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NANOSPONGES: PRESENT ASPECTS AND FUTURE CHALLENGES

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Abstract:
*Efficacious targeted drug delivery systems have been a dream for a long time but the chemistry hold complex form had made conditions complicated butthe expansion of new colloidal carrier called **Nanosponges** likely circumvent these problems. They consist of nanoporous particles that can suspend or entrap a wide variety of substances, and then be engulfed into a dosage form. They release their active components on a time mode and also in response to other stimuli (rubbing, temperature, pH etc.). They can be crafted for targeting drugs to specific site, prevent drug and protein degradation and prolong the drug release in a controlled manner. They can circulate around the body and release the drug in a controlled and predictable manner at the specific target site.Another feature of nanosponges which makes them a carriers for poorly water soluble drugs is their good aqueous solubility.Both lipophilic as well as hydrophilic drugs can be loaded into nanosponges.Various applications of nanosponges like enhancing bioavailability of drug molecule and delivery of drugs into oral, topical, parentral as well as nasal route make them a good candidate for targeted delivery of drugs. This review is focusing on the fabrication and characterization of nanosponges, their advantages,applications and their future scenario.*

Keywords: *Nanosponges, Controlled release, Polymers, Cross linkers, Cyclodextrin*

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INTRODUCTION:

The pharmaceutical and health care industry has been fabricating and using nano-scale materials for solving many physical, chemical and biological problems related with the treatment of disease. Since 1950's, nanotechnology has dominated technology.[1] So far nanotechnology resulted in variants of formulations like nanoparticles, nanocapsules, nanospheres, nanosuspensions, nanocrystals, nano-erythosomes etc.[2] Nanoparticles are obtainable in various forms like polymeric nanoparticles, solid-lipid nanoparticles, nanoemulsions, nanosponges, carbon nanotubes, micellar systems, dendrimers etc [3].

Nanosponges are tiny mesh-like structures in which a large variety of substances can be enveloped [3,4]. They have a size of about a virus with an average diameter below 1µm. These nanoscopic sponges can move around the body until they accomplished the specific target site and stick on the surface and began to release the drug in a controlled and predictable manner [5]. Due to their small size and penetrable nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability by modifying the pharmacokinetic parameters of actives [6]. It is mixed in solution with little molecules called cross linkers that grasp different parts of the polymer together.The net effect is to form spherically shaped nano sized particles filled with cavities where drug molecules can be stored. The biodegradable polyester breaks down moderately in the body. By differing the proportion of cross linker to polymer, the nanosponge's particles can be made smaller or larger [7]. These particles are capable of handling both lipophilic and hydrophilic substances and of ameliorating the solubility of poorly water soluble molecules.The tiny shape ofnanosponges allows the pulmonary and venous delivery of nanosponges [8,]. The chemicals used for the synthesis of nanosponges are listed in Table 1 .

Table 1: Chemicals used for synthesis of nanosponges [10, 11]

• **Polymer**:Hyper cross linked polystyrene Cyclodextrin and its derivatives like Alkyloxy carbonyl Cyclodextrin, Methyl β Cyclodextrin, Hydroxypropyl β Cyclodextrin
• **Copolymer:**Poly(Valerolactoneallylvalerolactoneoxypane dione) , Ethyl cellulose , Polyvinyl Alcohol
• **Crosslinkers**:Diphenyl Carbonate, Diarylcarbonates,Diisocynates,Pyromelliticanhydride, Carbonyl diimidazoles, Epichloridrine, Glutaraldehyde, carboxylic acid dianhydrides , Dichloro methane
• **Polar solvents**: Methanol, Ethanol, Diethylformamide, Dimethylacetamide

BENEFITS OF THE NANOSPONGES [12-18]

