Nanosponges as Emerging Nanocarriers for Enhanced Solubility and Oral Bioavailability

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ABSTRACT

Nanosponges (NSs) are advanced, porous, nanoscale carriers designed to enhance drug solubility, stability, and bioavailability—particularly for poorly soluble drugs. With a 3D network structure containing hydrophilic interiors and hydrophobic exteriors, NSs can encapsulate both hydrophilic and lipophilic drugs and release them in a controlled, targeted manner. They protect drugs from degradation and support various administration routes, including oral, topical, parenteral, and nasal. This review highlights recent developments in NS preparation, drug loading, and their potential in improving oral drug absorption and systemic delivery for a range of therapeutic applications.

Keywords: Nanosponges, Cyclodextrins, Controlled release, Cross-linking agents, Oral drug delivery.

1. Introduction

The main goal of any drug delivery system is to transport an adequate amount of a drug to its intended site of action within the body while maintaining the necessary plasma concentration over a desired period of time [1,2]. An ideal system should enhance the drug's solubility and ensure therapeutic effectiveness at the target location, tailored to meet both the individual patient's needs and the progression of the disease [3]. Targeted drug delivery plays a key role in enhancing therapeutic outcomes, minimizing side effects, and optimizing dosage regimens—making it a major focus in modern drug delivery technologies [4–6]. Among the various advanced carriers, nanosponges (NS) have gained significant attention due to their ability to provide controlled and predictable drug release [7]. These nanoscale delivery systems offer precise drug targeting, contributing greatly to medical advancements, especially by enhancing the performance of existing pharmaceuticals.

Nanosponges (NSs) are playing a pivotal role in supporting the development of innovative therapies [8–10]. Structurally, NSs are tiny, three-dimensional, mesh-like frameworks featuring nanoscale cavities capable of encapsulating a broad spectrum of substances, such as volatile oils, anticancer agents, proteins and peptides, and even DNA [11–13]. The foundation of a nanosponge consists of a long polyester chain, which is blended in a solution with small molecules known as cross-linkers. These cross-linkers function like miniature grappling hooks, helping to bind different sections of the polymer together [14]. When cyclic oligosaccharides, particularly Cyclodextrins (CDs), interact with appropriate cross-linking agents, they form a unique nanoscale structure that enhances drug delivery capabilities.

A nanomaterial made from hyper-cross-linked cyclodextrins (CDs), commonly referred to as CD-based nanosponges (NSs), can be synthesized through this process [15,16]. To ensure biodegradability within the body, the polyester backbone of NSs must be capable of breaking down. Drug release begins as the structural backbone of the nanosponge starts to degrade [12].

NSs offer a range of significant advantages over other existing nanoparticulate systems [17]. They can be conveniently regenerated through various methods such as gentle heating, modifying pH or ionic strength, exposure to moderately inert hot gases, or rinsing with environmentally friendly solvents [18].

Due to these versatile properties, NSs have garnered considerable interest for applications across several industries, including pharmaceuticals, nutraceuticals, cosmetics, and cosmeceuticals [19–21].

NSs can be engineered in different forms, influenced by factors such as the type and strength of the polymer used, as well as the preparation technique. Numerous formulations have already been documented in scientific literature (Fig. 1). Among them, beta-cyclodextrin (β-CD)-based NSs are the most extensively researched and widely applied variants.

Structurally, NSs are solid, spherical colloidal particles with a porous surface. Owing to their unique inclusion and non-inclusion mechanisms, they possess exceptional solubilizing capabilities—particularly beneficial for poorly water-soluble drugs, especially those classified under BCS Class II and IV [22–24]. NSs can be easily integrated into various excipient matrices such as diluents, disintegrants, lubricants, and anti-caking agents for the development of oral dosage forms. Additionally, they can be formulated into parenteral, topical, or inhalable delivery systems [25,26].

When used in tablets or capsules, NSs offer several critical advantages: targeted retention at the site of action, reduced required dosage, minimized toxicity, improved patient adherence, and extended drug release [24,27]. NSs can be suspended in saline, sterile water, or other aqueous solutions for parenteral use. In topical applications, they can be effectively incorporated into hydrogels for enhanced delivery [28].

Nanosponges (NSs)

Nanosponges (NSs) are tiny, sponge-like particles that can carry both water-loving (hydrophilic) and water-repelling (hydrophobic) drugs because of their special structure—hydrophobic spaces inside and hydrophilic surfaces outside [8]. They look like small, three-dimensional networks. These structures are formed using long polymer chains connected by crosslinkers, which act like hooks to hold the network together [87]. The final product is a round particle with small holes inside where drugs can be stored [85].

NSs are often made by combining cyclodextrins (a sugar-based molecule) with crosslinkers, creating a tightly connected, nano-sized material. This process helps mask the bitter taste of some drugs and turns liquid forms into solids for easier use in oral medicines like tablets [88]. By adjusting how much crosslinker is used, scientists can control how much drug the NS can carry and how fast it is released [89].

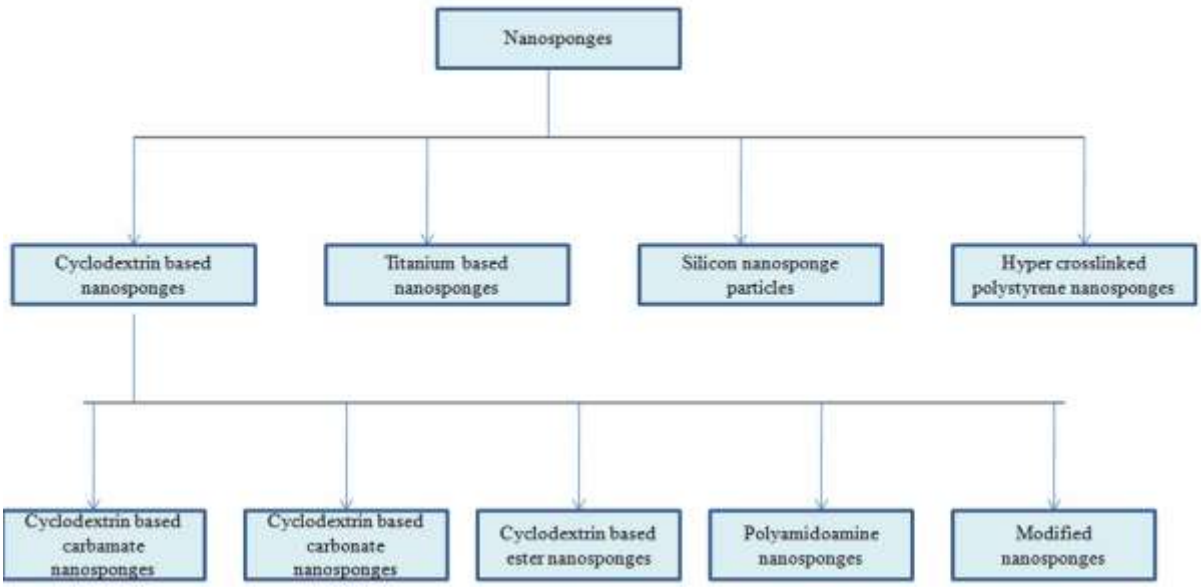
Depending on the type of crosslinker, NSs can be made to swell and can be either neutral or slightly acidic [90]. Their tiny porous structure allows drugs to be stored inside the cavities or attached on the surface, giving them better drug-carrying capacity than plain cyclodextrins [89]. NSs also protect the drugs from breaking down and can hold a wide range of medicines due to their high entrapment efficiency [91].

