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Recent Advances in Nanosponges as Drug Delivery System

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ABSTRACT:

The most recent developments in nanotechnology have led to the creation of a targeted medicine delivery system. A specialized medication delivery mechanism is necessary, nevertheless, in order to effectively target a molecule to a particular location. The development of nanosponge has been a significant stride in addressing issues like limited bioavailability and drug toxicity.Nanosponges, which are three-dimensional drug transporters at the nanoscale, are created by crosslinking polymers. The ability to hold a range of pharmaceuticals in various sizes is one advantage they provide. Because they may offer targeted drug delivery along with a regulated drug release pattern, nanosponges are better than alternative delivery methods. Nanosponges are microscopic sponges that are roughly the size of viruses (250 nm–1 μm). They have chambers that can hold a wide range of medications. When it comes to regulated drug distribution, nanosponge is essential. Because it can load water and lipid-soluble drug molecules and lessen their side effects, it can increase the aqueous solubility and penurious bioavailability of medications in a variety of dosage forms for controlled drug administration, including oral, parenteral, topical, rectal, and inhalational dose forms. This review explores the advantages and disadvantages, methods of preparation, variables that affect their preparation, methods of characterization, uses, and the latest developments in nanosponges. The preparation process, characterization, and potential usage in drug delivery systems are the main topics of the current review.

Keyword: Nanosponges, Targeted drug delivery, Controlled release, Bioavailability enhancement, Polymeric carriers, Nanotechnology in pharmaceuticals

1. INTRODUCTION

Nanosponges are tiny, sponge-like particles—typically made from biodegradable polymers—that can absorb, carry, and release drugs or other substances in a controlled way. Due to their porous, three-dimensional structure, they can encapsulate both hydrophilic and hydrophobic compounds, making them useful for targeted drug delivery, detoxification, and controlled release in pharmaceuticals.

Nanosponges are tiny, spherical particles with a large porous surface area that are used as porous polymeric forms of delivery. In order to achieve significant benefits including lowering the overall dosage, keeping the dosage form on the skin, and preventing systemic absorption, they are used to passively target cosmetic pollutants to the skin. By extending dose intervals, these nanosponges can be advantageously added to topical systems for prolonged release and skin retention, which reduces toxicity and variability in drug absorption whereas further improving patient compliance. [1]

Insoluble solid porous materials having exceptional absorption and complexation capabilities, as well as typical nonmetric porosity, are referred to as nanosponges (NS). Both organic and inorganic substances are used in its synthesis. The structure of this new class of microscopic sponges, which is as practical as a virus's size and has many voids where a medicine can be packed to target the tumor cell by joining an individual chemical linker.

The NS is regarded as a scaffold-structured or three-dimensional network. In order to clip different elements of polymer together, the NS polymer has cross-linking agents that resemble tiny grappling hooks and an extended polyester backbone. A spherically shaped particle with a pouch that can contain medicinal ingredients is created when the polyester and cross linker react. Because polyester is biodegradable, it comes down gradually in the body. The NS's length and cavity will change when different cross-linkers are used. Drugs that are poorly soluble may be captured by NS, which could improve delivery. It may be built by tweaking the cross linker ratio because to its broad palette of diameters (1μm or less) and the variable polarity of the cavities. [2]

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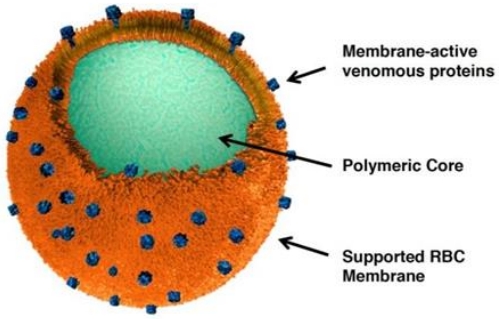

Fig: 1 Structure of Nanosponge [3]

The primary accomplishment of this medication delivery system is that it solves the issues associated with the drug's release at the designated location at a predetermined rate. Probably the most notable engineering achievement since the industrial era is nanotechnology.

Designing and manipulating materials at the nanoscale to produce products with superior qualities is known as nanotechnology. One billionth of a meter is called a nanometer. Physical substances with at least one percentage in the 1–100 nm range are referred to be nanomaterials.

Nanoparticles are pieces with an adjacent interfacial layer which varies in size from 1 to 1000 nm.

These nanoparticles come in a variety of forms, including dendrimers, carbon nanotubes, micellar systems, polymeric nanoparticles, hard phospholipid nanoparticles, nano emulsions, and nanosponges (NSs).

The colloidal structures known as NSs can encapsulate a wide variety of compounds, including DNA, proteins and peptides, volatile oil, anti-neoplastic drugs, and many more. Since NSs have a diameter of 10–25 µm and a void space of 5–300 µm, they are superior microsomes, which have a diameter of less than 1 µm.[4]

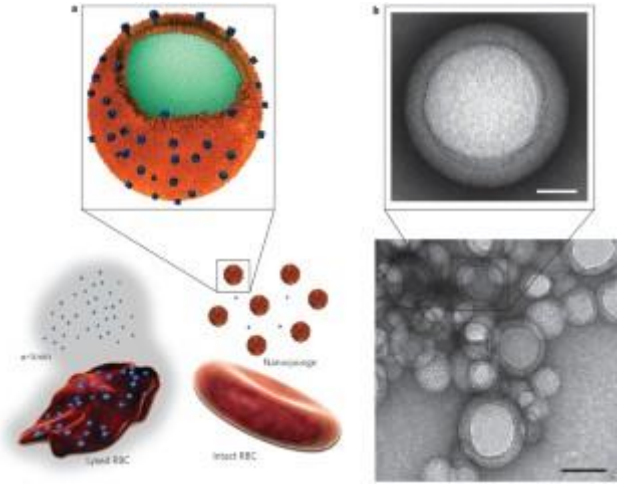

Fig: 2 Schematic Structure of Nanosponges [5]

Drug irritation can be considerably decreased using nanosponges without compromising the medications' effectiveness. The solid nanosponges can be prepared as topical, parenteral, oral, or inhaled dose forms. The Complexes can be distributed in a matrix of excipients, diluents, lubricants, and anti-caking agents appropriate for the production of capsules or tablets for oral administration. They can be successfully added to topical hydrogel for topical delivery. The long-held goal of creating efficient tailored medicine delivery systems has been largely dashed by the intricate chemistry required to create new systems.

Targeting drug delivery has long been a problem for medical researchers i.e., how to get them to the right place in the body and how to control the release of the drug to prevent overdoses. One potential solution to this issue is the creation of novel, intricate molecules known as nanosponges. [6]

Because of their many benefits, including the ability to transport poorly soluble medications, target molecules at specific locations, and prevent degradation, nano-drug delivery systems have recently emerged as a crucial component of the most innovative drug delivery systems. [7]

The way that nanosponges bind drugs can be used to categorize them. Some shield their selves from deleterious outside influences by encasing recuperation chemicals within their core. Covalent bonds are created between pharmaceuticals and conjugating nanosponges, guaranteeing a robust, long-lasting binding for regulated, prolonged release. In the meanwhile, complexing the nanosponges use electrostatic interactions to provide a versatile and flexible method of administering medication. [8]

1.1 SCOPE OF THE STUDY:

Thanks to their exceptional benefits in terms of stability, solubility, and controlled release of therapeutic drugs, Nanosponges constitute a new and adaptable class of Nano carriers in drug delivery systems. The porous, three-dimensional structure of nanosponges, which are mostly made of hyper-crosslinker cyclodextrins or other biodegradable polymers, enables the encapsulation of both hydrophilic and lipophilic therapeutics. [9]

Systems based on nanosponge have been investigated as potential substitutes for targeted drug administration and cancer treatment because of its exceptional porosity, straightforward functionalization procedures, distinctive topologies, affordability, and environmental friendliness. Their bio distribution and biocompatibility require more investigation. To create multifunctional systems with cancer/tumor theragnostic applications, more research is necessary to concentrate on the precise surface functionalization or modification of nanosponges utilizing different materials, such as fluorescent chemicals, magnetite nanoparticles, folic acid, etc. [10]

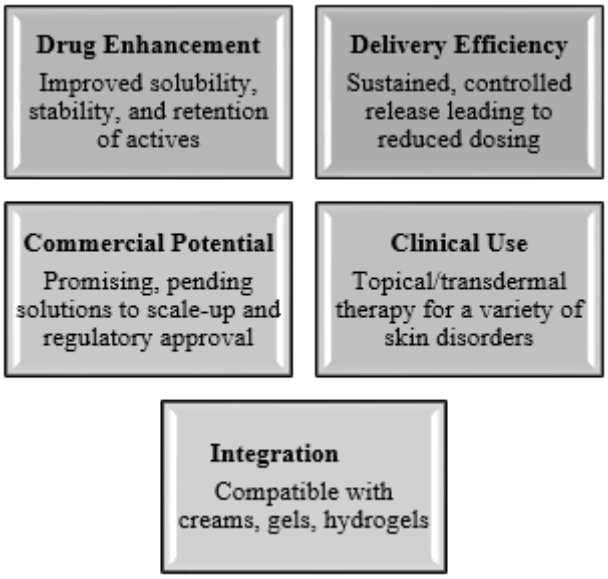

Fig: 3 Scope of the NS as Drug Delivery System [11]

1.2 TYPE OF NANOSPONGES-

There are many different kinds of NS that may be created and shaped based on the polymer used, its concentration, and the production method. Beta CD-based NS are the most commonly manufactured and utilized kinds of NS.

