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Nanosponges: In-sights into Fabrication, Design, Drug delivery and its Evolving Challenges

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Abstract

Nanosponges (NS) represent a promising advancement in drug delivery technology due to their unique porous structure, biocompatibility, and ability to encapsulate both hydrophilic and lipophilic drugs. These nanoscale carriers offer controlled and targeted drug release, improving therapeutic efficacy and reducing side effects. This highlights the potential of NS, particularly cyclodextrin-based formulations, in enhancing solubility, bioavailability, and sustained release of poorly water-soluble drugs like docetaxel. Various preparation methods—including emulsion solvent diffusion, quasi-emulsion, and melt techniques—affect the physicochemical characteristics of the final product. Studies demonstrate that β-cyclodextrin and carboxymethyl chitosan-based NS improve drug stability, loading efficiency, and release profile. The addition of cross-linkers and polymer blends further optimizes drug entrapment and release kinetics. NS applications include skin cancer therapy, antifungal treatment, rheumatoid arthritis management, and skin disease therapies. Innovative NS systems incorporating gold nanoparticles or photothermal agents show potential for multifunctional cancer therapies. Preclinical studies report enhanced therapeutic outcomes, biocompatibility, and minimal toxicity, although long-term biosafety and regulatory concerns remain areas for future exploration. Advances in surface functionalization and formulation optimization are expanding NS utility in personalized medicine. Despite the challenges in large-scale production and clinical translation, the evolving research underlines the vast potential of nanosponges as flexible, efficient, and safe drug delivery systems. This review encourages continued development and evaluation to realize their full application in pharmaceutical and biomedical fields.

Keywords: Nanosponges, Drug delivery, Emulsion solvent diffusion method, Loading capacity, Bio compatibility

Introduction:

Chronic Myeloid Leukemia (CML) is caused by a genetic abnormality known as the Philadelphia chromosome. This occurs when parts of chromosomes 9 and 22 swap genetic material, leading to uncontrolled cell growth. As a result, two genes—BCR and ABL1—combine to form the BCR-ABL1 fusion protein. This protein acts like an overactive enzyme (tyrosine kinase), constantly signaling cells to grow and multiply without regulation, which ultimately leads to CML[1].CML is relatively rare, affecting around 1 to 2 people per 100,000 each year and accounting for about 15% of new leukemia cases in adults [2]. The introduction of tyrosine kinase inhibitors (TKIs) has significantly improved treatment options, providing

targeted and effective therapies. However, some patients develop resistance to TKIs, particularly due to mutations in the ABL1 kinase domain, posing a major challenge in treatment [3].Tyrosine kinase inhibitors (TKIs), which specifically target the ATP binding site of the ABL1 gene, have completely changed the way Chronic Myeloid Leukemia (CML) is treated. Thanks to these drugs, CML has shifted from a life-threatening illness to a manageable chronic condition, allowing many patients to live as long as the general population.

However, treatment isn't always smooth—more than half of those with chronic-phase CML (CML-CP) who are prescribed imatinib eventually experience resistance to the drug or struggle with side effects that make it difficult to continue. CML stands out as a prime example of how targeted therapies can be game-changers in medicine, and TKIs have been central to this transformation. Before TKIs became available, CML was inevitably fatal over time [4].While these drugs have drastically improved survival rates, they come with their own challenges. Side effects can take a toll on a patient's quality of life, affecting their daily comfort and well-being. Another major concern is that most patients must continue taking TKIs indefinitely to prevent a relapse, meaning they’re exposed to the medication long-term [5].

Gallic acid is a naturally occurring compound with a small molecular size and a three-part phenolic structure. It can be found in a variety of fruits, including lemons, bananas, pineapples, berries, and grapes, as well as in certain hardwood plants like chestnuts and oak. Many other plants also contain this compound.Gallic acid is well-known for its wide range of biological and medicinal benefits. It exists in different forms, including free acids, esters, and catechin derivatives, but is most commonly present as hydrolyzable tannins[6].Gallic acid (GA) can be easily extracted from the tannins found in many plants using either alkaline or acidic hydrolysis. Its phenolic hydroxyl groups help neutralize reactive oxygen species (ROS) and break the chain reaction of radical formation [7]. These antioxidant properties make GA effective in preventing the oxidation of essential biological components like lipids, DNA, proteins, and enzymes that contribute to oxidative damage.