They are easy to make and can be reused, and they are also good at absorbing liquids into their sponge-like structure [92]. One limitation is that they work better for small molecules (less than 500 Da). The amount of drug they can carry also depends on how crystalline the drug is [93]. There's a small risk that the drug might be released too quickly (dose dumping), but this can be reduced by using special blends of polymers [94].

NSs are safe for both oral and injectable use [88, 95]. For oral delivery, they can be mixed with common tablet ingredients like fillers and lubricants to make capsules or tablets [96, 97]. Overall, NSs work by trapping drug molecules inside their core, acting as carriers that improve how drugs are delivered in the body [98].

Types of Nanosponges :

Nanosponges can be developed in various forms depending on the type and concentration of polymer used, as well as the chosen preparation method. Among these, β-cyclodextrin (β-CD)-based nanosponges are the most commonly synthesized and extensively studied. Their formulation is relatively simple and allows for multiple structural modifications (see Fig. 2) [127,128]



Chemicals Used in the Synthesis of Nanosponges

Polymers:

A variety of polymers are employed in the fabrication of nanosponges (NSs), including hyper-cross-linked polystyrene, different

forms of cyclodextrins such as standard, alkyloxy carbonyl-substituted, and 2-hydroxypropyl cyclodextrins, as well as copolymers like poly(valerolactone-allylvalerolactone) and poly(valerolactone-allylvalerolactone-oxepanedione) [85,86].

Crosslinkers:
Several crosslinking agents are utilized in NS synthesis, including diphenyl carbonate, diarylcarbonates, dicyandiamide, diisocyanates, pyrrolidine, carbonyldiimidazole, glutaraldehyde, carboxylic acid dianhydrides, 2,2-bis(acrylamido)acetic acid, and dichloromethane [85, 86].

NSS EDGES: [29-35]
1. Make the medication less annoying without sacrificing its efficacy.
2. Drug release that is targeted to a specific place.
3. Fewer negative side effects.
4. Biodegradable.
5. Controlled and predictable discharge.
6. Increasing adherence from patients.
7. The medication is shielded against deterioration.
8. By varying the amount of cross-linker added to the polymer, particle size can be changed.
9. Give the action a therapeutic start.

The composition of NSS: [36-41]

The arrangement process: The NSs are prepared using the following techniques:
1. Melt technique
2. Methods of solvent diffusion

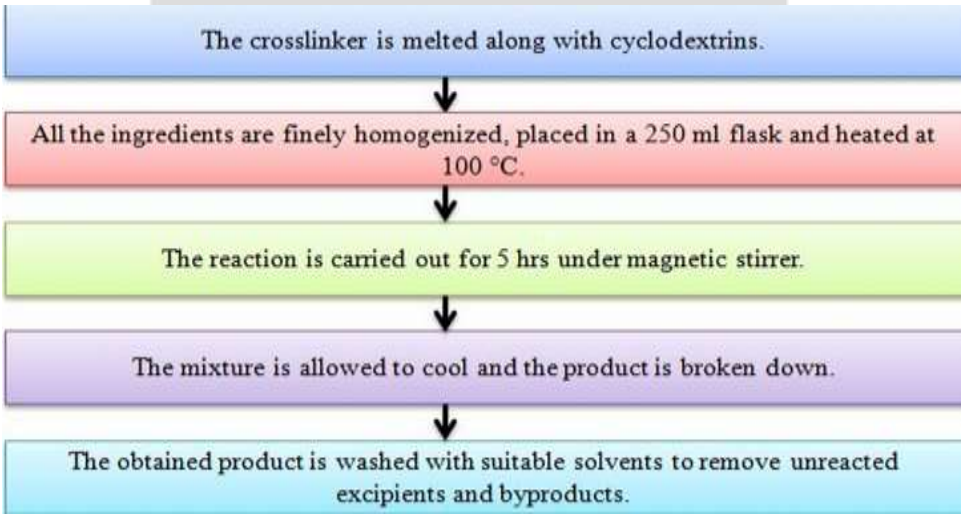
- Emulsion solvent diffusion method and
- Quasi-emulsion solvents

3. Solvent Method

4. Ultrasound Assisted Method

Melt Technique:

In this method, cyclodextrin is combined with an appropriate crosslinking agent, such as dimethyl carbonate, diphenyl carbonate, isocyanates, diaryl carbonates, carbonyldiimidazole ($C_7H_6N_4O$), or carboxylic acids. [42]The mixture is placed in a 250 mL flask and heated to 100 °C while continuously stirring using a magnetic stirrer. The reaction is maintained under these conditions for approximately 5 hours. Once the reaction is complete, the mixture is allowed to cool to room temperature. The solidified product is then ground and subjected to purification to eliminate any residual reactants or by-products.[43]



Solvent diffusion method :

Emulsion solvent diffusion technique –

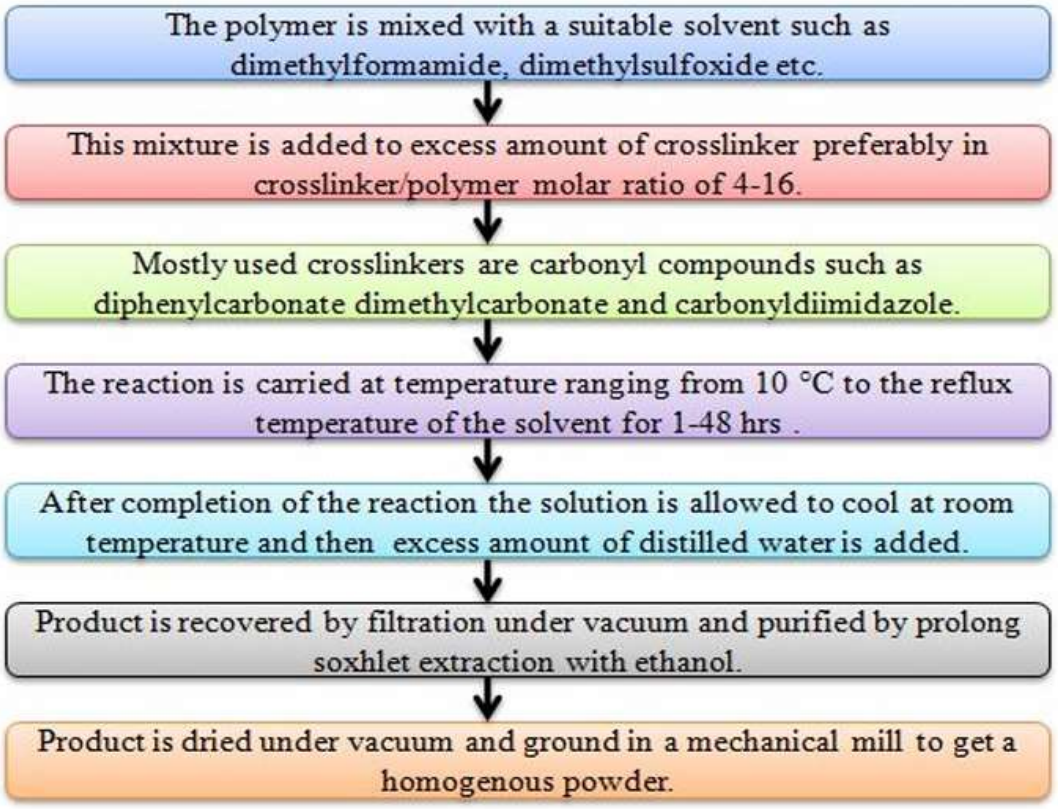
In this method, two distinct volumes of organic and aqueous phases are employed. The drug and polymer are dissolved in the organic phase, while the aqueous phase contains polyvinyl alcohol (PVA) [44]. Once the drug and polymer are fully dissolved in an appropriate organic solvent, this mixture is gradually added to the aqueous phase and stirred continuously for at least 2 hours at 1000 rpm using a magnetic stirrer [45]. The resulting nanosuspensions (NSs) are then collected by filtration, thoroughly washed, and dried either at room temperature in air or in a vacuum oven at 40°C for 24 hours.[46]