1. **Nanosponges with modifications**

2. **Nanosponges Based on Beta Cyclodextrins**

3. **Nanosponges Made of Titanium**

4. **Particles of silicon nanosponges**

5. Amino Nanosponges of Beta Cyclodextrins Baste Polyamide

6. Metallic Nanosponges Coated with Carbon

7. Polystyrene Nanosponges with Hyper Cross Linking

8. Nanosponges of beta cyclodextrins [12]

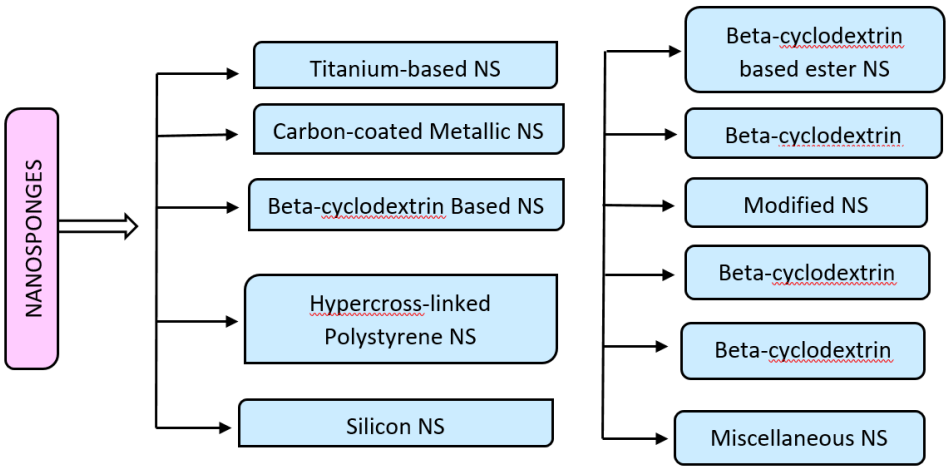

Fig: 4 Types of Nanosponges

There are numerous varieties of NS that may be created and manufactured according on the polymer used, its concentration, and the appropriate production technique in order to perform Beta CD-based neural networks are the most often used and constructed types of neural networks. The whole process of conceiving beta-CD NS is quite straightforward, and a number of variants are available. [13]

METAL - BASED NANOSPONGE (categories):

NS can be classified into a number of categories according to the production technique, concentration, and polymer.

Monometallic

It only has one metal precursor, which is the most basic kind of metal NS. Alkyl (trim ethyl) bromide was used as a 3 nm pore surfactant during the synthesis of TiO2, the first monometallic oxide in nonporous applications, as described by Antonelli and Ying in 1995. On the template-free single-metal NS, however, a number of metals are displayed, including copper, silver, gold, platinum, and palladium.

A two-metal nanosponge

Bimetal NS exhibits remarkable catalytic activity, stability, and a variety of pores. Pd is the recommended option because it is more affordable and readily available. For enhanced electrocatalytic activity, scientists have effectively created a three-dimensional, highly porous Pd-Cu bimetallic NS alloy with Al (NO3). Achieving the required porosity and catalytic activity during the synthesis process depends on efficient Al extraction.

Polymerized nanoparticle

Because of advancements in catalytic activity, the emphasis has switched in recent decades to the creation of polymetallic nanostructures. These NS may find use in catalysis, fuel cells, and water purification. Hydrogen bubbles act as a dynamic template in the template-free tremetol NS of Pt53Ru39Ni8, which is produced in part by NaBH4. Compared to bimetallic NS, polymetallic NS has greater catalytic activity.

Nanosponge made of metal oxide

The synthesis includes inorganic plastics like zeolite and alumina as well as organic plastics like polysaccharides, starches, and surfactants. These plastics are then used to apply strong acids and foundations, or to change or remove the template. The metal oxide NS must be synthesized using two different kinds of template-based methods.

Nanosponge nano casting

Strong, porous materials such as copolymer block, silica, alumina, zeolite, and polystyrene latex are used as support materials in the hard template technique. Using techniques including calcination, acid treatment, and basic treatment, the metal ions that fill the frame are removed. Because of its versatility and ease of usage, this technology is suggested for expanding architecture into different shapes, sizes, and lengths.

Nanosponge endo template

The soft template solution is a flexible framework composed of polysaccharides, surfactants, and cellulose-based ingredients. By forming mesopore or micropore-functioning micelles, surfactants enable the alteration of the size, shape, and content of nanostructures. In 1994, mesostructured metal oxides were produced using this method. Compared to hard templates, it is less costly, simpler to synthesize, and reasonably successful. [14]

1.3 Nanosponges' benefits include:

1. Improved Drug Solubility and Stability:

Hydrophobic pharmaceuticals can be encapsulated in Nanosponge's porous structure, increasing the drugs' solubility and stability in physiological settings. This characteristic improves the bioavailability of poorly soluble medications and lessens the need for solubilizing chemicals.

2. Targeted Drug Delivery:

By altering their surface characteristics, functionalized nanosponges can be made to target particular tissues, cells, or organs. This ability reduces systemic toxicity and minimizes off-target effects while improving therapeutic efficacy.

3 Controlled Release Profiles:

Over an extended period of time, nanosponges enable the controlled and sustained release of encapsulated medications. By keeping drug concentrations within the therapeutic window for extended periods of time, this controlled release profile can maximize therapeutic.

4. Biocompatibility and Reduced Immunogenicity

A variety of nanosponge materials, including lipid-based materials and biocompatible polymers, have low immunogenicity and high biocompatibility, which qualifies them for use in biomedical applications.

5. Formulation Versatility:

Nanosponges can be made to encapsulate a variety of medicines, such as proteins, peptides, small molecules, and nucleic acids, providing formulation design flexibility for a range of therapeutic uses.

1.4 Negative aspects of Nanosponges-

1.Complex Synthesis and Characterization:

Nanosponge synthesis frequently entails complex processes and calls for exact control over variables like template removal and polymerization conditions. Furthermore, comprehensive characterization is necessary to guarantee stability and homogeneity.

2. Possible Stability Problems:

Over time, certain nanosponge formulations may show signs of aggregation, disintegration, or a decline in the effectiveness of the encapsulated medication. Because of these difficulties, formulation characteristics and storage conditions must be optimized.

3. Scale-Up Challenges:

It can be difficult to increase nanosponge manufacturing to satisfy market demand while preserving batch-to-batch uniformity. One major obstacle to extensive clinical translation is still production scalability.

4. Biological obstacles and Clearance:

The mononuclear phagocyte system (MPS) and possible buildup in nontarget organs are two biological obstacles that nanosponges must get past. There is ongoing research into ways to increase circulation time and reduce systemic clearance.

5. A Look at Regulatory Aspects:

Regulatory approval procedures for nanosponge medication delivery systems necessitate thorough safety and efficacy assessments, just like for any product based on nanotechnology. Clinical translation and commercialization are hampered by the need to comply with regulations. [15]

1.5 Features and attributes of Nanosponges:

1. One important characteristic of these sponges that allows them to transport drugs with low solubility is their aqueous solubility.

2. Drugs that are hydrophilic (soluble in water) or lipophilic (soluble in fat) can be delivered by nanosponges.

3. The polarity of the holes in these nanosponges can be altered to meet particular needs, and they are typically less than 1 µm.

4 They are non-toxic, porous particles that do not dissolve in most organic solvents and can withstand temperatures of up to 300°C.

5. Nanosponges exhibit stability in the pH range of 1 to 11.

6. The particle size of nanosponges can be altered by varying the amount of cross-linker in the polymer.

7. They provide their effects a therapeutic start.

8. Because nanosponges are neither mutagenic nor irritating, they can be used safely in pharmaceutical and medical applications. [16]

2. MATERIALS FOR THE PREPARATION OG NANOSPONGES

2.1 Copolymers and polymerization

The kind of polymer used to make nanosponges has an impact on their development and functionality. The cavity of the created nanosponges should be able to hold a specific medicament in the complexation scenario. The kind of medicine to be encapsulated and the intended release profile also influence the polymer choice. Among the polymers utilized include acrylic polymers, Eudragit RS100, hyper crosslinked polystyrene, cyclodextrin and its derivatives, and others.

2.2 Crosslinking Agents:

The kind of crosslinker to use is determined by the drug whose nanosponges are to be made and the structure of the polymer. Crosslinking agents include carboxylic acid dianhydrides, carbonyl diimidazoles, dichloromethane, diphenyl carbonate, glutaraldehyde, and others. The degree of crosslinking, which depends on the concentration of the crosslinker, is an essential part of nanosponges because it affects the pattern of drug release and drug encapsulation. By adjusting the concentration of the crosslinker, it is possible to create hydrophilic and hydrophobic nanosponges for the delivery of active pharmaceutical compounds. Water-soluble or insoluble nanosponge structures can be created depending on the kind of crosslinkers used.

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2.3 The medicinal substance-

The medical substance should have a molecular weight of 100–400 Da. It is intended to be formed as nanosponges. With a melting point of less than 250 °C, the solubility should be less than 10 mg/ml in water. Additionally, medication compounds should have fewer than five condensed Rings. [17]

The synthesis's constituent chemicals-

Table: 1 Chemicals used for the synthesis

POYMER	COPOLYMER	CROSSLINKERS	POLAR SOLVENTS
Hyper crosslinked polystyrene	Poly (Valero lactone allyl Valero lactone)	Carbonyl diimidazole (CDI)	Ethanol
CD (alkoxycarbonylCD)	Poly (Valero lactone allyl Valero lactone oxypanedione	Carboxylic acid dianhydrides	Dimethylacetamide
Methyl β- CD	ECPVA	Diary carbonates	Dimethylformamide
Hydroxy propyl β-CD		Dichloromethane	
Poly- Valero lactone		Glutaraldehyde	
Eudragit RS100		Pyromellitic anhydride 2,2bis(acrylamide) acetic acid	
Acrylic Polymer		Epichloridine	

3. TECHNIQUES OF PREPARATION

3.1 The solvent technique

Polymers including β-CD, ethyl cellulose (EC), alginates, eudragit, and polyvinyl alco (PVA) are used in this process. Appropriate solvents, especially aprotic polar solvents like dimethylformamide and dimethyl sulfoxide, are combined to create a combination. Next, add enough cross-linker (CDI and dimethyl carbonate) to the mixture, ideally to a cross-linked polymer with a molar ratio of 4 to 16 for the formulation. At temperatures between 10°C and the solvent's reflux temperature, the reaction is carried out for one to forty-eight hours. The cooled solution is combined with a sizable volume of distilled water to create the final product. [18]

The product is recovered under vacuum using filtration, and it is further purified using long-term Soxhlet extraction. The final product was then vacuum-dehydrated and ground into a homogeneous powder by reducing its size in a mechanical mill.
Shorter extraction times and a higher percentage of manufacturing output are made possible by this straightforward and economical process.

