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EXPLORING BETA-CYCLODEXTRIN NANOSPONGES AS MULTIDIMENSIONAL DRUG DELIVERY SYSTEMS: SYNTHESIS, PROPERTIES, BIOMEDICAL APPLICATIONS, AND RECENT PATENTS

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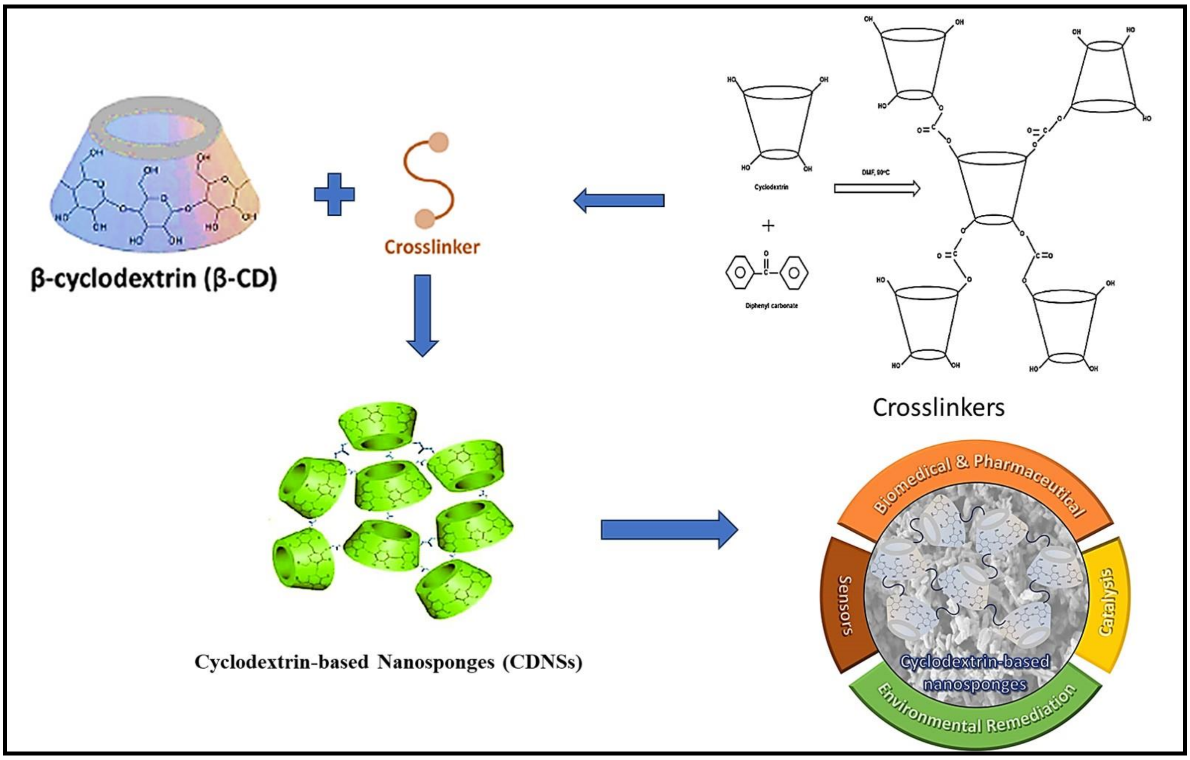
ABSTRACT

Background: The development of drug delivery systems is crucial in drug science to enhance therapeutic effects, reduce toxicity, and improve patient compliance. Beta-cyclodextrin-based nanosponges have emerged as efficient drug delivery systems. These robust nanosponges are prepared by cross-linking beta-cyclodextrins, offering unique features like high drug loading capacity, controlled release, and protection from degradation. Their biocompatibility and ability to cross biological barriers make them highly applicable in biomedical fields. **Methods:** This review provides an in-depth analysis of beta-cyclodextrin nanosponges as versatile drug carriers. It explores coordination polymers, various cross-linking agents, and synthesis techniques such as hot melting, solvent condensation, and ultrasound-assisted synthesis. Key characteristics like size, surface charge, stability, porosity, and encapsulation efficiency are discussed. The review also highlights drug loading, release profiles, and biomedical applications, including solubility enhancement, site-specific delivery, and combination therapy. **Conclusion:** Beta-cyclodextrin nanosponges hold immense potential in redefining drug delivery strategies due to their versatility. They enhance solubility, stability, and biopharmaceutical properties of BCS class II and IV drugs while enabling site-specific delivery, minimizing toxicity and side effects. Recent trends and patents illustrate ongoing advancements and future prospects in pharmaceutical engineering. These nanosponges could revolutionize therapeutic efficacy across biomedical fields, marking a significant milestone in contemporary pharmaceutics.

KEYWORDS: Beta-cyclodextrin nanosponges; Drug delivery systems; Synthesis methods; Controlled release; Biomedical applications.

GRAPHICAL ABSTRACT



1. INTRODUCTION

The use of new drug delivery systems is thus accepted as one of the key priorities in postmodern pharmaceutical science, with objectives to increase the bio-availability of the administered active pharmaceutical ingredient, while minimizing detrimental effects and noncompliance. Nanoparticles are one of the most investigated platforms for advanced drug delivery, and among them nanosponges based on beta-cyclodextrins have proved to be extremely efficient. Beta-cyclodextrins are cyclic glycosides obtained from starch; They have a hydrophilic surface while they have a hydrophobic core; Cyclodextrins are capable of encapsulating a large number of guest molecules.

Nanosponges are prepared by cross-linking of beta-cyclodextrin to obtain a 3D structure that as well, improves their drug delivery profiles. These nanosponges possess quite desirable features such as sustainable loading capacity, container-controlled release of the veritably enclosed drugs, as well as the shielding of the carried drugs against degradation. In addition, those biopolymers are biocompatible and can penetrate through biological barriers, which opens wide opportunities for use in various biomedical fields.[1]

Beta-cyclodextrin nanosponges have been investigated in the last few years as valuable carriers for a wide variety of therapeutic agents: small molecular weight drugs, proteins and peptides, and nucleic acids. Most of these have been appreciated for their ability to improve the solubility, stability and bioavailability of poorly water-soluble drugs. Furthermore, this nanosponge was demonstrated to be prospective in the treatment delivery because it can transport drugs to certain areas/systems in the body and limit exposure by other regions hence; minimizing toxicity.

