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DRUG DELIVERY VIA NANOSPONGES FOR THE MANAGEMENT OF HYPERTENSION

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ABSTRACT

Nanosponges have emerged as a highly promising and innovative approach to drug delivery, with the potential to revolutionize medicine. These nanoscale structures, composed of porous materials, including biocompatible polymers, present unique benefits for delivering therapeutic agents directly to targeted areas in the body. With their highly porous architecture, nanosponges can effectively encase various drug molecules, including small molecules, proteins, and nucleic acids. They are composed of three-dimensional networks or scaffolds filled with drugs and porous, insoluble nanoparticles, which can be either crystalline or amorphous and often have a spherical shape or exhibit swelling properties. Furthermore, the polarity and dimensions of the polymer mesh can be easily manipulated by changing the different type of cross-linker and the degree of cross-linking. These minuscule sponges, which are less than 1 μm in diameter, are capable of holding a diverse range of drugs. The encapsulation process not only safeguards the medication from deterioration, but additionally facilitates controlled release kinetics, enhancing therapeutic effectiveness while reducing potential side effects. Moreover, nanosponges can be specifically engineered with surface modifications to target certain tissues or cells, enabling accurate drug delivery to affected regions. The biocompatibility of nanosponges further highlights their suitability as drug carriers, ensuring ability to coexist with the biological environment and lowering the risk of adverse reactions. Additionally, their adaptability supports applications in a wide variety of therapeutic fields, such as oncology, infectious diseases, and regenerative medicine. In conclusion, nanosponges offer a compelling foundation for creating next-generation drug delivery systems. Their capacity to encapsulate,

target, and regulate the release of therapeutic agents possess significant promise for enhancing the management of numerous medical conditions while minimizing side effects.

KEYWORDS: Nanosponge, Hypertension, Controlled Release, Targeted Release, Novel drug delivery system.

1. INTRODUCTION

Hypertension is linked with a heightened risk of cardiovascular disease events such as stroke, heart failure, and coronary heart disease in addition to a higher risk of mortality.[1] It stands as the most substantial avoidable risk factor for CVD and overall mortality globally. As of 2010, hypertension was classified as a systolic blood pressure of 140 mmHg and a diastolic blood pressure of 90 mmHg, affecting 31.1% of the adult population worldwide, translating to around 1.39 billion individuals. The global prevalence of hypertension is on the rise, influenced by factors like an aging population and increased exposure to lifestyle risks, including unhealthy diets (marked by high salt and low potassium intake) and insufficient physical activity. However, variations in hypertension prevalence trends can be detected across different regions. Over the previous 20 years, there has been a substantial rise in hypertension rates in low- and middle-income countries (LMICs), while there has been a slight decline in high-income countries (HICs).[2]

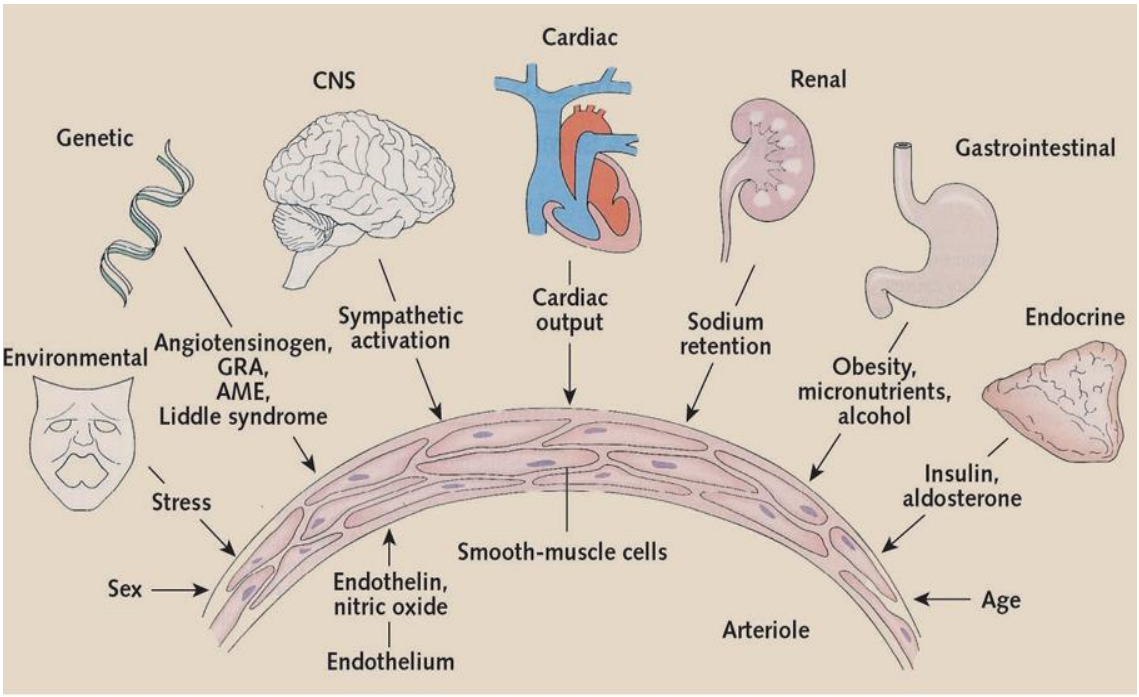

Fig 1: Pathophysiologic mechanisms of hypertension.[3]

Special definitions of hypertension[4]

1. White coat hypertension - This term, often observed in older adults, describes individuals who do not take antihypertensive medication but exhibit continually elevated blood pressure measurements in the office (≥ 140/90 mmHg) while having normal ambulatory blood pressure throughout the day (≤ 135/85 mmHg).

