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Review Article

Nanosponges: The Advant in Pharmaceutical Field for Optimial Delivery of Medications.

Zambare Swapnil D.*, Sontakke Shrikrushn B., Borkar Smita P., Shinde Snehal M., More Priti U.

Arvind Gavali college of Pharmacy, Jaitapur, Satara, Maharashtra, India.

A B S T R A C T

Fast developments in nanotechnology have given rise to a novel and promising medicine delivery method called nanosponges. These nanostructures meet the need for accuracy and controlled release in medication management by being able to carry a variety of tiny drug molecules and being delivered by oral, topical or parenteral methods.

In particular, because of their high selectivity, biocompatibility, degradability, and capacity to provide a sustained release of the medicines, nanosponges hold the potential to significantly enhance cancer therapy. The advantages of the nanosponge system extend beyond cancer treatment; it is suitable for treating a wide range of illnesses, such as infections and autoimmune diseases. The sponge-like structure of nanosponges, which can hold a wide range of drug molecules, is the main component of their drug delivery mechanism. The regulated release of the medication takes place at the target spot, which is reached after the pharmaceuticals are loaded into the nanosponges and circulate throughout the body.

Because of their similar size to viruses, which enables them to interact with cells at the minuscule scale and efficiently transport medications throughout the body, nanosponges are also good drug delivery vehicles. In the field of topical drug administration, their use is especially noteworthy for the treatment of skin diseases and fungal infections. All things considered, the nanosponge drug delivery system has many benefits over conventional medicine administration methods, such as the ability to deliver drugs precisely where they are needed, increased bioavailability, less adverse effects, and improved therapeutic efficacy. The pharmaceutical industry is still heavily researching this dynamic delivery system, which offers improved therapy alternatives for patients with a variety of ailments.

KEYWORDS: Nanosponges, β-cyclodextrin, Crosslinker, Poly vinyl alcohol, Polymer, Entrapment Efficiency.

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*Address for Correspondence:
Zambare Swapnil D.*, Research Scholar, Arvind Gavali college of Pharmacy, Jaitapur, Satara, Maharashtra, India.

INTRODUCTION

Targeting the delivery of drugs has long been a problem for medical researchers - how to get them to the right place in the body and how tocontrol the release of the drug to prevent overdoses. The developments of new and complex molecules called nanosponges have the potential to solve these problems.Targeting the delivery of drugs has long been a problem for medical researchers - how to get them to the right placein the body and how to control the release of the drug to prevent overdoses. The developments of new and complex molecules called nanosponges have the potential to solve these problems.Nanosponges are a new class of materials and made of microscopic particles with few nanometres wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the

solubility of poorly water-soluble molecules.Nanosponges are a new class of materials and made of microscopic particles with few nanometres wide cavities, in which a large varietyof substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water-soluble molecules. Nanosponges are a new class of materials and made of microscopic particles with few nanometres wide cavities, in which a large varietyof substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water-soluble molecules.

Medical researchers have suffered from difficulties with the delivery of drugs, figuring out how to transport them to the proper location in the body and regulate their release to avoid overdosing. These problems can be settled by the creation of novel, complex molecules called to as nanosponges.The nanosponges have a scaffold structure or "backbone" composed of naturally degradable polyester and they are roughly the size of viruses. Small molecules known as cross-linkers are added to the long polyester strands in solution; these molecules have a preference for particular regions of the polyester.To create a spherical shape with numerous pockets (or cavities) places where drugs are stored, they "cross link" segments of polyester. The polyester breaks down naturally in a predictable way. Therefore, it releases its drug payload in a predictable manner and breaks down gradually in the body. These tiny sponges have the ability to move throughout the body until they reach the precise location of the medication, stick to the outer layer and start to disperse the medication. [1]

Nanosponges represent a novel class of materials made from of minute particles possessing cavities a few manometers in diameter, which allow for the encapsulation of a broad range of chemicals. These particles possess the capacity to transmit one of lipophilic and hydrophilic compounds, additionally to increase solubility of molecules that are not very water soluble.[2].

Types of Nanosponges

Table 1: Types of nanosponges

Type	Description	Applications	Reference
Cyclodextrin based nanosponges	Nanosponges based on cyclodextrin are lyophilized. nanostructures that replicate sponges and possess the capacity of interaction with small molecules within their matrix, and the NSs were generated by cross-connecting various cyclodextrin varieties utilizing cross-linkers like dimethyl carbonate, carbonyl diimidazole and diphenyl carbonate. Cyclodextrins are produced by a particular amount of α-, β-, and γ-cyclodextrin cross-links that occur naturally. Usually manufactured from β-cyclodextrins, they offer highest levels of stability and difficulty because of their optimal cavity size using polymers that can cross-link.	Cyclodextrin-based NS's are mostly used as drug delivery vehicle in biological applications. It is also used in agriculture, beauty products and as a highly effective way to remove impurities from contaminated water. Reusable oil absorbents, electrodes, polluti on removal, supercapacitors, antibacterial use, biosensors and medication delivery are a few of these.	3
Titanium-based nanosponges	Titanium oxide (TiO2) is a few of the semiconductor elements that has been studied the most for energy and environment-related uses because of its fascinating chemical and electrical properties. It is used as a photocatalyst due to its not being toxic, highly stable photocatalytic capability, cost-effectiveness and capacity to generate charge through energy absorption.	Hybrid nanospheres of TiO2/ZnO are implemented as photoanodes in photo electrochemistry. Metallic nanoparticles (NS), such as silicon NS particles, carbon-coated metal-based NS, TiO2 NS's have several applications.	4
Silicon-based nanosponges	Metallurgical quality silicon powder was pulverised into particles that ranged in size from 1-4 microns in order to produce silicon nanosponges. After styrene and polymerizable surfactants were copolymerized, titanium-based nanosponges were applied to the resulting polystyrene microspheres.	Explosives, photosensitive compounds, adsorbents, catalysts, sensors, fuel cell electrodes are all transported via high-porous silicon nanosponges. It also acts as a starting point with relation to ceramic materials with a high surface area, such as SiNa and SiC.	4
Hyperlinked nanosponges originate from polystyrene	Each of the single coiled polystyrene was placed in suspension in diluted solvents, followed by large amounts when stiff intramolecular bonds were introduced, leading to the coils to create circular nanostructures (NSs) by forcefully constricting them. The NS solutions have low viscosity, a high degree of sedimentation, and diffusion. When a linear polystyrene nonsolvent is present, these NSs showed increased inner surface area and significant swelling.	NS that had been cross-linked were utilised to separate inorganic electrolytes according to the correct method using the size exclusion chromatography principles. Tissue scaffolds have been made using cyclodextrin-based and hyper-cross-linked polystyrene NS.	4

