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Nanosponge: A Prospective Nanocarrier for Novel Drug Delivery System

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ABSTRACT :
Bioavailability and solubility are both necessary for a medication to be therapeutically effective. About 70% of medications being researched in the pharmaceutical industry are BCS class II pharmaceuticals since they are not very water soluble. For medications with issues including limited bioavailability, poor water solubility, and a small absorption window, oral delivery is suggested. There are several different drug delivery mechanisms utilised to get over these restrictions. Nanotechnology is one of the most significant revolutions in this area. Nanotechnology is defined as manufacturing and conversion of materials at nanoscale level that create final products which shows novel properties. It includes various formulations like nanoparticles, nanocapsules, nanospheres, nanosponges, nanosuspensions, nanocrystals etc.Nanosponges are tiny mesh like novel class hyper crosslinked polymer based colloidal structures in which large variety of drug molecules encapsulated within its core. They have been a proved spherical colloidal nature, reported to have a very high solubilization capacity for BCS class II drugs (poorly soluble drugs) by their inclusion and non-inclusion behaviour.Nanosponges can be created using a variety of methods, including the hyper crosse linked CD approach, solvent method, emulsion solvent diffusion method, and ultrasound-assisted synthesis nanosponges.Nanosponge technology is used for topical application, oral drug delivery, cancer therapy, Ocular drug delivery and sustained delivery system.

Keywords : Bioavailability, solubility, Nanotechnology, Nanosponges.

INTRODUCTION :

The medical profession has developed at an astounding rate since the 19th century.Humans have been able to survive life-threatening illnesses and deforming diseases like Polio and many others thanks to the development of antibiotics, anticancer medications, transplant operations, and several other forms of treatment. However, there are still illnesses that cannot be addressed, which has allowed traditional medicine to take a new approach by utilising nanomedicine.[1]

Difference between Conventional and Nanomedicine:

Conventional small molecule medications can have major adverse effects, lack any particular selectivity, and require careful attention to dosage and frequency.They cannot cross some biological barriers, and their insolubility may have an impact on their effectiveness.In contrast, nanomedicines are focused, assist in lowering drug toxicity, and increase bioavailability.It can slow the release of medicines and increase their half-lives. More importantly, insoluble medications' permeability and solubility should be increased to enable them to pass through biological barriers. Nanomedicine has a lot of development potential and application possibilities in the therapeutic treatment of tumours today. Nanomedicine can be utilised to treat tumours as well as infections, neurological disorders, ophthalmic conditions, immunotherapy, and other conditions.[2]

Nanosponges are the small mesh-like structures that have an outside lypophilic branching structure and an interior hydrophilic pocket or opening that can encapsulate both aquaphilic and aquaphobic medicinesand increase the solubility of poorly water-soluble molecules.[3]Nanosponges are excellent candidates for the encapsulation of various substances because of their mesh-like/colloidal structures, including medications, phytochemicals, volatile oils, antineoplastic agents, genetic materials, proteins/peptides, and more[4].Nanosponge is a scaffold-like material that is naturally biodegradable and virus-sized[5].Depending on the ratio of the crosslinker to the polymer and whether they are made from an acidic or neutral synthetic material, nanosponges have a significant swelling property.In order to remove harmful substances from the body, such as indole, less frequently perform dialysis, and prevent toxicity to the hepatic and cardiac systems, cyclodextrin-based nanosponges were developed[4].Cyclodextrin-based nanosponges can be created by crosslinking cyclodextrin polymer in

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a hyper-cross manner with the appropriate crosslinking agent.These serve as diluents to boost the carrying capacity of the nanosponges.Nanosponges are considered safe for invasive and oral administration methods due to their solid nature, and their small size allows for pulmonic and venous drug delivery.These are the spherical, three-dimensional structures with numerous cavities for medicinal molecules[3].Early studies have demonstrated that they are five times more successful than conventional ways at directing medications to breast cancer cells, revolutionising the way that many diseases are treated[5].

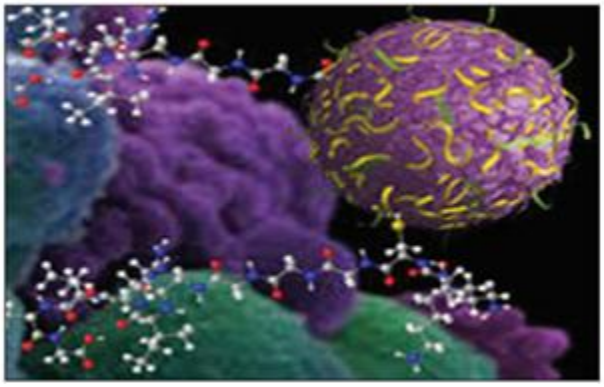

Table No.1: Examples of MarketedNanospongeFormulations

Name of Drug	Route of Administration	Brand Name	Dosage form	Reference
Iodine	Topical	Mena-Gargel	Solution	[6]
Alprostadil	Intravenous	Prostavastin	Injection	[6]
Dexamethasone	Dermal	Glymesason	Tablet	[6]
Piroxicam	Oral	Bervin	Capsule	[6]

- **Origin and History of Nanosponge :[7]**

1. Origin of Insoluble Crosslinked Cyclodextrin Polymers: 1960s to 1980s

In 1965, Solms and Egli published a study on the creation and inclusion characteristics of novel network polymers composed of CDs crosslinked with epichlorohydrin(EPI) which is the precursor to today's crosslinked insoluble CD polymers.CDs that had been dissolved in water were first activated using sodium borohydride and a hot solution of sodium hydroxide, and then EPI was added as a crosslinker. Comparing this unique substance's binding capabilities to those of EPI-dextran network polymers was done by the authors.According to this study, the separation of p- and o-nitrophenol based on differences in their inclusion behaviour could be an example of a separation strategy that uses the inclusion ability to separate molecules not only based on their size but also on their shape.