However, it has a number of drawbacks, such as a reduced spherical shape, a less uniform size distribution, larger particles, ineffective encapsulation, and a burst release effect, which have encouraged more research to identify alternate production techniques. [19]

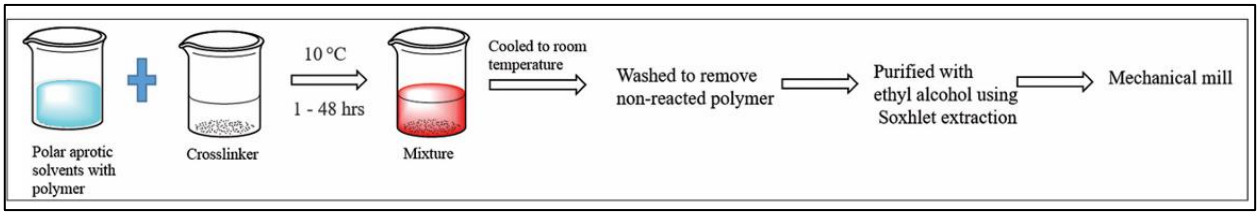

Fig: 5 Solvent Technique

3.2 Ultrasound-assisted synthesis

A flask was filled with the polymer and the cross-linker at a specific molar ratio, and it was then held for five hours under continuous effective sonication in an ultrasound bath device filled with water that had been heated to 90°C. 2. Ultrasound-assisted synthesis

NS is created using this technical method by sonicating the polymers with the cross-linkers without the use of a solvent. The NS resulting from this technique is spherical and uniform in size.

After adding too much water, the non-reacted polymer was successfully eliminated, and it was then extracted for a considerable amount of time using ethanol. The high-pressure homogenization process can produce NS with a tight particle size dispersion. The product was then vacuum-sealed and desiccated at 25°C. [20]

Some benefits include the method's ability to produce rapid, repeatable findings and the absence of solvent traces. In addition to requiring potentially harmful cross-linking chemicals, this approach simultaneously yields NS with an uneven particle size and an asymmetrical structure, which limits its use. [21]

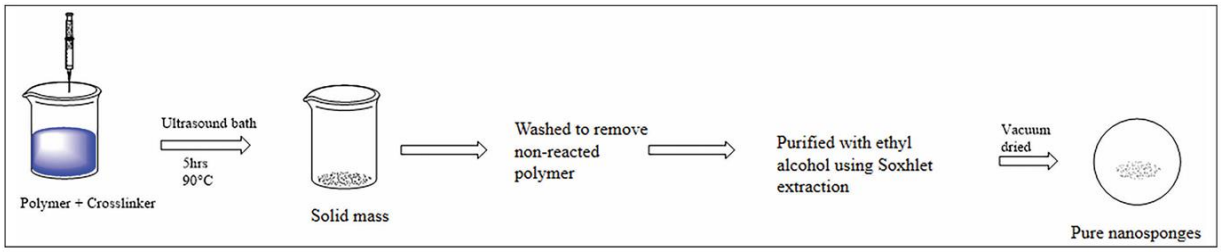

Fig: 6 Ultrasound-assisted synthesis method

3.3 β-CD that are hyper cross-linked

This approach used β-CD as the drug carrier to deliver the medication. By reacting β-CD and using a cross-linker, NS was created. While percentages of particles below 500 nm can be identified, its synthesis can take the shape of neutral or acidic forms with a mean diameter of less than 1 µm.

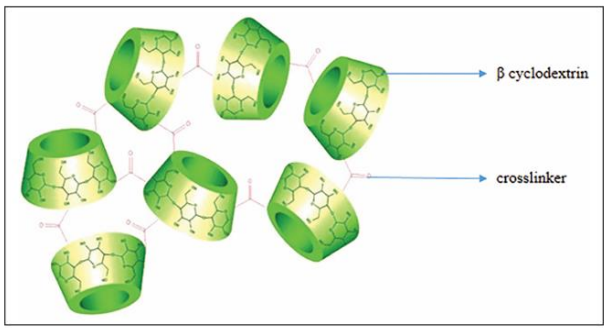

Fig: 7β- CD method

3.4 Solvent evaporation method

EC and PVA can be used to create NS. Here, the dispersed phase EC was dissolved in an organic solvent called dichloromethane before being extensively combined with the continuous aqueous phase, PVA aqueous solution. After that, the reaction is carried out for five hours using magnetic mixing. After filtering, the product was finally dried in an oven set to 40°C for 24 hours. [22]

Compared to alternative fabrication techniques, this straightforward and economical method has a number of advantages, including the use of acceptable organic solvents, a high formulation yield, exceptional batch-to-batch reproducibility, and a limited size distribution. This technique can precisely manage particle size, something that other approaches find challenging. Leakage of the water-soluble drug material into the external phase during the emulsification process is a major disadvantage of this approach that could reduce the effectiveness of encapsulation. [23]

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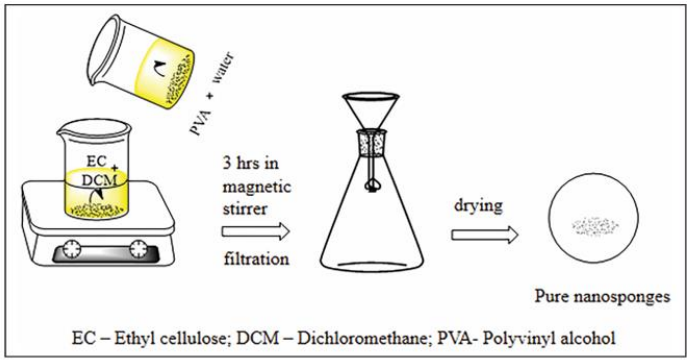

Fig: 8 Solvent evaporation method

3.5 Melt method

When the melting process is performed, the β-CDs and crosslinker fuse together. After being thoroughly mixed, the remaining ingredients are put into a 250 ml jar that has been heated to 100°C. After that, magnetic mixing is used to continue the reaction for five hours. After allowing the reaction mixture to cool, the result is broken down and thoroughly cleaned several times using appropriate solvents, such as ethanol, to get rid of any excipients and byproducts that haven't fully reacted. After then, these blank NSs were encased. [24]

It is a highly automated, efficient, repeatable, and continuous process. However, this technology is not appropriate for the manufacturing of NS due to the thermal degradation of heat-sensitive materials, increased production costs, and a lack of qualified and experienced staff. [25]

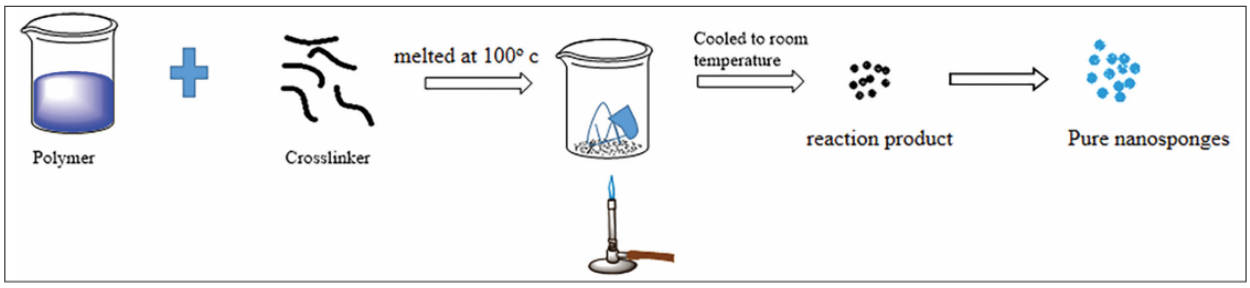

Fig: 9 Melt method

3.6 Bubble Electrospinning Method

According to several works of literature, a typical electrospinning setup consists of a syringe, syringe pump, high-voltage supply, and a grounded collector. Nonetheless, one of the main limitations limiting the use of nanofibers is the volume of their manufacture. PVA can also be used in the bubble electrospinning process as a polymer. The 10% polymer solution was to create a one-phase mixture, it was first arranged by adding distilled water and then agitated for two hours at 80°C to 90°C. After cooling, the polymer solution was used to create NS fibers. [26]

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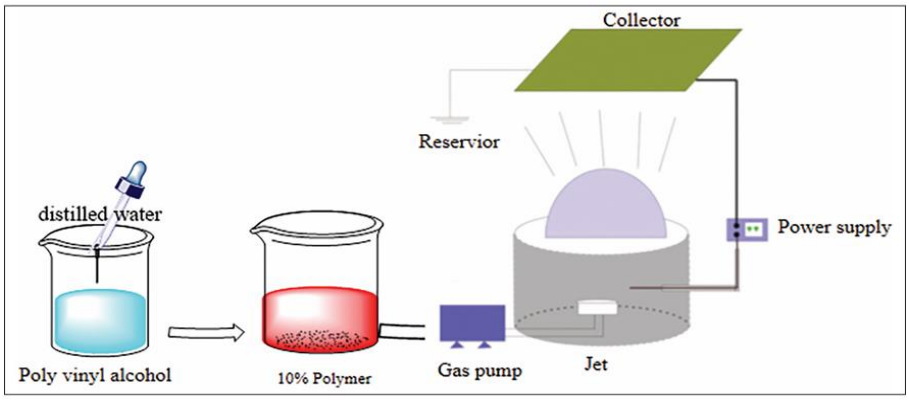

Fig: 10 Bubble Electrospinning Method

3.7 Quasi-emulsion solvent method

The polymer was used to assemble the NSs in various sums. The inner stage is made and added to a reasonable dissolvable stage using Eudragit RS 100. Under ultra-sonication, the medication produced a response and degraded at 35°C.
This internal procedure is used in the polyvinyl alcohol-containing external phase as an emulsifying operator. The mix is blended for three hours at 1000–2000 rpm at room temperature, and then it is dried for twelve hours at 40°C in an air-warmed oven. Significant advantages of this approach include spherical particle form, reduced solvent traces, and high drug loading capacity. By adjusting the stirring speed utilized in this process, the size of NS may be readily controlled. The primary obstacles to using this technology to a considerable degree are the lengthy time required for the monomer reaction and the inability to load water-soluble medications.[27]