CHARACTERISTICS OF NANOSPONGES [5-10] [79-82]

- Nanosponges offer a variety of diameters (1 µm or less) with adjustable cavity polarity.
- They can be replicated using straight forward thermal desorption, solvent extraction, microwaves and ultrasounds.
- Nanosponges are capable of carrying hydrophilic and lipophilic medications.
- They guard the medication against physicochemical deterioration.
- The materials that are called nanosponges has a pH range from 1 to 11 and can withstand temperatures exceed as much as 130°C.
- Nanosponges are non-toxic, non-allergic, non-irritating, and biodegradable.
- Drug profiles may differ based on the dose therapy, from rapid, medium or slow release.
- By creating complexes of inclusion and non-inclusion, nanosponges can encapsulate various kinds of compounds.
- When compared to chemical linkers, nanosponges are more successful at attaching to the target site.
- A variety of compounds can be transported, captured and released selectively than to their 3D structure.
- When utilising nanosponge, very little of the medication comes in contact with healthy tissue, so the side effects are reduced.
- The ability of nanosponge to deliver drugs under controlled conditions is one of its key advantages.
- The crosslinker to polymer ratio can be changed to make virus-sized nanosponges.
- The crosslinker's functional groups and concentration have an impact on the NSs' porosity and provide adaptable polarity.
- NSs medicines are available in oral, parenteral, topical and inhalational forms. When preparing oral formulations, excipients such as lubricants, diluents, anticaking agents and NSs are distributed collectively as a kind of a matrix.
- Their nature might be either crystalline or procrystalline. In addition to producing transparent, milky-coloured colloidal combinations in water, they can be easily re-developed using solvent-extraction, microwave and thermal desorption.

ADVANTAGES OF NANOSPONGES [11-16]

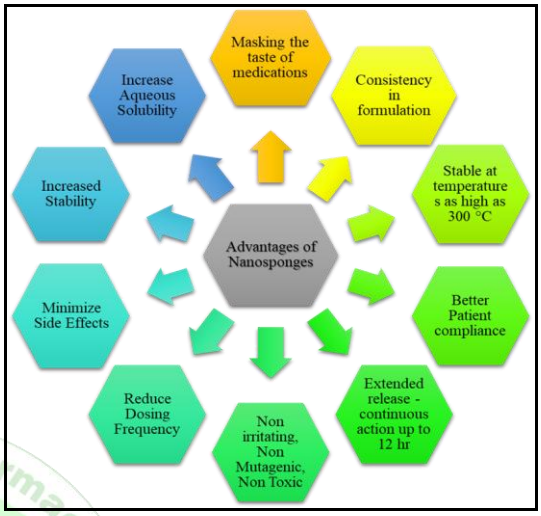


Figure 1: Advantages of Nanosponges

COMPONENTS OF NANOSPONGES

Figure 2: Components of Nanosponges

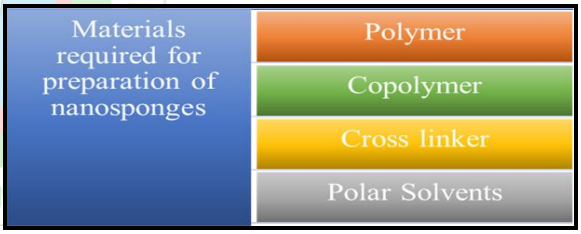
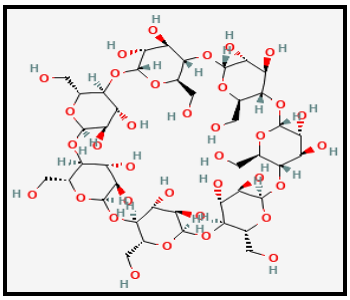
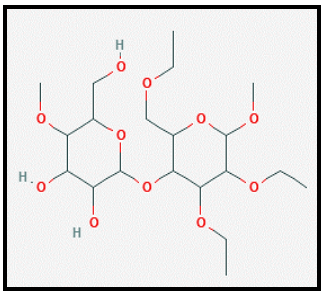
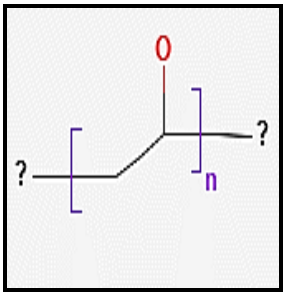


Table 2: Composition of nanosponge [16]

Polymer		
A specific kind of polymer can have an impact on the production process and functionality of nanosponges. The probability that the medication needs to be released from its capsule determines which polymer to use. It is essential to choose a polymer that can form a connection with a ligand. Examples include hyper cross-linked polystyrene, copolymers like ethylene cellulose as well as PVA, cyclodextrins and their by-products such methyl β-cyclodextrin.		
Structures of Polymers		
β-cyclodextrin [54] 	Ethyl cellulose [53] 	Polyvinyl Alcohol [55] 
Cross linking agent		

A crosslinking agent may be determined depending on the polymer's structure and the medication that has to be produced. Among the numerous examples are diary carbonates, dichloromethane, diphenyl carbonate and diisocyanatos.