2. Investigation on Polymer Properties and Applications : 1980s to the 1990s

In 1980, researchers looked at insoluble porous polymers such polyurethane-CD network polymers.Hexamethylene diisocyanate (HMDI), 1,3-bis (isocyanatomethyl) cyclohexane, and 1,3-bis (isocyanatomethyl) benzene were used as crosslinkers to produce them. Diisocyanate was heated in pyridine while CDs were stirred during the production.Thermal analysis, Brunauer, Emmett, and Teller (BET) surface area measurement, elemental analysis (detection of unreacted -OH groups in CD), and gas chromatography were used to study the interactions between CD polymers and organic compounds,

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such as benzene, toluene, cyclohexane, ethanol, methyl ethyl ketone, propanol, and others.

3. In the Beginning Was the Word, 1999 :

In 1999, Min Ma and De Quan Li used the term "nanosponge" for the first time.They discussed innovative nanoporous polymers consisting of CDs joined by diisocyanate linkers.It was fairly easy to prepare: CDs were combined with the crosslinker in DMF and heated for 24 hours. These NSs showed an unexpectedly high adsorption capability despite having a little surface area, which created new opportunities for the water remediation industry.Their advantages over existing purification techniques, such as reverse osmosis and adsorption on activated carbon or zeolites, included their high adsorption capacity, tunability, and low cost.The ability to alter these polymers' characteristics by varying the degree and type of crosslinking was a significant benefit.

4. The New Era Brought New Applications from : 2000 to 2009

The new era brought exciting chances for NSs in various industries. The use of CD NSs in known applications was not, however, disregarded**.**CD NSs gained popularity due to their intriguing features, which can be attributed to their distinct structure.The initial focus of the research was on their ability to encapsulate various types of drugs.Since they were made for human use, special attention was devoted to their safety, low level of toxicity, and biodegradability.In order to fully characterise these novel drug delivery systems, FTIR and HPLC techniques were used to examine the structure and loading properties. These techniques were also used in conjunction with DSC thermal analysis, X-ray diffraction, photon correlation spectroscopy, optical microscopy, TEM, hemolysis, cytotoxicity, and in vitro release experiments.For the first time, Cavalli et al. tested the ability of carbonate CD NSs to load drugs that are both hydrophilic (e.g., doxorubicin) and lipophilic (e.g., dexamethasone or flurbiprofen) and succeeded in achieving a sustained release of the drugs.

5. Intensify the use of nanosponges as delivery systems: 2010 to 2015

These years saw intensive research into CD NSs' capacity to load compounds of medicinal relevance.They have been discovered to be effective for carrying gases like oxygen and carbon dioxide in addition to serving as drug carriers.Since 1987, when the encapsulation of carbon dioxide with CDs was patented in Japan, researchers have known that cyclodextrins had the ability to store gases in their cavities. This was done in anticipation of the application of the CDs in cosmetics, cleaning products, and personal care items.The last few years have seen the development of numerous NSs-based drug delivery systems using various CDs and crosslinkers.They made a contribution to the enhancement of permeability, sustained release, solubility, stability, bioavailability, and activity of drugs.Additionally, they made it possible to choose between several administration methods, favouring patient compliance and minimising adverse effects; they included ocular and transdermal distribution.

6. Current State and Future Prospects of Nanosponges from : 2016 to the Present :

The rise in CD-based NS publications with time indicates that they began to appear in the previous ten years.They have captured the interest of academics in many fields globally. In the field of nanomedicine, CD NS_S have been employed mainly as drug delivery system.Acute and repeated dose toxicity studies by Shende et al. in 2015 showed that NSs are not dangerous, despite their capacity to host different types of medicines and so increase their bioavailability.All four CD-based nanosponge generations have been studied in the pharmaceutical industry over the past few years, from 2016 to 2019.In the first generation, beta cyclodextrin crosslinked with DMC, CDI, DPC, PMDA, and CA (citric acid) has been used in pharmaceutical research.In their 2016 study, Patel and colleagues looked into the capacity of -cyclodextrin/DPC NSs to accommodate both hydrophilic medicines like gemcitabine and lipophilic pharmaceuticals like bicalutamide, paclitaxel, and letrozole.In 2017, erlotinib (an epidermal growth factor receptor tyrosine kinase inhibitor) and camptothecin (a DNA topoisomerase-I inhibitor) were loaded into β-CD/CDI NSs to boost their oral bioavailability, solubility, and dissolution, decreasing the dose-related side effects.Curcumin, resveratrol, and a combination of the two were loaded into β-CD NSs and evaluated. Pushpalatha et al. coupled curcumin and resveratrol in 2019 to take advantage of their synergistic efficacy against breast cancer by transdermal administration.In 2019, pH-sensitive NSs (CyCaNS) were created by combining cyclodextrins and calixarenes, and their adsorption

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and release properties were examined using a model drug for tetracycline antibiotics.