Quasi-emulsion solvent diffusion

In this technique, the polymer is first dispersed in a suitable solvent, forming what is known as the inner phase [47]. The drug is then added to this solution under ultrasonication at 35°C to ensure proper mixing [48]. This inner phase is subsequently introduced into the outer phase, which consists of an aqueous solution of polyvinyl alcohol (PVA) [49]. The resulting suspension is stirred using a magnetic stirrer at 1000 rpm for 60 minutes. Afterward, the nanosuspensions (NSs) are collected by filtration and dried in a hot air oven at 40°C for 2 hours [50].

Solvent method

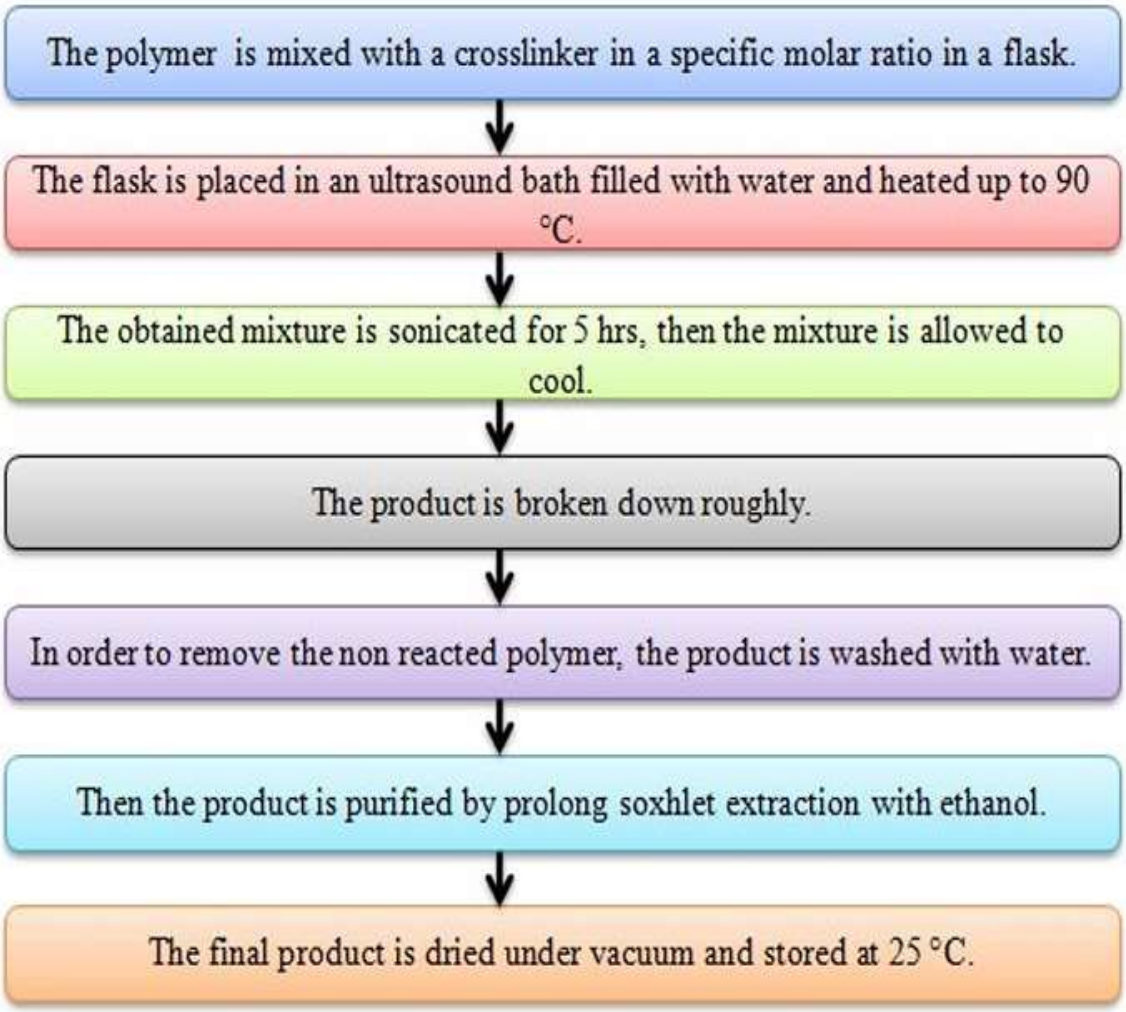
In this method, a polar aprotic solvent such as dimethylformamide or dimethyl sulfoxide is combined with an appropriate polymer. This mixture is then reacted with a large excess of a crosslinking agent, typically in a molar ratio ranging from 4:1 to 16:1 [51]. The reaction is carried out at temperatures between 10°C and the solvent's reflux point, for durations ranging from 1 to 48 hours. Commonly used crosslinkers include carbonyl-based compounds like dimethyl carbonate and carbonyldiimidazole ($C_7H_6N_4O$) [52]. Once the reaction is complete, the mixture is allowed to cool to room temperature before being poured into an excess of distilled water. The resulting product is collected via vacuum filtration and purified through extended Soxhlet extraction using ethanol. Finally, the purified product is vacuum-dried and ground into a fine powder using a mechanical mill [53].



Ultrasound-assisted technique

In this approach, the polymer is reacted with crosslinking agents without the use of a solvent and under ultrasonic treatment [54]. The resulting nanosuspensions (NSs) are typically spherical, uniform in size, and less than 5 µm in diameter [55]. Crosslinkers such as diphenyl carbonate or pyromellitic anhydride are used in the process. A suitable amount of anhydrous cyclodextrin is combined with molten diphenyl carbonate at 90°C and maintained for 5 hours [56]. After the reaction, the mixture is allowed to cool and is then coarsely ground. The crude product is washed with water and further purified using Soxhlet extraction with ethanol to remove residual and unreacted diphenyl carbonate [57]. Following purification, the NSs are stored at 25°C until further use [58].