Recently, polyphenolic compounds have gained attention for their positive impact on health and well-being. They are recognized for their ability to combat diseases associated with oxidative stress, including cardiovascular conditions, neurodegenerative disorders, and cancer. GA has shown anti-cancer potential through several biological and chemical mechanisms. These include activating ATM/Chk2/p53 pathways to stop cell division and trigger apoptosis, inhibiting H2A.X and ribonucleotide reductase to reduce DNA synthesis by neutralizing free radicals and altering dNTP balance, suppressing COX-2/NF-kB pathways to lower inflammation, and depleting GSH to enhance antioxidant effects [8].

Nanosponges are tiny, three-dimensional structures with a unique ability to hold and transport large quantities of drugs. Their porous framework allows them to efficiently trap and deliver therapeutic agents, making them highly valuable in medical treatments.These microscopic carriers are made up of tightly crosslinked polymer networks, creating nano-sized cavities that can securely encapsulate active pharmaceutical ingredients, ensuring controlled and effective drug delivery [9]. Nanosponges stand out from traditional nanoparticles due to their porous structure, non-toxic composition, and exceptional ability to endure extreme temperatures up to 3000°C [10]. They are made from long, linear macromolecules that are intricately cross-linked, forming tiny spherical structures similar in size to proteins. This unique design not only enhances flexibility in their applications but also reduces potential harmful effects.

The materials used to make nanosponges are highly soluble and can break down at the molecular level, helping protect their structure from damage caused by light, oxygen, and chemicals [11]. Compared to conventional nanoparticles, nanosponges offer distinct advantages. Their simple peptide and polyester crosslinking chemistry makes them easy to manufacture using various methods, while their water solubility and chemical durability in liquid environments make them suitable for diverse applications.Nanosponges are extremely small drug delivery systems with significant potential in cancer treatment. These minuscule carriers, much smaller than a single cell, feature a highly porous structure that effectively traps and delivers bioactive compounds, making them promising tools for targeted therapy [12].

Nanosponges are incredibly small drug delivery systems with significant potential for cancer treatment. These microscopic carriers, far tinier than a single cell, have a highly porous structure that allows them to efficiently trap and transport bioactive compounds. As they gradually break down, they release the stored medication in a controlled manner, providing a more precise and sustained drug delivery compared to traditional methods [13,14].

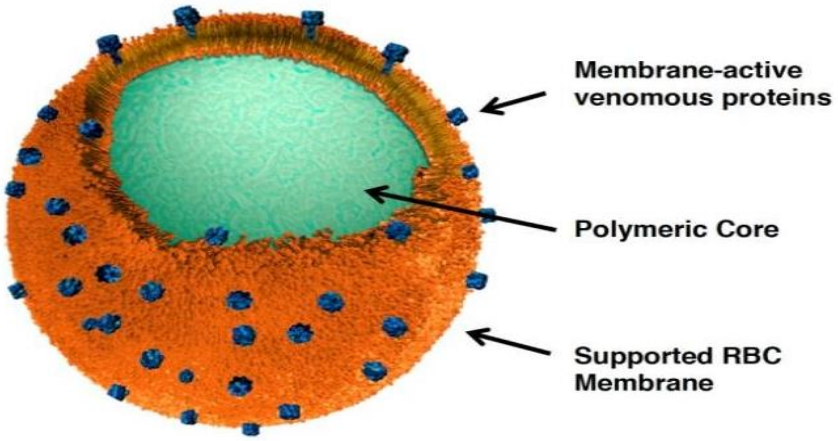

Fig.1: Structure of Nanosponges

Fabrication of Nanosponges:

The solvent evaporation method results in NS with an amorphous structure and a uniform size distribution, while the melt method produces nanosponges with a crystalline form. This structural difference significantly impacts their solubility and drug release, ultimately influencing the effectiveness of the encapsulated drug [15]. This study successfully developed and optimized BNS using the Box-Behnken design. The resulting BNS demonstrated excellent drug entrapment efficiency (83.12 ± 1.2%) and had a recorded particle size of approximately 114 ± 2.32 nm, with a PDI value of 0.11 ± 0.01, indicating uniform size distribution.