2. Masked hypertension - Research shows that exhibiting elevated blood pressure at home while maintaining normal levels at work is linked to an increased risk of cardiovascular incidents. A significant vascular profile is related to masked hypertension, frequently observed in older adults. These findings need to inspire more widespread use of home blood pressure monitoring within this population.

3. Pseudo hypertension -Vascular changes related with aging, such as atherosclerosis, contribute to the increased systolic blood pressure (SBP). The Osler maneuver, although it has low sensitivity and specificity, should be performed if there is a suspicion of pseudohypertension; this maneuver involves checking for a noticeable radial artery pulse after inflating the cuff beyond systolic pressure. To verify the presence of pseudohypertension, blood pressure should be directly measured using intra-arterial methods.

4. Resistant hypertension - Even when taking three different antihypertensive medications concurrently, it is characterized by blood pressure that stays higher than the desired level. All three medications should be administered at their suggested dosages, and preferably, one of them should be a diuretic.

Table 1: Standard medications used to treat hypertension.[5]

Diuretics
Loop diuretics: Ethacrynic acid, Torsemide, Bumetanide, Furosemide
Thiazide-like diuretics: Chlorthalidone, Metolazone, Indapamide
Thiazide diuretics: Epitizide, Chlorothiazide, Bendroflumethiazide, Hydrochlorothiazide
Potassium-sparing diuretics: Triamterene, Spironolactone, Amiloride
Adrenergic receptor agonists:
Alpha-2 agonists: Methyldopa, Guanfacine, Clonidine
Adrenergic receptor antagonists:
Alpha blockers: Phenoxybenzamine, Prazosin, Terazosin, tolazoline, Doxazosin, Phentolamine, Indoramin
Beta blockers: Oxprenolol, Pindolol, Propranolol, Timolol, Atenolol, Metoprolol, Nadolol
Mixed Alpha+ beta-blockers: Carvedilol, Labetalol, Bucindolol,
ACE inhibitors: Quinapril, Captopril, Ramipril, Benzapril, Enalapril, Fosinopril, Lisinopril, Perindopril, Trandolapril

Angiotensin II receptor antagonists: Olmesartan, Telmisartan, Valsartan, Candesartan, Eprosartan, Irbesartan, Losartan
Calcium channel blockers:
Dihydropyridines: Nifedipine, Nimodipine, Lercanidipine, Nicardipine, Nitrendipine, Amlodipine, Felodipine, Isradipine
Non-dihydropyridines: Diltiazem, Verapamil
Aldosterone antagonists: Spironolactone, Eplerenone
Centrally acting adrenergic drugs: Methyldopa, Moxonidine, Clonidine, Guanabenz
Vasodilators: Hydralazine, Sodium nitroprusside

Various lifestyle modifications are recommended to help prevent hypertension: For maintaining general health men should consume alcohol in moderation to a maximum of 30 milliliters daily, while women should restrict theirs to 15 milliliters; engage in aerobic exercises for 30 to 45 minutes on most days of the week; discontinue smoking; restrict daily sodium chloride consumption to under 6 grams; ensure sufficient dietary potassium intake (around 90 mmol/d); and lessen the consumption of saturated fat and cholesterol to support overall cardiovascular health.[6] As individuals grow older, the incidence of hypertension tends to rise and can act as a risk factor for ailments such as dementia, ischemic heart disease, stroke, and kidney failure.[7]

Nanosponges are used as an innovative method of medication delivery for treating hypertension. The telmisartan-loaded nanosponges, produced through the acetone-based solvent evaporation method as the solvent along with PLGA, Tween80, glutaraldehyde, and pluronic, demonstrated effective drug encapsulation and release characteristics for hypertension treatment.[8] Olmesartan medoxomil (OLM), a widely recognized medication for hypertension, has low water solubility, which results in low bioavailability and slow degradation rate. To enhance the bioavailability of oral OLM, a delivery system incorporating ethylcellulose (EC), a biobased polymer, in the form of nanosponges (NSs) was developed and its cytotoxicity was evaluated.[9] The advancement and evaluation of nebivolol-loaded nanosponges mark an important development in the delivery of oral medications that enhances therapeutic efficacy.[10]