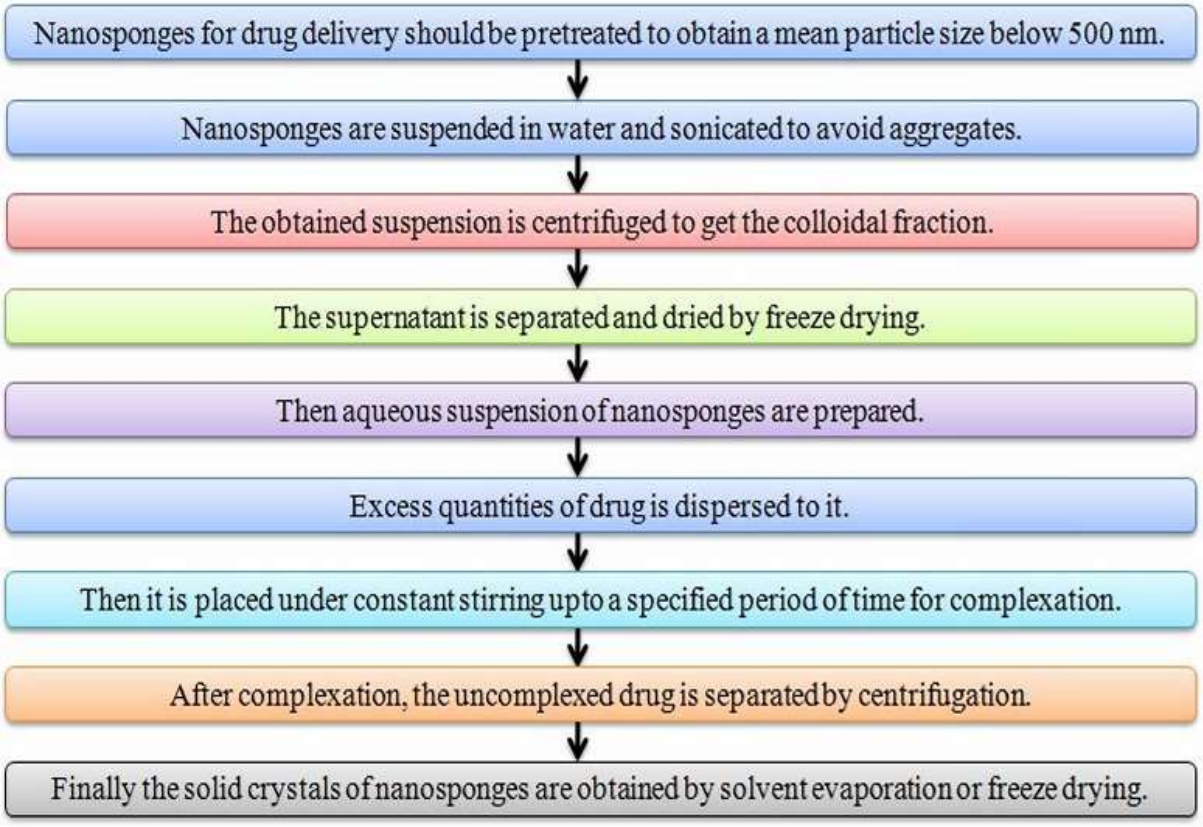
Fig: Schematic Representation of Ultrasound-Assisted Synthesis[133]



Loading of Drugs Into Nanosponges:[133]

Figure: Schematic Representation of Loading of Drugs in to Nanosponges

Note: Crystal structure of nanosponges plays a key role in complexation with drug. Drug loading is better in crystalline nanosponges when compare to paracrystalline one



Methods to load drugs in nanosponges:

Particle size—ideally under 500 nm—is a critical factor for effective drug delivery using nanosuspensions (NSs). To prevent particle aggregation, the NSs are first suspended in water and subjected to sonication. The resulting dispersion is then centrifuged to form a colloidal solution, which separates into a supernatant and solid NSs after freeze-drying. The drug is added in excess to this system and stirred continuously for a defined period, promoting complexation and aiding the formation of NSs within the aqueous medium. Any uncomplexed drug is removed by repeating the centrifugation step [59]. The final NSs are obtained by either solvent evaporation or freeze-drying of the solid crystals. A key objective is the integration of the drug into the NSs' crystal structure. Notably, para-crystalline NSs exhibit higher drug-loading capacity than their fully crystalline counterparts. In crystalline NSs, drug incorporation occurs via inclusion complexes, whereas in poorly crystalline forms, the drug is held as a mechanical mixture [60].

Drug release mechanism via nanosponges

Nanosuspensions (NSs) contain multiple pores within their core structure, which enable the free movement of drug molecules. When the surrounding liquid medium becomes saturated with the drug, and the formulation is applied either topically or orally, the encapsulated drug is released into the vehicle and subsequently absorbed by the skin or body [61]. This release lowers the drug concentration in the vehicle, creating an unsaturated state that disrupts the equilibrium. This cycle continues until the entire drug dose has been absorbed. Understanding this mechanism is essential for selecting appropriate carriers for NS formulation. However, as the formulation is prepared, the increased solubility of the drug may reduce the intended sustained-release effect, making the drug act more like a freely dissolved molecule rather than one that is encapsulated [62].

Progress of nanosponges in improving oral absorption of drugs

Advancements in Nanosuspensions (NSs) for Enhancing Oral Drug Absorption

Alongside the rapid progress in nanomedicine, nanosuspensions (NSs) have emerged as a promising approach for delivering active pharmaceutical ingredients. Due to their ultrafine size, typically with a mean particle diameter of less than 1 µm—and narrow size distribution, NSs form colloidal systems that appear opalescent when dispersed in water. Carbonate-based NSs often possess a zeta potential around −25 mV, which is high enough to maintain dispersion stability over time by preventing particle aggregation [63]. This stability also facilitates easier passage across physiological barriers.

A key advantage of reducing particle size is the significant increase in surface area, which improves the dissolution rate of poorly soluble drugs and enhances their absorption across the gastrointestinal (GI) tract's monolayer epithelium [64]. β-Cyclodextrin-based NSs are frequently used to enhance the oral bioavailability of various drugs. Research has shown that β-cyclodextrin can modulate the activity of P-glycoprotein (P-gp), a key efflux transporter, through complex mechanisms such as altering cell membrane fluidity, inhibiting ATPase activity, reducing P-gp expression, and modifying cholesterol levels [65].

Another notable advantage of NSs is their high entrapment efficiency (EE), which allows them to serve as reservoirs for therapeutic compounds, helping to protect the drugs from premature degradation [66]. Additionally, due to the protective effects of crosslinkers and other formulation materials, drugs encapsulated in NSs can evade first-pass metabolism, improving their systemic availability [67]. For instance, gamma-oryzanol encapsulated in NSs has demonstrated potent antioxidant activity and resistance to photodegradation [68]. Overall, NSs represent a versatile and effective drug delivery system that has been applied in the treatment of various diseases.

Anti-cancer drugs

Nanosuspensions (NSs) are emerging as a promising nanocarrier system for enhancing the effectiveness of anti-cancer drugs, especially given the challenges of low oral bioavailability and poor tumor-targeting specificity often seen in cancer therapies. For instance, when paclitaxel-loaded NSs were administered orally to rats via gavage, using the commercial formulation TAXOL® as a control, the drug's oral bioavailability increased by approximately threefold compared to the control [69].

Similarly, tamoxifen-loaded NSs with optimal particle size were developed using the conventional inclusion complexation method. These formulations led to a significant improvement in the pharmacokinetic profile of tamoxifen compared to its citrate form. Oral administration of tamoxifen via the NS formulation resulted in significantly higher plasma concentrations ($P<0.01$), showing a 1.44-fold and 1.38-fold increase over the plain drug at the same dose [70].