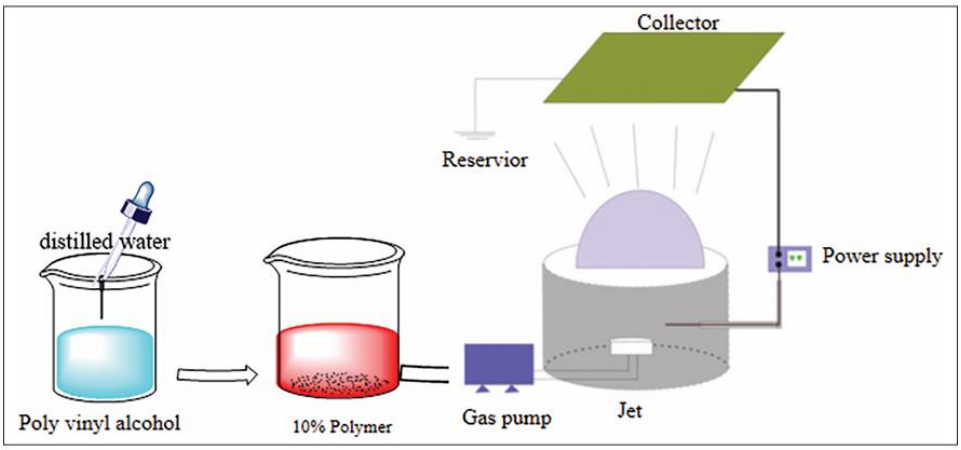

Fig: 11 Quasi-emulsion solvent method

3.8 Synthesis by the use of microwave radiation

The loading capability of CD NS produced with microwave aid was increased in comparison to conventionally produced nanoparticles. According to this group, using microwave technology to create CD NS quickly is very efficient, simple, reproducible, scalable, and reasonably priced.

Created CD NS using a microwave-mediated method to boost rilpivirine hydrochloride's bioavailability. This group used DPC as the crosslinker and optimized the solvent volume, the crosslinker, and the polymer-to-watt power ratio. The development of Para crystalline CD NS during the study greatly improved the drug rilpivirine hydrochloride's oral bioavailability.

The reaction time for CD-based NS is significantly accelerated by this microwave irradiation synthesis method. These NS have outstanding crystallinity. The microwave synthesis of NS reduced reaction time by four while producing a homogeneous particle

size distribution and crystallinity as compared to traditional heating techniques. Evaluated the benefits of using a microwave-assisted heating method over traditional heating for the synthesis of CD-based NSs.

The results showed that NSs created with microwave aid quadrupled the model drug's ability to retain pharmaceuticals. The NSs generated by microwave synthesis are highly complex, have a narrow size range, and are highly crystallized. Reaction times were drastically shortened and reaction products were greatly improved with microwave-assisted heating. The benefit of using microwave irradiation for synthesis is that it can precisely supply the targeted molecules with direct energy. As the reaction develops, the true impact becomes apparent. [28]

4. DRUG LOADING INTO NS

To attain an average particle size of less than 500 nm, drug loading NS as a drug delivery carrier needs to be pre-treated. To prevent aggregation formation, the NSs are hung in water and then subjected to sonication. Colloidal fractions are obtained by centrifuging the resulting suspension. The lyophilization principle is used to separate the liquid supernatant and dry the material.
The excess amount of medication is dispersed throughout the formulation of the NS-containing aqueous suspension. For a specified amount of time, the formulation is continuously stirred until complexation occurs. [29]

It is necessary to decrease these NS to particle sizes less than 500 nm. The suspension is then centrifuged to create a colloidal section. Centrifuging the suspensions for 10 minutes at 3,000 rpm allowed the uncompleted medication to separate from them as a residue underneath the colloidal supernatant. The resultant supernatant was then freeze-dried using a lyophilized.
This solid, freeze-dried form of NS is essential for the creation of the drug's complex, and crystalline NS has a larger drug loading range (62.8 ± 0.22 to 73.1 ± 0.39), compared to Para crystalline NS.In weak crystalline NS, the drug loading takes place as a mechanical mixing. The following table lists the medications that have been delivered in NS formulation.

Table: 2 Drug loaded in NS [30]

DRUG	THERAPEUTIC ACTIVITY	NS VEHICLE	ATTRIBUTES	ROUTE OG ADMINISTRATION
Itraconazole	Antifungal	B-CD, copolyvidonum	Enhanced drug solubility	Oral, topical
Dexamethasone	Anti-inflammatory	B-CD, DPC	Enhanced drug solubility	Oral, parenteral
Doxorubicin	Antineoplastic	B-CD,DPC	Sustained release drug	Parenteral
Nelfinavir mesylate	Antiviral	B-CD, dimethyl carbonate	Enhanced drug solubilization	Oral
Gamma- oryzanol	Antioxidant	B-CD,DPC	Enhanced drug stability, solubility, permeation	Topical
5-Fluorouracil	Antineoplastic	B-CD	Enhanced drug stability	Parenteral, topical
Tamoxifen	Antiestrogen	B-CD,CDI	Enhanced bioavailability and solubility	Oral

4.1 Capacity to incorporate medications into nanosponges

The NSs are sonicated and suspended in water to stop them from aggregating. After that, the dispersion is centrifuged to produce a colloidal solution, which separates into supernatant and dries the NSs when it is freeze-dried.
In order to facilitate the complexation process and help generate NSs in an aqueous suspension, the drug is then disseminated in excess and continuously agitated for a predetermined period of time in the following step.
Following complexation, centrifugation is repeated to separate the uncompleted medication. Finally, the NSs were obtained using the solvent evaporation method or the freeze-drying method.

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5. MECHANISM OF DRUG RELEASE FROM NANOSPONGES

The drug molecule can freely move through the numerous holes in the NSs' structures that are located at their core, and the liquid has reached the drug molecule's saturation point. When the final product is applied topically or ingested, the encapsulated moiety is free to enter the vehicle and be absorbed by the skin. This helps to lower the drug concentration in the vehicle, which results in unsaturation and upsets the equilibrium. This procedure continues until the body has absorbed all of the drug.

The above-mentioned technique helps to prepare a variety of cars for the NS. During the preparation process, the drug molecule becomes more soluble in the liquid, decreasing the benefit of its progressive release and making the drug moiety appear to have been added in its free form rather than its trapped form. [31]Since there is no continuous barrier surrounding the nanosponges due to their open structure, the active component is administered to the vehicle in an encapsulated state. Until the vehicle is saturated and equilibrium is achieved, the encapsulated active component can freely move from the particles into the vehicle.
As soon as the product is applied to the skin, the active ingredient's carrier becomes unsaturated, disrupting the balance. Therefore, the flow of active chemicals from nanosponge particles into vehicles starts at the epidermis and continues until the vehicle is either absorbed or dried. Even when the nanosponge particles are trapped on the stratum corneum, the skin's outermost layer, the active ingredient continues to be released into the skin for a significant period of time. [32]

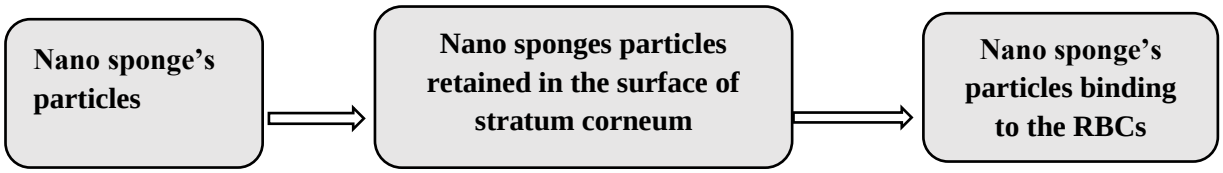

Fig: 12 Mechanism of Drug Release from NS

5.1Pharmacokinetics and the mechanism of in vitro drug release from NS

The open structure of the nanosponge allows the encapsulated active ingredient to easily exit the tiny vehicle until equilibrium is achieved. After local application, the equilibrium shifts, causing the vehicles holding the active component to become unsaturated. As a result, the active medicine in the vehicles starts to move toward the stratum corneum of the skin until the vehicle is completely dried up or absorbed. With time, the NS remained on the stratum corneum's surface, continuously supplying the skin with active chemicals, leading to pseudo-zero-order kinetics.

5.2 Kinetics of release

For the NS in-vitro release testing, a rotating multi-compartment cell with a dialysis membrane is used. The donor phase contains drug-loaded NS complexes in distilled water. A UV-visible spectrophotometer is then used to analyze the receptor phase at pre-arranged intervals after it has been fully extracted and diluted with water. Additionally, depending on the composition, USP Apparatus II can be employed in a variety of situations.

6. Assessment and description of NS:

(Characterizations of Nanosponges)

6.1 Solubility studies

The approach most commonly employed to study inclusion complexation was the phase solubility method, which was put out by Higuchi and Connors. These investigations looked into how NS affected the solubility of medications. Phase solubility diagrams are used to determine the complexity level.
This approach determines the solubility studies using an Erlenmeyer flask. To do this, a mechanical shaker was used to shake the flask of medications with an aqueous solution that included different amounts of NS at 37°C. After the suspension reached equilibrium, a 3,000-dalton it was clarified using a molecular filter. With the use of high-performance liquid chromatography (HPLC) analysis, the drug content in the solution was determined.

6.2 Effectiveness of trapping and loading

The un-entrapped drug is subtracted from the total amount of drug to get the prepared nanosponge loading efficiency. Separating the un-entrapped drug, as measured by any appropriate analytical technique, will reveal the drug entrapment efficiency. The process that uses ultra-centrifugation, dialysis, and gel filtering to separate the unentrapped medication.[33]

To calculate the loading efficiency, divide the actual drug content in the nanosponge by the theoretical drug times 100.