Alongside exhibiting good tolerance with red blood cells and minimal hemolysis, in vitro cytotoxicity tests demonstrated safety for both liver and kidney epithelial cells, especially at lower dosages. This underscored the safety and enhanced bioavailability of the nano-sponge formulation.[11] The polyphenolic compound hesperetin (HT) possesses anti-oxidant, anti-cancer, and anti-tumor necrosis properties. This study discusses the development,

optimization, and evaluation of HT-loaded nanosponges (HTN)-based gel (HTNG) aimed at providing sustained anti-inflammatory effects.[12] Ocular hypotensive treatments can be effectively delivered in a consistent and linear manner for up to 32 days following a single injection of NS. Furthermore, NS can effectively target retinal ganglion cells (RGCs), which are the neurons that deteriorate in glaucoma.[13]

Nanotechnology may represent the most significant engineering transformation since the onset of the industrial era. To date, nanotechnology has led to various formulations such as nanoparticles, nanocapsules, nanospheres, nanosuspensions, and nanocrystals, alongwith nano-erythosomes. It is described as the process of creating and modifying materials at the nanoscale to produce items that exhibit unique characteristics.[14] Nanosponges are porous solid particles that can be formulated for use as topical, parenteral, oral, or inhalable dosage forms. They have the ability to encapsulate drugs and other active substances within their nanocavities. This innovative class of colloidal structures known as nanosponges consists of solid nanoparticles with nanosized voids and is based on hyper-crosslinked polymers. Among the most notable nanosponges are those crafted from cyclodextrin, silicon nanoparticles, titanium, and hyper-crosslinked polystyrene.[15] The size of silicon nanosponge particles, derived from metallurgical-grade silicon powder, typically ranges from about 1 millimeter to around 4 microns. Each silicon nanosponge particle is comprised of numerous nanocrystals that include pores throughout the particle and between the nanocrystals.[16] Approximately 25% of the existing inventory of commercially available nanoproducts consists of nanoscale silver. Products made from silver nanoparticles are known to have their unique physiochemical properties and biological functions, enhancing their application as treatments for antibacterial, antiviral, and anti-inflammatory purposes. Historically, silver has been availed for its medicinal advantages.[17]

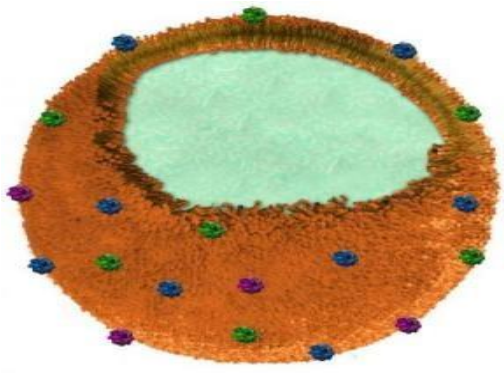

Figure 2: Nanosponges.

Initially, nanosponges were developed for administering medication topically. They typically have a diameter of less than 1 μm, making them tiny sponges that resemble viruses. These microscopic sponges can navigate throughout the body until they reach the exact target location, where they adhere to surfaces and begin releasing the medication in a controlled and predictable manner. The effectiveness of the drug is enhanced for a specific dosage since it can be released at the exact target site instead of spreading throughout the body.[18] Nanosponges are constructed from hyper-cross-linked cyclodextrins, incorporating α, β, and γ cyclodextrins, either individually or in combination with suitable amounts of linear dextrin and a cross-linking agent.[19]

Nanosponges are considered to be non-mutagenic, non-irritating, non-allergenic, and non-toxic.[20] These microscopic structures bear a mesh-like appearance and are coated with a diversity of materials. Because of their ability to include and exclude substances, these spherical colloids are highly effective at solubilizing medications that are poorly soluble.[21] Nanosponges are essentially three-dimensional networks or scaffolds. Generally, these scaffolds are composed of polymers and other substances that are used historically in medication delivery methods. The collaboration between material scientists and healthcare professionals has prompted the creation of scaffolds with improved qualities for medicament delivery that possess clinically relevant capabilities. Nanosponges can be categorized into two types: crystalline and paracrystalline. The extent of crystallization impacts their capacity for entrapment.[22] NS formulations can remain stable at temperatures up to 130°C and across a pH scale of 1 to 11.[23]

Ascribed to their sponge-like structure, cyclodextrins, which are the primary components of nanosponges, can entrap hydrophilic and hydrophobic active medicinal ingredients (drugs) within their core. Their openings, measuring 0.7 nm in diameter, facilitate the formation of complexes with medicinal molecules. The therapeutic agent can be accommodated within the cavities of the nanosponges and subsequently delivered to biological systems. When dissolved in water, cyclodextrin-based nanosponges, characterized by their high porosity and hyperbranched cyclodextrin polymers, can swiftly achieve nanometer sizes, appearing sponge-like when viewed under a microscope.[24] Cyclodextrin-based nanosponges serve as excellent carriers for the adsorption of proteins, enzymes, antibodies, and macromolecules. Particularly, utilizing enzymes enhances their efficacy and activity, extends their operational range in terms of pH and temperature, and allows for continuous flow processes.