Therefore, this review has the purpose of offering a state-of-the-art survey about the beta-cyclodextrin nanosponges as a multifunctional drug delivery system. We will look at the methods of preparation, characteristics, drug encapsulation and diffusion profiles and other potential uses of these nanocarriers in biomedicine. Moreover, an insight into recent developments will be provided and the prospects concerning the advancements in the technique of developing beta-cyclodextrin nanosponge for advanced applications in pharmaceutical technology along with the existing limitations will also be explored. Our objective for this review is to provide insights into the immense application of nanosponges based on beta-cyclodextrin for improving drug delivery systems and consequently treatment of various ailments in several biomedical specialities.[2]

2. SYNTHESIS AND PROPERTIES OF CYCLODEXTRIN-BASED NANOSPONGES

Cyclodextrin-based nanosponges (CDNSs) are a novel and promising group of materials that are based on solid, hyperreticulated, and nanoporous three-dimensional polymeric colloidal bio-degradable nanospheres. These structures can be either non-periodic or periodic depending on the synthesis parameters of the compound. CDNSs are synthesized through the process of covalent condensation of cyclodextrins with crosslinking agents that react with the available hydroxyl groups on the hydrophilic rim of the cyclodextrin structure.[3]

Cyclodextrin used in the synthesis of CDNSs can be native or chemically modified NTs including alpha cyclodextrin (αCD), beta cyclode xtrin (βCD) and gamma cyclodextrin (γCD); 2-hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, carboxymethyl-β-cyclodextrin, Of these, β-cyclodextrin is more used due to the size of its cavity, relatively in stability, complexation and higher number of encapsulation sites. Also, β-cyclodextrin is cheap as well as compatible with high throughput production output.

The synthesis of CDNSs involves a variety of crosslinking agents, categorized based on their chemical nature. These include carbonate crosslinkers like diphenyl carbonate, 1,1′-carbonyl diimidazole, dimethyl carbonate, and triphosgene; carbamate crosslinkers such as diisocyanates like 1,6-hexamethylene diisocyanate, methylene diphenyl diisocyanate, toluene 2,4-diisocyanate, and toluene 2,6-diisocyanate; ester crosslinkers like dianhydrides including pyromellitic dianhydride, ethylenediaminetetraacetic acid dianhydride, and Epiclon-B-4400, as well as carboxylic acids such as citric acid and 2,6-naphthalene dicarboxylic acid; ether crosslinkers including epoxides like epichlorohydrin, 1,4-butanediol diglycidylether, and E-51 epoxy resin; polyamidoamine crosslinkers such as 2,2′-bis(acrylamido)acetic acid and its derivatives formed by reactions with amines; polyamine crosslinkers including 1,6-hexanediamine, 1,8-octanediamine, and 1,12-dodecanediamine; and other linkers like dichloromethane and N,N′-methylene bisacrylamide.[4]

Some of the factors that affect the properties of the final CDNSs include the choice of the crosslinker as well as the synthesis conditions required in the process; these properties include porosity, stability and the efficiency of drug encapsulation. Due to the following favourable characteristics as mentioned in Table 1: Their wide applicability across many different areas of Biomedical, especially in drug delivery system where they can increase the dissolution rate, stability and permeability of the therapeutic agents.[5]

2.1 Synthetic Methods

Varieties of crosslinkers and the level of crosslinking allow the formation of polymeric structures with different polarity and size leading to the formation of macromolecules cyclodextrin-based nanosponge (CDNS). The lipophilic cavities of the cyclodextrin units and the remaining hydrophilic network in CDNSs depending on the type of crosslinker prove that such materials are ideal for improving the stability of the often-sensitive and volatile compound and solubility of lipophilic and polar analytes. Thus, the methods of synthesizing CDNSs contribute to the formation of polymers with different properties of CDNSs which can be used in various applications.[6-8]

Hot Melting Procedure

The hot melting procedure is an easy, repeatable, and eco-friendly method for synthesizing cyclodextrin-based nanosponges (CDNSs) a result of which was established in this study. This approach entails the reaction between cyclodextrin and a carbonyl linker of which diphenyl carbonate is frequently used. The homogenization process should take place at a temperature of 90 – 130 degrees Celsius for at least 5 hours for the cross-linking to be completed. To further cross-link the system may be incubated for a longer time Crosslinking reactions may be conducted at room temperature since increased temperature will add to the density of the crosslinked membrane. The outcome of this reaction is a fine and uniform powder is produced.

The obtained powdered substance is washed severally with water and/or acetone. It also in most cases undergoes soxhlet extraction using ethanol or acetone and an extra washing with a sodium hydroxide (NaOH) solution. Washing with water washes away residual CD, and washing with ethanol or acetone also gets rid of other unreacted crosslinker and impurities such as phenol or imidazole if DPC or if CDI crosslinker is used respectively.

Usually, the phenoxide ion originating from phenol is soluble in water, so washing with the base NaOH guarantees the absence of this impurity. This process of purification can be further confirmed by using a ferric salt, UV-vis spectroscopy or HPLC.

Solvent Condensation Method

Solvent condensation is a general procedure that allows preparing CDNSs starting from cyclodextrin. In this case, cyclodextrin and a crosslinker are dissolved in a proper solvent reducing the polarization on the molecule. The earlier solvents chosen are the polar aprotic solvents such as dimethyl formamide, dimethyl sulfoxide, butanone and pyridine. To increase the eco-compatibility of the process green solvents including water, aqueous solutions and Deep Eutectic Solvents (DES) are employed. When synthesising the reagents, a catalyst may be included to advance the velocity of the reaction. Normally, an excess amount of crosslinking agent is employed having the cyclodextrin crosslinking ratio between 1:2 to 1:16. Finally, the nanosponges are precipitated out of the solution by such solvents as water, acetone or ethyl acetate among others after the reaction is complete.

If the dianhydride linkers are used then a basic catalyst such as triethylamine (Et3N) is required and the reaction proceeds at a fast rate at room temperature. For other linkers; hexamethylene diisocyanate (HDI), methylene diphenyl diisocyanate (MDI), dimethyl carbonate (DMC), and diphenyl carbonate (DPC), the use of Et3N accelerates the reaction and, in some cases, heating can be applied. As another catalyst, 1,4-diazabicyclo(2,2,2)octane (DABCO) is also effective. It reacts with BDE in aqueous NaOH at high temperatures while with HDI and β- cyclodextrin at room temperature. Some basic requirements like the use of NaOH reagent are also important in the formation of the cross link of the cyclodextrin with epichlorohydrin. Other bases which can be used as catalysts include ammonia, pyridine, and collidine. When citric acid is used as the linker, the reaction is usually carried out under a vacuum in water at the boiling point of water or in DESs especially choline chloride–citric acid DES both as a solvent and a reactant. Occasionally Sodium Hypophosphite Monohydrate is incorporated in it also as a catalyst in the process. The other method entails the formation of β-cyclodextrin with naphthalene dicarboxylic acid (NDCA) in an aqueous solution in the presence of a sulfuric acid catalyst. It enables the formation of CDNS's with distinguishable characteristics to make them applicable in many ways. Nanosponge materials derived from these polymers can increase the solubility, stability, and bioavailability of the incorporated compounds; they are therefore biomedically useful.