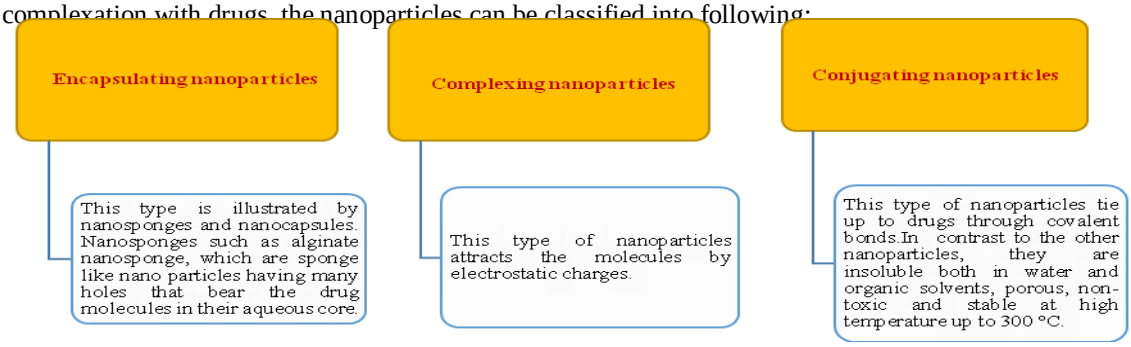
- Deliver the drug molecule at the targeted site
- This sponges provide entrapment of active contents and side effects are less
- It provides improved stability, elegance and formulation flexibility.
- Non-irritating, non-toxic, non-mutagenic.
- It provide prolong release condition which is continuous action up to 12hr.
- Drug is protected from degradation
- Formulations are cost effective and provide therapeutic onset of action.
- Less baleful side effects since smaller quantities of the drug have contact with healthy tissue.
- The encapsulation can be done within the nanosponges by the addition of chemical called an adjuvant reagent, because nanosponge's particles are soluble in water.
- Particles can be made smaller or larger by altering the proportion of cross-linker to polymer.
- Easy scale-up for commercial production.
- Biodegradable.
- The drug profiles can be made from fast, medium to slow release, preventing over- or under-dosing of the therapy.
- These formulations are stable over range of pH 1 to 11.
- One of the major advantages of this system is its capacity to produce predictable and controlled drug release.

SALIENT FEATURES OF THE NANOSPONGES [3,8, 14,29]:

- Nanosponges have the dimensions in the range of 1 µm or less with adjustable polarity of voids.
- Nanosponges can either be crystalline or paracrystalline in nature. Thecrystalline structure of nanosponges is very important for drug complexation because the degree of crystallization affects the loading efficiency of nanosponges.
- Nanosponges are stable at the pH range of 1-11 also upto temperature 130^0 C.
- They are nontoxic, biodegradable and porous polymeric entities which can resist in higher temperature.
- Nanosponges give clear to opaque colloidal suspension in water, and could be easily regenerated via solvent extraction.
- The targeted delivery of encapsulated moieties can be achieved due to the ability of nanosponges to link with different functional groups, which can be further improved through chemical linkers primarily binding to the the target sites.

CLASSIFICATION OF NANOSPONGES [7,9]

Nanosponges are a type of nanoparticles which incorporate the drug molecules within its core. By the method of complexation with drugs, the nanoparticles can be classified into following:



METHODOLOGY FOR PREPARATION OF THE NANOSPONGES:

The various methods used for the preparation of Nanosponges are given below:

SOLVENT DIFFUSION METHODS [19-21]

1.Quassi emulsion solvent diffusion:

Polymer is dissolved in suitable solvent(inner phase)

↓

Drug can be added to solution and dissolved under ultrasonication at 35^0C

↓

Inner phase is poured into the polyvinyl alcohol solution in water

↓

After 60 min of stirring, the mixture is filtered

↓

Prepared nanosponges are dried in an air heated oven at 40^0 C for 12 h

2. Emulsion solvent diffusion method:

Preparation of aqueous phase and organic phase:
Aqueous phase contain copolymer
Organic phase contain drug and polymer

↓

Organic phase is slowly added to the aqueous phase and Stirred for 2-3 hrs at 1000rpm

↓

Prepared nanosponges are collected by filtration, washed and then dried in air at room temperature or in vacuum oven40^0C for 24 hrs

ULTRASOUND ASSISTED SYNTHESIS [8,22,23]

Polymer is mixed with cross linker in balanced ratio in a flask

↓

Then flask is placed in an ultrasound bath filled with water and temp. is maintained at 90^0 C

↓

Sonicate the mixture for 5 hrs

↓

To remove non reacted polymer, product is washed with water

↓

Then the product is purified with ethanol by soxhlet extraction

↓

Allow the product to dried under vaccum at 25^0 C

NANOSPONGES PREPARED FROM HYPER CROSS LINKED CYCLODEXTRIN:In this method cyclodextrin is reacted with a cross linker such as di-isocianates, diaryl carbonates, carbonyl di-imidazoles etc. The size of the sponges is controlled according to porosity, surface charge density for the attachment to different molecules.Depending upon the cross linker nanosponges are synthesized in neutral or acidic form. Capacity of nanosponges to encapsulate drug having different structures and solubility. They are used to enhancement of aqueous solubility of poorly-water soluble drugs mainly BCS class II drugs [24-26].