Additionally, cyclodextrin nanosponges have the capability to encapsulate or adsorb proteins and other macromolecules for transport.[25]

Nanosponges are small, mesh-like particles shaped like cups that are safe for biological systems and can break down in biological fluids. They offer a solubility that is five times greater than that of current drug delivery techniques. Various methods such as complexation, encapsulation, and conjugation can be employed to produce nanosponges that enclose drug molecules within their core.[26] Before creating a nanosponge dosage form, it is essential to determine key physical and chemical characteristics of the medication, both alone and when combined with excipients. This preliminary phase is cited as pre-formulation. The objective of pre-formulation is to gather data that will assist the formulator in creating dosage forms that are bioavailable, stable and suitable for mass production. The objectives of pre-formulation studies include the following:

- To assess the drug substance through analytical methods and identify its essential properties.
- To determine its suitability with various excipients.[14]

Pharmaceutical principles can be applied to nanosponges to improve the water solubility of hydrophobic drugs, protect degradable substances, and form medicament delivery systems for non-oral administration methods.[27] The particle size was determined to be in the range of 200 and 500 nm. The entrapment effectiveness for various formulations varied from 91.56% to 99.12%.[28] A recent investigation from Vanderbilt University and Emory University introduced a controlled-release nanoparticle drug delivery system. This approach has the ability to enhance the administration of anticancer therapies, like direct injections into tumors. Upon engaging with the surface of tumor cells, these nanoparticles adhere to them and start to deliver the medication in a controlled and predictable fashion.[20]

The drug molecules are enclosed within the core of the nanosponges, which consist of encapsulating nanoparticles. The method by which the nanoparticles attach to the medications enables their classification into:

- **Complexing nanoparticles** attract molecules through electrostatic interactions.
- **Conjugating nanoparticles** are attached to drug molecules via a robust covalent bond.
- **Encapsulating nanoparticles**, which include nanosponges and nanocapsules, are intended to transport drug molecules. For example, alginate nanosponges feature numerous pores that trap the drug substances. In contrast, nanocapsules like

poly(isobutyl-cyanoacrylate) (IBCA) envelop drug substances within their aqueous interiors.[29]

2. Key characteristics of nanosponges[18,30]

- Nanosponges are accessible in various sizes, typically 1 µm or smaller, and feature adjustable cavity polarity.
- The amount of crosslinker to polymer can be altered to create nanosponges of a certain size.
- Their shapes can be either crystalline or paracrystalline, contingent on the parameters of the procedure. The way that nanosponges complex with medications is greatly influenced by their crystal structure.
- The level of crystallization influences the capacity for drug loading.
- Paracrystalline nanosponges can exhibit various capabilities for drug loading.
- These particles remain stable up to 300 °C, are nontoxic, porous, and insoluble in most organic solvents.
- They maintain stability across a pH range of 1 to 11.
- In water, they form an opalescent and transparent suspension.
- Solvent extraction, microwaving, simple thermal desorption and ultrasonics can all be used to replicate them.
- A variety of compounds can be selectively captured, transported, and released due to their three-dimensional structures.
- Their ability to connect with various functional groups enables them to be targeted to different sites.
- Chemical linkers facilitate the targeted binding of nanosponges to their desired location.

3. Materials used in nanosponge preparation[31]

- **Cross linkers:** Diphenyl Carbonate, Epichloridine, Gluteraldehyde, Pyromellitic anhydride, 2,2-bis (acrylamido) Acetic acid, Carbonyl diimidazoles, Carboxylic acid di anhydrides, Diarylcarbonates, Di chloromethane, Diisocyanates

- **Polymers**: Eudragit RS 100, and Acrylic Polymers, Methyl β-Cyclodextrin, Hypercrosslinked Polystyrenes, Cyclodextrins and their derivatives such as Alkyloxycarbonyl Cyclodextrins, Hydroxypropyl β-Cyclodextrins, Ethyl Cellulose, Polyvalerolactone.

- **Copolymers:** Poly vinyl alcohol, Ethyl Cellulose, Poly(valerolactoneallylvalerolactone), Poly (valerolactone-allylvalerolactone oxepanedione)

4. Advantages and disadvantages of nanosponges[32]

Advantages

- The drug profiles can vary in release speed: fast, medium, or slow.
- The drug is safeguarded against degradation.
- Non mutagenic
- Non-toxic
- Non-irritating
- It offers enhanced stability, refined elegance, and greater flexibility in formulation.

Disadvantages[18]

- Nanosponges consist solely of small molecules.
- Paracrystalline nanosponges can exhibit varying loading capacities.

5. Factors influencing nanosponge formation[15,33]

Various categories of Polymers - The kind of polymer utilized may influence both the creation and functionality of nanosponges. A drug molecule of a specific size should be able to fit in the nanosponge's cavity size for complexation.[15]

Category of medications - Molecules intended for complexation with nanosponges need to possess specific characteristics outlined below.