- **Features of nanosponges:[8]**

1. Their aqueous solubility, which is a key characteristic of these sponges, enables the successful application of these systems for medicines with limited solubility.
2. The nanosponges may transport both lipophilic and hydrophilic medications.
3. They have been utilised as Nano-carriers for biomedical applications, as well as for the elimination of organic pollutants from water.
4. This method provides trapping of chemicals, decreased adverse effects, increased elegance, and higher formulation flexibility.
5. Nanosponges are extremely soluble materials that may disperse at the molecular level, stabilising and shielding their structures from substances like chemicals, light, and oxygen.

- **Advantages of nanosponges :[8]**

1. These formulations maintain their stability between PH 1 and 11.
2. Nanosponges aid in the removal of poisonous and venomous substances from the body.
3. The nanosponges function as a self-sterilizer since bacteria cannot pass through their tiny (0.25 m) pore size.
4. They increase the bioavability of drug.
5. They increase the solubility of poorly soluble drug.

- **Disadvantages of nanosponges :[9]**

1. Nanosponges can encapsulate small molecules but are not appropriate for larger molecules.
2. Sometimes there may be dose dumping.

- **Composition and Structure of Nanosponges :[10]**

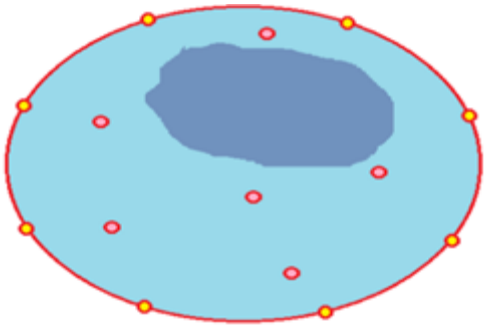

Fig. Structure of a nanosponge showing a cavity for drug loading

The structure of nanosponges is intricate. They are made of long, linear molecules that are folded into a protein-sized, roughly spherical structure by cross-linking.Nanosponges mainly consists three components. They are,

A. Polymer.
B. Cross linking agent.
C. Drug substance.

A. Polymer :

The type of polymer employed in the formulation of NS is crucial because it can affect both the substance's formation and functionality.A drug molecule of a specific size should fit comfortably inside the nanosponge's cavity in order to generate a complex structure.The functional groups and active groups that will be substituted determine whether the polymer can be cross-linked.The choice of polymer is determined by the needed release and the medicine to beenclosed.It is possible to employ the polymers to interact with the drug material or to enclose the drug.For targeted medication release, the polymer should have the ability to bind with the appropriate ligands.

B. Cross linking agent :

The polymer's structure and the medication being developed must be taken into consideration while choosing cross linking agents.The list of polymers and crosslinking agents used for the synthesis of nanosponges are presentedin Table no.2

Polymers	Co-polymers	Cross-linkers
Hypercrosslinkedpolysterene and its derivatives -Methyl β-cyclodextrine. -Alkyloxy Carbonyl CD. -2-Hydroxy propyl β-CD	Poly(valerolactone allyl valerol acetone)	Dichloromethane

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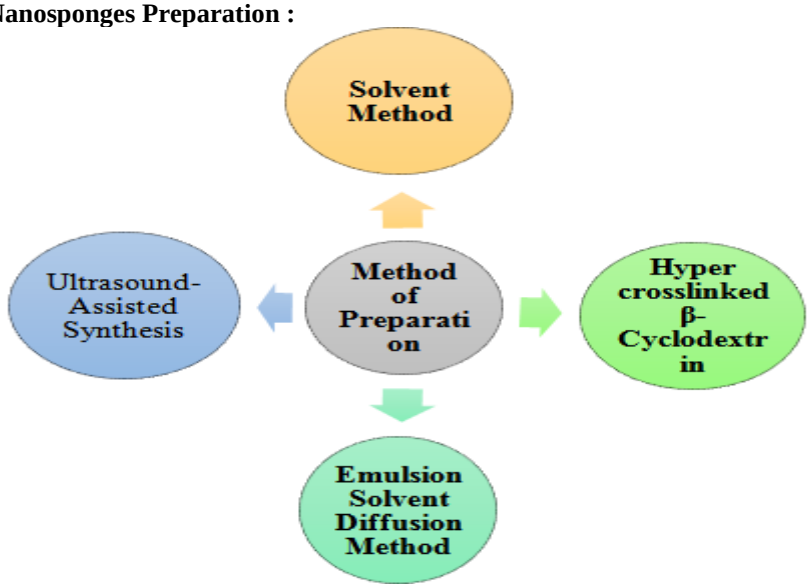
2- propyl β-CD	Poly(valeroacetone allyl valerol acetone oxepanedione)	Di phenyl carbonate
Ethyl cellulose	Ethyl cellulose	Acrylamide
Acrylic polymer	PVA	Glutaraldehyde
Eudragit RS 100		Carboxylic acid dianhydride
		Carbonyl di imidazole
		Diaryl carbonate
		Epichlorohydrin

C.Drug Substances :
The molecules of drugs should be readily miscible or can be made to be miscible by adding water or a solvent.During formulation, the mixture's viscosity shouldn't be increased by inert to monomers substances.