The study also integrated BNS into an in situ gelling system containing poloxamer and HPMC, creating a formulation specifically designed for ocular application. Safety evaluations confirmed that the gel was non-irritating and non-toxic, making it suitable for eye-related treatments.Additionally, in vitro studies showed a drug release rate of 60 ± 2.1%, while ex vivo studies recorded a flux of 5.308 ± 0.09 mg/cm². The release profile followed a non-Fickian pattern, suggesting a controlled and sustained drug release mechanism [16].

Nanocarriers enhance the effectiveness of treatment by directing the drug deep into the skin layers, ensuring complete elimination of fungal infections. The newly developed BTF-loaded nanosponges (NS) incorporated into a carbopol-based polymeric gel show promise as an efficient drug delivery system (DDS) for antifungal medications. By providing sustained drug release, this system helps reduce the frequency of dosing and minimizes the chances of recurrent skin fungal infections (SFI).Fungal infections, such as Candidiasis and Aspergillosis, are known for their high recurrence rates. Given its ability to maintain drug effectiveness over time, the BNS3 topical gel could serve as a potential DDS for managing skin-related fungal infections more effectively [17].

NS demonstrated satisfactory quality and efficient drug delivery. FTIR confirmed chemical compatibility, while XRD and SEM indicated reduced crystallinity and a spongy structure in NS. Incorporation of β-cyclodextrin (β-CD) improved percentage yield, drug entrapment, and release due to enhanced solubility. Ethyl cellulose (EC) ensured a sustained release profile, although β-CD accelerated drug release. Among all formulations, F1 showed an initial burst release, while others exhibited prolonged effects. The drug release followed the Korsmeyer-Peppas model, indicating a non-Fickian diffusion mechanism. Statistical analysis revealed that polymer concentration significantly influenced the drug release rate, with EC providing effective sustained drug delivery [18].

Nanosponge-based systems, known for their porosity, eco-friendliness, and cost-effectiveness, are emerging as promising tools for targeted drug delivery and cancer therapy. Cyclodextrin nanosponges are particularly notable due to their high biocompatibility, low toxicity, and ease of surface modification. They can enhance drug solubility, protect therapeutic agents from degradation, and be tailored for multifunctionality by adjusting polymer concentrations and cross-linker ratios. Future research should focus on improving biosafety, specificity, and functionalization, along with assessing their biodistribution, long-term safety, and scalability. Additionally, incorporating materials like fluorescent dyes, magnetite nanoparticles, and folic acid can help develop advanced nanosponges with potential applications in cancer diagnosis and therapy. Optimization and commercialization efforts remain essential for their clinical success [19].

Nanosponges (NS) loaded with furosemide were developed to provide a sustained release effect, particularly beneficial for elderly patients requiring diuretics. The NS were prepared using the emulsion solvent diffusion method with ethyl cellulose, polyvinyl alcohol, and dichloromethane as key components. Characterization was carried out using SEM, FTIR, PXRD, and DSC, revealing high drug entrapment efficiency and a good production yield. In vitro studies demonstrated sustained drug release over 10 hours, following a non-Fickian, erosion-controlled mechanism. Drug–polymer interactions were explored using molecular docking and simulation studies. The resulting sustained release system offers reduced dosing frequency and improved patient adherence [20]. NS offer a versatile platform for targeted and controlled drug delivery. They can encapsulate a wide variety of drugs, supporting both oral and topical administration, and are effective in carrying both hydrophilic and lipophilic compounds. Beyond drug delivery, they show potential in improving solubility, capturing gases like oxygen, and serving roles in cosmetics, diagnostics, and toxin adsorption. Various tests are conducted to ensure their structural and chemical stability. As research progresses, the applications of nanosponges are expected to grow, making them valuable across multiple fields in the future [21].

NS offer a promising drug delivery system, enhancing the solubility of BCS class II drugs while ensuring controlled, site-specific release. This study utilized their ability to improve aqueous solubility to address LPT's rate-limiting step. Eudragit RS100-based NSs were formulated, demonstrating excellent stability, high drug encapsulation (88.25%), and minimal drug loss. Compared to pure LPT, NSs significantly boosted solubility, dissolution rate, and pharmacokinetics (Cmax, AUC). The formulation presents a potential lower-dose alternative and may improve bioavailability for poorly soluble drugs [22]. The nano-based gel formulation is highly effective in treating fungal infections because the nanocarrier can deliver the drug deep into the skin layers, reaching areas that traditional topical treatments might not. Nanocarriers enhance therapeutic efficacy by directing the drug precisely to the affected site, ensuring thorough elimination of the infection.The newly developed TBF-loaded nanosponges incorporated into a carbopol polymeric gel serve as an efficient drug delivery system for antifungal treatment. By enabling sustained drug release, this formulation helps reduce dosing frequency while improving treatment effectiveness [22].