- The drug's molecular weight should ought to be within the limit of 100 to 400 Daltons.
- The drug molecule contains fewer than five condensed rings.
- The solubility of the substance in water should not exceed 10 mg/ml.
- The material must have a melting point that is less than 250°C.[15]

Temperature - Variations in temperature can influence the interaction between drugs and nanosponge materials. In general, an increase in temperature leads to a decline in the apparent stability constant of the drug/nanosponge complex. This decline may occur due to contact forces between the drug and nanosponge, like van der Waals and hydrophobic interactions, tend to weaken.[15]

Degree of substitution - The type, number and position of the substituent on the polymeric molecule affect the complexation ability of nanosponges. The degree of crosslinking and the

total number of substitutions present are directly correlated. The likelihood of experiencing increased crosslinking increases with the number of substituents. Since there are more connections between the polymers creating a mesh-like network, a higher degree of crosslinking will result in highly porous nanosponges.[33]

Method of preparation - The method in which the drug is incorporated into the nanosponge can impact the drug/nanosponge complexation. Although the efficacy of various approaches may fluctuate depending on the particular drug, and polymer used, freeze drying has often proven to be the most effective technique for drug complexation.[33]

6. Method of preparation of nanosponges

Table 2: Comparison of various nanosponges preparation methods based on their physicochemical properties.[34]

Methods	Particle size	Shape of particles	Stability	Zeta potential	Porosity
Emulsification diffusion method	105-842.2 nm	Spherical shaped nanosponges	Stable	-1.35mV	Extremely porous featuring small-sized pores.
Solvent method (Liquid- liquid extraction or leaching)	316.4-911.6nm	Spherical structure	Stable at 40ºC up to 3 months	-18.5 to -11.8	Porous surface
Polymerization	190 ± 20nm	Sphere like particles	Stable		Porous
Hyper crosslinked method	350- 500nm	Approximately spherical	Stable at 4ºC up to 6 months	Between 31.70& -35.35	Porous
Sonochemistry	97.10-325.90 nm	A porous structure that is advantageous for enhancing drug loading.	Physically stable	>20mV	Porous structure
Microwave irradiation method	153-400nm	Spherical shaped	Stable up to 325ºC.		Highly porous

6.1. Spherical crystallization method (Quasi-emulsion solvent diffusion method)

Nanosponges were prepared using varying quantities of ethyl cellulose and polyvinyl alcohol (PVA). The process began by dissolving the medication along with ethyl cellulose in 20

milliliters of dichloromethane. This scattered phase was gradually combined with a specified volume of polyvinyl alcohol within 150 milliliters of an aqueous continuous phase. The mixture was agitated at a speed of 1000 rpm for two hours. Following agitation, the nanosponges were collected through filtration and oven-dried at 400ºC for 24 hours. To totally eliminate any remaining solvent completely, the dried nanosponges were placed in vacuum desiccators.[27]

In an alternative approach, nanosponges can be manufactured using this technique with varying quantities of polymer. The inner phase is formed by dissolving Eudragit in an appropriate solvent. The drug is immersed in this solution and dissolved at 350ºC through ultrasonication. The outer phase, comprised of a PVA solution in water, is then merged with the inner phase. After mixing for 60 minutes, the resulting mixture is filtered to yield the nanosponges, which are then dried in an oven with air-heating at 400ºC for 12 hours.[35]

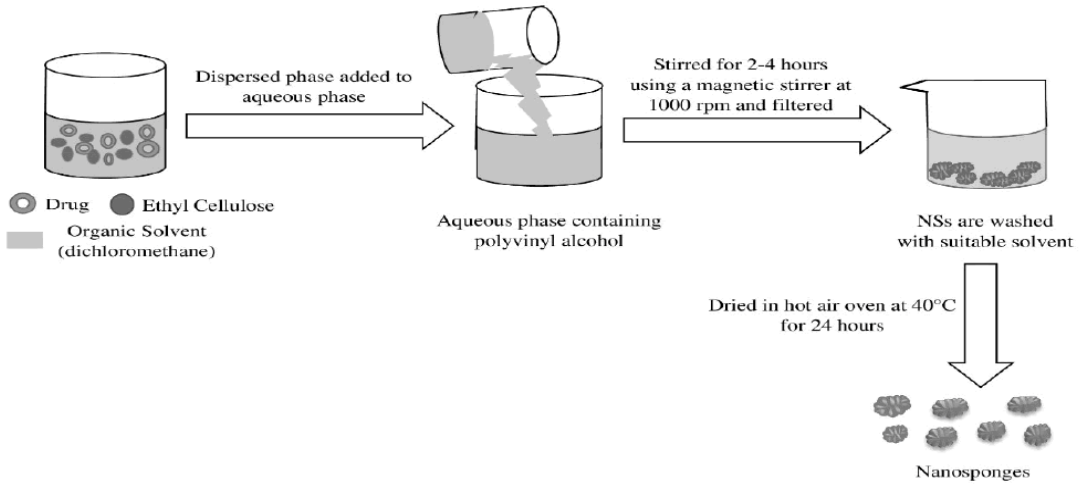

Figure 3: Fabrication of nanosponges using the spherical crystallization technique.