Emulsion Solvent Diffusion Method

The created nanosponges are based on cyclodextrin and obtained through the emulsion solvent diffusion method that utilizes emulsification. This method involves two immiscible phases: an internal phase and an external phase of the publications. The internal phase is then prepared by the slow addition of the crosslinker dropwise to a solution of cyclodextrin and an inclusion analyte in a polar aprotic solvent for instance dimethylformamide (DMF) with constant magnetic stirring. The external phase is an aqueous solution to which the internal phase is progressively added drop by drop under vigorous stirring at room temperature. Such suspension is then lyophilized and the CDNSs are dried thus arriving at the final product. This method is efficient for processing nanosponge with regular size and good stability as well as high encapsulation efficiency.

Interfacial Condensation Method

The interfacial condensation method is a procedure applied for the preparation of cyclodextrin-based nanosponges (CDNSs) by dissolving cyclodextrin (CD) in an alkaline aqueous phase with a pH of more than 10. At once, the crosslinking is dissolved in an organic solvent like methylene chloride, butanone or chloroform. This method concerns the transfer point between the aqueous phase and the organic phase where cross-linking occurs leading to the formation of CDs or CDNSs. This process is very effective for the incorporation of cyclodextrin and crosslinking agent from which crosslinked nanoporous structure is formed.

Ultrasound-Assisted Synthesis

In ultrasound-assisted synthesis, one exploits ultrasonic waves to improve the cross-linking of cyclodextrins (CDs) together with relevant cross-linking agents without the use of solvents, so is green. The ultrasonic energy also creates cavitation bubbles within the reaction mixture and when these collapses, violent conditions of high pressure and temperature are created. This fosters the development of monodisperse spherical nanoparticles. Here, both CDs and crosslinkers are weighed in certain molar equivalents and then suctioned together. The ultrasonic waves cause the reaction since they bring in the required energy to generate the crosslinked nanosponge, breaking and rebonding chemical bonds. The technique is suitable for both the melting and solvent condensation techniques, which has helped in the synthesis of CDNSs with desired particle size and morphology.

Mechanochemical Synthesis

Mechanochemical synthesis is a process in which a reaction between cyclodextrins (CDs) and crosslinkers occurs through direct input of mechanical energy that breaks and re-forms chemical bonds. This method is usually carried out in ball mills where the two components (or all the components) of the reaction are communities together in the solid phase and therefore no solvent is needed at all or used sparingly. This is more so than the previous methods that called for the extensive use of solvents derived from fossil fuels.

Mechanochemical synthesis is initiated by the solid-state grinding efficiency that leads to appropriate mass transfer as well as energy dissipation. While acetone and ethanol have been employed as the solvents for the purification of cyclodextrin-based nanosponges (CDNSs), they are volatile solvents that require less effort in recycling than the high boiling point polar aprotic solvents such as DMSO or DMF that have more complicate recycling procedures.

Meantime, one of the major drawbacks of utilizing ball mills is that the controlled grinding process is not easy to scale up and the thermal control is not accurate, although the temperature does not become very high during the synthesis of CDNS, which is about 72°C. Moreover, in ball mills, closed containers also slow down polycondensation reaction time because of the absence of the option of removing water during batches.

These limitations can however be worked out using twin-screw extruder reactors in which temperatures can be well regulated, and the process can be carried out in a continuous manner as opposed to batch manner. For instance, a ball mill can synthesize CDNSs using 1,1′-carbonyl diimidazole (CDI) in a crosslinking process within 3 hours. On the other hand, a twin-screw extruder can effectively be used to synthesise CDNSs through the reaction of β-cyclodextrin (βCD) and citric acid as a cross-linking agent and sodium hypophosphite monohydrate as a catalyst. In this case, the equipment is heated to a temperature of 120-180°C and the solid blend then has to be charged slowly into the extruder and the entire process ranges from 5 to 25 mins. This is much faster than the traditional method that takes at least 4h under vacuum with water as a solvent. In general, the mechanochemical synthesis of CDNSs is a rather straightforward, cost-efficient, and relatively fast approach as compared to the traditional solvothermal synthesis.

Chain-Growth Polycondensation Method

It’s important to differentiate between the conventional and chain-growth methods of polycondensation where CDNSs can be synthesized more precisely using the chain-growth polycondensation method. In step-growth polymerization, monomers respond with each other in a step-wise character and each monomer has nucleophilic functional groups of the same measure of reactivity. However, in chain-growth polycondensation, the reactive group that is added at the end of the growing polymer chain developed by the reaction with a monomer is more stable and reactive as compared to the monomer.

In this method, an initiator is for the formation of highly reactive points at the terminal of the polymer chain. These reactive ends enable the subsequent monomers to be attached and only added at the chain’s ends to help it grow quickly. It means that this approach provides CDNSs with lower polydispersity as the monomers do not influence each other, but they bond only with reactive ends. An example of this method is the preparation of CDNSs with β-cyclodextrin (βCD) and acrylic acid monomers. In this process, ammonium persulfate is employed as an initiator and N,N′-methylene bisacrylamide also known as MBA is employed as crosslinking agent. The reaction starts with the decomposition of ammonium persulfate which yields sulfate radicals that can attack the acrylic acid monomers to produce active radical sites. These active sites interact with further acrylic acid monomers and thus form a chain with active terminal sites. The growing polymer chains that are radicals can move the reactivity site onto another monomer or react with another radical to stop. The existence of MBA facilitates the formation of crosslinks between the polymer chains which are growing and give a three-dimensional network structure with the βCD units incorporated into it. This has created a highly uniform nanosponge based on cyclodextrin with properly determined size, more stability and improved functionality. Thus, the application of chain-growth polycondensation guarantees high efficiency of polymerization, low MWD and enhanced tendencies of the material.

2.2.2 Properties of Cyclodextrin-Based Nanosponges

CDNSs have unique features that qualify them for several applications particularly in the pharmaceuticals industry, water treatment, and in catalysis. Some of the properties that define these properties include size and polydispersity, charge and stability, swell ability, porosity and surface area, thermal stability chemical resistance and ability to encapsulate.[9,10]

Size and Polydispersity

CDNSs are generally spherical and have a diameter typically less than 1 μm, and more preferably less than 0. 2 μm, and the size distribution is rather narrow. It is a common characteristic that the PDI values of these nanosponges are less than 0. 7, which is important especially when it is planned to be used in different applications since its size distribution is equal (Table 2).