NS were developed using the melting method for arthritis pain and inflammation management. The optimized CAPNS batch exhibited improved solubility, controlled release, efficient drug encapsulation, and stable particle properties while retaining anti-inflammatory and antioxidant effects. CAPNS4 significantly inhibited RAW 264.7 macrophage cells, reducing toxicity compared to plain CAP. It also suppressed TNF-α, a key inflammatory marker. The findings suggest CAPNS4 as a promising, safe, and effective nanoformulation for arthritis treatment, with potential for further in-vivo research [23].Inspired by the RCC immune microenvironment, we developed M2 macrophage-derived nanosponges that actively move toward RCC-specific chemokines using membrane receptors. These nanosponges, enriched with CSF-1R, TGF-βR, and IL-10R, act as cytokine decoys, neutralizing excess cytokines to shift M2-TAMs toward the pro-inflammatory M1 phenotype, inhibiting tumor angiogenesis, and boosting CD8+ T cell activity. By adding M2pep for targeted recognition and encapsulating the TLR7/8 agonist R848, we enhanced immune remodeling, achieving strong therapeutic effects. These biocompatible nanosponges offer promising applications in cancer and autoimmune disease treatment [24].

We developed a novel AuNR-S-PEG.β-CD NS-DOX nanocomposite for chemo-photothermal cancer therapy and thoroughly analyzed its properties. This nanocomposite is highly biocompatible, offers efficient photothermal conversion, and has a strong DOX loading capacity for targeted chemotherapy. It demonstrated dual pH/NIR-responsive drug release, rapidly releasing DOX in tumor-like acidic conditions and under NIR stimulation. In A549 lung cancer cells, it showed superior cancer-killing effects when combined with NIR irradiation, making it a promising candidate for further in vivo studies[25].

The analgesic effect of Piroxicam (PXM) was enhanced by incorporating it into β-cyclodextrin nanosponges. Twelve formulations were developed, testing different β-cyclodextrin-to-crosslinker and drug-to-nanopore ratios. The optimal formulation was achieved at a 1:8 crosslinker ratio and 1:2 drug-to-nanoparticle ratio, significantly improving solubility and dissolution. The optimized PXM nanosponge demonstrated superior analgesic activity and pharmacokinetic bioavailability compared to standard tablets, proving its potential for more effective pain management [26].This study successfully developed DPC-crosslinked β-CD nanonetworks (NNs) to enhance the bioavailability and sustained release of BAR. The optimized formulation (B-CDN3) demonstrated ideal size, PDI, ZP, and %EE, ensuring controlled drug release, confirmed through in vitro studies. Pharmacokinetic analysis showed improved bioavailability over pure

BAR, highlighting its superior therapeutic potential for arthritis treatment as a promising oral drug delivery system [27].

Developing DBF-loaded DPC-crosslinked β-CD nanosponges (NSPs) to enhance bioavailability and ensure sustained drug release. The optimized β-CD NSPs had ideal size, PdI, Z.P, and E.E, enabling effective drug delivery, as confirmed by in vitro release, permeation studies, and pharmacokinetic evaluations. These NSPs demonstrated higher bioavailability than the pure drug and showed superior therapeutic efficacy due to their porous nanoscale structure. Our findings highlight their potential as an oral delivery system for cancer treatment [28].