Analgesics and anti-inflammatory drugs

Acetylsalicylic acid (ASA), a non-steroidal anti-inflammatory drug (NSAID) belonging to BCS class III, was formulated into pyromellitic dianhydride cross-linked β-cyclodextrin (β-CD) nanosuspensions (NSs) [71]. Transmission electron microscopy (TEM) analysis revealed that the ASA-loaded NSs had an average particle size of 40 to 60 nm and maintained a consistent spherical shape. The zeta potential was sufficiently high, allowing the formation of a stable colloidal system. Both in vitro and in vivo studies demonstrated that the pyromellitic cross-linked β-CD NSs released ASA slowly and continuously over a 24-hour period. In an in vivo study, when administered via oral gavage to rats with carrageenan-induced paw edema, the ASA-loaded NSs significantly reduced inflammation ($P<0.01$ and $P<0.05$) compared to plain ASA and the control group, respectively. These results suggest that ASA-loaded NSs may be effective for oral drug delivery [71].

Meloxicam, a Cox-2 inhibitor used to treat osteoarthritis, suffers from limited solubility and stability, leading to poor oral absorption. To address this, Shende et al. [72] investigated the use of NSs to enhance meloxicam's bioavailability. They prepared meloxicam-loaded NSs by combining meloxicam with a 1:8 molar ratio of β-CD crosslinked with pyromellitic dianhydride (PMDA). This formulation demonstrated improved aqueous solubility. Similarly, piroxicam (PXM), another highly effective NSAID used for conditions such as osteoarthritis and post-surgery pain, is also classified as a Class II drug due to its low solubility and high permeability. The low solubility of PXM results in poor bioavailability after oral administration. However, the formation of inclusion complexes with β-CD improved PXM's analgesic effect in mice and increased the relative bioavailability of PXM-loaded NSs by 1.42 times compared to commercial tablet formulations [73].

Antidiabetic drugs

Gliclazide, a BCS Class II anti-diabetic drug, was formulated into nanosuspensions (NSs) using the emulsion solvent diffusion method with Eudragit S100 as the polymer. Various drug-to-polymer ratios were tested, and the resulting NSs showed improved bioavailability of the drug [74].

Glibenclamide, another oral anti-diabetic agent with very low water solubility, has only about 45% oral bioavailability. However, its complexation into NSs significantly enhanced its drug release profile. NSs of Glibenclamide, prepared using the emulsion solvent diffusion technique with a high-speed homogenizer, demonstrated a more controlled and increased drug release compared to the pure drug [75].

Similarly, Nateglinide, also classified as a BCS Class II drug due to its poor solubility, was successfully incorporated into NSs to enhance its solubility. This was achieved using ethyl cellulose as the polymer and dichloromethane as the cross-linking agent [76].

Central nervous system drugs

Carbamazepine, a BCS Class II drug characterized by low solubility and high permeability, was formulated into nanosuspensions (NSs) using the emulsion solvent diffusion method to enhance its solubility and dissolution rate. The NS formulation demonstrated improved solubility and a faster dissolution rate compared to the unprocessed drug. Additionally, the development of Carbamazepine NS tablets was successful, and the final formulation was found to be stable [77].

Cardiovascular drugs

Telmisartan, a BCS Class II antihypertensive drug, has limited bioavailability due to its extremely low water solubility, estimated at just 9.9 µg/mL. Research showed that when telmisartan formed a ternary complex with carbonate-based nanosuspensions (NSs) and sodium bicarbonate ($NaHCO_3$), its dissolution rate significantly improved [78].

Atorvastatin, another poorly water-soluble drug, was formulated into β-cyclodextrin-based NSs. When complexed with β-CD NSs, atorvastatin exhibited a biphasic release profile and showed a 2.13-fold increase in bioavailability compared to the unformulated drug. In pharmacodynamic studies conducted on rats with fatty liver, this formulation led to a notable reduction ($P < 0.05$) in total cholesterol, triglycerides, and LDL, while increasing beneficial HDL-C levels. Histological examination further confirmed an improvement in liver steatosis [79].

Carvedilol (CRV), a non-selective third-generation beta-blocker used in the treatment of angina, heart failure, and hypertension, suffers from low oral bioavailability (approximately 25%) due to extensive first-pass metabolism. To overcome this, CRV was incorporated into bilosomes, which were then formulated into buccal NSs using a carboxymethyl cellulose/hydroxypropyl cellulose (CMC/HPC) composite. The resulting NSs displayed high porosity (67.58%) and enhanced swelling capacity, as confirmed by morphological analysis. In vivo studies in rats demonstrated that CRV-loaded NSs significantly improved systolic and diastolic blood pressure, reduced oxidative stress, enhanced lipid profiles, and exhibited strong cardioprotective effects [80].

Fungal infection

Griseofulvin (GRI), an antifungal agent derived from the mold *Penicillium griseofulvum*, is administered orally to treat dermatophyte and ringworm infections, particularly those affecting the scalp, hair, nails, and skin when topical treatments are ineffective. GRI has limited water solubility (8.64 mg/L) and a log P value of 2.15, placing it in BCS Class II, where its absorption is primarily hindered by a slow dissolution rate. Additionally, GRI is known for its unpleasant taste, which can be a challenge, especially in pediatric formulations where liquid dosage forms are preferred for ease of administration. However, the drug's poor solubility complicates the production of such liquid formulations.

Nanosuspension (NS) formulations of GRI significantly improved its performance compared to the plain drug. The dissolution efficiency increased by 3.19 times, while pharmacokinetic parameters such as maximum plasma concentration (Cmax) and area under the curve ($AUC_{0–48}$) rose by 2.13 and 3.78 times, respectively. Moreover, taste-masking studies confirmed that GRI NSs effectively concealed the drug's bitter taste [81].

Anti-oxidants

Resveratrol, a potent antioxidant, is found in significant amounts—both in free and conjugated forms—in natural sources such as grape juice, peanuts, mulberries, and various plant extracts. It has long been utilized in medicine to treat a wide range of conditions, including inflammation, cardiovascular disorders, dermatitis, gonorrhea, fever, and high cholesterol. Resveratrol also contributes to the cardiovascular benefits associated with moderate consumption of red wine and is well-known for its cancer chemopreventive effects

In addition to its health-promoting activities, resveratrol exhibits antibacterial and antifungal properties, which are especially relevant in treating human skin infections. However, its hydrophobic nature results in poor water solubility, making dissolution the primary limiting step for oral absorption and, consequently, bioavailability. This issue was addressed by formulating resveratrol into β-cyclodextrin-based nanosuspensions (CD-NSs), which significantly enhanced its in vitro release profile and stability compared to the unformulated drug.

Cytotoxicity studies conducted on HCPC-I cells indicated that the NS formulation of resveratrol was more effective than the pure compound. Permeation studies further demonstrated that the NS formulation had superior penetration capabilities in pig skin. Additionally, accumulation studies using rabbit mucosa showed that the NS form of resveratrol achieved higher tissue retention than the plain drug [82].