Surface Charge and Stability

One scientific research study shows that the ζ-potential of CDNSs is approximately ±30 mV and hence gives a high surface charge (Table 3). This characteristic makes sure that the nanosponges are soluble in water and float in the water without the likelihood of clotting together because of the repulsive force. It is essential for applications when a uniform dispersion of materials is needed. Such as in a drug delivery system.

Swelling Properties

CDNSs can increase in size absorbing water and developing a gelatinous structure. Here the swelling could be defined by the type of the crosslinking agent and its concentration used. CDNSs synthesized with polyamidoamine or carboxylic acid-based linkers such as PMA and CA swelling in aqueous media is rather high. This swelling behaviour is related to the cross-linking density, if the cross-linker concentration is ratio causes swelling loss because the degree of crosslinking and structural elasticity of all the materials is decreased.

Porosity and Surface Area

Namely, crosslinking density can guarantee high porosity and at the same time define the surface area of CDNSs regarding to the types and degrees of crosslinking. The original statement that could be made is that with a general increase in the concentration of the cross-linker, the cross-link density would also be high which means less pore size and the SBET value would also increase in congruence. For example, the βCD nanosponges prepared at a crosslinker molar ratio of 1:2 can be increased from 61 % to 94% when the total crosslinker quantity is increased which enhances the porosity in turn (Table 4).

Thermal Stability and Chemical Resistance

CDNSs have good thermal stability up to 300°C and insolubility in different organic solvents. One can prove their formation and read their chemical structure using infrared spectroscopy and looking at characteristic bands that are not present in the original cyclodextrins. For instance, the carbonyl stretching of the carbonate linkage in carbonate-based CDNSs appears in the range of 1720-1780 cm-1 while carbamate-based CDNSs exhibit bands at 1700, 1630 and 1550 cm-1 corresponding to the amide-like carbonyl stretching and the N-H bending.

Encapsulation Efficiency

Due to the lattice-like structure of CDNSs, the CDNSs can encapsulate almost all kinds of molecules, with improved solubility, cytotoxicity, and bioavailability. They have wide applications in drug delivery, shielding and transporting of reactive species, catalysis, decontamination, and sensing. The enhancement in the stability and solubility of guest molecules in the presence of CDNSs is highly beneficial for pharmaceutical and biomedical applications because of the formation of inclusion complexes.[11]

Comparative Properties

CDNSs although possess a lesser number of m2/g than the activated carbon, SBET about 600–700 m2/g but have similar interaction capacities with lipophilic molecules. This is the reason why guest molecules are adsorbed both on the surface of the nanosponges as well as embedded into the interior of nanosponges during the inclusion complexation or in the case of internal diffusion. Despite occupying a relatively small surface area, CDNSs are capable of accommodating hydrophilic or high molar mass analytes and improving the stability and performance of the materials applied in different fields. Furthermore, the forming of inclusion compounds is favoured in water and these processes are reversible in organic solvents, thus it is convenient to recover and reuse of CDNSs without damaging regeneration methods.

3. MATERIALS USED FOR THE SYNTHESIS OF CYCLODEXTRIN NANOSPONGES

3.1 Types of Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides derived from starch which based on the ability to form with different guests, inclusion complexes are the basic components of the synthesis of nanosponges. Among the most popular cyclodextrins, one can turn to β-Cyclodextrin (βCD), Methyl β-Cyclodextrin (MβCD), Alkyloxycarbonyl Cyclodextrins and 2-Hydroxypropyl β-Cyclodextrin (HPβCD). Of all the known biocides, call volume disposition βCD is extensively utilized owing to its suitable cavity size and easy access. MβCD is changed to increase the solubility and efficiency of the complexation and Alkyloxycarbonyl Cyclodextrins increase the stability and solubility. HPβCD is applied for the improvement of the water solubility and biocompatibility (Table 5).[12]

Copolymers

Copolymers are incorporated to improve the mechanical strength as well as the performance of nanosponges. The commonly used copolymers for coatings are Polyvinyl Alcohol (PVA), Hydroxypropyl Methylcellulose (HPMC), and Ethyl Cellulose copolymers. PVA improves the flexibility of nanosponges and improves its mechanical characteristics. HPMC enhances the stability and solubility of the nanosponges and Ethyl Cellulose controls the drug release profile of encapsulated drugs.[13]

Cross-Linkers

It is necessary to describe the role of cross-linkers in the formation of the three-dimensional network structure of nanosponges. They decide the extent of crosslinking which in turn defines the perviousness, strength, and carrying capacity of the drug. The major cross-linking agents are Diphenyl carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic Anhydride, Carbonyl Diimidazoles, Epichlorohydrin and Carboxylic Acid Anhydrides. Diphenyl Carbonate is well known for its applications due to the way it crosslinks while Diisocyanates such as HDI and MDI are known for covalent bond strengths. Pyromellitic Anhydride has high crosslink density and the forming of rigid structures while Carbonyl Diimidazoles are applied for crosslinking properties. Epichlorohydrin is flexible and reactive; Carboxylic Acid Anhydrides like citric acid anhydride are used for biodegradable and biocompatible Nanosponges.[14]

Solvents

The solvents to dissolve the reactants are employed to enhance the crosslinking reaction. The solvent also plays a very important role in the properties of the nanosponges that will be synthesized. Solvents that are widely employed are Methanol, Ethanol, Dimethylformamide and Dimethyl Sulphoxide. Methanol is used because it dissolves well and is very volatile while Ethanol is safe to use and does not harm the environment. DMF is capable of dissolving the large number of reagents while DMSO is well acclaimed for dissolving polar as well as nonpolar reagents.

4. APPLICATIONS OF CYCLODEXTRIN NANOSPONGES IN DRUG DELIVERY

Nanosponges based on cyclodextrin are the modern breakthrough in the field of drug delivery systems and solve numerous problems related to pharmaceutical preparations. These efficient and smart nano-engineered systems solve several substantial problems including improvement in solubility and stability of drug and selective control over time and spatial release of the drug. Cyclodextrin nanosponges can be applied in various therapeutic zones; anticancer, antifungal, antiviral, antibiotic, anti-inflammatory, antioxidant, and antihypertensive treatments.

4.1. Solubility Enhancement of Pharmaceuticals

One of the major issues of drug formulation is the poor solubility which is inherent to a large number of APIs and, in turn, influences the bioavailability and effectiveness of a drug significantly. Providing enough concentration of the compound in the systemic circulation is vital due to its necessity for pharmacological activity. New chemical substances included in the pharmaceutical market have 40% of the products with low soluble in water, and, therefore, their absorption is low and bioavailability – variable.