Types of Nanosponges :[3]
These are one of the essential types of nanosponges that can characterise or unite the calm components in its midsection. The distribution of the nanosponges into three classes using the method of drug complexation is

- **Encapsulating nanosponges:**These are amalgamate nanosponges, which have many holes like alginate nanosponges and encapsulate the medications in the middle.
- **Complex nanosponges:**Electrostatic charges are used in these to draw the drug molecules.
- **Conjugating nanosponges:**These require a powerful covalent bond to bind the medication to the nanoparticles.

- **Method of Nanosponges Preparation :**



A. Solvent Method :[13]
1) In the solvent method, the polymers are dissolved in an appropriate polar aprotic solvent, such as dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) etc.
2) The cross-linker is added in excess to the mixture at a molar ratio of 1:4. (polymer and crosslinker).
3) The reaction is conducted for 1 to 48 hours at a temperature range from 10°C to the solvent's reflux temperature.
4) When the reaction is finished, it is allowed to cool at room temperature before being cleaned with extra bi-distilled water, recovered by vacuum filtering, and purified using a soxhlet extraction method with ethanol.

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5) The preparation is finished with vacuum-assisted product drying.

B. Hyper Crosslinked β-Cyclodextrin Method :[13]

1) Crosslinking various cyclodextrin forms allows for the development of nanosponges with a carbonyl as a crosslinker.
2) They are created by mixing cyclodextrin with a cross-linker like diphenyl carbonate di-isocyanates.
3) A block of hyper cross-linked cyclodextrin that is transparent is coarsely ground, and excess water is used to wash away the solvent.
4) The product is purified by soxhlet extraction using ethanol, and the product is dried at 60 C in an oven overnight.

C. Emulsion Solvent Diffusion Method :[14]

1) This approach uses various concentrations of polyvinyl alcohol and ethyl cellulose.
2) The medication and ethyl cellulose-containing dispersed phase were dissolved in 20 ml dichloromethane and slowly added to a predetermined quantity of polyvinyl alcohol in 150 ml of the aqueous continuous phase.
3) For two hours, the aforementioned reaction mixture was agitated at 1000 rpm.
4) The NS that had developed was afterwards collected by filtering and dried for 24 hours at 400°C in the oven. In vacuum desiccators, the dried NS was kept, making sure that any remaining solvent was eliminated.

D. Ultrasound-Assisted Synthesis :[15]

1) This approach produces evenly spherical particles by sonicating the polymer and cross-linker without the need of a solvent.
2) The process begins with combining the polymer and cross-linker in a flask at a specific molar ratio before placing it in an ultrasound bath for sonication at 90°C for a short period of time.
3) After the reaction is finished, the mixture is cooled, the result is roughly crushed, washed with water to remove the unreacted polymer, and then purified by extended soxhlet extraction with ethanol.
4) The nanosponges will become available after additional drying.

➢ **Loading of drug into nanosponges :[16]**

The produced Nanosponges were suspended in water, sonicated to remove any aggregates, and then the suspension was centrifuged to separate out the colloidal fraction.An excessive amount of the medication was added to the Nanosponge's aqueous suspension, and the suspension was kept constantly stirred for the 24 hours necessary for complexation.The uncomplexed medication was separated from the suspension after 24 hours by centrifuging it at 2000 rpm for 10 minutes.Then, by solvent evaporation or freeze drying, acquire the solid crystals of Nanosponges.It was kept at room temperature in vacuum desiccators.The nanosponge's crystal structure is crucial for the complexation of drugs.When compared to crystalline nanosponges, paracrystallinenanosponges exhibit differing loading capacities.Crystalline nanosponges have a higher drug loading than paracrystalline ones.

➢ **Mechanism of drug release from nanosponges :[17]**

The NSs have a number of pores in their core structures that let the free passage of the drug molecule, and the liquid has reached the point of drug molecule saturation.When the final product is applied to the skin or ingested, the moiety enclosed is free to flow into the vehicle and is subsequently absorbed by the skin which leads to a decline in the drug concentration in the vehicle, generating the state of unsaturation and upsetting the balance.This continues until the body has absorbed all of the drug.The procedure examined above helps in the selection of cars appropriate for NS preparation.As the liquid is being prepared, the drug molecule's solubility rises, decreasing the benefit of its progressive release and making the drug moiety behave as though it had been added in its free form rather than its trapped form.

➢ **Factors Influence Nanosponge Formation :**

1) Polymers :

Nanosponges' ability to develop and function can be impacted by the type of polymer employed [18].Depending on the need for drug release and drug containment, the polymer is chosen. The choose polymer should have some quality to couple with ligands.

Examples include highly cross-linked polystyrene, cyclodextrins and their derivatives, such as methyl cyclodextrin, and copolymerssuch as ethyl cellulose and PVA[19].