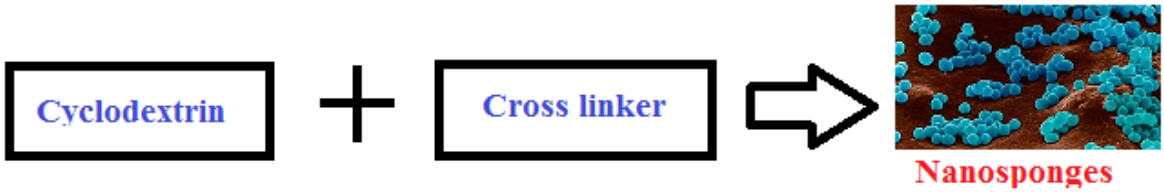
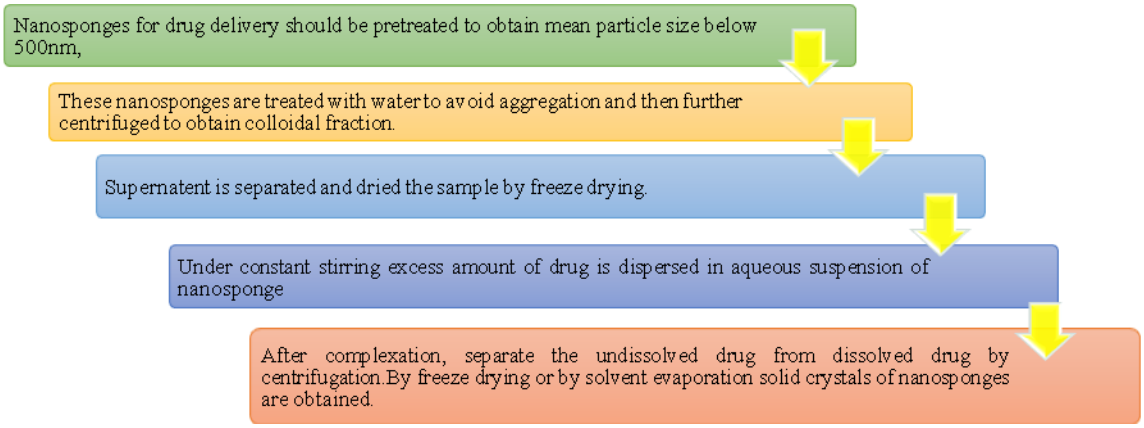


Figure1: Formation of Nanosponges

Loading of Drug into the Nanosponge [9,27-29]



FACTORS AFFECTING THE FORMATION OF NANOSPONGES:

Type of Polymer: Type of polymer used has a serious impact on development of Nanosponges. Hydroxy propyl β-cyclodextrinhasgood affinity to form inclusion complex as compared to α, β and γ-cyclodextrin. Uniform and small particle of nanosponges depends on polymer complex [31,32].

Type of Drug:The drug molecule should be complexed with nanosponges should have certain featureslike:molecular weight between 100-400 daltons, drug molecule should contain not more than five condensed ring, solubility in water is less than mg/ml,melting point of the drug substance should be below 250°C [31,33].

Temperature: Changes in the temperature can affect the drug / nanosponges complexation.By increasing the temperature the magnitude of stability constant of drug/nanosponges decreases which may be due to the possible reduction in drug/nanosponges interaction forces like van der wall forces [34,35].

Medium used for interaction: The interaction between nanosponges cavities and drug molecules fully depends on the medium; a hydrophilic medium will carry the organic guest molecules into hydrophobic cavities, while an organic solvent tends to release the organic molecules which are hold by nanosponges. These strong interactions between host and guest molecules depend on mutual matching of polarity, size, hydrophobic environment and structural properties [36].