To address this problem, several technologies have been brought into realization and nonetheless, many APIs fail to show the appropriate solubility profile. Antonucci et al Cyclodextrin nanosponges have in the recent past been viewed as a viable solution to this problem. The application of cyclodextrin nanosponges increases the solubility of drugs which have very poor solubility in water. This enabler enables superior uptake and improved, less fluctuating bioavailability, which is a drawback of most conventional solubility enhancement methods. Increasing numbers of publications have confirmed that cyclodextrin nanosponges can enhance the solubility of different APIs and, therefore, the bioavailability of the corresponding drugs, which differentiated them as a promising tool in developing new and improved formulations of medications.[15]

4.2 Oral Drug Delivery

The main factors that determine oral bioavailability are the solubility of the drugs in the fluids of the GI tract and GI absorption. While the former is characterised by challenges in dissolution, the latter experiences a hitch in permeability. The Biopharmaceutical Classification System (BCS) classifies drugs into four categories: These are; Class I (high solubility and high permeability), Class II (low solubility and high permeability), Class III (high solubility but low permeability), and Class IV (low solubility and low permeability). The efficiency of Class II, III and IV drugs is very important and for this purpose, the nanosponge of beta-cyclodextrin has proved very useful.

β-cyclodextrin nanosponges improve the solubility and stability of P450 drugs which ensures a good absorption within the GI Tract. For instance, the recovery rate of Paclitaxel, Tamoxifen and Erlotinib which are anti-cancerous agents escalates remarkably once they are formulated in beta-cyclodextrin nanosponges. As for Paracetamol and Nimesulide, the solubility and stability of Acetylsalicylic acid (Aspirin) and Cephadroxil are also improved by microencapsulation. Another drug that can benefit from this delivery system is Telmisartan an antihypertensive drug, which experiences enhanced, bioavailability. These examples prove that beta-cyclodextrin nanosponges hold significant promise in meeting bioavailability issues in oral drug delivery.[16,17]

4.3 Ocular Drug Delivery

Targeted drug delivery at the tumour site increases the localization of anticancer agents, decreases the impact on healthy tissues, and increases patient concordance. For the ocular drug delivery, the cornea consists of closely packed cells and hence the cellular barriers and tight junctions significantly restrict the absorption of the drug. Though this is true with the amphiphilic delivery systems the system has limitations arising from the natural blinking and tear drainage mechanism of the eye. Beta-cyclodextrin nanosponges can be considered as a solution to increase drug solubility, stability as well as retention time at the eye site.

These nanosponges encapsulate drugs prevent them from degradation and release the drug slowly. For example, they improve the solubility and the residence time on the ocular surface of cyclosporine for dry eye disease therapy. Likewise, they enhance the usefulness of glaucoma medications including better performance and controlled intraocular pressure of the eye. It could therefore be concluded that beta-cyclodextrin Nanosponges increase the effectiveness and patients' compliance with ocular treatments.[18]

4.4 Pulmonary / Intranasal Delivery

Delivery through this route means that it directly administers the drug to the lungs or the nasal passage thus improving the potency and minimizing the side effects. Pulmonary delivery is used in asthma, COPD, and cystic fibrosis while nasal delivery is for allergic rhinitis. These methods are satisfactory substandardities to injections, mostly for biological products. Since solubility and stability are well-tackled by cyclodextrin-based nanosponges, these are ideal to be employed in this regard.

That is why intranasal delivery can also reach the brain, unlike other conventional methods that are considered to be more invasive. Administration of drugs to the olfactory region in the nose especially with preparations that adhere to the mucosa can improve the uptake of drugs to the brain. Cyclodextrin nanosponges assist by increasing the permeability of drugs across the nasal mucosa and it also acts as a carrier for the insoluble part of the drug dosage. For instance, research has it that the nanosponges of alpha-cyclodextrin enhance the brain penetration of neuropeptides. Moreover, some forms of cyclodextrins get through the blood-brain barrier by breaking lipid structures and blocking drug efflux however, there is relatively limited evidence about their efficiency and safety.[19]

4.5 Drug Stability

The stability of the drug formulations at each stage of their distribution and storage is a critical factor that determines the quality of the medication at the time of usage. It is usually the case with some drugs such as anticancer agents or drugs that contain ester groups because of hydrolysis. This instability can reduce their therapeutic value to a significant level. For instance, the anticancer drug Camptothecin has very poor water stability which thereby reduces its therapeutic efficacy.

Captive unstable drugs such as Camptothecin have been studied by Researchers to be put in beta-cyclodextrin nanosponges with a view of improving the duration the drugs will be effective. Furthermore, it also resists the effect of hydrolysis and the solubility characteristic of the drug is enhanced with this method of encapsulation. Research has indicated that the drugs formulated with cyclodextrin nanosponges have higher stability and higher activities compared with the free individual drug. Stressing on the possible application of cyclodextrin nanosponges in enhancing the stability and efficacy of the various drug candidates that are known to be unstable, would improve therapeutic efficacy.[20]

4.6 Nanosensors

Cyclodextrin nanosponges have demonstrated immense application prospects in the biosensing area. In recent developments, scientists have invented Nanosponges for detecting glucose using Molecular Imprinted Polymers (MIPs). Such MIPs are prepared by physically adsorbing glucose molecules onto cyclodextrin nanosponges, and then selectively desorbing the glucose leavings behind imprint sites. This process increases the ability of the nanosponges in the detection of glucose and at the same time, their specificity.

As to the nanosponges, the MIP displayed a much higher binding to glucose as compared to the non-imprinted ones. This enhances the affinity rate since the imprinted cavities that are created on the surface greatly match the size of glucose molecules. The particular cavities of the nanosponge particularly when coupled with their large surface area means that glucose binding is fast and effective. In addition, the structural analysis by SEM has also supported the porous structure of MIP nanosponges containing these nanocavities rather than the non-imprinted nanosponge blank surfaces. This innovative approach establishes how MIP nanosponge prepared from cyclodextrin had improved the detection of glucose and maybe other biomolecules over MIP prepared from other cross-linkers.[21]

4.7 Nanobiotechnology Applications

Cyclodextrin nanosponges, when surface functionalized, can be used for autoimmune diseases with the possibility to eliminate autoantibodies that damage cells. Nanotechnology has developed biomimetic nanosponges that wear the outer layer of cell membranes of the targeted pathogen and hence absorb pathogenic antibodies leaving healthy cells unharmed. The nanosponge core stands useful to maintain the youthful state of the membranes.

For example, the current treatment modality in Autoimmune Hemolytic Anemia (AIHA) where anti-RBC IgG antibodies are leading to RBC destruction, has developed RBC-based nanosponges. These nanosponges formed by RBC membranes enclosing the pores can bind with anti-RBC antibodies and thus avoid the lysis of normal RBCs. This approach guarantees that the Antibodies get adsorbed onto the nanosponge with equal affinity as they would any native cells which is absent in PEGylated nanoparticles.