2) Cross linking agent :

Depending on the polymer's structure and the medicine that needs to be developed, the crosslinking agent might be chosen[19].Effective crosslinkers create three-dimensional, nanoporous structures from nano-cavities

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molecules.Hydrophilic or hydrophobic components that can bind the target molecules are created by varying the crosslinking rate.Nano-sponge structures that are soluble or insoluble are created depending on the crosslinkers' composition.Epichlorohydrin (24), when utilised as a crosslinker, produces hydrophilic nanosponges.Hydrophilic nanosponges can alter the amount of drug release and can be utilised to enhance drug absorption across all biological barriers, acting as a strong drug carrier even in fast-release products.Diphenyl carbonate (4, 19, 20, 28, 29, 34), pyromellitic anhydride (32), diisocyanates (31, 55), and carbonyl diimidazoles (19, 30, 35) are all useful for the synthesis of hydrophobic nanosponges that could be used as crosslinkers[18].

3) Types of drugs :[19]

To be efficiently absorbed into nanosponges, drug molecules that will be coupled with nanosponges must meet specific requirements.

a) In the nanocavity of sponges, molecules with a ring size of fewer than five and a molecular weight of between 100 and 400 Da can be captured with ease.
b) There is less than 10 mg/ml of water solubility.
c) The substance's melting point is lower than 250 °C.

4) Temperature :

Drug/Nanosponge complexation can be impacted by temperature fluctuations.Generally, when temperature rises, the strength of the apparent stability constant of the drug/nanosponge complex diminishes. This may be because drug/nanosponge contact forces such van-der Waal forces may be reduced as a result.So when preparing nanosponges, complete temperature control should be kept[20].

5) Method of preparation :

Drug/Nanosponge complexation may be impacted by the way the drug is loaded into the nanosponge.However, depending on the type of drug and polymer used, freeze drying has often been shown to be the most successful approach for drug complexation [20].

6) Degree of substitution :

The class, number, and position of substituents on the parent molecule may have a significant impact on the nanosponge's capacity for complexation [20].The type of replacement is crucial because there are numerous ways in which the active groups on the surface of the cyclodextrin output might access the b-CD output.Different functional groups can combine to form various complex substances (β-CD nanosponges, CD-carbamate nanosponges, CDcarbonate nanosponges, etc.) with the aid of a crosslinker [18].

➢ **Characterization of Nanosponges :**

1) Particle size determination : [5]

Controlling the size of the particles during polymerization will make it feasible to produce free-flowing powders with fine aesthetic qualities.The particle size can be determined by dynamic light scattering using a Malvern Zeta particle size analyzer with MAS OPTION particle size analysis software, a laser diffractometer, or the 90 Plus particle size analyzer.This allows for the calculation of the polydispersity index and average diameterandvalue of polydispersity index is given in Table 1.

Polydispersity Index	Type of Dispersion
0-0.05	Monodispersed standard
0.05-0.08	Nearly monodisperse
0.08-0.7	Midrange polydispersity
>0.7	Very polydisperse

2) Determination of loading efficiency and production yield :[5]

The following formula can be used to determine the loading efficiency (%) of the nanosponge.

Loading Efficiency= Actual drug content in NS/Theoretical drug content ⍰ 100

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The manufacturing yield of the nanosponge can be determined using the following formula after accurately calculating the initial weight of the raw materials and the final weight of the created nanosponge.

Production yield = Practical mass of NS/Theoretical mass (Polymer + drug) × 100

3) Zeta Potential : [5]

Zeta potential is measured utilising additional electrodes in the particle size measuring equipment.In this procedure, the sample containing the nanosponge should be removed, diluted with 0.1 mol/L KCl, and then placed in the electrophoresis cell with a 15 V/cm electric field applied.After averaging all of the measured values, the average hydrodynamic diameter and polydispersity index are calculated.

4) Microscopy Studies: [5]

Drugs, nanosponges, and products (drug/nanosponge composites) can be studied from a microscopic perspective using scanning electron microscopy (SEM) and transmission electron microscopy (TEM).The creation of clathrates(inclusion complexes) is indicated by the difference in the crystalline condition of the raw materials and products that was seen under an electron microscope.

5) Resiliency:[5]

The resilience (viscoelasticity) of the sponge can be altered to generate softer or stronger beads depending on the requirements of the final formulation.The release rate often slows down as cross-linking increases.Therefore, the elasticity of the sponge will be investigated and optimised in accordance with requirements by taking the release as a function of crosslinking over time.

6) X-ray diffractometry and single crystal X-ray Structure analysis : [8]

Inclusion complexation in the solid can be found using powder X-ray diffractometry.The diffraction pattern of a newly created material clearly differs from that of an uncomplicated Nanosponge when the drug molecule is liquid because liquids do not have their own diffraction patterns.The complex creation is indicated by the variation in the diffraction pattern. When the drug compound is a solid, it is necessary to compare the diffractograms of the mechanical combination of the drug and polymer molecules with the complex that is supposed to exist.While the diffraction pattern of complexes appears to be distinct from each member and results in a "new" solid phase with a separate diffractogram, the diffraction pattern of a physical combination is frequently the sum of that of each component.The chemical decomposition and complex creation of a mixture of substances can be determined from their diffraction peaks.Drug diffraction patterns and the crystalline nature of the drug are both changed by the complex formation of the drug with nanosponge.A few new peaks develop, some existing peaks become sharper, and some peaks move as a result of the complex creation.The exact inclusion structure and manner of interaction can be determined via single crystal X-ray structural analysis.It is possible to determine how the host and guest molecules interact and to establish their exact geometric connectionstudies on solubility.The phase solubility method established by Higuchi and Connors, which investigates the impact of a Nanosponge on the solubility of medication, is the most used method for studying inclusion complexation.Diagrams of phase solubility show the level of complexation.