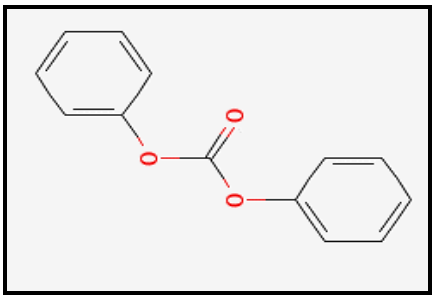
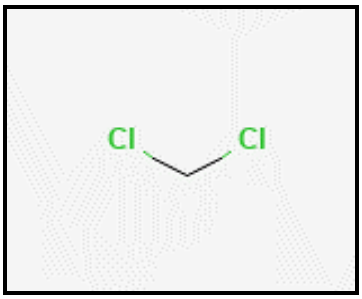
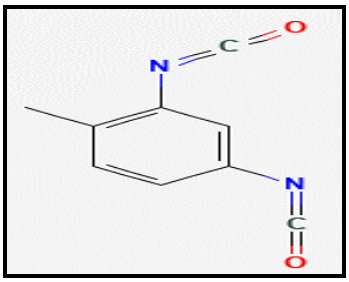
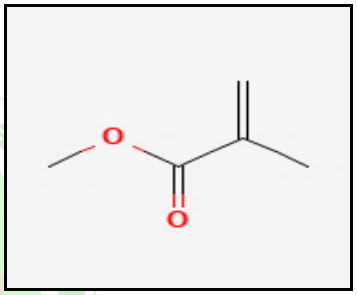
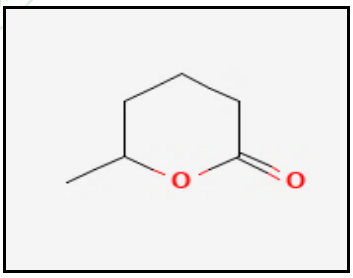
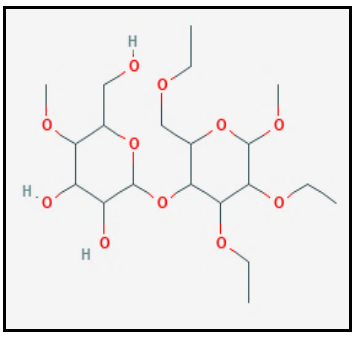
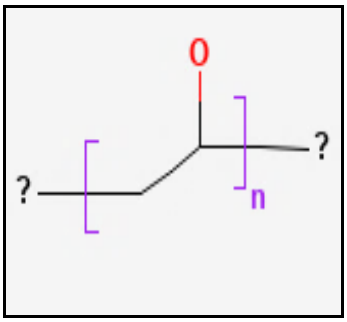
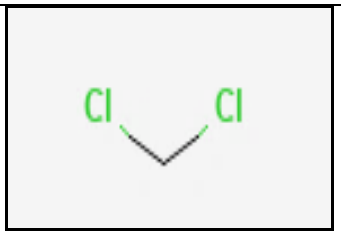
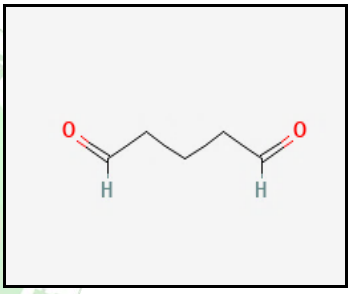
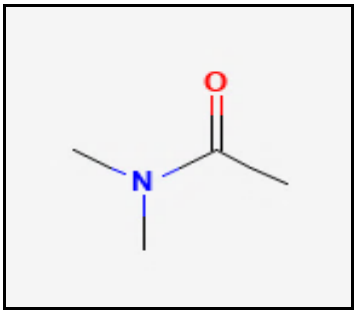
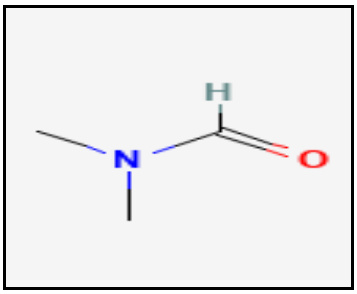
Diphenyl carbonate [56]	Dichloromethane [57]	Di-isocyanates [58]
		

Table 3: Components of Nanosponges

Component Name	Description	Structure	References
Polymer			
Eudragit RS100	Copolymers including an ester of methacrylic acid, methyl methacrylate, and ethyl acrylate containing quaternary ammonium groups (trimethyl ammono ethyl methacrylate chloride) at low concentration make up EUDRAGIT® RS 100. Granules are colourless, clear to hazy and they possess a mild amine-like smell. pH-independent swelling, limited permeability, insoluble. distinguished release characteristics by blending in various amounts with EUDRAGIT® RS. For sustained/extended release, functional coating polymer and matrix former are used in matrices.		59
Copolymer			
Poly (Valerolactone allyl Valerolactone)	The poly(δ-valerolactone-co-allyl-δ-valerolactone) (PVL-co-PAVL) is an entirely new polymeric substance which has been utilised to create microparticles (MPs) for long-lasting drug delivery. A redesigned oil-in-water method was employed to produce PVL-co-PAVL MPs and a UV-initiated cross-linking procedure was then carried out. The prepared MPs indicated a smooth, spherical shape and it was discovered that the copolymer's cross-linking enhanced the MPs' integrity and thermal sustainability.		31, 61
Ethyl cellulose	A portion of those hydroxyl molecules attached to repetitive glucose units change into ethyl ether groups, resulting in the manufacturing of ethyl cellulose, also referred to as ethyl cellulose. Different standards may be set by the manufacturer for the quantity of ethyl groups. Its main uses include as a thin-film material for coatings for paper, vitamin, medicine pills, as well as thickening agents in manufacturing processes and cosmetics. Food-grade Among the ethyl cellulose, the few safer films and thickening agents that are not soluble in water. This property allows substances that are water-resistant.		53

Polyvinyl Alcohol	Artificial polymer poly vinyl alcohol (also known as PVA, PVOH or PVAI) dissolves in water. The envisioned formula for it is $[CH_2CH(OH)]_n$. It is utilised in the manufacturing of paper, textile warp sizing, thickening and stabilising emulsions in poly vinyl acetate (PVAC) adhesive preparations coatings and 3D printing. It has no colour and no smell (it is white). Typically, it comes like beads or water-soluble solutions. PVA solution can be gelled by repeatedly freezing and thawing it without the need for an external crosslinking agent. This results in extremely strong, ultrapure, biocompatible hydrogels that are useful for a range of applications, including contact lenses, cartilage and vascular stents.		32, 33, 34, 55
Cross linker			
Dichloromethane	The formula for dichloromethane, often known as methylene chloride, methylene bichloride or DCM, is CH_2Cl_2. A common solvent is this colourless, vaporous liquid with a sweet, chloroform-like smell. It is fairly polar and miscible with a broad selection of organic solvents, despite not being miscible with water.		57
Glutaraldehyde	A molecular organic group having molecular formula $(CH_2)_3(CHO)_2$ is glutaraldehyde. The molecular structure is made up of a five-carbon chains that has formyl (CHO) groups on both ends. Usually utilised as a mixture in water, it takes the form of various condensation products, hydrates and cyclic derivatives, some of which are interconvertible. The molecular structure is able to serve as a cross-linking agent for any material containing main amine groups and form imine linked linkages because it has two carbonyl groups which exhibit reactivity towards primary amine groups (as well as their hydrates). Glutaraldehyde solutions are employed as fixing agents and biocides because crosslinking causes numerous biological processes to become stiff and inactive.		38, 39, 60
Polar Solvents			
Dimethylacetamide	The chemical molecule dimethyl acetamide, commonly referred to as DMAc or DMA, has the formula $CH_3C(O)N(CH_3)_2$. In the process of chemical synthesis, this colourless, highly boiling solution which is water soluble can often be employed as a solvent that is polar. DMA is not very soluble in aliphatic hydrocarbons; however, it is miscible in the majority of other solvents. It can withstand to bases, though. Because of this, Dimethylacetamide is frequently utilised in the glue manufacturing business or as a dissolving agent for fibres (such as spandex and polyacrylonitrile). [40]		62
Dimethylformamide	The formula for the chemical substance dimethylformamide is $(CH_3)_2NC(O)H$. This colourless liquid, commonly referred to as DMF (while this abbreviation is also occasionally used to refer to dimethylfuran or dimethyl fumarate), is soluble with water and most other organic solvents. A typical solvent for chemical processes is DMF. Dimethylformamide has no odour, although samples that are technical-grade or degraded usually smell like fish because of dimethylamine contaminants. DMF and water are mixable. At 20 °C and the vapour pressure is 3.5 hPa.		39, 40, 63