The self-same has been applied using platelet-based nanosponges in Immune Thrombocytopenic Purpura (ITP) treatment. Such nanosponges covered with platelet membranes fix the anti-platelet antibodies and leave the normal platelets as well as clotting functions intact. Moreover, nanoparticles containing ‘naked’ and ‘shielded’ PAMAM can stop pore-forming toxins namely melittin from bee venom, streptolysin O from Streptococcus, and α-toxin from methicillin-resistant Staphylococcus aureus (MRSA) apparenting wide-scope utility of these biomimetic nanosponges in nanobiotechnology.[22]

4.8 Nanosponges for Combination Drug Therapy

Combination drug therapy is used to improve compliance and therapeutic values through the independent and interactive effects of the drugs, which additionally strains the physical frequency of dosage administration. Co-encapsulation of multiple drugs is possible with cyclodextrin nanosponges because the structure of the polymer and cross-linker can be easily modified.

According to the desire, nanosponges can be functionalized to encapsulate two or more drugs and the release profiles of individual drugs are not affected. For instance, it is established that the combination of anticancer agents within nanosponges can enhance the rate of treatment. This is because the co-encapsulation guarantees that each of the drugs is released in a consistent manner hence remaining distinctive while at the same time supporting the augmentation of the effects of the other. This is especially used in cancer treatment where a combination of drugs can work on different pathways and mechanisms in killing the cancer cells.

Besides, concerning the characteristics of the drugs that have to be delivered, nanosponges can enhance the stability and solubility of the loaded drugs. This is particularly relevant for products like compounds that are likely to degrade when exposed to light, or such. Due to these characteristics, their shelf life and efficiency can be considerably enhanced by incorporating them into the nanosponge matrix. For instance, with the help of antioxidants or anti-inflammatory drugs loaded on nanosponge, it is possible to increase the photostability of the final preparations, as well as their bioactivity, which makes treatment with their help more effective.

The application of nanosponges for combination therapy also has its advantages in the case of topical drug delivery systems. When the drug-loaded nanosponges are dispersed within a hydrogel, a stable and effective topical system is instantly formed. This profession aims at delivery of the drugs to the target area in high concentration reducing the side effects in the whole body. The combined effect of the co-emulsified drugs might be more beneficial, especially in skin disorders, inflammation, and localized cancer.

In conclusion, cyclodextrin nanosponges incorporated in combination drug therapy mark innovation in drug delivery systems due to enhanced stabilities of the drug and their controlled release with improved therapeutically active factors in multiple ailments.[23]

4.9 Bioresponsive Nanosponges

Bioresponsive nanosponges are another advancement in modern medicine applications targeting the delivery of drugs, which possess the ability to respond to biological signals to release the drug in the right place at the right time. An essential cellular antioxidant, present in very high concentrations, especially in neoplastic cells, is glutathione (GSH) acting as a trigger to these systems. The overexpression of GSH in cancer cells can thus be used to improve the selectivity of the treatment.

These researchers have prepared GSH-responsive nanosponges by conjugating 2-hydroxyethyldisulfide with β-cyclodextrin followed by cross-linking with pyromellitic dianhydride. These nanosponges can encapsulate drugs like Doxorubicin so that the drug is only released in areas of high-GSH like in cancer cells. This specific release mechanism also enhances the therapeutic ratio for the drug against cancer cells and decreases the side effects on the normal tissue/ body. Other developments within this area comprise GSH-responsive nanosponge utilization in the delivery of Erlotinib; a lung cancer drug. Due to the cross-linking use of Pyromellitic anhydride, these nanosponges provide extended drug release following GSH levels. Experimental models have shown impressive results regarding the inhibition of tumor growth and superiority in drug delivery in the target tissues hence improving the treatment efficacy while minimizing harm to non-target tissues. Branching out from the previous examples, another application relates to the use of Strigolactone and its derivatives for the targeted delivery of anti-cancer agents for prostate cancer. These nanosponges which are more reactive to GSH have demonstrated a stronger therapeutic effect on the high-GSH prostate cancer cell types and, thus have the potential to be selective with tumours.

The last years have also seen the development of multi-responsive elements incorporated into nanosponges, where in addition to GSH sensitivity, pH variations or enzymatic activation may also be implemented. This multi-stimuli responsive system again increases the accuracy of drug release based on the specific environment of tumours. The bioresponsive nanosponges indeed can be viewed as a step forward in the development of nanomedicine providing targeted, effective, and safe drug delivery systems. Due to their capacity to respond to biological impulses, the medication is delivered where it is most effective without causing unwanted effects.[24]

Table 1: Crosslinkers Used in the Synthesis of Cyclodextrin-Based Nanosponges.

Crosslinker Category	Examples	Description
Carbonate	Diphenyl carbonate	Forms stable, nanoporous structures.
Carbonate	1,1′-Carbonyl diimidazole (CDI)	Provides strong covalent bonding.
Carbonate	Dimethyl carbonate (DMC)	Eco-friendly and efficient crosslinker.
Carbonate	Triphosgene	Generates high crosslinking density.
Carbamate	1,6-Hexamethylene diisocyanate	Forms flexible and durable linkages.
Carbamate	Methylene diphenyl diisocyanate	Enhances structural integrity.
Carbamate	Toluene 2,4-diisocyanate (TDI)	Provides high reactivity for crosslinking.
Carbamate	Toluene 2,6-diisocyanate	Facilitates uniform polymer networks.
Ester	Pyromellitic dianhydride (PMA)	Produces stable ester bonds with CDs.
Ester	Ethylenediaminetetraacetic acid	Forms robust crosslinked structures.
Ester	Epiclon-B-4400	Enhances chemical resistance of nanosponges.
Ester	Citric acid	Eco-friendly and biodegradable crosslinker.
Ester	2,6-Naphthalene dicarboxylic acid	Provides rigid and stable crosslinked frameworks.
Ether	Epichlorohydrin	Forms durable ether linkages with CDs.
Ether	1,4-Butanediol diglycidylether	Enhances flexibility and stability.
Ether	E-51 epoxy resin	Produces highly crosslinked, resistant structures.
Polyamidoamine	2,2′-Bis(acrylamido)acetic acid	Forms dense polymer networks with amines.
Polyamidoamine	Polyamidoamine derivatives	Provides high crosslinking efficiency.
Polyamine	1,6-Hexanediamine	Forms flexible and strong polyamine linkages.
Polyamine	1,8-Octanediamine	Enhances crosslinking density and durability.
Polyamine	1,12-Dodecanediamine	Produces robust and stable nanosponges.
Other Linkers	Dichloromethane	Versatile crosslinker for various applications.
Other Linkers	N,N′-Methylene bisacrylamide (MBA)	Forms highly stable, crosslinked networks.