Loading efficiency = Actual drug content in nanosponge / Theoretical drug × 100 [34]

6.3 Studies using microscopy

The microscopic characteristics of the drug and drug/NS combination are investigated using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Under an electron microscope, inclusion complexes are created when new components and byproducts from different crystallization stages come together.

6.4 Particle size and polydispersity

Dynamic light scattering can be used in order to estimate particle size with a 90 Plus particle sizer and the MAS OPTION particle sizing application. This understanding can be used to calculate the mean diameter and polydispersity index (PDI). The particle size distribution's variance or dispersion is measured by the PDI. If a sample's PDI value is lower, it is said to be monodisperse; if it is higher and exhibits a greater range of particle sizes, it is said to be polydisperse. Table 4 provides the polydisperse index of dispersion. Utilize the following formula to determine PDI:

PDI is equal to Δd/dvg.

The average particle size, represented by MV (nm), is indicated by (d Avg) on the particle size data sheet, whereas (d) is the width of the distribution, indicated by SD. Particle size can be measured using the following techniques: Atomic Force Microscopy, Freeze Fracture Electron Microscopy, SEM, and TEM.

6.5 Potential for Zeta

The zeta potential is used to detect surface charge. One way to find it is to employ an extra electrode in particle size measurement equipment. For zeta potential analysis, NS samples were diluted with 0.1 mol/l KCl and then placed in an electrophoretic cell with an electric field of around 15 V/cm.

6.6 Methods of Thermoanalysis

Peak broadening, peak shifting, and the appearance and disappearance of specific peaks are the three methods most commonly used with thermograms. These thermo-analytical techniques can be used to track the NS's thermal degradation. Examples of this degradation include melting, evaporation, disintegration, oxidation, or polymorphic change. The drug substance's changes are what caused the complex to develop.

6.7 Infrared spectroscopy

Infrared spectroscopy is used to assess how NS interacts with medicinal substances in the solid state. The peaks of NSs frequently fluctuate just little when a complex arises. If less than 25% of the visitor molecules were encapsulated in the complex, the peaks of the NS spectrum blatantly hide peaks that could have been attributable to the guest molecules' involved portion. The method does not offer as much detail as other methods and is less frequently employed to find the inclusion complexes.

6.8 Chromatography using thin layers

Thin-layer chromatography was used to determine the RF values in this NS complex drug molecule. The lower RF value was greatly shown, confirming the complex's identification between the NS and drug molecule.

6.9 Tests of resilience

Depending on the requirements of the finished product, NS's toughness (viscoelastic characteristics) can be altered to create softer or tougher beadles. With increasing crosslinking, the release rate progressively slows down.

Thus, the resilience of sponges can be examined and improved as necessary by taking into account the release pattern as a function of crosslinking over time. [35]

6.10 The porosity

To determine the extent to which Nano channels and Nano cavities have formed, a porosity analysis is conducted. A helium pycnometer is used to measure the porosity of nanosponges since helium gas can pass through both intra- and inter-particular material channels. The helium displacement method determines the material's actual volume. Nanosponges are more porous than the parent polymer that was utilized to create the system because of their porous nature. The following equation provides the percent porosity:

% Bulk volume - True volume / Bulk volume × 100 is the porosity.

6.11 Uptake of water and swelling

By immersing the produced nanosponges in an aqueous solution, the water uptake of swellable polymers, such as polyamidation nanosponges, can be measured. Equations can be used to calculate swelling and water uptake:

% Swelling = Marking of cylinder at a specified time point / Initial marking before soaking × 100

% Water uptake = Mass of hydrogel after 72 hrs. / Initial mass of dry polymer × 100

6.12 Studies of Compatibility

The polymers that are utilized to make nanosponges should be compatible with the medication. Fourier Transform Infra-red Spectroscopy (FT-IR) and Thin Layer Chromatography (TLC) can be used to assess a drug's compatibility with adjuvants. Differential Scanning Calorimetry (DSC) and powder X-ray diffraction (XRD) are two methods for studying crystalline properties.

6.13 Studies on penetration

To analyze the dissolution release of nanosponge across a cellophane membrane, diffusion studies of the manufactured nanosponge can be conducted in a Franz diffusion cell. 250 ml of phosphate buffer (pH 7.4) was used as the dissolution media for the diffusion studies, which were conducted at 37 ± 1° using a nanosponge sample (0.5g) in a cellophane membrane. At intervals of 1, 2, 3, 4, 5, 6, 7, and 8 hours, 5 ml of each sample can be taken out, and each sample will be replaced with an equivalent volume of brand-new dissolving medium. Phosphate buffer can then be used as a blank to evaluate the samples for drug content. [36]

6.14 Studies of Thermodynamics

Any changes that drug molecules or particles undergo prior to the heat-induced annihilation of nanosponges can be detected using the thermo-chemical method. Drug particles can change by a variety of processes, including polymeric changes, oxidation, and melting. Widening, shifting, the addition of new peaks, and the removal of certain peaks can all be examined using the thermograms produced by differential scanning calorimetry and differential thermal analysis. Variations in weight loss can provide additional information for the establishment of inclusion complexes. [37]

6.15 In vitro cytotoxicity studies on NS

a) In their 2019 study, Pushmataha et al. examined the cytotoxicity of curcumin NS and resveratrol NS in combination against Michigan Cancer Foundation-7 (MCF-7) cell lines. Cell viability was evaluated using the (3 (4, 5 dimethyl thiazole-2yl)-2, 5-diphenyl tetrazolium bromide) (MTT) test. The 3:1 mixture of curcumin NS and resveratrol CD NS significantly boosted the cytotoxicity impact ($p < 0.05$) in a concentration-dependent manner when compared to the single treatment of curcumin NS and resveratrol CD NS. In blank NS, there was no cytotoxicity.

b) Using the MTT assay, Kumar et al. (2018) examined the cytotoxicity of Bakuchi oil in CD-based NS against HaCaT cell lines. According to these findings, cytotoxicity was produced by treating these cell lines with 320 g/ml of Bakuchi oil-loaded NS, with an IC50 of 191.4 g/ml, and by treating blank, pure Bakuchi oil, with an IC50 of 172.3 g/ml. The cytotoxicity of Bakuchi oil and Bakuchi oil NS is not significantly different, however this implies that NS releases enough medications to harm cells. The MTT experiment revealed that the generated nano formulation was less harmful to human skin cells than bakuchi essential oil.

c) (Ansari and colleagues, 2011) The cytotoxicity of the Paclitaxel NS complex in the MCF-7 cell line was assessed using the vMTT test. The paclitaxel-NS combination suppressed cell proliferation at least 10% more effectively than the free drug counterpart at all tested dosages. Cytotoxicity tests on MCF-7 cell line cultures provide compelling evidence that NS may contribute to either inhibiting the P-glycoprotein and increasing the effectiveness of paclitaxel or somehow disrupting cell permeability. However, as NS were examined for cytotoxicity in MCF-7 cell line culture and found to have minimal impact on cell toxicity, increasing cell permeability seems less possible.

d) To examine the in vitro cellular cytotoxicity of bortezomib CD NS and bortezomib free against MCF-7 cells, Allahyari et al. (2020) employed the MTT assay. The MTT results also suggest that a blank nanocarrier is safe, even at higher concentrations. Bortezomib demonstrated a concentration and time-dependent effect, as can be shown. These results could be explained by CD NS's persistent release feature.

6.16 Studies on toxicology

Determining the safety of medications and their excipients, as well as maximizing the most effective dosage form for each individual, requires toxicological testing. The key discovery is that the fate of parent CDs in the gastrointestinal tract is determined by enzymatic degradation and hydrolysis resistance.

B-CDs are resistant to pancreatic amylases and stomach juice, which enables them to enter the colon and undergo full hydrolysis. The study, which involved ileostomies and clinical research participants, found that although β-CDs are completely broken down in the colonic microbiota, their breakdown in the alkaline pH of the intestine is inadequate. Glucose or maltodextrins can be used to enzymatically screen for β-CDs in the human colon.

In vitro testing has already assessed the safety of NS, and results on numerous cell lines showed no cytotoxicity or hemolytic activity. Furthermore, the ability of NSs to withstand chemical degradation in vitro was evaluated. The findings of the LD50 test indicated that oral administration had the least degree of toxicity, with an initial dosage of 300 mg/kg. At all available dosage levels, neither the control nor treatment groups experienced any fatalities during the trial period. According to recent research findings, the NS formulation was supplied at a low-toxicity dose of 2,000 mg/kg per body weight, which did not indicate any adverse effects that had not yet been observed.

7. Factors that influencing NS -

7.1 Polymer types

The type of polymer utilized can have an impact on the NS structure's formulation and functionality. For a drug molecule to be accommodated and for the drug to complex with the NS,

The pore diameter size of the NS needs to be in the proper specific size.

7.2 Drug types

Drug molecules must have certain characteristics in order to complex with NS, such as having less than five condensed rings and a molecular weight between 100 and 400. The medication should have a melting point of less than 250°C and an aqueous solubility of less than 10 mg/ml.

7.3 The temperature

The medication or NS complexation may also be impacted by temperature variations. The amount of the apparent stability constant complex may decrease as the temperature rises due to the weakening of drug/NS contact interactions like van der Waals and hydrophobic forces.

7.4 The preparation technique

The drug-NS complexation can be broken by loading the active drug molecule into the NS. The medication molecule and the type of polymer determine the procedure's skill. Freeze drying is the most effective technique for drug complexation. [38]

7.5 The extent of substitution

The kind, quantity, and location of the substituent on the parent molecule may have a significant impact on the nanosponge's capacity for complexation. [39]

8. RECENT ADVANCES IN NANOSPONGES-

Over the past few years, the NSs medication delivery system has undergone numerous developments and enhancements. Both the list of medications they have been loaded with and their preparation technique have grown. There has also been a growth in the EE and the kind of polymers utilized as the components.[40]

Discrete solid porous nanoparticles with superior drug absorption and complexation capabilities, nanosponges are made of hyper-cross-linked polymers. Typically, their molecular structure consists of distinct polymer chains that can create particular micro domains that are appropriate for co-encapsulating two medications with dissimilar chemical structures. Tamoxifen and quercetin have been co-encapsulated using polyester nanosponges. By adding the two-molecule solution to a pre-made nanosponge suspension, co-loading was achieved.