CHEMICAL STRUCTURE OF CD'S

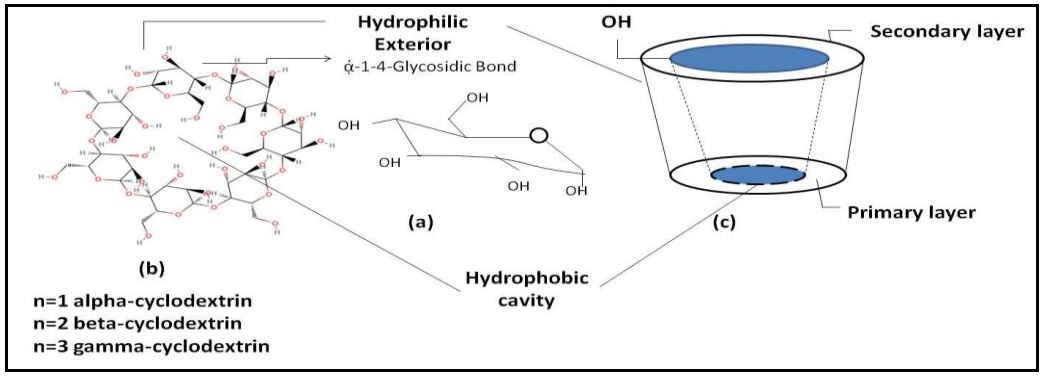


Figure 3: Diagrams depicting the overall chemical structure (a), the chemical structure and dimensions of α-, β-, and γ-cyclodextrin (b), and the three-dimensional (3D) structure of cyclodextrins respectively [43]

Cyclodextrin Polymer with Cross-linkers

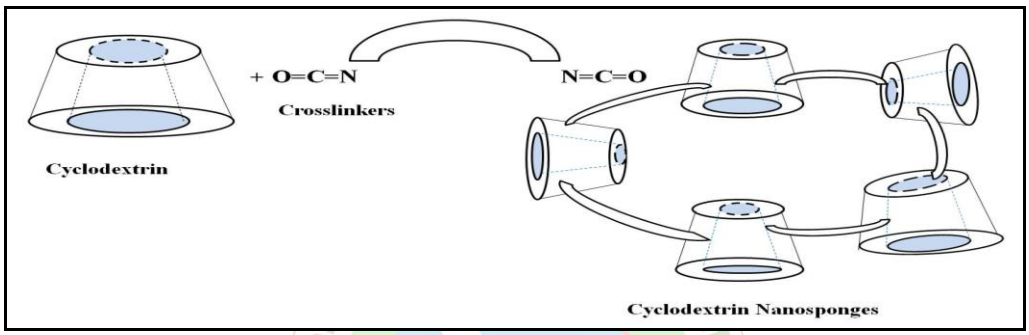


Figure 4: Cyclodextrin Nanosponge is created by crosslinking polymer with cyclodextrins.[43]

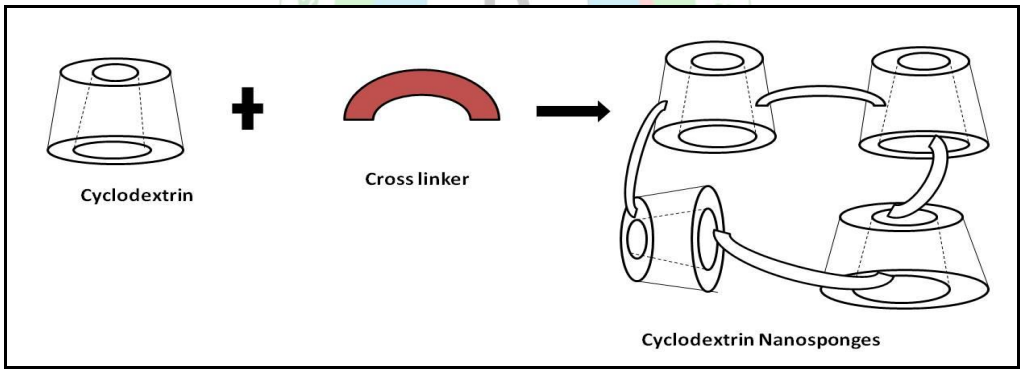


Figure 5: Cyclodextrin Nanosponges and several cross-linking agents [43]

METHOD PREPERATION OF NANOSPONGES

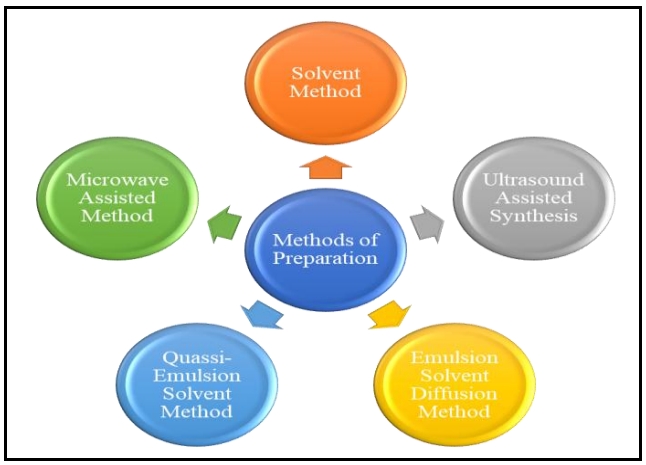


Figure 6: Methods of preparation of nanosponges.[19-24] [69-73]

1. **Solvent Method** [19][20]

- The solvent approach is used to make nano sponges by mixing polar aprotic solvents with the polymer such as DMF and DMSO stand for dimethyl sulfoxide and dimethylformamide.
- Next, a cross-linker is added to this mixture at a ratio of 1:4. Therefore, mentioned reaction is required to be executed at 10˚C in order to reflux the temperature of the solvent for a period of 1 to 48 hrs.
- Following the completion of the reaction, after allowing the mixture to reach room temperature, bi-distilled water is added to the finished product.
- After the filtration of product under vacuum and refined by using Soxhlet extraction method with ethanol and drying, the product is recovered.