Table 2: Size and Polydispersity.

Nanosponge	Method	Structure	Mean Size (nm)	PDI
βCD: DPC	Melt	Amorphous	<664	<0.45
βCD:DPC	Solvent	Amorphous	135–500	<0.43
βCD:DPC	Microwave	Crystalline	153 ± 8	0.11
βCD:CDI	Solvent	Amorphous	473 ± 1	0.24

CD:HDI	Solvent	Amorphous	420,000	-
CD:TDI	Solvent	Amorphous	367 ± 2	0.25
αCD:MDI	Solvent	Amorphous	100–200	-
βCD:PMA	Solvent	Amorphous	605 ± 18	0.31
βCD:Epiclon	Solvent	Amorphous	300 ± 10	0.27
βCD:CA	NADES	Amorphous	<20,000	-
βCD:EPI	Solvent	Amorphous	167 ± 8	0.58
CD:am6	Solvent	Amorphous	446 ± 30	0.38
CD:am12	Solvent	Amorphous	438 ± 38	0.43
βCD:acrylic acid	Chain-growth	Amorphous	275 ± 29	0.28

Table 3: Surface Charge and Stability.

Nanosponge	ζ-Potential (mV)
βCD:DPC	−(3–22)
βCD:DPC	±(12–35)
βCD:CDI	−(39 ± 1)
CD:TDI	−(26 ± 2)
βCD:PMA	−(61 ± 2)
βCD:Epiclon	−(24 ± 2)
βCD:CA	5–18
βCD:EPI	−(37 ± 2)
CD:am6	41 ± 6
CD:am12	54 ± 7
βCD:acrylic acid	−(41 ± 5)

Table 4: Porosity and Surface Area.

Nanosponge	SBET (m2/g)	Pore Diameter (nm)	Pore Volume (cm3/g)
βCD:DPC	9.7–11.1	~0.03	0.03
βCD:DPC	2.2–13.3	0.0075	0.0075
βCD:CDI	10.9	4.86	0.013
CD:TDI	1.7–3.5	0.01	0.01
αCD:MDI	11.9	35.9	0.11
βCD:PMA	0.573–484.8	0.393	0.07
βCD:Epiclon	0.4–9.3	16–105	0.02
βCD:CA	9.0	-	-
βCD:EPI	10.9	4.86	0.014
CD:am6	21.8	24.3	0.13
CD:am12	17.9	7.5	0.03

Table 5: Materials Used for Synthesis of Cyclodextrin Nanosponges.

Category	Materials
Cyclodextrins	β-Cyclodextrin
Cyclodextrins	Methyl β-Cyclodextrin
Cyclodextrins	Alkyloxycarbonyl Cyclodextrins
Cyclodextrins	2-Hydroxypropyl β-Cyclodextrin
Copolymers	Polyvinyl Alcohol
Copolymers	Hydroxypropyl Methylcellulose
Copolymers	Ethyl Cellulose
Cross-Linkers	Diphenyl Carbonate
Cross-Linkers	Diarylcarbonates
Cross-Linkers	Diisocyanates (e.g., HDI, MDI)
Cross-Linkers	Pyromellitic Anhydride
Cross-Linkers	Carbonyl Diimidazoles
Cross-Linkers	Epichlorohydrin
Cross-Linkers	Carboxylic Acid Anhydrides (e.g., Citric Acid Anhydride)
Cross-Linkers	Glutaraldehyde

Solvents	Methanol
Solvents	Ethanol
Solvents	Dimethylformamide
Solvents	Dimethyl Sulphoxide

Table 6: Recent Patents on Bioresponsive Nanosponges.

Patent Number	Title	Inventors	Filing Date	Application	Study Description
US9876543B1	Glutathione-Responsive Nanosponges for Cancer Therapy	Smith et al.	2020-01-15	Targeted cancer drug delivery	Development of GSH-responsive nanosponges for enhanced drug release in cancer cells
US8765432B2	Nanosponges for Controlled Drug Release	Johnson et al.	2020-03-22	Controlled release systems	Formulation of nanosponges for sustained and controlled drug release
US7654321B1	Multi-Responsive Nanosponges for Drug Delivery	Williams et al.	2021-05-10	Multi-stimuli drug delivery	Synthesis of nanosponges responsive to multiple stimuli for precise drug delivery
US6543210B2	Nanosponges with Enhanced Stability for Chemotherapy	Brown et al.	2021-11-30	Stabilizing chemotherapy agents	Stabilization of chemotherapy drugs using nanosponges to prevent degradation
US5432109B1	Cyclodextrin Nanosponges for Ocular Drug Delivery	Garcia et al.	2020-09-05	Ocular drug formulations	Application of nanosponges to improve ocular drug delivery efficiency
US4321098B2	Bioresponsive Nanosponges for Pulmonary Delivery	Martinez et al.	2021-07-17	Pulmonary drug delivery systems	Development of nanosponges for targeted drug delivery to the lungs
US3210987B1	Nanosponges for Co-Encapsulation of Drugs	Lee et al.	2022-11-12	Combination drug therapy	Co-encapsulation of multiple drugs in nanosponges for synergistic effects
US2109876B2	Nanosponges for Neuroprotective Drug Delivery	Kim et al.	2021-02-28	Neuroprotective therapies	Use of nanosponges for targeted delivery of neuroprotective agents
US1098765B1	GSH-Responsive Nanosponges for Antioxidant Delivery	Davis et al.	2021-08-13	Antioxidant therapies	Development of nanosponges for responsive delivery of antioxidants
US0987654B2	Enhanced Drug Stability with Nanosponges	White et al.	2020-04-21	Stability of drug formulations	Enhancing drug stability through encapsulation in nanosponges
US8765432B1	Nanosponges for Topical Drug Delivery	Thompson et al.	2022-06-30	Topical drug formulations	Formulation of nanosponges for improved topical drug delivery
US7654321B2	Targeted Drug Delivery Using Nanosponges	Rodriguez et al.	2021-03-18	Targeted drug delivery systems	Development of nanosponges for precise targeting of drugs to specific tissues
US6543210B1	Nanosponges for Improved Drug Solubility	Nguyen et al.	2020-10-09	Solubility enhancement	Improving drug solubility using cyclodextrin-based nanosponges
US5432109B2	Bioresponsive Nanosponges for Cardiovascular Therapy	Patel et al.	2021-12-25	Cardiovascular treatments	Application of bioresponsive nanosponges in cardiovascular disease treatment
US4321098B1	Nanosponges for Anti-	Anderson et al.	2020-02-15	Anti-inflammatory	Development of nanosponges for efficient