CHARACTERIZATION OF NANOSPONGES:

1) **Particle size analysis**: Particle size can be determined by laser light diffractometry or Zeta sizer. Cumulative percentage drug release from nanosponges of different particle size can be plotted against time to study effect of particle size on drug release [31,37].
2) **Zeta potential:** The surface charge of Nanosponge can be determined by using Zeta sizer [27].
3) **Loading efficiency:** The loading efficiency of formed nanosponges is determined by subtracting the un-entrapped drug from the total amount of drug.The drug entrapment efficiency will be determined by separating un-entrapped drug estimated by any suitable

method of analysis like gel filteration, dialysis and ultra centrifugation.The loading efficiency (%) of Nanosponge can be determined by using the formula given below [38,39].

$$\textbf{Loading Efficiency} = \frac{\textit{Actual Drug Content in Nanosponge}}{\textit{Theoretical drug content}} \times 100$$

4) **Production yield:** The production yield can be determined by calculating initial weight of raw materials and final weight of nanosponges obtained [8].

$$\textbf{Production yield} = \frac{\textit{Practical mass of Nanosponge}}{\textit{Theoretical mass of Nanosponge (polymer + drug)}} \times 100$$

5) **Porosity:** Porosity study is performed to check the extent of nanochannels and nanocavities formed. Helium pycnometer is used to assess porosity of nanosponges, since helium gas is able to penetrate inter- and intra-particular channels of materials. Percent porosity is given by equation [28].

$$\%\,\textbf{Porosity} = \frac{\textit{Bulk Volume} - \textit{True Volume}}{\textit{Bulk Volume}} \times 100$$

6) **In Vitro release studies:** Drug release from Nanosponges can be determined by using dissolution apparatus USP xxiii with a modified basket consisted of 5m stainless the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions.Samples from the dissolution medium can be analyzed by a suitable analytical method.In most cases Franz diffusion cell can also be used depending upon the formulation [40]**.**

7) **Microscopystudies:** 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) [27].

8) **Infra redspectroscopy:** Infra-Red spectroscopy is used to judge the interaction between nanosponges and the drug molecules in the solid state. Nanosponge bands often changes moderately upon complex formation and if the fraction of the guest molecules encapsulated in the complex is less than 25%, bands which could be allotted 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 recognize the inclusion complexes and is less clarifying than other methods. The application of the Infra-red spectroscopy is finite to the drugs having some characteristic bands, such as carbonyl or sulphonyl groups. Infrared spectral studies give information regarding the involvement of hydrogen in various functional groups [41].

9) **Accelerated stability studies:** Stability studies are performed by charging the freshly prepared formulation in stability chamber maintained at 25 ± 0.5^0C and under accelerated storage conditions at 37 ± 0.5^0 C/75%RH in humidity controlled ovens. The formulations subjected to stability tests areanalyzed for six months for its physical appearance, size,% drug entrapment and in vitro drug release [55].

10) **Drug release kinetics:** The mechanism of drug release from nanosponges was analysed by using Zero order, First order, Higuchi model, KoresmeyerPeppas model. The mathematical expressions that describe the dissolution curve are summerized below: [31].

Model	Equation
Zero order	$Q_t = Q_0 + K_o t$
Higuchi model	$Q_t = Q_0 + K_h t^{1/2}$
Koresmeyerpeppas model	$Q_t = K_{kp} t^n$

11) Drug content: Formulation is taken in 100 ml volumetric flask containing 50ml methanol and stirred for 30 minutes and allowed to stand for 2h. The volume was made up to 100 ml with methanol. 1ml of the above solution was further diluted to 10 ml with6.8 pH phosphate buffer. The drug content was determined by measuring the absorbance using UV Visible spectrophotometer.[43]

APPLICATIONS OF NANOSPONGES:

1. **Nanosponges for Drug delivery:** Because of their nanoporous structure, nanosponges can preferably 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. As compared to direct injection β -cyclodextrin based nanosponges are reported to release the drug to the target site three to five times more efficaciously. Drugs having low solubility can be successfully delivered by loading into the nanosponges. Due to their solid nature and can be formulated as oral, parenteral, topical or inhalation dosage forms depending [44, 45].

