosponges are dried in an air-heated oven at 40˚c for 12 hrs.

5.From hyper cross- linked β-cyclodextrin:

β- Cyclodextrin can be used as carrier for drug delivery. Nanosponges can be obtained by reacting cyclodextrin with a cross linker. Due to this 3D networks are formed which may be a roughly spherical structure about the size of a protein having channels and pores in the internal part. Reacting cyclodextrin with a cross linker such as di- isocianates, diary carbonates etc. sponges size is controlled according to porosity, surface charge density for the attachment to different molecules. Nanosponges can be synthesized in neutral or acid forms. The average diameter of a nanosponge is below 1µm but fractions below 500 nm can be selected. They are used to increased aqueous solubility of poorly-water soluble drugs. They consist of solid particles and converted in crystalline form.

6:From hyper cross- linked β-cyclodextrin Polymerization:

A solution of non polar drug is made in the monomer, to which aqueous phase, usually containing surfactant and dispersant to promote suspension is added. Polymerization is effected, once suspension with the discrete droplets of the desired size is established, by activating the monomers either by catalysis or increased temperature. The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores.

Applications of Nanosponges:

Nanosponges have many applications in the pharmaceutical field due to their biocompatibility and versatility. Some of them are as follows.

1.Nanosponges in Solubility Enhancement:

Presence of crosslinking agent and cyclodextrin cavities in the nanosponge structure favours interaction with active molecules. These features permit several substances to be included and get solubilized in the formed cavities. Reduction in drug crystallinity occurs by preparing inclusion complexes or solid dispersions with cyclodextrins which enhances drug solubility or rate of dissolution of poorly water soluble drugs. The hydrophobic functionality of the complex hides in the interior cavity of the cyclodextrin while hydrophilic hydroxyl groups on the external surface remain exposed to the environment, the net effect is that a water soluble complex is formed.

Swaminathan et al. studied a formulation of itraconazole (BCS Class II drug that had a dissolution rate limited poor bioavailability) in nanosponges. Nanosponges improved the solubility of the drug more than 27- fold and exceeded to 55-fold when copolyvidonum was added as a supporting component of the nanosponge formulation. Nanosponges solubilized the drug by possibly masking the hydrophobic groups of itraconazole, by increasing the wettability of the drug, and/or by decreasing the crystallinity of the drug.

2.Nanosponges in Drug Delivery:

Nanosponges have spherical shape and nanomeric in size making them ideal in preparing various dosage forms like topical, parenteral, aerosol, tablets and capsules10. Telmisartan (Telmisartan is a BCS Class II drug having dissolution rate limited bioavailability) is incorporated into the nanosponges. It is found that highest solubility and in vitro drug release is observed in inclusion complex47. Paclitaxel (BCS Class II drug having dissolution rate limited bioavailability) used for cancer chemotherapy having poor water solubility. β- Cyclodextrin based nanosponges, to deliver paclitaxel is used as an alternative to cremophor EL because cremophor reduces the paclitaxel tissue penetration. The biological effect of paclitaxel in vitro is highly enhanced by nanosponges, not only its cytotoxicity but also the intracellular paclitaxel concentration is significantly enhanced when compared to plain paclitaxel after 72 hrs incubation48. Econazole nitrate which is an antifungal agent used topically to relive the symptoms of superficial candidasis, dermatophytosis and skin infections. When econazole nitrate is applied to the skin, adsorption is not significant and requires high concentration of active agents to be incorporated for effective therapy. Thus, econazole nitrate nanosponges are prepared by emulsion solvent diffusion method and these nanosponges are loaded in hydrogel as a local depot for sustained drug release.

3.Nanosponges for Protein Delivery:

The major obstacle in protein formulation development is the maintenance of the native protein structure both during the formulation process and upon the long term storage49. Swaminathanet al. reported that new swellable cyclodextrin based poly (amidoamine) nanosponges named nanosponges 10 and nanosponges 11, were synthesised by cross-linking β-cyclodextrins with either 2, 2-bis-acrylamido aceticacid or a short polyamido-amine chain deriving from 2, 2-bisacrylamido acetic acid and 2-methyl piperazine respectively. The prepared β-cyclodextrin based poly (amidoamine) nanosponges were found to be stable at 300 °C and high protein complexation capacity was also observed.