6.2. Ultrasound assisted synthesis

Sonification occurs when a polymer reacts with cross linkers without incorporating a solvent to form nanosponges. In a flask, the polymer and cross linkers are blended in an appropriate ratio. This mixture undergoes sonication for five hours while positioned in a water-filled ultrasonic bath maintained at a temperature of 90ºC. The resulting product is vacuum-dried at 25 degrees Celsius until it is needed again.[36]

6.3. Solvent method

An appropriate aprotic polar solvent, like dimethyl formamide or dimethyl sulfoxide, was blended with the polymer in this method. This combination was augmented to an excess of crosslinker in a molar ratio ranging from 4 to 16. The reaction took place for a duration of one to forty-eight hours at temperatures varying from 10°C to the reflux temperature of the solvent. The recommended crosslinkers are carbonyl compounds, specifically dimethyl carbonate and carbonyl diimidazole. After the reaction was complete, prior to adding the product to a large volume of bi-distilled water, the solution was allowed to cool to room temperature. The product(result) was subsequently obtained through vacuum filtration, followed by purification using ethanol and an extended Soxhlet extraction process. To produce a consistent powder, the drying procedure was performed under vacuum, and then it was ground in a mechanical mill.[37]

6.4. Nanosponges formulated by hyper cross-linked β-cyclodextrin

A cross-linking agent, such as carbonyl diimidazoles, diphenyl carbonate, diisocyanates, diaryl carbonates, carboxylic acid anhydrides, dimethyl carbonate, and 2,2-bis(acrylamido)acetic acid, is combined with cyclodextrin to produce nanosponges. By modifying their surface charge density, porosity and pore sizes various molecules can be infused into the nanosponges.[38]

6.5. Microwave Irradiation Method

Cata's scientific microwave apparatus was operated to carry out microwave procedures. A fiber optic probe instrument was introduced into the reaction vessel to track the temperature of the reaction mixture. Cyclodextrin nanosponges were formed using diphenyl carbonate as agent for crosslinking and diphenyl formamide as the solvent. In summary, a combination of cyclodextrin and diphenyl carbonate in dimethylformamide was immersed in a 250 millilitres flask and subjected to microwave heating for a specific duration under defined conditions. After a certain period, the solvent was completely extracted. The final product was thoroughly purified through Soxhlet extraction with ethanol. This process yielded a white powder that was oven-dried at 60 °C to render it usable. In an experiment, Singireddy explored the benefits of using microwave heating for cyclodextrin-based nanosponges compared to conventional heating methods. The results of the study indicated that microwave-assisted synthesis enhanced the model drug's capacity for drug retention by 50%. High-resolution TEM studies revealed that the nanosponges produced via microwave

synthesis exhibited a narrower size distribution, a more complex structure, and higher crystallinity. One significant advantage of employing microwave irradiation in synthesis is the precise energy distribution it provides to the targeted molecules.[39]

6.6. Polymerization

After mixing a non-polar drug with the monomer, an aqueous phase—typically containing dispersants and surfactants to assist with suspension—is introduced. Once a solution with distinct droplets of the desired size is formed, polymerization occurs by either raising the temperature or using a catalyst on the monomers. This polymerization process yields a reservoir-type system that opens at the surface through pores. For the formulation of glutathione pH dual-bioresponsive degradable doxorubicin, a one-pot polymerization of acryloyl-6-ethylenediamine-6-deoxy-cyclodextrin, acrylic acid, and N, N-bis(acryloyl)-cystamine as a crosslinker was utilized, leading to the creation of nanosponges based on β-Cyclodextrin-appended hyper-cross-linked polymer. This method provided enhanced doxorubicin loading within a three-dimensional network of nanosponges.[34]

7. Incorporating the drug into nanosponges

To acquire a mean particle size of less than 500 nm, pretreatment of nanocarriers (NSs) is essential for drug delivery. To prevent the formation of aggregates, the NSs were dispersed in water, subjected to sonication, and then centrifuged to isolate the colloidal fraction. After the supernatant was removed, the sample underwent freeze-drying.[33] An aqueous suspension of the NSs was prepared, the excess medication was evenly distributed, and the suspension was constantly stirred for the exact duration required for complexation. After complexation, centrifugation was employed to isolate the uncomplexed (undissolved) drug from the complexed form. Subsequently, either solvent evaporation or freeze-drying methods were utilized to generate solid crystals of NSs. For the NS to interact with the drug, its crystal structure is essential. Research indicated that paracrystalline NSs demonstrated different loading capabilities compared to crystalline NSs. In crystalline NSs, the drug loading is more substantial than in paracrystalline types. In weakly crystalline NSs, drug loading occurs through mechanical mixing rather than forming an inclusion complex.[40] When drug molecules are placed into beta-CD nano-cavities, the interactions between the guest molecules and additional β-CD units may arise due to further crosslinking. Additionally, the creation of nano-channels in the NS structure might also stem from the existence of a crosslinked network. This particular structural configuration could account for the enhanced

solubilization and protection abilities of NSs compared to the original CD. Along with the drug candidate, the nanosponges are suspended in drug dispersions and subsequently freeze-dried. An alternative loading method involves the evaporation of the solvent, where the medication is dissolved in a suitable organic solvent. Therefore, the mentioned drug dispersion is then combined with the prepared NSs and ground until the solvent has evaporated. The ratio of medication to NS is determined based on the solubility of the medication.[41]