Table 1: Some Biopharmaceutical classification system class II drugs

Category of Drugs	Name of the drug
Antiarrythmic agents	Amiodaron hydrochloride
Antibiotics	Azithromycin ,Ciprofloxacin,Erythromycin,Ofloxacin
Antianxiety drugs	Lorazepam
Anticonvulsants	Carbamazepine,Clonzepam,Felbamate,Primidone
Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole,Ketoconazole, Voriconazole
Antihistamines	Terfenadine
Antihypertensive drugs	Felodipine, Nicardipine,Nifidipine
Antineoplastic agents	Camptothecin,Docetaxel,Etoposide,Exemestane,Flutamide, Tamoxifen
Antipsychotic drugs	Chlorpromazime hydrochloride
Antiulcer drugs	Lansoprazole, Omeprazole
Antioxidants	Resveratrol
Anthelmintics	Albendazole, Mebendazole,Praziquantel
Cardiac drugs	Talinolol, Digoxin,Carvidilol
Immunosupressants	Cyclosporine,SirolimusTacrolimus
NSAIDs	Dapsone,Diclofenac,Flurbiprofen,Ibuprofen,Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin,Piroxicam
Steroids	Danazole,Dexamethazone
Antiepileptic drugs	Phenytoin
Antidiabetic and Antihyperlipidimic drugs	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone
Anticoagulants	Warfarin

2. **Nanosponges as Solubility Enhancer:** Nanosponge is the carrier system, which entrap the drug into its core and provide improved solubility as well as the bioavailability of lipophilic drugs [46].
3. **Nanosponges as a carrier for biocatalysts:** It has been found that Cyclodextrin based nanosponges are essentially a suitable carrier to adsorb enzymes, antibodies, proteins, and macromolecules. Specifically when enzymes are used, nanosponge formation can maintain their activity, efficiency, extend their operation, pH and temperature range of activity and allows the conduct of continuous flow processes. Moreover, proteins and other macromoleculs can be carried by adsorbing or encapsulating them in cyclodextrin nanosponges [10].
4. **In Antiviral Therapy:** They can be useful in the ocular, nasal and pulmonary administration routes. The selective delivery of antiviral drugs to the nasal epithelia and lungs can experienced by nanocarriers in order to target viruses that infect the RTI such as respiratory sinctial virus, influenza virus and rhinovirus. The drugs which are formulated in nano delivery systems are zidovudine, saquinavir, interferon-α, acyclovir, nelfinavir etc [37].
5. **In AntimycoticTherapy:** Nanosponges can be used as an Antimycotic. Example Econazole nitrate, an antifungal agent used topically to relive the symptoms of superficial candidiasis, dermatophytosis and skin infections available in cream, ointment, lotion and solution. By emulsion solvent diffusion method econazole nanosponges were originated and were loaded in hydrogel as a local depot for sustained drug release [19].
6. **In Cancer Therapy:** It has been claimed that nanosponges as anticancer drug delivery are three to five times more effective in reducing tumour growth as compared to direct injection. These tiny sponges are filled with a drug and expose a targeting peptide that binds to radiation-induced cell surface receptors on the tumour. When the sponges confront tumour cells they stick to the surface and are activated to release their drug at the targeted site with reducing side effects [48].
7. **In Encapsulation of gases:** Three different gases can be encapsulate in the cyclodextrin based nanosponges like1-methylcyclopropene, oxygen and carbondioxide. The oxygen filled Nanosponges provide oxygen to the hypoxic tissues which are present in various diseases. These formulations can able to store oxygen and release it in a controlled manner. In future, they could be one useful tool for the delivery of some vital gases.[30]
8. **Nanosponges as protective agent:** Gamma-oryzanol is a ferulic acid ester mixture, is a natural antioxidant and usually used to stabilize pharmaceutical raw material and food, moreover as a sunscreen in the cosmetics industry. Its major drawback isits high instability and photodegradation. But,if Gamma oryzanol is encapsulated in nanosponges, showing a good protection from photo degradation. A gel and an O/W emulsion were formulated with the gamma-oryzanol-

loaded nanosponges [50].