7) Infra-Red spectroscopy :[8]

The interaction between Nanosponge and the drug molecules in the solid state is estimated using infrared spectroscopy.When a complex is formed, Nanosponge bands frequently vary only little, and if fewer than 25% of the guest molecules are encapsulated in the complex, bands that may be attributed to the included portion of the guest molecules are quickly covered up by the bands of the Nanosponge spectrum.The method is often unsuitable for detecting inclusion complexes and is less illuminating than alternative approaches.The use of infrared spectroscopy is only applicable to medications with certain distinguishing bands, such as carbonyl or sulfonyl groups.The presence of hydrogen in different functional groups is shown by infrared spectral investigations.As a result of the stretching vibration of the group responsible for the creation of the hydrogen bonds, the absorbance

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bands are often shifted to a lower frequency, intensified, and widened.The stretching vibration band's biggest change is caused by a hydrogen bond at the hydroxyl group.

8) Thermo-analytical methods :[8]

Thermo-analytical techniques evaluate whether the drug substance changes in any way prior to the Nanosponge's thermal degradation.The drug substance can change by melting, evaporating, decomposing, oxidizing, or going through a polymorphic transition. The alteration of the drug substance denotes the development of a complex.The thermogram generated by DTA and DSC can be studied for broadening, shifting, emergence of new peaks, or elimination of certain peaks.The development of inclusion complexes can also be supported by changes in weight loss.

9) Thin Layer Chromatography :[8]

The Rf values of a drug molecule significantly decrease in thin layer chromatography, which aids in recognising the complex formation between the drug and nanosponge.

10) Solubility Studies:[5]

Higuchi and Connors describe a technique for analysing inclusion complexation, also known as a phase solubility method, which is used to determine whether drugs are soluble in nanosponges.The level of complexation is indicated by the phase solubility diagram.This approach employs an Erlenmeyer flask.The flask was filled with medications containing varying concentrations of nanosponge aqueous solution.After reaching a steady state, the Erlenmeyer flask was stirred on a mechanical shaker at room temperature. The suspension was then centrifuged through a 3000 Dalton molecular filter (MICRON YN 30, Millipore Corporation, Bedford MA 1730 USA) to remove any remaining particles.High-performance liquid chromatography was used to evaluate the solution and determine the medication concentration.

11) Raman spectroscopy :[17]

Raman spectroscopy is a helpful tool for analysing the behaviour of CD NSs as they transition from a dry to swollen condition.Raman peaks are sensitive to the conformational changes in molecules and the strength, quantity, and distance of intermolecular interactions.It can also be applied to the investigation of molecule structure.Additionally, it provides information on how the water is acting between the nanoporous structure and the dissolved solution. The vibration modes of the dissociated OH and CH groups from water can be used to investigate the dynamics of hydration in relation to bulk water.

12) Stability studies :[17]

The NSs have been the subject of stability research under accelerated settings and photodegradation experiments.The formula is annually evaluated for three months.The features of the substance are generally examined by changes in appearance, size, and physical characteristics.The photodegradation analysis is conducted for one hour while stirring in the dark and under the UV lamp.The NSs are situated at a distance of 10 cm from the lamp. The sample is taken out and examined using HPLC.

13) Dissolution test :[17]

The USP XXIII dissolving apparatus can be used to examine the dissolution profile of NSs with the use of a modified basket made of 5 m of stainless steelwire and rotating at 150 rpm.When examining the solubility of active chemicals, the chosen dissolve medium ensures sink conditions are maintained. The final samples are examined using the analytical methods that are available.

14) Drug Release Kinetics:[5]

We used zero-order, first-order, Higuchi Kosemeyer-Peppas, Hixon Crowell, Kopcha, and Makoid-banaker models to analyse the drug release data in order to study the mechanism of drug release.Utilizing the software graph pad prism, the data may be examined.The programme gives a good fit between the parameters of non-linear functions andnon-linear functions and experimental findings.A good fit between experimental observations and non-linear functions is provided by the programme, which also calculates the parameters of non-linear functions.

- **Recent Development in Nanosponges :**

The drug delivery method for NSs has undergone numerous upgrades and innovations throughout the years.Both the list of medications that have been placed into them and the preparation process have grown.There has also been an increase in the EE and the class of polymers used in the components.The recent advancements seen in NSs have been mentioned in Table.