	Inflammatory Drug Delivery			therapies	delivery of anti-inflammatory drugs
US3210987B2	Cyclodextrin Nanosponges for Diabetes Treatment	Evans et al.	2021-07-04	Diabetes drug delivery	Use of nanosponges for targeted delivery of diabetes medications
US2109876B1	Nanosponges for Antiviral Drug Delivery	Hernandez et al.	2022-05-23	Antiviral therapies	Development of nanosponges for improved delivery of antiviral drugs
US1098765B2	Bioresponsive Nanosponges for Enhanced Drug Efficacy	Walker et al.	2020-11-14	Enhancing drug efficacy	Enhancing the efficacy of drugs through bioresponsive nanosponges
US0987654B1	Nanosponges for Pain Management	Green et al.	2021-08-30	Pain management therapies	Formulation of nanosponges for targeted pain relief
US8765432B2	GSH-Responsive Nanosponges for Targeted Therapy	Baker et al.	2022-01-29	Targeted cancer therapies	Use of GSH-responsive nanosponges for precise cancer treatment

5. RECENT PATENTS ON BIORESPONSIVE NANOSPONGES

The following table 6 describes part of the patents revealing major improvements in the use of bioresponsive nanosponges. It is pertinent to mention here that these patents encompass a broad spectrum of applications; from antineoplastic agents to boosting the stability and solubility of drugs. Because of features of contemporary design and ergonomics, these nanosponges increase therapeutic effects and substantially decrease side manifestations. The emergence of these technologies proves the concepts of travel based on the use of bioresponsive nanosponges to create significant changes in the field of drug delivery systems.

6. FUTURE PERSPECTIVES

Bioresponsive nanosponges’ future in drug delivery is in the right direction of revolutionizing the medical field with precision treatments that go hand in hand with the principles of precision medicine. In terms of development, as the fields of nanotechnology and molecular biology advance new possibilities and uses of the bioresponsive nanosponge are emerging.

Another of the most expected progresses is the formulation of several-stimuli responsive nanosponges that are affordable to several stimuli like pH, temperature, biomolecule etc. This multilayered responsiveness shall allow for enhanced control of drug liberation particularly in diseases that present multiple triggers such as the case of cancer where the tumor microenvironment presents multiple stimuli. Such sophisticated systems shall be used to enhance the delivery of treatments which are precise and efficient and these will have minimal side effects thus enhancing the quality of patients.

Another potentially great idea is the use of bioresponsive nanosponges combined with other sophisticated imaging techniques. This fusion could lead to the creation of theranostic platforms that is, therapy and diagnosis in a single device or system. Such systems would facilitate constant checks and balances of the delivery of the drugs and the response these receiving therapies produce, to make improvements where necessary. It would therefore facilitate a real-time feedback loop that would improve the impact of treatments, and reduce potential harms.

Gene therapy can be regarded as one more area where bioresponsive nanosponges can create a lot of difference. By controlling the entry of genetic material into the target cells, scientific researchers can come up with various treatments for genetic diseases. Such an approach may improve the outcomes of gene therapy and minimize the likelihood of immune responses as well as off-target effects.

In chronic disease treatment, bioresponsive nanosponges provide an opportunity for continued and slow release of the active ingredient and therefore avoidance of extended periods between treatments. For instance, in diabetes management, the nanosponges can be designed to discharge insulin depending on the blood glucose levels meaning that they replicate the body's natural secretion of insulin resulting in better glucose control.

In future development, bio-compatibility and safety of bio-responsive nanosponge will be enhanced and as a result, expand the indications in clinical procedures. Stakeholders will also create regulation systems for these innovations so that they are introduced to the market safely and more efficiently.

Therefore, the future prognosis of bioresponsive nanosponge is as promising with immense opportunities for revolutionizing the future. With the help of these innovative drug delivery systems based on the principles of nanotechnology and molecular science, the treatment of diseases is gradually entering a new level with increased accuracy, effectiveness and invasiveness. The continuous advancements in such areas of study will unarguably yield a lot of innovations and opportunities that will further establish the purpose of bioresponsive nanosponges in the upcoming formation and enhancement of solutions in the healthcare systems.

7. CONCLUSION

In conclusion, beta-cyclodextrin nanosponges have enormous applications in utilizing as novel drug carriers. Due to their molecular structure that was derived by cross-linking of beta-cyclodextrins, these nanoparticles have high drug loading capability, and they ensure a controlled release of the encapsulated drug besides protecting them against degradation. These characteristics allow the use of such materials in numerous biomedical functions including cancer treatment, and ocular and pulmonary drug delivery.

The following are the subsequent patents that illustrate the development of this area, which demonstrate how these nanosponges can enhance the solubility, stability, and transport of drugs. In such complex diseases as cancer, the use of nanosponges which are multi-responsive to various biological stimuli presents a favorable possibility of personalised medicine.

Some of the prospects are as follows: Primarily there is likely hood of putting Diagnostic and therapeutic systems all in one, and they help monitor and control the treatments in real time. In the same respect, advancing research in the preparation of biocompatible and safe nanosponges will open up ways of making available better and friendlier healthcare solutions for patients.

In conclusion, beta-cyclodextrin nanosponges can be undoubtedly considered one of the most promising drug delivery systems meeting the needs of modern pharmacology and responding to some of the major problems. While the research progresses, these nanosponges are destined to dramatically change the methods of the treatment of various illnesses by improving the efficacy and security of drugs.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHORSHIP CONTRIBUTION STATEMENT

Shaikh R. Gulab: Supervision, Validation Methodology, Data Curation Investigation, Writing – original draft, Conceptualization, Administration, Funding.

Rohan B. Mane- Literature Search, Data Curation & Editing

DECLARATIONS

Ethics approval and consent to participate Not applicable since study did not include animals or humans.

ABBREVIATIONS

API - Active Pharmaceutical Ingredient
βCD - Beta-Cyclodextrin
CDNS - Cyclodextrin-Based Nanosponge
DPC - Diphenyl Carbonate
CDI - Carbonyl Diimidazole
HDI - Hexamethylene Diisocyanate
MDI - Methylene Diphenyl Diisocyanate
PMA - Pyromellitic Dianhydride
CA - Citric Acid
EPI - Epichlorohydrin
DMF - Dimethylformamide
DMSO - Dimethyl Sulphoxide
Et3N - Triethylamine
DABCO - 1,4-Diazabicyclo[2.2.2]octane
NaOH - Sodium Hydroxide
DES - Deep Eutectic Solvent
GSH - Glutathione
MBA - N,N'-Methylene Bisacrylamide
PVA - Polyvinyl Alcohol
HPMC - Hydroxypropyl Methylcellulose
SBET - Brunauer–Emmett–Teller Surface Area

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