Viral infection

Acyclovir, a synthetic nucleoside analogue derived from guanosine, is widely used as an antiviral agent, particularly for the treatment of herpes simplex virus infections (O'Brien and Campoli Richards, 1989). However, current commercial formulations of acyclovir—whether administered orally or parenterally—struggle to deliver the drug at therapeutically effective concentrations to target tissues. This is largely due to its poor and inconsistent absorption in the gastrointestinal tract, resulting in highly variable pharmacokinetics and low oral bioavailability, ranging from just 10% to 30%. As a result, high doses of up to 1.2 g per day are often required, with approximately 80% of the administered dose remaining unabsorbed.

To overcome these limitations, carboxylated cyclodextrin-based nanosuspensions (Carb-CD-NSs), which contain carboxylic groups in their structure, were developed as advanced carriers for acyclovir. These Carb-CD-NSs demonstrated improved drug loading capacity and more sustained drug release compared to conventional nanosuspensions. Additionally, in vitro studies showed that acyclovir encapsulated in Carb-CD-NSs exhibited superior antiviral activity [83].

Antimicrobial agents and anti-infectives:

Bacterial infection

Trimethoprim is an antibiotic primarily prescribed for the treatment of urinary tract and bladder infections. However, its low water solubility contributes to poor oral bioavailability. To address this issue, trimethoprim-loaded nanosuspensions (NSs) were developed and formulated into extended-release tablets aimed at enhancing solubility and ensuring a sustained release of the drug to the urinary tract.

The NSs were prepared using ethyl cellulose as the encapsulating polymer and dichloromethane as the cross-linking agent, applied in various ratios. These formulations were evaluated for several parameters, including powder flow properties, yield percentage, entrapment efficiency, particle morphology, zeta potential, particle size, and in vitro drug release profiles. Results indicated that the maximum drug release achieved was 98.43 ± 0.1% across all formulations. The study concluded that the extended-release tablets containing trimethoprim-loaded NSs successfully prolonged drug release for up to 10 hours while significantly improving solubility and dissolution rates [84].

Estimation of Nanosponges (NSs) –

Solubility Studies :
The phase solubility method, introduced by Higuchi and Connors, is the most widely used technique to study how inclusion complexes form. This method helps determine how a formulation affects the solubility of a drug. The extent to which a drug forms a complex with the carrier is represented by a phase solubility diagram.[99,100]

Particle Size Evaluation:
The particle size of both drug-loaded (burdened) and empty (unburdened) nanosponges was measured using laser light diffraction or a Malvern Zeta Sizer, along with zeta potential analysis. Each sample was tested three times, and the average of these measurements was used for further analysis.[101,102]

Microscopy Studies :
To examine the shape, surface structure, and microscopic features of the API/NSs complex, techniques such as scanning electron microscopy (SEM) and transmission electron microscopy (TEM) can be used.[103,104]

Entrapment Efficiency (Paraphrased):
A measured amount of drug-loaded nanosponges is dispersed in methanol and then centrifuged at 1000 rpm for 30 minutes. The resulting supernatant is collected, appropriately diluted with methanol, and analyzed using ultraviolet (UV) spectroscopy to measure its absorbance against a methanol blank. The percentage of drug entrapment in the nanosponges is then calculated using a specific formula.[105-107]

Entrapment Efficiency (%) = (Actual Drug Content / Theoretical Drug Content) × 100

Zeta Potential (Paraphrased):
The zeta potential, which indicates the surface charge of the prepared nanosponges, is measured using a zeta sizer. For this analysis, the nanosponge emulsion is diluted with water and then placed into an electrophoretic cell for evaluation.[108-110]

Porosity (Paraphrased):
This analysis helps verify the formation of nanochannels and nanocavities within the nanosponges. A helium pycnometer is used to assess the porosity, as helium gas can penetrate both the internal and external channels of the material. The percentage of porosity is calculated using the following formula:[111,112]

% Porosity = (Bulk Volume − True Volume) / Bulk Volume × 100

Fourier Transform Infrared (FTIR) Analysis (Paraphrased):
FTIR analysis is performed to investigate any interactions between the drug and polymer at the chemical bond level. The powdered sample is scanned over a wavelength range of 400 to 4000 cm^{-1}, including the region corresponding to carbon black.[113,114]

Polydispersity Index (PDI) (Paraphrased):
The polydispersity index (PDI) indicates the range of particle size distribution. A lower PDI reflects a more uniform particle size, while a higher PDI suggests a broader size distribution among the particles.[115,116]

Production Yield (PY) (Paraphrased):
Production yield is determined by comparing the total weight of the final nanosponges to the initial weight of the raw materials used. It is calculated using the following formula:[117,118]

PY (%) = (Practical Mass of Nanosponges / Theoretical Mass of Polymer + Drug) × 100

Dissolution Studies (Paraphrased):
900 ml of phosphate buffer at pH 6.8 is added to the vessel, and the USP Apparatus Type II (paddle method) is set up. The medium is allowed to equilibrate to a temperature of 37°C ± 0.5°C. The prepared nanosponges powder is then placed in the

vessel, and the system is run for 12 hours at 75 rpm. At specified time intervals, 5 ml of the receptor fluid is withdrawn, filtered, diluted, and analyzed using spectrophotometry.[119-121]

Drug Content (Paraphrased):
The formulation is placed in a 100 ml volumetric flask containing 50 ml of methanol and shaken for 30 minutes, then allowed to stand for 2 hours. The volume is adjusted to 100 ml with additional methanol. 1 ml of this solution is then further diluted to 10 ml with a pH 6.8 phosphate buffer. The drug content is determined by measuring the absorbance using a UV-Visible spectrophotometer.[122,123]

Drug Release Kinetics (Paraphrased):
The in vitro drug release mechanisms of nanosponges are examined to understand their kinetic behavior and the mechanisms involved in the drug release. Various models, including Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models, are applied to determine how the drug is released from the nanosponges.[124]

Swelling and Water Uptake (Paraphrased):
The water absorption and swelling behavior of swellable polymers, such as polyamidomine nanosponges, can be measured using the following formula. [125]

Percentage of swelling =

Marking of the cylinder at the specified time point / Initial marking before swelling × 100

Percentage of water uptake Mass of hydrogel after 72 hours/ Initial mass of polymer× 100

Characterization of Nanosponges:[133]

S. No.	Charecterization parameters	Objective
1	Solubility study	Determines the drug concentration by using HPLC.
2	Porosity	Performed to check the amount of nanochannels and nanocavities formed.
3	Microscopic studies	To study the morphology and surface topography Scanning electron microscopy and Transmission electron microscopy are used.
4	Loading efficiency	Determined by the quantitative estimation of drug loaded into nanosponges.
5	Particle size and polydispersity	By dynamic light scattering using 90Plus particle size reequipped with 'MAS OPTION' particle sizing software, the particle size is determined. By using this mean diameter and polydispersity index are determined.
6	Zeta potential	Zeta potential measurement involves examination of the electric potential. Stability of the formed nanosponges is estimated by zeta potential.
7	Drug release kinetics	Drug release is calculated to determine the release pattern.
8	Swelling and water uptake	These are determined by soaking the prepared nanosponges in aqueous solvent.
9	Saturation state interaction	This study is carried out to find out the drug loading in a saturated state using UV-spectroscopy.
10	Thermo analytical methods	This method examines whether the drug substance undergoes any changes (like melting, evaporation, decomposition, oxidation or polymorphic transition) before the thermal degradation of the nanosponge.
11	X-ray diffractometry	It is used to detect inclusion complexation in the solid state.
12	Infrared spectroscopy	It is used to determine the interaction between nanosponges and the drug molecules in the solid state.
13	Thin layer chromatography	It helps in identifying the complex formation between the drug and nanosponge.
14	Raman spectroscopy	It is used to study the molecular structures.