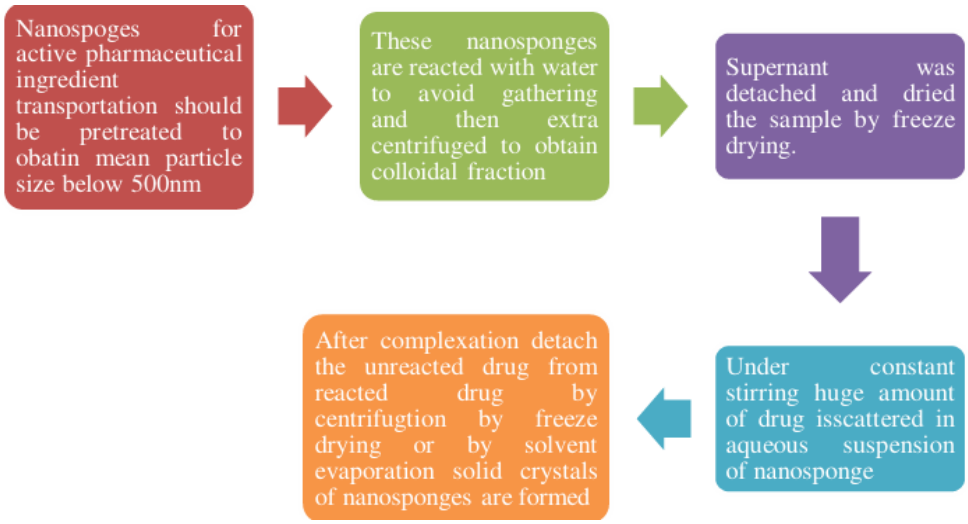

Figure 4: Incorporating the drug into nanosponges.[42]

8. Assessment of Nanosponges

8.1. Polydispersity index and particle size: Dynamic light scattering technique can be employed to assess particle size utilizing the Malvern Zeta sizer, laser light diffractometry, or the 90 Plus particle sizer furnished with MAS OPTION particle sizing software. This enables the calculation of the mean diameter and polydispersity index.[18] The variation in particle size is indicated by the polydispersity index. Samples that are monodispersed typically exhibit a lower polydispersity index value, whereas samples that are polydispersed show a higher polydispersity index value, indicating a broader particle size distribution. Particle size can be determined using techniques such as Transmission Electron Microscopy (TEM), Atomic Force Microscopy (AFM), Freeze Fracture Electron Microscopy (FFEM), and Scanning Electron Microscopy (SEM).[43]

Table 3: Polydispersity index.[44]

Polydispersity Index	Form of dispersion
0-0.05	Monodisperse standard
0.05-0.08	Nearly monodisperse
0.08-0.7	Mid-range polydispersity
>0.7	Very polydisperse

8.2. Surface topography and morphology: Transmission Electron Microscopy (TEM) and Scanning electron microscopy (SEM) can be employed to analyze the surface topography and morphology of the medication, nanosponges, and the yielded product (drug/nanosponge complex). This analysis involves coating the samples with a gold–palladium mixture in an argon environment at room temperature. Under the electron microscope, the contrast between the crystallization states of the raw materials and the final product clearly illustrates the formation of inclusion complexes.[45]

8.3. Zeta Potential: The zeta potential analyzer is used to assess the surface charge. To arbitrate the zeta potential, an additional electrode can be assimilated into the particle size measurement device. Moreover, both laser Doppler anemometry and a zeta potential meter can be employed.[43]

8.4. Single crystal X-ray structure analysis- employed to arbitrate the exact configuration of the inclusion and interaction technique. It is feasible to recognize and differentiate the specific geometric relationship between the guest and host molecules.[46]

8.5. Loading efficiency / Entrapment efficiency- The measured amount of the loaded nanosponge complexes should be dissolved in a suitable solvent, subjected to sonication to break them up, appropriately diluted, and then analyzed using either HPLC or a UV spectrophotometer.[47]

8.6. Loading efficiency and production yield- The percentage of loading efficiency (%) for the nanosponges can be determined using the subsequent equation.

Loading Efficiency = Actual drug content in NS÷ Theoretical drug content × 100

The yield of the product can be determined using the following equation, once the precise initial weight of the raw materials and the final weight of the obtained nanosponge are established.

Production yield (PY) = Practical mass of NS ÷ Theoretical mass (polymer+Drug) × 100[44]

8.7. Resiliency (Viscoelastic properties)- The resilience of sponges can be adjusted to produce beadlets that are either softer or firmer, depending on the requirements of the final formulation. Increased crosslinking typically reduces the rate of release. Consequently, by considering the release as it relates to cross-linking, the resilience of sponges will be explored and altered as required.[27]

8.8. Porosity- To assess the formation of nanochannels and nanocavities, a porosity analysis is performed. A helium pycnometer measures the porosity of nanosponges, as helium gas is capable of flowing through both intra- and inter-particular channels. The helium displacement technique is used to ascertain the actual volume of the material. Due to their porous characteristics, nanosponges exhibit greater porosity than the original polymer used to synthesize the system.