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Name of Researchers	Year of Research	Title of project	Conclusions
Madhuri Shringirishi et al.	2017	Fabrication and characterization of nifedipine loaded β-cyclodextrin nanosponges: An in vitro and in vivo evaluation	In this study, the manufactured batch showed improved oral bioavailability of the drug (Cmax 0.02 g/ml for test and 0.055 g/ml for control formulation), and AUMC and AUC were 4.8 g/hr2 and 0.056 g/hr2 respectively with a mean residence time of 8.57 hrs.
Yijie Chen et al.	2018	Broad-Spectrum Neutralization of Pore-Forming Toxins with Human Erythrocyte Membrane-Coated Nanosponges	In this study, hRBC nanosponges and showed how well they could detoxify a variety of poisons that formed hemolytic pores. The resulting hRBC nanosponge, which is composed of a biocompatibleand biodegradable polymeric core and a natural hRBC membrane shell, exhibits a stable core-shell structure in both serum and PBS solution.
Wang et al.	2019	Nonviolent Self - Catabolic DNAzyme Nanosponges for Smart Anticancer Drug Delivery	The current DNAzyme NS framework could be developed to show remarkable applications in bioengineering and medicine.
Mohamed Aly Kassem et al.	2020	Design, evaluation and bioavailability of oxybutynin chloride nanosponges on healthy human volunteers	OXC was effectively added to EC nanosponges (N3, N4) before being compacted into tablets. When compared to Uripan XR®, the bioavailability of tablets administered to healthy human volunteers was higher.

Name of Researcher	Year of Research	Title of Project	Conclusion
Mohammed Muqtader Ahmed et al.	2021	Formulation and in vitro evaluation of topical nanosponge-based gel containing butenafine for the treatment of fungal skin infection.	The created BTF loaded NS impregnated carbopol polymeric gel may be an effective drug delivery system (DDS) of an antifungal agent for the successful treatment of fungal infections by prolonging the drug release and lowering the need for repeated dosing and the occurrence of SFI.
Roberta cavalli et al.	2022	Dextrin-Based Nanohydrogels for Rokitamycin Prolonged Topical Delivery	The outcomes indicated that these nanohydrogels are promising for the topical delivery of rokitamycin and might open the door for the delivery of other macrolide antibiotics.

- **Patents :** New patents have recently been submitted and approved in the field of NSs, where they have

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been used to enhance the preparation procedure and so make the process effective.The patents have been submitted for their usage as biocatalyst studies, growth preservation, enzyme release, and toxin absorption agents.Additionally, they have demonstrated promising antitumoral effects. As a novel drug delivery method, NSs are now more in demand thanks to the new patents that have been awarded by the authority and which are mentioned below.

Sr.No.	Patent/App no.	Applicants	Title
1.	W02006002814A1	Francesco Trotta, Wander Tumiatti, Orfeo Zerbinati, Carlo Roggero, Roberto Vallero	Ultrasound-assisted synthesis of cyclodextrin-based nanosponges
2.	W02009149883A1	Gianfranco Gilardi, Francesco Trotta, Roberto Cavalli, Paolo Ferruti, Elisabetta Ranucci, Giovanna Di Nardo, Carlo Mario Roggero, Vander Tumiatti	cyclodextrin nanosponges as a carrier for biocatalysts, and in the delivery and release of enzymes, proteins, vaccines and antibodies
3.	ITMI20071321A1	Giovanni Nicolao Berta, Roberta Cavalli, Barbara Mognetti, Carlo Maria Roggero, Francesco Trotta, Vander Tumiatti	Nanosponges based on cyclodextrins as a vehicle for anticancer drugs.
4.	W02012147069A1	UniversitaDegliStudi Di Torino, Sea Marconi, Technologies Di	Method of preparing dextrin nanosponges
5.	CA2692493A1	Sea Marconi, TechnologiesDi Vander Tumiatti, S.A.S, Francessco Trotta, Vander Tumiatti, Roberta Cavalli, Carlo Mario Roggero, Barbar Mognetti, Giovanni, Nicolao Berta	Cyclodextrin-based nanosponges as a vehicle for antitumoral drugs
6.	ITTO20110873A1	Vecchi Marco DeCarlo Stefano DiShubhenKapilaCarlo Maria RoggeroValentina ScariotMichela Tumiatti	Use of nanosponge functionalized for growth, preservation, protection and disinfection of plant organisms
7.	US9574136B2	Kun Lian	Nanoparticles, nanosponges, methods of synthesis, and methods of use
8.	US20170152439A1	Kun Lian	Nanoparticles, nanosponges, methods of synthesis, and methods of use
Sr.No.	Patent/App no.	Applicants	Title
9.	US8828485B2	Kun Lian, Qinglin Wu	Carbon-encased metal nanoparticles and sponges as wood/plant preservatives or strengthening fillers
10.	WO2007095454A2	Kun Lian, Qinglin Wu	Carbon-encased metal nanoparticles and sponges, methods of synthesis, and methods of use

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11.	WO2009138998A3	Eswaramoorthy Muthusamy, Saikrishana Katla	A template free and polymer free metal nanosponge and a process thereof
12.	WO2012147069A1	Francesco Trotta, Pravin Shende, Miriam Biasizzo	Method for preparing dextrin nanosponges

➢ **Application of Nanosponges :**

NS produced with CD have been used in a variety of pharmacological, enzymological, and environmental applications. The following is a summary of NS's pharmaceutical uses.

1. Improved dissolution :[21]

Drugs that are poorly soluble can be combined with NS to create inclusion complexes that will improve their solubility in water.Due to NS's limited solubility, the drug is shielded against precipitation and agglomeration by avoiding over saturation in the fluid.The medication is integrated so that its hydrophobic properties inhabit the hydrophobic interior chambers of CD units within the NS, while its hydrophilic groups associate with the hydrophilic external surface that is left open to the environment. Drug-loaded NS with increased thermodynamic energy and decreased crystallinity, as shown by an XRPD study.The overall result is improved medication solubility, which leads to an increase in drug bioavailability.