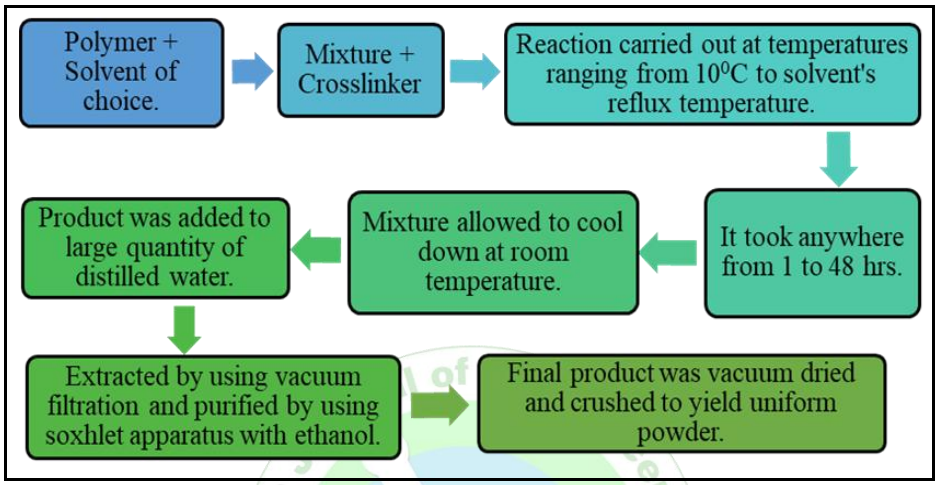


Fig 7: Solvent method.

2. **Ultra-sound assisted synthesis**[21].

- Without the use of a solvent, the polymers are designed to interact with cross-linkers in a flask.
- The mixture is withdrawn from the flask after it has been submerged in an ultrasonic bath that has been filled with water, heated to 90˚C, and sonicated for five hours.
- After the mixture reached room temperature, the result is roughly divided into pieces.
- Finally, the product is cleaned with water to eliminate the non-reacting polymer and ethanol is used in a Soxhlet device to refine the product and create nanosponges.

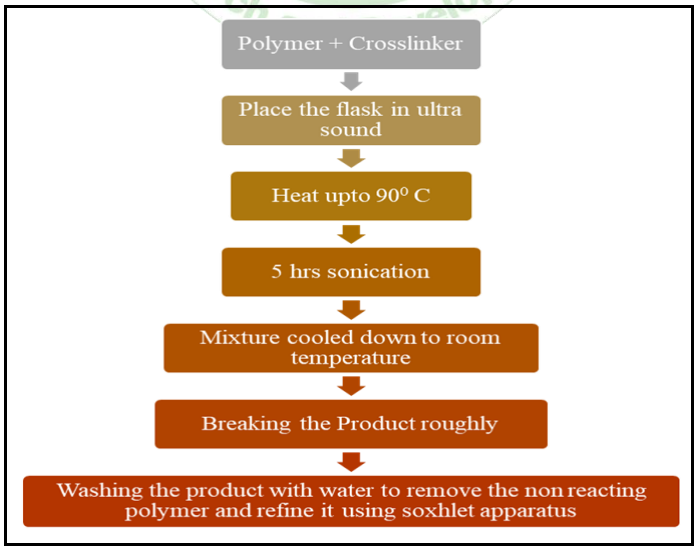


Figure 8: Ultrasound assisted synthesis.

3. **Emulsion-solvent diffusion method** [24].

- The technique involves manufacturing nanosponges using various ratios or quantities of polyvinyl alcohol and ethyl cellulose.
- This method uses two phases: continuous and dispersed, the drug and ethyl cellulose constitute the dispersed phase.
- The drug was dissolved in 20 millilitres of dichloromethane & 150 millilitres (ml) of the continuous

phase (aqueous) are mixed with a little quantity of polyvinyl alcohol (PVA).

- After that, the mixture was agitated for approximately 2 hours at a speed of 1000 revolutions per minute.
- The product was gathered through filtration process.
- At 40˚C, the product finally dried in an incubator.

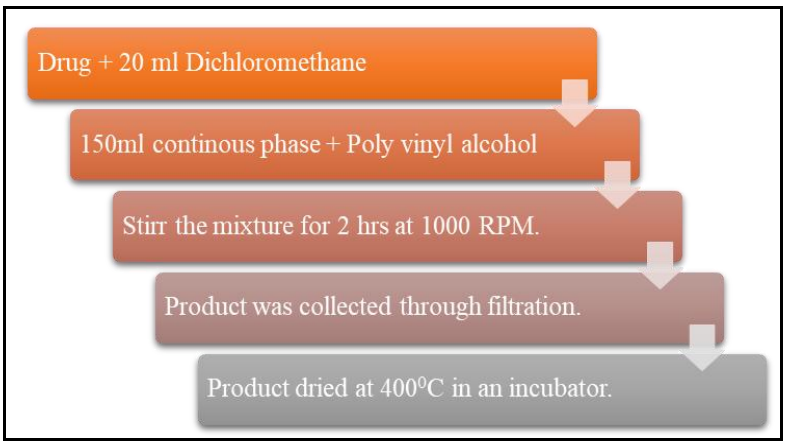


Figure 9: Emulsion-Solvent Diffusion Method.

4. Quasi-Emulsion Solvent Diffusion [22] [23]

- Nanosponges can be made with different quantities of the polymer.
- Eudragit RS-100 is used to produce the inner phase, which is then combined with a compatible solvent.
- The medicinal product was dissolved at 35 ºC using ultrasonication and a solution.
- This inner phase functions as an emulsifying agent when added to the external phase that contains PVA.
- After three hours of stirring at 1000–2000 rpm at ambient temperature, the mixture is dried for 12 hours at 40 ºC in an air-heated oven.