Percent porosity is given by equation:

% Porosity = Bulk volume - True volume / Bulk volume × 100[31]

8.9. Infra-Red Spectroscopy: It is employed to assess the interaction between drug molecules and nanosponges in their solid form. This method offers crucial information about the role of hydrogen within different functional groups. Generally, when hydrogen bonds form, the absorbance bands tend to shift to lower frequencies, gain intensity, and broaden. The greatest shift in the stretching vibration band is detected in the hydroxyl group as a result of hydrogen bonding.[43]

8.10. Swelling and water uptake: Immersing the produced nanosponges in a water-based solvent enables the assessment of water absorption by swellable polymers like polyamidoamine nanosponges. Formulas can be applied to determine the swelling and water absorption rates:

% 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[31]

8.11. Compatibility Studies: 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 Colorimetry (DSC) and powder X-ray diffraction (XRD) can be used to study crystalline properties.[20]

9. Application of nanosponges

9.1 Nanosponges for drug delivery- Nanosponges are capable of transporting medications that are not soluble in water (class-II pharmaceuticals as classified by the Biopharmaceutical Classification System) due to their unique nanoporous structure. These complexes can convert liquids into solids, mask unpleasant smells, and enhance the dissolution rate of medications, making them more soluble and stable. Reports indicate that β-Cyclodextrin-based nanosponges can deliver drugs to the target area with three to five times more efficiency than direct injection. By incorporating drugs into the nanosponges, formulation is significantly improved for those medicaments that are critical regarding their solubility.[48,43] Naturally solid, the nanosponges can be formulated into dosage forms including topical, parenteral, oral, or inhaled applications. The complexes can be integrated into a blend of excipients, anticaking agents, diluents and lubricants suitable for producing tablets or capsules intended for oral use. This combination can be readily transported in saline, sterile water, or other aqueous mediums for parenteral administration.[19]

Table 4: List of BCS Class II dugs which can be developed as nanosponges.[33,50]

CATEGORY	DRUG
Antianxiety drugs	Lorazepam
Antiarrhythmic agents	Amiodarone hydrochloride
Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethoxazole
Anticoagulant	Warfarin
Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone
Antidiabetic and Antihyperlipidemic drugs	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone
Antiepileptic drugs	Phenytoin
Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole, Lansoprazole, Vericonazole
Antihistamines	Terfenadine
Antihypertensive drugs	Felodipine, Nicardipine, Nifedipine, Nisoldipine
Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan, Paclitaxel, Raloxifene, Tamoxifen, Temozolamide, Topotecan
Antioxidants	Resveratrol
Antipsychotic drugs	Chlorpromazine Hydrochloride
Antiretrovirals	Indinavir, Nelfinavir, Ritonavir, Saquinavir
Antiulcer drugs	Lansoprazole, Omeprazole
Anthelmintics	Albendazole, Mebendazole, Praziquantel
Cardiac drugs	Carvedilol, Digoxin, Talinolol
Diuretics	Chlorthalidone, Spironolactone
Gastroprokinetic agent	Cisapride
Immunosupressants	Cyclosporine, Sirolimus, Tacrolimus
NSAIDs	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin, Piroxicam
Steroids	Danazol, Dexamethazone
Miscellaneous	Atovaquone, Melarsoprol, Phenazopyridine, Ziprasidone

9.2 Nanosponges as chemical sensors- Titania nanosponges, a kind of nanosponge categorized as a "metal oxide," serve as chemical sensors and are used for the highly sensitive identification of hydrogen. Because the nanosponge structure lacks initial contact points, electron transport encounters less resistance, resulting in more effective 3D interconnected titania nanosponges that are responsive to H2 gas.[24,49]

9.3 Nanosponges in solubility enhancement- A study conducted by Swaminathan et al. investigated a formulation of itraconazole utilizing nanosponges. Itraconazole is classified as a BCS Class II drug, characterized by low bioavailability and a slow dissolution rate. The solubility of the medicament was enhanced by over 27-fold because of the use of nanosponges. This enhancement increased to 55 times with the usage of copolyvidonum as an auxiliary component in the nanosponge formulation. Nanosponges solubilize drugs by improving the drug's wetting properties, reducing its crystallinity, or potentially masking the hydrophobic sections of itraconazole.[25,51]

10. CONCLUSION

Nanosponges serve as an effective vehicle for drug delivery in the management of hypertension, enhancing the solubility of certain hypertensive medications. This system offers controlled and targeted drug delivery capabilities. It is suitable for carrying both lipophilic and hydrophilic drugs. The porous design of nanosponges enhances their effectiveness in drug administration. They represent a stable form of dosage. Compared to current drug delivery methods, nanosponges provide five times greater solubility. The drug release profiles can be tailored to be fast, medium, or slow, depending upon the dosing therapy. Additionally, the drug is safeguarded against degradation.

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