4.Nanosponges in Enzyme Immobilization:

The enzyme immobilization is particularly relevant for lipases, as it improves their stability and modifies properties like enantio selectivity and reaction rates51. As a consequence, the demand for new solid supports, suitable for family of enzymes is constantly growing. For this Boscolo et al. reported that high catalytic performances of Pseudomonas fluorescens lipase adsorbed on a new type of cyclodextrin based nanosponges.

5.Nanosponges as a Carrier for Delivery of Gases:

In diagnostic, treatment purpose gases play a key role in medicine. Hypoxia (deficiency of adequate oxygen supply) is related to various pathologies, from inflammation to cancer. Sometimes it can be difficult to deliver oxygen in appropriate form and doses in clinical practice. Cavalli et al. developed nanosponge formulations as oxygen delivery systems for topical application which were having the ability to store and to release oxygen slowly over time.

6.Nanosponges as Protective Agent Against Photo Degradation:

Sapino et al. reported that gamma-oryzanol (a ferulic acid ester mixture), an anti-oxidant and usually employed to stabilize food and pharmaceutical raw materials, moreover, used as a sunscreen in the cosmetics industry. Its applications are limited due to its high instability and photodegradation. Nanosponges are prepared by encapsulating gamma-oryzanol showing a good protection from photodegradation. With the gamma- oryzanol loaded nanosponges a gel and an O/W emulsion are formulated.

7.Modulating Drug Release:

The major drawback of most of the conventional, commercially available drug delivery systems is frequent administration. However, a drug loaded into the nanosponge is retained and released slowly over time. Vyasetal. reported that hydrophilic cyclodextrin nanosponges are employed to modify the drug release rate, to enhance the drug absorption across biological barriers, as a potent drug carrier in immediate release formulations. Hydrophobic cyclodextrin nanosponges are utilized as sustained release carriers for water soluble drugs, including peptide and protein drugs and also used as carriers of drugs such as doxorubicin (an anticancer drug), and also they may protect the drug during its passage through the stomach. This drug is released very slowly at pH 1.1, whereas release is faster if pH is raised to 7.455. h).

8.Effective Delivery Carriers:

Antitumor drugs such as paclitaxel, camptothecin and tamoxifen shows bioavailability problem (because of poor aqueous solubility) hence cyclodextrin nanosponges can be used as vehicles inorder to improve their solubility as well as bioavailability. Torne et al. investigated antiproliferative effect of drugs incorporated into nanosponges and studied on various cell lines. Complexes showed high effect than that of the drug alone15. After loading the drug in nanosponges the mean absolute bioavailability of paclitaxel was increased and found to be 2.5-fold higher than the plain drug.

FUTURE PROSPECTS OF NANOSPONGES:

The increasing number of CD-based NS articles in the last decade has indicated that researchers in many domains have caught the world's attention.Nanomedicine, where CD NSs are used primarily as drug delivery systems, is the primary field of the research. Since NS has been able to host different types of medicines, NSs has gained significant popularity, enhancing their bioavailability and their lack of toxicity. All four generations of CD nanosponge were examined in the pharmaceutical sector in the last several years (2016–2019). - CD related to first generation DMC, CDI, DPC, PMDA and CA (citric acid) have been used in drug studies.

Roy Biswas (2016) examined NSs capability for bicalutamids, paclitaxel, and letrozole, both for gemcitabine and for lipophile medications. Due to the large numbers of Lipophilic sites available for medicinal complexation lipophilic medicines were able to load more medicines than hydrophilic drugs. Dose-related adverse effects of NSs loading with anticancer medication (e.g. erlotinib) and camptothecin (a DNA TopoisomeraseI inhibitor) have been increased by oral bioavailability, solubility and dissolution for 2017. In addition to these effects, dose-related adverse events have been increased. The inherent absence of the cellular binding capability of Nss was attempted in 2018 to resolve, restricting their use in medicinal products.

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