5. Microwave-Assisted Synthesis Method [69]

- Because thermal gradients exist during conventional and ultrasonic heating processes, non-uniform transformations result, causing longer reaction times and scalability issues.
- As a result, reactions are accelerated 4 times faster by microwave radiation than by the melting process & more scalable and reproducible as a result of the microwave irradiation's controlled and uniform heating.
- Thus, extremely crystalline materials can be produced by microwave synthesis. CDNS's by reacting CD with a suitable crosslinker (usually DPC) in polar aprotic solvents like DMF, resulting in a narrow particle size distribution.
- According to a report, tin octanoate catalyst was used to encourage the reaction between β-CD and HDI crosslinker using DMF as the solvent in a microwave system at 80°C for 30 minutes.

- This solvent condensation synthesis can be carried out utilising microwave irradiation.

LOADING OF DRUGS IN NANOSPONGES [35]

- Pre-treatment of nanosponges It's important to accomplish mean particle sizes below 500 nm for drug delivery. To prevent aggregates from forming, sonicate the nanosponges in water and then centrifuge the mixture to separate the colloidal fraction.
- Freeze-dry the supernatant soon after removing it from the sample, make a solution of Nanosponges in water, distribute the excess medication and in order to facilitate complexation, stir continuously.
- Centrifugation should be used to separate the complexed drug from the insoluble (undissolved) drug during complexation. Solvent evaporation or freeze-drying can then be used to generate solid crystals of nanosponges. Drug complexity necessitates crystal structure. According to one study, crystalline and para-crystalline nanosponges have different loading capabilities.
- Drug loading is higher in crystalline nanosponges as compared to para-crystalline nanosponges. Rather than a drug inclusion complex, drug loading happens mechanically in weakly crystalline nanosponges.

STRUCTURE OF NANOSPONGES

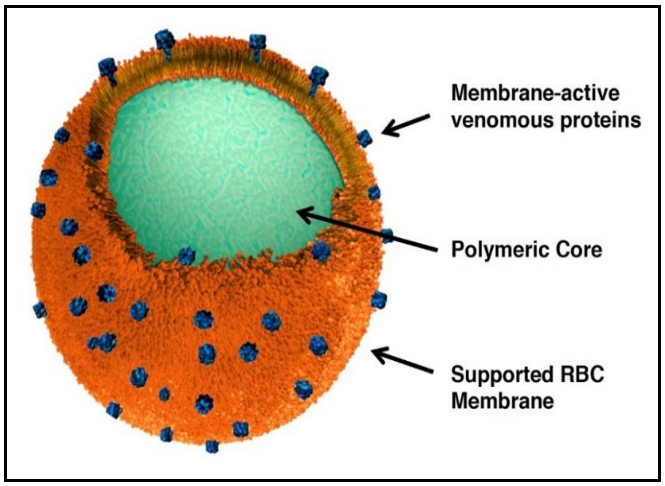


Figure 10: Structure of nanosponge. [16]

APPLICATIONS OF NANOSPONGES [24]

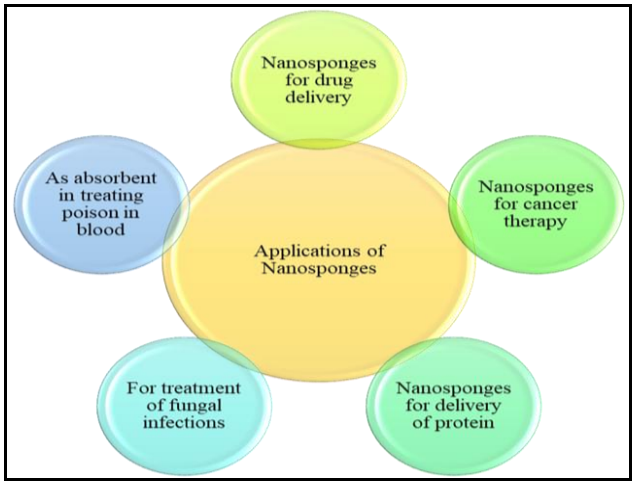
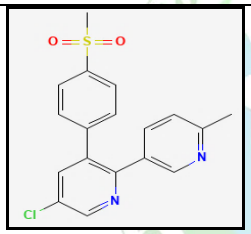
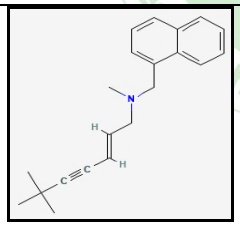
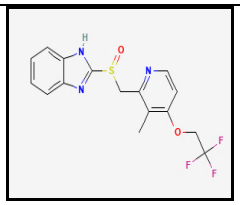
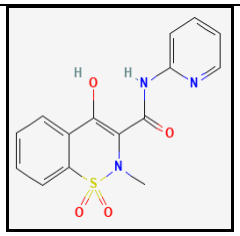
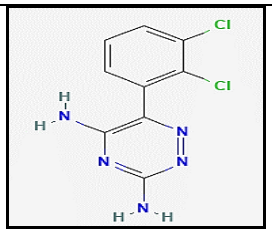
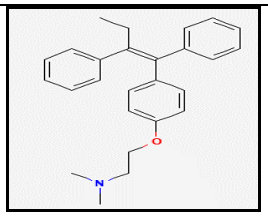
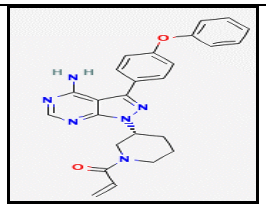


Figure 11: Applications of Nanosponges

Table 4: Synthetic drugs used in Formulation of Nanosponges.