The in vitro release tests demonstrated similar linear release kinetics for quercetin and tamoxifen, respectively, and the resulting drug loading was in the same order of magnitude. This behavior demonstrates that the individual drug release kinetics were unaffected by the dual loading. On the 4T1 cell line, a synergistic anti-cancer impact was seen in vitro, with the combined anti-cancer activity of the two drugs being higher than that of the individual drugs.

Interestingly, because of its low cytotoxicity, biocompatibility, and biodegradability, cyclodextrin-based nanosponges have garnered a lot of scientific interest as drug delivery vehicles. Because of its unique structure, this kind of nanosponge—which is made up of a cluster of cross-linked cyclodextrin—has the potential to absorb and hold both tiny and large molecules. In fact, the cross-linked network creates the cyclodextrin cavities and Nano channels that make up the nanosponge nanostructure. This supramolecular Nano system can be regarded as a versatile platform for the transport of either lipophilic or hydrophilic compounds since it contains two domains with varying lipophilicity. To adjust the network interaction sites for drug integration, the cross-linker agent's chemical nature (neutral, positive, or negatively charged) can be chosen. The complexation capability can then be enhanced by the collaboration of different cyclodextrin cavities found in the nanosponge network.

Furthermore, various cyclodextrins may be employed as the building blocks of nanosponges, opening up new avenues for the incorporation of medications into the nanostructure. Because of these unique characteristics, cyclodextrin-based nanosponges can be used to create co-delivery drug delivery systems. This nanocarrier has a number of advantages, and there have been some co-delivery examples documented in the literature. [41]

Of all the innovative medication delivery technologies based on nanotechnology, the nanosponge can be regarded as an efficient carrier. It is a more recent class of Nano particulate system with a nanometric cavity size and a three-dimensional scaffold structure. The capacity to entrap various active moieties, load hydrophobic and hydrophilic pharmaceuticals, improve drug solubility, which in turn promotes drug molecules' bioavailability, and demonstrate programmable release are just a few advantages that Nanosponge's highly porous nature can provide.[42]

According to numerous studies, nanosponges' unique porosity architectures provide great promise for encasing or trapping medications and therapeutic substances, lowering their toxicity and potential adverse effects. Additionally, in contrast to traditional drug delivery systems, they have demonstrated a prolonged and programmed release of medicines. According to one study, chitosan Nanosponges were created to increase drug absorption through the skin while posing no discernible toxicity. In light of this, skin penetration was improved in comparison to the free model medication, resulting in effective trans-epidermal drug administration.[43]

Longer therapeutic action, fewer doses, and better patient compliance are all made possible by nano drug delivery systems, which greatly aid in regulated and sustained drug release. Another significant benefit is that it enables medications to reach previously unreachable locations by overcoming biological barriers like the blood-brain barrier.[44]

By inhibiting gene expression, siRNA containing or producing NSs holds promise as an effective cancer treatment technique. Zhang et al. recently demonstrated that intracellular miR-21 may be absorbed and eliminated by self-assembled DNA NSs. This is accomplished by applying antisense oligonucleotide to the NSs, which improves DOX transport into the cells. This strategy aims to increase the efficacy of anticancer treatment.[45] Oral drug administration using Nanosponges can increase the stability and bioavailability of medications in the gastrointestinal system. [46]

Nanosponges with narrow size distributions, excellent entrapment efficiency, and three-dimensional (3D) porous architectures are frequently designed for drug delivery and cancer treatment. Notably, new nanosponge-based systems for biomedical purposes can be developed using 3D printing technology. Analytical evaluation should be done on the effects of polymers, cross-linkers, drug type, temperature, loading and drug release mechanism, fabrication techniques, and degree of substitution. [47]

9. APPLICATIONS OF NANOSPONGES

9.1 Nanosponges for drug delivery

Nanosponges can effectively transport water-insoluble medications (class-II pharmaceuticals according to the Biopharmaceutical Classification System) due to their nano porous shape. These complexes can be used to turn liquids into solids, mask off offensive odors, and speed up the rate at which medications dissolve, become more soluble, and remain stable. Compared to direct injection, β-Cyclodextrin-based nanosponges are said to transport the medicine to the target site three to five times more efficiently.

List of some BCS Class II dugs which can be developed as nanosponges are given below: - BIOPHARMACEUTICAL CLASSIFICATION SYSTEM CLASS II DRUGS

Table: 3 Class II BCS drugs that have the potential to be transformed into nanosponges

Sr. No	CATEGORY	DRUGS
1	Antianxiety drugs	Lorazepam
2	Antiarrhythmic agents	Amiodarone hydrochloride
3	Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin
4	Anticoagulant	Warfarin
5	Anticonvulsants	Carbamazepine, Clonazepam, Felbamate
6	Antidiabetic	Atorvastatin, Fenofibrate,
7	Antihyperlipidemic drugs	Glibenclamide, Glipizide, Lovastatin, Troglitazone
8	Antiepileptic drugs	Phenytoin
9	Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole
10	Antihistamine	Terfenadine
11	Antihypertensive drugs	Felodipine, Nicardipine, Nifedipine, Nisoldipine
12	Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane,
13	Antioxidants	Resveratrol
14	Antipsychotic drugs	Chlorpromazine Hydrochloride
15	Antiretroviral	Indinavir, Nelfinavir, Ritonavir,
16	Antiulcer drugs	Lansoprazole, Omeprazole
17	Anthelmintic	Albendazole, Mebendazole, Praziquantel
18	Cardiac drugs	Carvedilol, Digoxin, Talinolol
19	Diuretics	Chlorthalidone, Spironolactone
20	Gastroprokinetic agent	Cisapride
21	Immunosuppressant	Cyclosporine, Sirolimus, Tacrolimus
22	NSAIDs	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib

The solid Nanosponges can be prepared as topical, parenteral, oral, or inhaled dose forms. The complexes can be distributed in a matrix of excipients, diluents, lubricants, and anti-caking agents appropriate for the production of capsules or tablets for oral administration (Jenny et al., 2011).The compound can be easily transported in sterile water, saline, or other aqueous solutions for parenteral delivery. They can be successfully added to topical hydrogel for topical delivery. [48]

Because of the holes in their composition, NSs can carry medications that are insoluble in water. These complexes can be used to increase the velocity of mixing, the dissolubility and constancy of the moiety, the masking of unwanted flavors, and the conversion of liquids into solids. It is claimed that β-NSs based on CD can deliver the medication to the target site three to five times more

efficiently than direct injection. The NSs are hard by nature and have the potential to be developed as topical, parenteral, oral, and inhaled medicinal forms. [49]

9.2 Sustained delivery system

It was formed in a top-down manner by crosslinking β-CD with PMDA and then forming the insulin NS. The NS's pH sensitivity was demonstrated by the minimal in-vitro release of insulin at stomach pH ≤ 2% but sustained at intestinal pH (Appleton et al., 2020). Customized active release. For example, NS's consistent release of glipizide (99.71%) after 12 hours.

9.3 Improvement of Solubility

An example of a BCS Class II antifungal medication is itraconazole, which has a poor bioavailability and a dissolving rate. A drug's solubility can be increased by almost 27 times with NS formulation. When polyvidone was added as an adjuvant to the NS formulation, this rose by a factor of 55. et al., Swaminathan, 2010a, 2010b. The drug's solubility was enhanced by lowering its crystallinity, improving its wetting qualities, and successfully masking the hydrophobic groups. In 2007, Swaminathan et al. NS was designed to include hydrophilic medications (doxorubicin) or lipophilic medications (dexamethasone or flurbiprofen) with a high solubility capacity. They greatly increased the medicines' rate of solubility and dissolution.

9.4 Delivery of proteins

Long-term stability is essential for the successful creation of medications, particularly macromolecular ones like proteins (Klibanov and Jennifer, 2004). Proteins can, however, undergo irreversible (or perhaps permanent) denature during lyophilization and adopt conformations that differ greatly from their original states. Therefore, maintaining the original protein structure during preparation and long-term preservation is a major difficulty for developing protein formulations.

The protein known as bovine serum alubin (BSA) is preserved in lyophilized form since it is unstable in solution. Proteins such as BSA were made more stable by a poly (amidoamine) nanosponge based on swellable cyclodextrin. Additionally, protein encapsulation and enzyme immobilization, followed by controlled distribution and stabilization, have been accomplished using nanosponge.

9.5 Immobilization of enzymes

Since it improves stability and regulates properties like enation selectivity and reaction rates, the problem of enzyme immobilization is especially significant for lipases. (Mateo and others, 2007). In order to continuously expand, a suitable family of enzymes needed a new stable foundation. Pseudomonas fluorescent lipase's excellent catalytic activity when adsorbed on a new kind of CD-based nanosponge.

9.6 A vehicle that delivers gas

In order to diagnose and cure medical diseases, gases are essential. Insufficient oxygen supply is associated with a number of diseases, such as inflammation and cancer. Hypoxia is the term used to describe this situation. In practical practice, it might be difficult to administer oxygen in the right form and dose since topical oxygen delivery techniques can store and release oxygen slowly over an extended period of time. Cavalli et al. (2010) developed formulations for NS that can store and release oxygen progressively over time to deliver oxygen topically.

9.7 Agent for light or degradation protection

Gamma oryzanol is a ferulic acid ester combination that has attracted a lot of attention lately because of its potential as a natural antioxidant. In the cosmetics business, it is usually used to stabilize sunscreen and food and pharmaceutical raw materials. Its use is limited due to its high instability and photodegradation. Gamma-oryzanol NS is very resistant to photodegradation. The NS loaded with gamma-oryzanol was used to make an O/W emulsion and a gel.