2. Targeted Drug Delivery :[22]

The unique toxicity of the chemotherapeutic agent caused by non-target drug distribution is the major burden connected with it. The use of nanoparticles can solve this problem. Active or passive targeting are the tactics that are most frequently used. The site-specific ligand is coupled to the nanoparticles to achieve active targeting. Regarding passive targeting, the increased permeability and retention effect (EPR) in the tumour microenvironment can be used to deliver targeted drugs. In the removal of nanoparticles from the biological system, the reticuloendothelial system (RES) is one of the main areas of concern. It can only be attributed to the presence of macrophages in RES. Targeting different parts of the biological system is made possible by tailored NSs with the right polymers because they can prevent RES uptake.Regarding the NSs, a porous mesh-like structure can provide more targeted and regulated release compared to other nanoformulations. Several investigations have reported keeping NSs in the systemic circulation until they reach the target site, according to the review . This can lessen the negative effects and decrease the frequency of dose.

3. Topical Drug Delivery :[22]

Drugs that are very hydrophilic or lipophilic do not penetrate as well with standard topical formulations. The treatment effectiveness may be negatively impacted by this. The NSs are special drug delivery systems that, because of their nano-porous nature, may be able to penetrate the skin and administer a variety of medications, including antibiotics, antifungals, and local anaesthetics. The most advantageous property of NSs is that they can be impregnated in a variety of topical formulations, including cream, lotion, gel, ointment, and patches.For enhanced antifungal action, Ahmed et al. (2021) created NSs based on polyvinyl alcohol and ethylcellulose that were butenafine-loaded. Additionally, it was added to 1% carbopol gel. The topical gel formulation including NSs demonstrated 0.18 mg/cm2.h flux rate and 89% drug diffusion in 24 h. This might take the place of traditional gel formulations.

4. Ocular Drug Delivery :[22]

The drawbacks of currently available conventional ocular formulationsinclude poor corneal permeability, less residence time, and more side effects.

All these drawbacks can be circumvented by encapsulating the drugsubstances using NSs.To increase the permeability of diclofenac sodium to the cornea, Hayiyana et al. (2016) created ester-based NSs. In an ex vivo investigation employing excised pig cornea, NSs and free medication showed 75% and 28% corneal penetration, respectively. This is in favour of NSs being used to overcome the limitations of conventional ocular formulations.

5. Oral Drug Delivery :[22]

In order to achieve maximal patient compliance, the oral route of drug delivery is the most frequently approved mode of administration globally. However, the problem of bioavailability must be addressed. Amidon created the Biopharmaceutics Classification System (BCS) in 1995 to forecast the degree of medication

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absorption following oral delivery.For medications in BCS classes 2 and 4, the rate of dissolution is a rate-limiting phase in the oral drug delivery process, whereas for drugs in BCS classes 3 and 4, the rate-limiting step is absorption. Through the use of an appropriate polymer, the NSs can increase the medicinal compounds' solubility and permeability. By making the tablet using CD-based NSs, Moin et al. (2020) increased the solubility of three regularly used painkillers, including caffeine, paracetamol, and aceclofenac. For caffeine, paracetamol, and aceclofenac NSs, respectively, the particle sizes were 185, 181, and 199 nm, with improved entrapment efficiency. Overall, the NSs increased the combinational dose form's rate of dissolution.

6. Delivery system for oxygen :[17]

Through the employment of CD and NSs, an oxygen delivery system was created. To achieve this, NSs made up of alpha and -CD are combined in water, then exposed to oxygen before being characterised in vitro . Using a CD NS/hydrogel combo device, oxygen can be infused through a silicone film. The ability of NS to release oxygen in a controlled pattern has been observed over time in research. When oxygen-deficient cell mass is present in various diseases, oxygen-encapsulated NSs can adhere to it.

7. As absorbent in treating blood toxicity :[17]

By eliminating the poison, NSs are used to extract toxic substances that are bad for the blood. When administered intravenously, NSs can absorb poisons and are superior to antidotes.NS makes a red blood cell-like appearance in the bloodstream, deceiving toxins into devouring them. Depending on the poison, NSs are able to absorb toxin molecules.

- **Future Trends and Challenges:**

The delivery of drugs using nanosponges is an exceptional and effective class of biocompatible delivery system. The presence of flexible crosslinked polymers enables a smooth conversion of traditional drug delivery methods to a distinctive and adaptable delivery system that exhibits the unique characteristics, making it flexible to design and develop novel product forms.Their unique structure makes it necessary to do in-depth research on their function in downstream processing. Removal of harmful compounds from industrial wastes and the removal of organic solvent vapour from the air are just a few potential applications that may be investigated. The bitter components of food and medicine items could be captured by nanosponges.The development of oral peptide delivery techniques and other sensitive biomers is the real challenge for the future. The safe administration of the active ingredients via various routes is authorised by the use of bioerodible and biodegradable polymers for medication delivery. The cytotoxicity of the nanoparticles or the byproduct of their disintegration is still a significant problem, and increasing bioavailability is one of the main goals of future study.

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