Sr. No.	Drug Loaded Nanosponges	BCS class	Drug Structure	Polymers used in the preparation of nanosponges	Crosslinker	Method Used	Therapeutic Activity	References
1	Etoricoxib	II		Ethyl Cellulose	Dichloromethane	Ultra-sonication Method	Anti-inflammatory	50, 76
2	Terbinafine	II		Ethyl Cellulose	Dichloromethane	Solvent Emulsion Evaporation Method	Anti-fungal	45, 49, 77
3	Lansoprazole	II		Ethyl Cellulose	Dichloromethane	Solvent Emulsion Evaporation Method	Proton Pump Inhibitor	44, 78
4	Piroxicam	II		β-cyclodextrin	Carbonyl Diimidazole	Solvent Emulsion Evaporation Method	Anti-inflammatory	51, 64

5	Lamotrigine	II		Ethyl Cellulose	Dichloromethane	Emulsion Solvent Diffusion Method	Anti-epileptic	66, 67
6	Tamoxifen	II		Ethyl Cellulose	Carbonyl Diimidazole	Emulsion Solvent Diffusion Method	Anti-cancer	68, 69
7	Ibrutinib	II		Ethyl Cellulose, Poloxamer 188 and Eudragit RL 30 D	Dichloromethane	Emulsion Solvent Evaporation Method	Anti-cancer	74, 75

HERBAL NANOSPONGES

Throughout the years, traditional herbal therapy has been used and is still widely used in healthcare systems across the globe. Herbal medicines can have limited therapeutic potential and efficacy because to a number of problems, including non-specific targeting, instability and inadequate absorption. Recent years have seen the rise of nanotechnology as a viable means of overcoming these obstacles and transforming the herbal medicine industry. This article examines the use of nano drug delivery systems to increase the effectiveness of herbal treatments. The initial stage in using nanotechnology in herbal medicine is to develop and produce nano-sized carriers that can encapsulate and distribute herbal bioactive components to the target locations in a targeted and regulated manner [25].

For thousands of years, humans have used natural plant-based heals for a variety of health issues as part of herbal medicine. However, issues like low bioavailability, insufficient targeted distribution and unstable active ingredients have frequently restricted the effectiveness and beneficial effects of herbal remedies. Recently, a ground-breaking method for overcoming these barriers and realising the complete effectiveness of herbal therapy has been revealed: nanotechnology [26].

The control and alteration of materials at the nanoscale, usually within 1 to 100 nanometres, is the focus of nanotechnology [27]. It features special qualities and capacities that can be used to improve medication delivery systems. Nano drug delivery methods have the potential to enhance the targeted release, absorption, distribution of bioactive substances derived from herbal sources within the realm of herbal medicine [28].

By resolving the drawbacks of conventional herbal treatments, herbal medicine and nanotechnology together have the power to significantly alter the field. Herbal compounds that have been nano encapsulated not only have increased stability & bioavailability but also enable the synergistic blending of several herbal constituents to maximise their treatment outcomes. This strategy creates new opportunities for personalised medicine by enabling the customization of herbal remedies to meet the needs of specific patients [29].

NEED OF THE NANOPARTICLES IN HERBAL REMEDIES

- For the following reasons, herbal nanoparticles have been chosen to circumvent the disadvantages of conventional herbal medications [41].
- The use of nanoparticles to target specific organs boosts the safety, efficacy, selectivity and delivery of herbal medicines.
- The nanoparticles can be employed to improve the ability of herbal medications to dissolve and facilitate localization to a particular location, hence enhancing their efficacy.
- The special size and high loading capabilities of nanoparticles enable them to transport large amounts of medication to infections areas.
- Demonstrates an elevated effect of both retention and penetration, meaning that retention is caused by insufficient lymphatic drainage and improved permeation occurs via the barriers due to their tiny size [42].

- Reflects no specific ligand moiety insertion and passive targeting towards the area of action within the disease.
- Reduces any adverse effects.

Need Of Novel Drug Delivery System "Nano Carriers" For "Herbal Remedies" [25]

- Herbal medicine ingredients have to overcome barriers in order to enter the bloodstream. Some may be metabolised in the liver, while others may be broken down in the stomach's extremely acidic environment.
- Due to this, the intended dosage of herbal medications might not enter the circulatory system adequately.
- The intended result cannot be accomplished if the medication does not get to the affected area in sufficient quantity to have a therapeutic impact.
- Herbal medicines that use nanocarriers can deliver the right amount of medication to the intended region of action while avoiding obstacles like the stomach's acidic pH and the metabolism of the liver [30].
- In addition, the medication circulates in the bloodstream for a longer period of time because to these nanocarriers' small size.
- In the area of herbal treatments, there is a novel medicine delivery is necessary, particularly nano carriers, for a number of reasons.

Table 5: Herbal drugs used in Formulation of Nanosponges

Sr. No.	Herbal Extract	Active Ingredients	Polymers used in the preparation of nanosponges	Crosslinker	Method used	Therapeutic Activity	Reference
1	Turmeric	Curcumin	β-cyclodextrin	Dimethyl Carbonate	Emulsion-Solvent Diffusion Technique	In the treatment of Ulcerative colitis	37
2	Cinnamon oil	Cinnamaldehyde, Cinnamate, Cinnamic Acid, etc.	Ethyl Cellulose	Dichloromethane	Emulsion-Solvent Diffusion Method	Anti-Bacterial	48
3	Turmeric and Coffee Beans	Curcumin and Caffein	β-cyclodextrin	Dimethyl Carbonate	Hot Melt Method	In the psoriasis treatment	52
4	MurrayaKoenigii	α-Terpinene, β-Ocimene, Myrcene, Elemol, Geranyl Acetate, and Linalool	Eudragit RS 100	Dichloromethane	Quassi-Emulsion Solvent Diffusion Method	For Burn Wound Healing	84, 85
5	WrightiaTictoria	β-amyrin, wrightiadione, wrightial and Lupeol	β-cyclodextrin	Dimethyl Carbonate	Melt Dispersion Method	In the Psoriasis treatment.	86, 87, 88, 89
6	Curcuma longa and Vitis vinifera	Curcumin and Resveratrol	β-cyclodextrin	Pyromellitic Dianhydride	Emulsion-Solvent Diffusion Method	Breast Cancer	90
7	Rutin	Rutin	Ethyl Cellulose	Dichloromethane	Emulsion-Solvent Diffusion Method	Antioxidant, Anti-allergic, Antiviral	91

FACTORS INFLUENCING NS'S FORMATION [69]

There are some Key components that have a role in the creation of NS.