9. **Nanosponge in protein drug delivery:** Nanosponge has also been used for enzyme immobilization, protein encapsulation and subsequent controlled delivery and stabilization Bovineserumalubin (BSA) protein is unstable in solution form so stored in lyophilized form. Swellablecyclodextrin based poly (amidoamino) nanosponge's enhaced the stability of proteins like BSA [51].
10. **Nanosponges that soaks up toxins:** The blood stream based on polymeric nanoparticles that can neutralize and remove a broad range of toxins from forming toxins (PFTs),which attack cells by boring holes in their membranes and altering their permeability, are one of the most common toxins produced by bacteria as well as venomous species of bees scorpions and snakes inhibiting pore forming toxins can reduce the severity of *Staphylococcusaureus* infections and has therapeutic potential for treating other common pathogen such as *Escherichia coli* (*E. coli*) [54].
11. **Other applications:** As Hydrogen is considered as an alternative energy for future, but one of the problems is its storage. A team of scientists from the Universities of Newcastle and Liverpool have discovered a new class of materials which composed of long carbon chains linked by metal atoms. These molecules form cavities that are less than a nanometer, which are connected by "windows" that are even smaller than a molecule of hydrogen.

Nanosponges can also be used in the purification of the water by removing the organic pollutants in raw water which is a major concern in industries requiring ultra pure water like pharmaceutical and electronic sector [7,52-54].

FUTURE DIRECTIONS AND CHALLENGES:

Nanosponges drug delivery represent an exceptional and effectual class of biocompatible delivery system, and the presence of flexible cross-linked polymers allows a smooth transformation of conventional means of drug delivery to a unique and versatile delivery system that exhibits the unique characteristics; which makes it supple to design and develop novel product forms. Owing to their special structure, their role in downstream processing requires in- depth research. Some applications that could be explored include, but are not limited to, removal of toxic substances from industrial wastes and organic solvent vapour from air. Nanosponges could be acquired forentrapping bitter constituents from food and drug products.The actual challenge in future is the progression of the delivery systems for oral peptide and other susceptible biomers. The use of bioerodible and biodegradable polymers for drug delivery is authorizing it for the safe delivery of the actives via multiple routes.The cytotoxicity of the nanoparticles or their degradation product remains a major challenge and improvement in bioavailability are a main concern of future research.

MARKETED FORMULATIONS:

Drug	Administration route	Dosage form	Market	Trade name
Dexamethasone	Dermal	Ointment	Japan	Glymesason
Iodine	Topical	Solution	Japan	Mena-Gargle
Alprostadil	I.V	Injection	Europe,Japan ,USA	Prostavastin
Piroxicam	Oral	Capsule	Europe	Brexin

PATENT REPORT ON β CYCLODEXTRIN NANOSPONGES [56-59]

Patent/App. No.	Applicant	Tittle
W02003041095A1(2003)	Alberto Bocanegra Diaz	Process of composites preparation between particulate materials and cyclodextrin and/or their derivatives
W02003085002A1(2003)	Sea Marconi Technologies Diw	Cross-linked polymer based on cyclodextrin for removing polluting agents.
EP0502194A1(1992)	Toppan Printing Co. Ltd.	Cyclodextrin polymer and cyclodextrin film formed.
W02012147069A1	Universita'DegliStudi Di Torino	Method of preparing dextrin nanosponges
W02009003656A1	Sea Marconi,Technologies Di VanderTumiatti, S.A.S	Cyclodextrin based nanosponges as a vehicle for antitumoral drugs
CA2692493A1	Sea Marconi,Technologies Di VanderTumiatti, S.A.S, FrancesscoTrotta, Vander Tumiatti,RobertaCavalli, Carlo Maria Roggero BarbarMognetti,Giovanni,Nicolao Berta	Cyclodextrin based nanosponges as a vehicle for antitumoral drugs

CONCLUSIONS: From the above points , it may be concluded that

Nanosponges possessing a myriad of beneficial attributes ,can serve as a promising tool for the efficient delivery of drugs, and can be adopted as a new fangled carrier in drug delivery and therapeutics. They offer encapsulating of both lipophilic and hydrophilic drugs, and allow controlled as well as predictable release of the drug at the effective target site, thereby improving bioavailability and efficacy.The required particle size and release rate can be attained by controlling polymer to cross linker ratio. Moreover, Nanosponges based delivery system also protects the active moiety from degradation.The small size and spherical shape of the delivery system allows formulating into different dosage forms like parentral, aerosol, topical and as well as oral dosage form as per the requirement and advanced approaches.

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