Table 1: Characterization Parameters along with their Objectives

Conclusion:

Nanosponges (NSs) represent a promising nanocarrier system characterized by a porous, mesh-like structure capable of encapsulating both hydrophilic and hydrophobic drug molecules. Their nanoscale size facilitates incorporation into diverse pharmaceutical formulations, including oral, parenteral, topical, and inhalation systems. NSs have demonstrated superior drug delivery performance, enhancing solubility, stability, permeability, and enabling controlled and site-specific release, particularly for poorly water-soluble drugs such as those classified under BCS Class II. Cyclodextrin-based NSs have shown considerable potential in improving the bioavailability of therapeutics for conditions like cancer and diabetes. Despite their advantages, comprehensive evaluation of their biocompatibility and in vivo metabolic pathways remains essential to ensure safety. Continued research is warranted to develop optimized, non-toxic NS formulations for clinical application.

Figure 1: Formation of Nanosponges

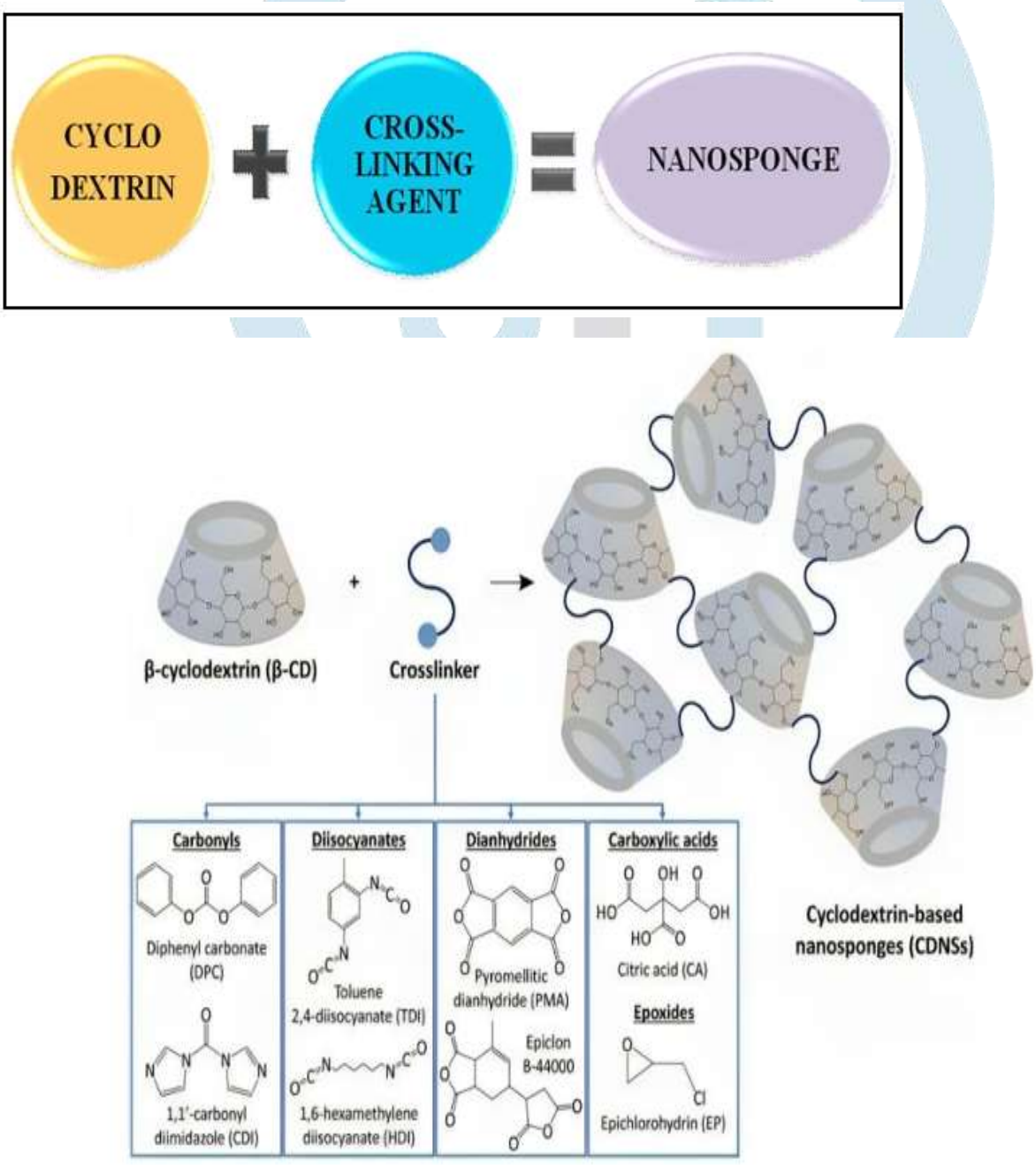


Fig. 2: Formation of cyclodextrin-based nanosponges (CD-NSs) occurs via a reaction between β-cyclodextrin and crosslinking agents such as carbonyl compounds, diisocyanates, dianhydrides, carboxylic acids, or epoxides [126].

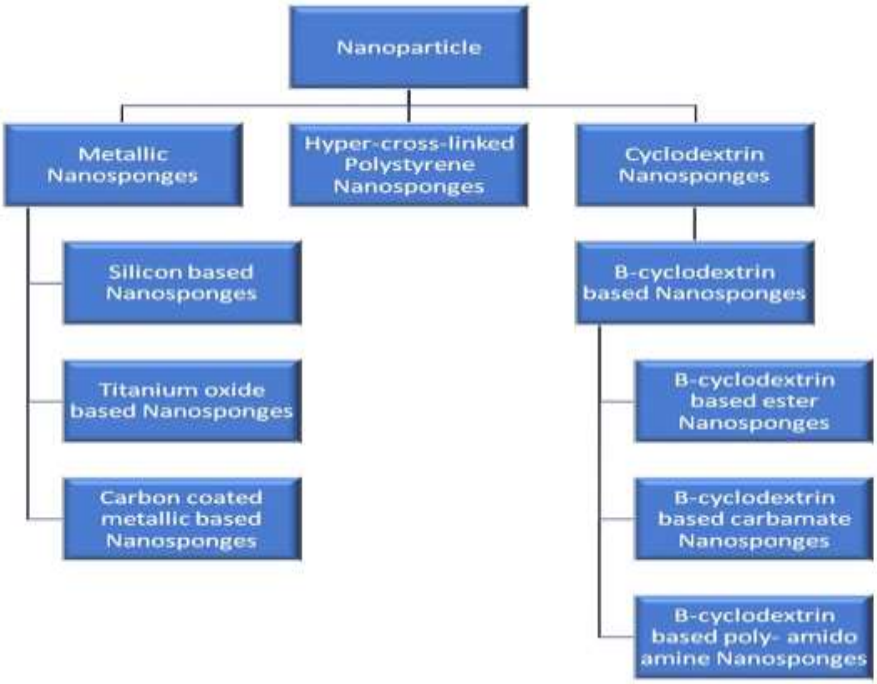


Fig. 3: Types of nanosponges based on composition [129]