These are the following:

a) **Type of Drug:** In addition to their hydrophilic or hydrophobic nature, the medications' "Five rules of Lipinski" characteristics influence how NSs develop.

b) **Crosslinkers and Type of Polymer:** The synthesis of NSs is significantly influenced by the kind of CD (α, β, γ-CD) and the crosslinkers employed. The exact size of NS particles is determined by the molar ratio of the cross-linker & CD; cross-linker types are crucial in developing NSs into a 3D structure that is appropriate for hydrophilic or hydrophilic drugs.

c) **Temperature:** Raising the temperature, for instance, may specifically cause the drugs and NSs to interact through lowering or decreasing intermolecular hydrophobic forces (such Van der Waal's force).

d) **Technique for Preparing Nanosponges:** Depending on the drug's composition and the polymer utilised in the formulation, the method's efficacy affects both the incorporation of the drug in the NS's and the development of the NS and drug complex. The freeze-drying method is among the most helpful for the formation of drug/nanosponge complex.

e) **Degree of Substitution:** Depending on the quantity, location, and configuration of the substituent on the parent polymer, different nanosponge complexes may be produced. As an example, greater cross-linking between CD and the crosslinker is possible as the higher the degree of substitution on the parent polymer.

f) Nanosponge Toxicity: In order to assess the utility of the structure, toxicity tests are vital in order to determine whether the drug dose employed and the nanocarrier intended for drug delivery are harmful to people and animals. Studies on the toxicity of NS have not revealed any harmful or toxic consequences. For example, the acute systemic toxicity of NS's has been demonstrated to be safe between 500 and 5000 mg/kg by injecting it into Swiss albino mice, and it exhibits no toxicity or adverse responses. Furthermore, mice used in the investigation of oral nanosponge treatment showed no appreciable adverse effects. NSs had no harmful effect, according to in-vitro toxicity studies employing cell cultures such as MCF-7, COS, and H.E.L.A and the MTT test.

EVALUATION OF NANOSPONGES [44] [45]

Particle size, drug polymer compatibility, % yield, in-vitro drug release, entrapment efficiency, and scanning electron microscopy was evaluated for the obtained nanosponges.

Physical appearance, skin irritability, pH and drug release, drug content, and extrudability and spredability as rheological characteristics were evaluated for the manufactured hydrogel formulations.

1. Fourier Transform Infrared Spectroscopy (FTIR) studies [46]

FTIR spectroscopy is used for evaluating drug loading within the formulation, cross-linking, polymerization, and drug-excipient interaction. The sample's scanning range was 4000-400 cm-1.

2. Analysis of particle size [47]

Particle size was evaluated using the Malvern Zetasizer. The poly-dispersity index (PDI) was additionally calculated. The PDI of a poly-disperse system is 1, whereas the value for a monodisperse system was 0.

3. Percentage Entrapment Efficiency: [65]

A volumetric flask containing 10 mg of nanosponges and 5 ml of methanolic HCl was shaken vigorously for one minute. Methanolic HCl was used to raise the volume to ten millilitres. The Drug content was recorded using spectroscopy at 220 nm after the solution was thoroughly filtered and properly diluted. Each formulation's percentage Drug content was recorded in triplicate, and the average results were reported.

4. Scanning Emission Microscopy: [92]

SEM is used at various magnifications to observe the morphological characteristics of produced nanosponges.

5. Determination of the particle size, polydispersity index, and zeta potential:

HORIBA scientific nanosponges (Nano particle size analyzer) SZ-100 was used to measure the characteristics of the nanosponges, including size distribution, zeta potential, and particle size diameter. The particle size distribution's width curve or the polydispersity index (PDI), was calculated as an indicator for homogeneity. Using the following formula, the polydispersity of drug-loaded nanosponges with non-uniform size was determined:

Polydispersity = [D 0.9 – D 0.1] / D 0.5

where,

Particle diameters D 0.9, D 0.1, and D 0.5 are found at the 90th, 50th& 10th percentiles of unwanted particles, respectively. A uniform population is indicated by low PDI values, whereas a highly heterogeneous population is indicated by high PDI values.

6. In-vitro drug release: [92]

Using a USP paddle apparatus, the in vitro release study of the substance from the nanosponges equivalent to 10 mg of drug was determined. A temperature of 37 ± 0.5°C was maintained & speed of the paddle rotation was kept at 50 rpm. As a separate dissolution medium, A pH 6.8 phosphate buffer solution (900 mL) was utilised for the release study. To keep the sink condition, 5 ml of sample were taken out at pre-arranged intervals and replaced with the equivalent amount of new dissolving medium. After filtering, the withdrawn liquids were measured at 220 nm for a pH 6.8 test.

7. Differential Scanning Calorimetry: [65]

DSC analysis of rutin and various nanosponges ratios is carried out on each sample in an equivalent environment with alumina serving as a reference, a temperature range of 0 to 420º C, at heating rate of 20ºC/min, and a nitrogen atmosphere of 20 ml/min. Samples were heated and DSC measurements were carried out by using Shimadzu DSC-60.

8. Entrapment Efficiency: [92]

It can be calculated to determine the effectiveness of any method, which aids in choosing the most suitable manufacturing strategy. Following formulation preparation, the ratio of the total amount of starting material (Theoretical yield) to the number of nanosponges collected from each preparation were utilised to calculate the Practical yield.

9. **In-vitro drug diffusion studies:** [92]

Employing the dialysis membrane approach, in-vitro drug release tests were conducted for each formulation. The membrane was kept to stir on a magnetic stirrer after being bathed in a 7.4 pH buffer for 24 hours. The receptor compartment was also filled with buffer. A 100 mg dose of NS powder was put into the membrane. For 12 hours, the stirring speed of 600 rpm was maintained. Every hour, 5 ml of the drug sample was removed and the same amount of freshly made buffer was substituted. A UV Spectrophotometer set at 550 nm was used to analyse the drug. Quantity of drug released was computed. An optimised formulation was selected, and the SEM studies were carried out, based

on the evaluation results mentioned above.This formulation was incorporated into gel and further evaluation studies for nanogel were carried out.

CONCLUSION

Nanosponges are a subject of intensive research due to their unique morphology, which among other effects contributes to an electrodynamic field. Cyclodextrin nanosponges have shown potential for enhanced anti-melanoma activity of silymarin, with antioxidant and anti-inflammatory properties, offering promise for the treatment of skin cancer. Additionally, a study aimed to enhance the aqueous solubility and bioavailability of lapatinib through the formulation of lapatinib nanosponges.

Nanosponges have gained significant attention for topical drug delivery, especially as a potential strategy for treating fungal infections. The development of cervix-targeted hydrogel carriers containing carboplatin-loaded nanosponges is being explored for mucosal application in the treatment of cervical cancer. Furthermore, quercitrin-loaded cyclodextrin-based nanosponges have been investigated for their potential in the management of lung cancer and COVID-19.

It is important to note that cyclodextrins are extensively employed in drug delivery systems such as inclusion complexes, metal-organic frameworks, and functionalized nanoparticles, offering new opportunities for high-quality biomedical applications. The integration of cyclodextrins and associated toxicities is also an essential aspect to consider in the roadmap for their biomedical applications.

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