9.8 SARS-CoV-2 suppression

The NS allows the use of biocompatible nanomaterials to prevent and treat a number of serious illnesses, including the Zika virus, COVID-19, and SARS (Singh and Chauhan, 2021; Yang et al., 2021). The spike glycoprotein, an "S" protein (SARS-CoV-2) virus that promotes cellular contact and entry, is the cause of severe acute respiratory syndrome. It interacts with glycosaminoglycans like heparin and human angiotensin converting enzyme 2 receptors. Polymeric cores wrapped in plasma membranes derived from human

lung epithelial type II cells or macrophages were used to create ACE2-containing NS (Xu et al., 2022). The cell membrane-coated nanoparticles (cellular NS) imitate the host cells to capture and neutralize SARS-CoV-2 via natural cellular receptors. This leads to a thorough antiviral strategy. [50]

9.9 Treatment for Cancer

Nanosponges that can be used to transport anticancer drugs to tumors. According to them, the technique reduces tumor growth three to five times more effectively than administering the medications directly. The drug-loaded small nanosponges reveal a targeting peptide that attaches to radiation-induced tumor cell surface receptors. The sponges adhere to the surface of the tumor cells they come into contact with, which causes them to release their cargo. Less adverse effects and more effective treatment at the same dose are two advantages of targeted medicine delivery. To date, paclitaxel has been used as the sponge load in studies conducted on animals.

9.10 Topical medications

A novel technique for the controlled release of topical medicines with delayed drug release and drug form retention on skin is the nanosponge delivery system. Medications that are easily manufactured as topical Nanosponges include antibiotics, antifungals, and local anesthetics. When active substances permeate the skin, they may cause rashes or more severe side effects. This technique, on the other hand, permits a steady and uniform rate of release, minimizing discomfort while preserving effectiveness.

A designed product can have a wide range of ingredients, including gel, lotion, cream, ointment, liquid, and powder. Econazole nitrate, an antifungal that comes in cream, ointment, lotion, and solution form, is applied topically to alleviate the symptoms of skin infections, dermatophytosis, versicolor, and superficial candidiasis. When econazole nitrate is given topically, adsorption is negligible, and a high concentration of active ingredients is necessary for an effective course of treatment. As a result, emulsion solvent diffusion was used to create econazole nitrate Nanosponges, which were then placed into hydrogel to act as a local depot for prolonged drug release. [51]

9.11 Rare blood cancer marker harvesting

It has been demonstrated that rare blood cancer marker harvesting NSs with different kinds of bait molecules inside may effectively trick particular blood protein families and protect them from blood enzyme breakdown.[52]

9.12 When biological stuff is removed to provide ultrapure water for power regeneration

The existence of natural contaminants in water is a serious worry for sectors like the pharmaceutical industry that need extremely clean water. An important function of the water-insoluble CD polymers is to effectively remove waste from collected water at a certain power plant. The CD polymers have also demonstrated the ability to extract liquified organic carbon from raw water by up to 84%, however the overall removal of organic carbon was comparatively low.

9.13 Use of antivirals

Currently used medications in nano-supply devices include acyclovir (based on eudragit), zidovudine, saquinavir, and interferon-5-007.

9.14 In the immobilization of enzymes

Pseudomonas fluorescence lipase's strong hydrolytic efficiency when adsorbed to a novel kind of CD-dependent NS has been validated by recent research.

9.15 Agent that prevents photodegradation

Gamma-oryzanol is encapsulated with robust protection against photodegradation to create NSs.

9.16 Transitions in the release of drugs

Constant administration is the main drawback of the majority of conventional, commercially available medication delivery methods. On the other hand, a substance placed into an NS is gradually released and stored. Water-soluble medications, including as peptide and protein medications, are delivered continuously by hydrophobic CD NSs.

9.17 As absorbent in treating poison in blood

In order to remove toxic substances that are detrimental to the blood, NSs are utilized as absorbents in the treatment of blood poisoning. When administered by injection, NSs are superior to antidotes because they can absorb poisons. In the bloodstream, NS resembles a red blood cell that deceives toxins into devouring and targeting it. NSs have the ability to absorb several types of toxins.

9.18 Nanosponges' function in treating fungal infections

Fungal infections are among the world's most dreaded illnesses. Due to its many advantages, including the ability to target medications to a particular disease site and lessen side effects, topical therapy is a significant alternative for the management of many cutaneous infections. Econazole nitrate, which comes as cream, ointments, lotions, and solutions, is an efficient antifungal or fungicide that is applied topically to treat a variety of skin conditions, including vaginal thrush, tinea pityriasis Versicolor, ringworm, jock itch, and athlete's foot.

Econazole nitrate works best when administered topically and combined with a high concentration of active ingredients. In order to achieve this, econazole nitrate NSs were created using an emulsion solvent method and subsequently injected into a hydrogel to release the medication continuously for topical usage.

9.19 Nanosponges' application as a diagnostic instrument

A variety of diagnostic materials are manufactured using β-CD. CD NSs are good diagnostic agents because of their great biocompatibility, prolonged blood circulation, homogeneous size distribution for permeability, and ease of access to the target.

Blood Poison Treatment

Nanosponges provide a novel approach to blood detoxification. By infusing the toxins into their bloodstream, Nanosponges can absorb them without the need for an antidote. By mimicking red blood cells, these nanosponges trick toxins into attacking them, absorb them, and change their course away from the intended cell. Chhabria et al. created nanosponges by combining poly (d, l-lactic-co-glycolic acid) cores with ovine erythrocyte vesicles. Ovine erythrocytes were more susceptible to lysis by streptolysin-O. The cholesterol-binding toxin streptolysin-O was absorbed by ovine nanosponges at 37 and 40 °C. [53]

9.20 Blood Poison Treatment

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9.21 Photothermal treatment

It was discovered that conventional phototherapy was useless since it was damaging not only cancer cells but also other cells. Nanocarrier-based photothermal therapy appears promising since the light-activated heating nanocarrier can be targeted at the tumor site. By restricting the thermal ablation to the tumor site, this lessens the destruction of healthy, normal tissues or cells.

Jin et al. used the FDA-approved dye indocyanine green for photothermal therapy to create deoxy ribozyme Nanosponges. Compared to the indocyanine green group, the temperature rose significantly greater in the Nanosponges' group. According to antitumor results, photothermal therapy might halt tumor growth following a nanosponge-indocyanine green injection without producing any adverse side effects. This suggests that photothermal therapy is a promising method for gene silencing. [54]

9.22 Versatile Therapeutic Applications

Because of their adaptable porosity structure and surface chemistry, Nanosponges have demonstrated extraordinary versatility across medicinal domains, including cancer therapy, wound healing, antiviral formulations (particularly COVID-19), and neurological diseases.

9.23 Bioavailability & Solubility Enhancement Major issues in drug formulation are addressed by Nanosponges, which significantly increase the water solubility and bioavailability of hydrophobic medicines, particularly chemotherapeutic agents. [55]

9.24 Functionalized & Stimulus-Responsive Designs

Nanosponges that react to physiological stimuli, such as pH variations, temperature changes, or enzyme activity, are recent inventions that enable highly targeted release of medicines at the site of sickness.

9.25 Eco-Friendly Production Methods

To increase manufacturing efficiency, scalability, and lessen environmental impact, novel preparation techniques are being investigated, such as solvent-free melting, emulsion-solvent diffusion, ultrasound-assisted synthesis, and even 3D printing. [56]

9.26 Targeted Medication Administration in Cancer Treatment

To accomplish tumor-targeted medication delivery, nanosponges have been functionalized with ligands such as folic acid or antibodies. These formulations minimize negative effects while improving drug accumulation at the tumor location.
For instance, doxorubicin-loaded β-cyclodextrin nanosponges demonstrated increased cytotoxicity against MCF-7 breast cancer cells. [57]

9.27 Viral Neutralization of COVID-19

Human lung cell membranes were used to create biomimetic Nanosponges that function as decoy targets and destroy SARS-CoV-2.
Mechanism: By drawing in and binding viral particles, they stop actual host cells from becoming infected. [58]

9.28 Delivery of Antibiotics and Mitigation of Resistance

Antibiotics have been delivered via sustained-release Nanosponges to fight germs that are resistant to many drugs.
As an illustration, ciprofloxacin-loaded cyclodextrin nanosponges demonstrated improved bacterial suppression and sustained release. [59]

9.29 Environmental Cleanup: Purification of Water

Heavy metals and organic contaminants are extracted from wastewater using nanosponges.

• One illustration would be the use of magnetic cyclodextrin nanosponges for the selective adsorption of dyes and phenols.[60]

9.30 Regeneration of Tissue and Wound Healing

Hydrogel-embedded Nanosponges facilitate regulated medication delivery and hasten wound healing.
• One example is the use of silver-loaded Nanosponges to treat diabetic sores and have antibacterial properties. [61]

Topical Nanosponges of Simvastatin for the Healing of Wounds Simvastatin-loaded ethyl cellulose Nanosponges demonstrated improved preferred skin retention and faster healing in comparison to controls when tested on full-thickness rat wounds. [62]

9.31 Delivery of Genes

In order to provide protection and tailored release, Nanosponges are also being investigated for siRNA or DNA delivery.[63]

Table: 4 Summary Table of Applications

Application Area	Key Benefit	Example Material
Cancer Therapy	Targeted delivery, reduced toxicity	β-CD Nanosponges + Doxorubicin
COVID-19 Neutralization	Decoy strategy against SARS-CoV-2	Lung-membrane-coated Nanosponges
Antimicrobial Delivery	Overcome resistance, prolonged release	Ciprofloxacin-loaded Nanosponges
Water Purification	Remove dyes and metals	Magnetic cyclodextrin nanosponges
Wound Healing	Antibacterial and regenerative effects	Silver-loaded Nanosponges in hydrogel
Gene Therapy	Protect and deliver genetic material	DNA/siRNA-loaded cyclodextrin sponges

9.32 Mupirocin-Loaded Nanosponges for Diabetic Foot Ulcers

Mupirocin-loaded nanosponges were developed to treat diabetic foot ulcers using Carbopol 940 gel. Studies conducted in vivo shown better efficacy and quicker healing than commercial formulations. [64]