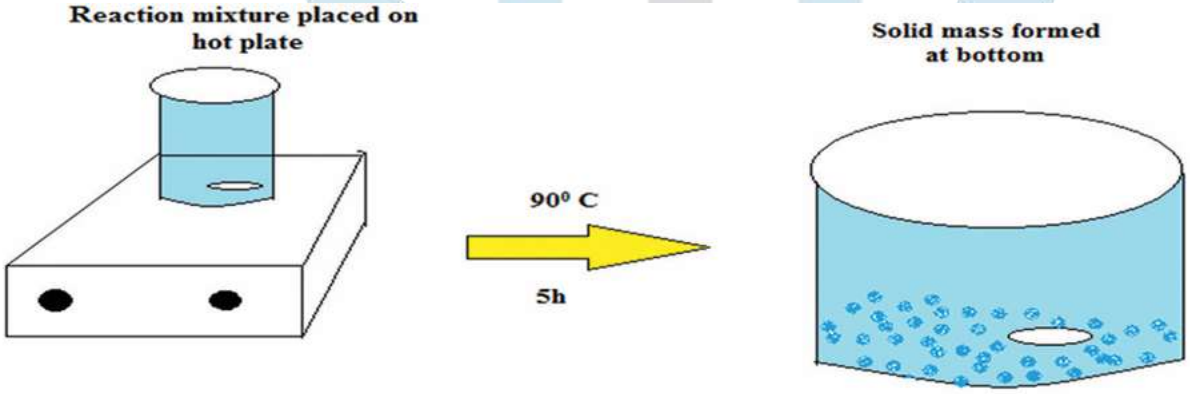


Fig. 4: Factorial representation of fabrication of nanosponges by melt technique

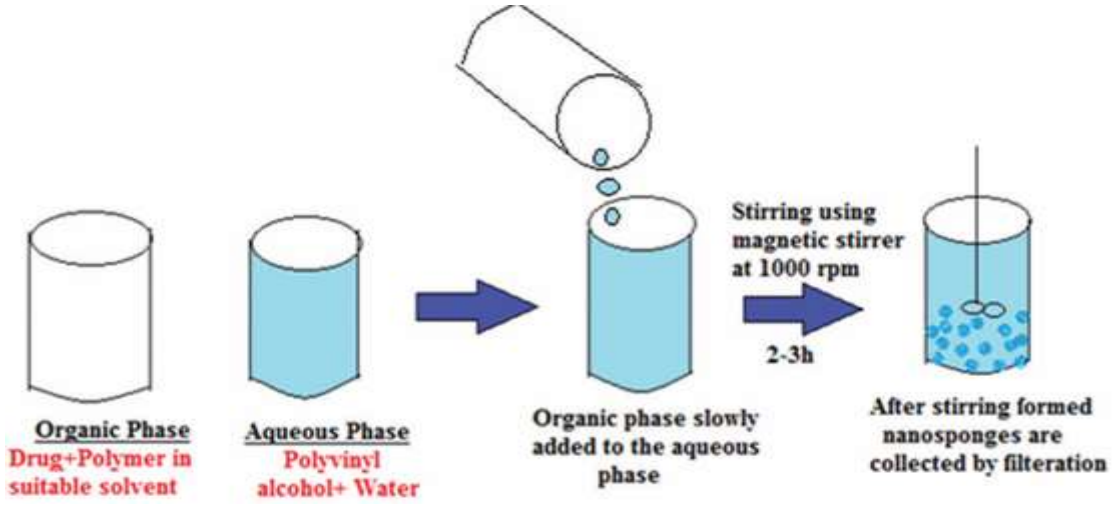


Fig. 5: Fabrication of nanosponges by emulsion solvent diffusion technique

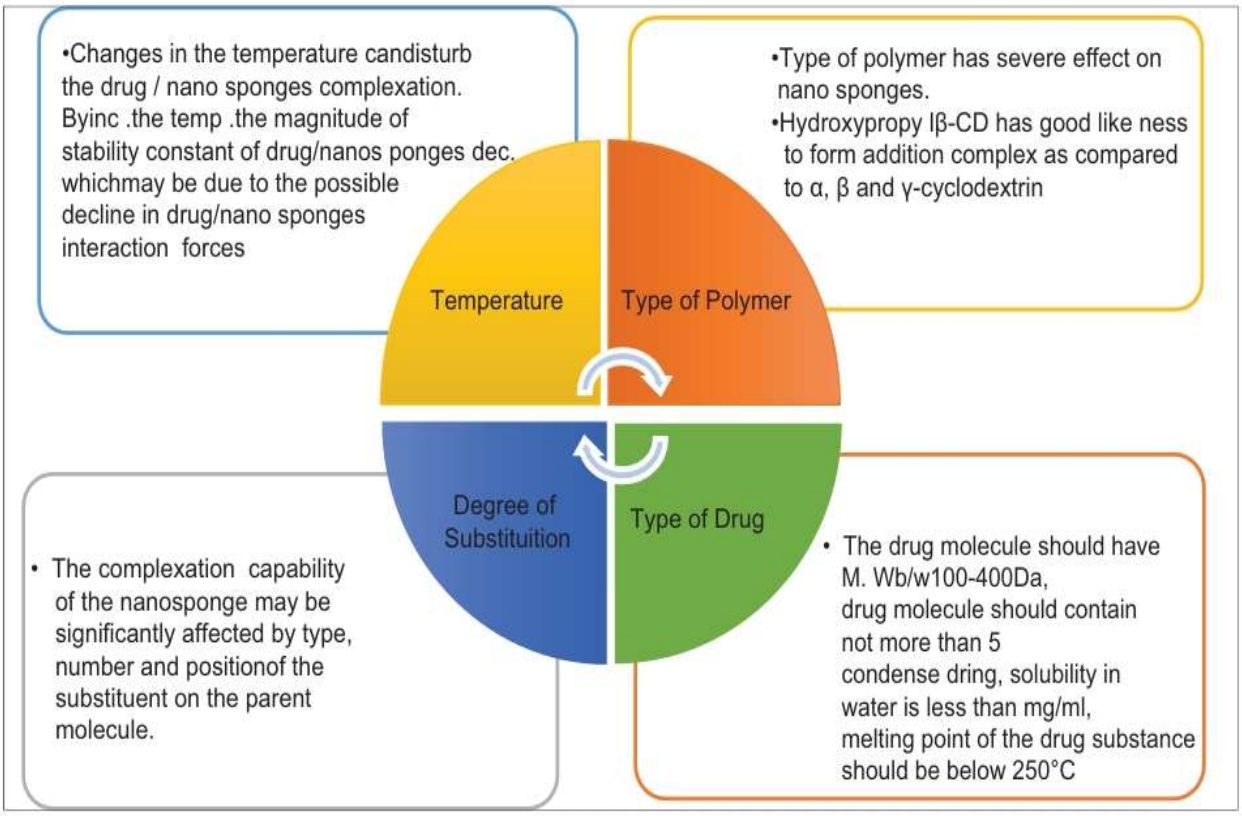


Fig. 6: Factors disturbing nanosponges preparation[130-132]

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