9.33 Nanosponges of Diflunisal for Rheumatoid Arthritis

Diflunisal-loaded polymeric Nanosponges were refined and incorporated into Carbopol gel. They showed regulated medication release and markedly decreased inflammation over a 12-hour period in a rabbit arthritis model.[65]

9.34 Buccal Quercetin Nanosponges Tablets

To improve bioavailability and offer prolonged release, quercetin-loaded nanosponge buccal tablets were created. These showed encouraging in vitro results and were intended for oral mucosal administration. [66]

9.35 Fluconazole and Tacrolimus Nanosponges in Hydrogel for Skin Disorders

Fluconazole and tacrolimus hydrogel-based nanosponge formulations were created for topical therapy of atopic dermatitis and fungal infections, respectively. Early tests revealed improved skin retention and medication release. [67]

9.36 Antifungal Nanosponges in Hydrogel

Nanosponges encapsulating a selected antifungal drug were developed in a topical gel. This system achieved **enhanced drug delivery** through the skin compared to conventional formulations. [68]

Example- Topical Antifungal Nanosponge Gel with Tazarotene

For the treatment of acne, a cyclodextrin-based nanosponge gel containing tazarotene was refined, showing enhanced skin penetration and therapeutic effectiveness. [69]

9.37 Budesonide Nanosponges Targeted to the Colon

For colon-specific delivery, budesonide-loaded cyclodextrin nanosponges were developed; in simulated gastrointestinal circumstances, they demonstrated great trapping efficiency and sustained release. [70]

Table: 5 A Summary Table of Above Recent Advances[71]

Application Area	Year	Description
Wound healing (simvastatin)	2025	Enhanced topical retention & healing
Diabetic ulcer treatment	2024	Mupirocin-nanosponge gel outperforms market standard
Rheumatoid arthritis	2025	Diflunisal-NS gel reduces inflammation sustained
Buccal delivery of antioxidants	2023	Quercetin nanosponge tablets improve bioavailability
Fungal/dermatological treatments	2024	Fluconazole & tacrolimus hydrogel formulations
Acne therapy	2024	Tazarotenenanosponge gel improves penetration
Topical antifungal therapy	2024	Enhanced delivery of antifungals via NS hydrogel
Colon-specific drug delivery	2024	Budesonide CDNS sustain release in GI conditions

10. PATENTS

Recently, new patents in NSs were filed, approved, and utilized to increase the efficiency of the manufacturing process. The patents, which show potential as anticancer medicines, span growth preservation, enzyme release, toxin absorption agents, and biocatalyst studies. The authorities have also awarded patents that will help shift demand to NSs as a revolutionary pharmaceutical delivery method. [72]

Recent years have seen the filing and approval of new patents in the field of NSs, which have been used to enhance the preparation technique and increase process efficiency. The patent applications include growth preservation, enzyme release, biocatalyst research, and toxin-absorbing agents. Additionally, they have demonstrated encouraging outcomes as antitumoral drugs. The authority also grants new patents, which are detailed below and contribute to the shift in demand for NSs as a novel drug delivery technology. [73]

Table: 6 Recent Patents [74]

Sr.No	PATENT/APP. NO	APPLICANT	TITLE
1	**W02006002814A1**	Francesco Trotta, Wander Tumiatti, OrfeoZerbinati, Carlo Roggero, Roberto Vallero	Ultrasound-assisted synthesis of CD-based NS
2	**W02009149883A1**	Gianfranco Gilardi, Francesco Trotta, Roberto Cavalli, Paolo Ferruti, ElisabettaRanucci, Giovanna Di Nardo, Carlo Mario Roggero, Vander Tumiatti	CD NS 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	NS based on CD as a vehicle for anticancer drugs
4	**W02012147069A1**	University DegliStudi Di Torino, Sea Marconi, Technologies Di	Method of preparing dextrin NS
5	**CA2692493A1**	Sea Marconi, Technologies Di Vander Tumiatti, S.A.S, Francessco Trotta, Vander Tumiatti, Roberta Cavalli, Carlo Mario Roggero, BarbarMognetti, Giovanni, Nicolao Berta	CD-based NS as a vehicle for antitumoral drugs
6	**ITTO20110873A1**	Vecchi Marco DeCarlo Stefano DiShubhenKapilaCarlo Maria RoggeroValentina Scariot MichelaTumiatti	Use of nanosponge functionalized for growth, preservation, protection and disinfection of plant organisms
7	**US9574136B2**	Kun Lian	Nanoparticles, NS, methods of synthesis, and methods of use.
8	**US20170152439A1**	Kun Lian	Nanoparticles, NS, methods of synthesis, and methods of use.
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
11	**WO2009138998A3**	EswaramoorthyMuthusamy, SaikrishanaKatla	A template free and polymer free metal nanosponge and a process thereof
12	**WO2012147069A1**	Francesco Trotta, PravinShende, Miriam Biasizzo	Method for preparing dextrin NS

11. PROMOTED NS FORMULATIONS

Numerous NS-based formulations are available for purchase, and several medications, including brexin, glymesason, mena-gargle, prostavastin, and others, are undergoing clinical trials.

The following table lists a few of the commercially available NS formulations.

Table: 7 List of some marketed formulations of NS.

Drug name	Trade name	Trade name	Route of administration	Dosage form
Iodine	Mena-gargle	Iodine and β CD	Topical route	Solution
Alprostadil	Prostavastin	Prostaglandin E1 and α CD	IV route	Injection
Piroxicam	Brexin	Piroxicam and β-CD	Oral route	Capsule
Dexamethasone	Glymesason	Dexamethasone and β CD	Dermal route	Tablet

12.FUTURE TRENDS-

Medical science has undergone a revolution as a result of the development of nanoscale NS. A movement in medical research has been initiated by the use of technology to reach the nanoscale. Drug toxicity is reduced as a result of improved therapeutic outcomes when a targeted and drug release regulated mechanism is used. It is impossible to overestimate the significance of NS in the advancement of nanotechnology and medicine. In the future, it might be employed as a simple water filter. One of the most important concerns is lowering production costs, which necessitates developing novel polymers, cross linkers, and manufacturing processes. [75]

A revolution in medical science has been brought about by the development of NSs, which have been reduced to nanoscale. The employment of technology to reach the nanoscale has sparked a revolution in the field of medical science. Drug toxicity is decreased when a controlled and targeted drug release mechanism is employed because better therapeutic outcomes can be obtained. NSs play a crucial role in the development of nanotechnology and medicines. NS may eventually be employed as a common water purifier. The primary challenge is reducing production costs, which will call for the development of new production techniques as well as the investigation of novel polymers and crosslinkers.

Increased yields, cost-effective production, and reproducibility are the current trends, and they will all aid in rapid mass production. The presence of residual liquids or reaction residues in the final product, which can very likely result in harmful effects, is a significant fault in the chemical process, even though the current NS preparation methods are straightforward. [76]

It has been established that Nanosponges are the most widely used drug delivery technique in the pharmaceutics industry. Future research should focus on effectively functionalizing Nanosponges to reduce toxicity, increase selectivity, and improve biosafety. Novel Nanosponges with a variety of characteristics and multiple uses can be produced. To create multifunctional systems with cancer theranostic applications, more research is required to concentrate on the precise surface functionalization of Nanosponges utilizing different materials, such as fluorescent chemicals, magnetite nanoparticles, etc. Using 3D printing processes, Nanosponges can be made more swiftly and easily. [77]

Because of their distinct properties in terms of synthesis, particle size, crystallinity, porosity, and the gradation of crosslinking following drug release, NS will be able to dominate the pharmaceutical and medical industries. However, conventional NS synthesis protocols are unsustainable due to the utilization of hazardous organic carriers, homogenous catalysis techniques, and the creation of chiral stereo genic metal complexes. Due to its conventional approach, ultrasound assisted synthesis is thought to be the most effective preparation method; nevertheless, new techniques such as solvent evaporation and bubble electrospinning are also being developed and updated. [78]

Intelligent and Stimuli-Responsive Nanosponges

In order to facilitate on-demand medication release, future Nanosponges are being developed to react to physiological stimuli including pH, temperature, redox environment, or enzymes. As an illustration, consider cyclodextrin-based Nanosponges that respond to redox for targeted cancer treatment. [79]

Functionalization with Targeting Ligands

Active targeting to certain tissues or cellular receptors will be made possible by surface-functionalized Nanosponges containing aptamers, peptides, or antibodies. Folic acid-conjugated Nanosponges for tumor targeting are one example. [80]

In the field of gene therapy

Nanosponges are being studied in the field of gene therapy as non-viral delivery systems for RNA-based and CRISPR/Cas9 treatments, providing biocompatibility and decreased immunogenicity. [81]

Because of their high surface area and functional group tenability, Nanosponges are now being researched for environmental uses, such as pollutant adsorption and oil spill cleanup, in addition to biomedical ones. [82]

It is anticipated that the combination of 3D printing technology and Nanosponges would make it possible to create customized drug delivery systems and scaffolds for tissue engineering that are suited to the requirements of each patient. [83]

These developments point to a bright future for Nanosponges in a variety of interdisciplinary fields, from sustainable environmental solutions to precision medicine.

13. CONCLUSION

NS are an efficient carrier for the delivery system, including sustained delivery, target drug delivery, and increased therapeutic efficacy of a number of pharmaceutical medications. NS can deliver medications to the designated site in a predictable way by a variety of methods, including parenteral, topical, oral, and rectal. Excellent uses of β-CD NS can be found in several specialized drug delivery systems. Additionally, it makes biopharmaceutical class II medications more soluble. The synthesis techniques, many variants, characterization techniques, formulation development, and applications—such as in vitro cytotoxicity studies, patents in this area, and certain commercial formulations—are all included in this review of NS.

By trapping components, this method reduces negative effects, improves stability, adds elegance, and boosts formulation flexibility. At the designated site, they can safely and accurately deliver the drug. Although Nanosponges have shown encouraging results in a number of fields, including medication delivery, cancer, and COVID-19, further study and development are required to fully understand their characteristics, maximize their effectiveness, and guarantee their safety.

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