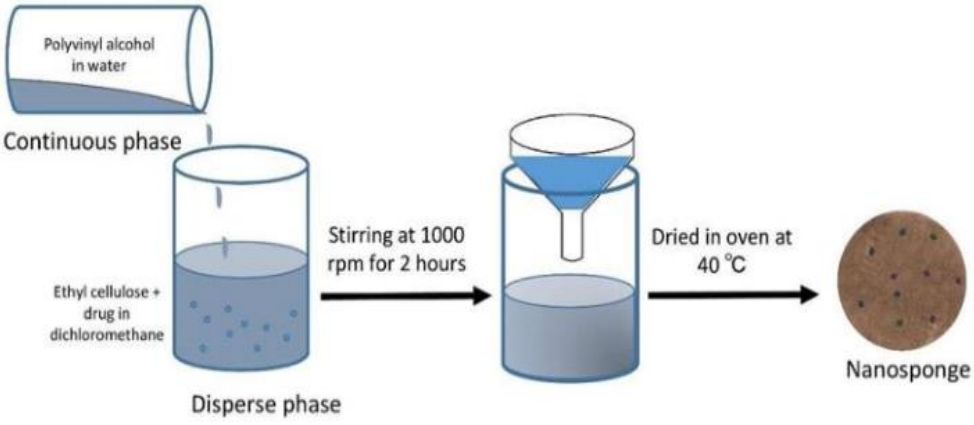

Fig.2: Fabrication of nanosponges in general

Drug Delivery:

Nanosponges offer a flexible and efficient platform for controlled drug delivery. They can carry both hydrophilic and lipophilic drugs, making them suitable for oral, topical, and therapeutic applications. Their porous structure also allows encapsulation of gases like oxygen. With potential uses in diagnostics, cosmetics, and detoxification, their structural and chemical integrity is rigorously tested. Ongoing research is expanding their future applications [29].

The formation of βCDNS with therapeutic agents PhEA and AT showed high drug loading efficiency and improved solubility compared to native βCD. Gold nanoparticles were also incorporated, achieving 85% immobilization. SEM confirmed porous nanosponge structures with effective drug attachment. These systems hold promise for drug delivery due to their biocompatibility, enhanced drug transport, and potential for controlled release, especially under laser activation, supporting further studies on permeability, toxicity, and pharmacological effects [30].

A novel chitosan-based nanosponge (CNS) optimized for enhanced drug penetration through the skin. The CNS maintained stability for four weeks under physiological conditions and showed no cytotoxicity, with over 90% cell viability. Notably, CNS3K (8:2) significantly improved drug permeation compared to free drug, highlighting its potential as an effective transepidermal drug delivery system [31].We developed GSH/pH dual-responsive degradable nanosponges using β-CD-appended hyper-cross-linked polymer to efficiently deliver doxorubicin into tumor cells. These nanosponges enhance drug release in response to

endosomal pH and cytoplasmic GSH, boosting anti-tumor effects. They exhibit low cytotoxicity, good drug-loading capacity, high stability with minimal drug loss (11% over 96 hours), and rapid release in acidic conditions, making them a promising cancer drug delivery system [32]. The nanosponge-based drug delivery system enhances therapeutic efficacy by ensuring predictable drug release, unlike conventional nanoparticle systems prone to burst release. A polymeric nanosponge system for luliconazole was developed using factorial design, optimizing ethyl cellulose and polyvinyl alcohol ratios. The formulations demonstrated excellent stability, controlled drug release for up to 8 hours, and superior antifungal activity. The optimized nanosponge gel was non-irritant, had improved skin permeability, and showed enhanced efficacy against fungal infections, confirming its therapeutic potential [33].

β-CD-based NS derivatives using various crosslinkers to eliminate toxic molecules from gastrointestinal (GI) fluids. Toluene diisocyanate cross-linked CD-NS demonstrated over 90% adsorption of indole, making it highly effective for detoxification. Stability studies confirmed its superior resilience, and safety evaluations showed promising results. These NSs could help remove toxins, aid in renal failure prevention, and provide a cost-effective treatment for chronic kidney disease (CKD) patients [34]. successful encapsulation of MPH and CUR within nanosponge (NS) cavities, achieving 89% and 63% encapsulation, respectively. Characterization confirmed their stability and suitability for drug delivery. Gold nanorods (AuNRs) retained their absorption band in the NIR-II window, making them ideal for photothermal therapy. NSs–MPH and NSs–CUR demonstrated lower cytotoxicity and improved drug release, highlighting their potential for safe, efficient drug delivery in future biomedical applications [35].

Docetaxel-loaded bi-polymeric nanosponges using free radical polymerization to improve its poor aqueous solubility. Characterization confirmed successful polymer cross-linking and a porous, stable structure. The nanosponges enhanced solubility by up to 14-fold and showed rapid drug release, particularly at pH 6.8. Toxicity studies showed no adverse effects, indicating safety. This delivery system offers a promising approach for improving oral bioavailability of poorly soluble drugs like docetaxel [36]. This study explored the potential of nisin, a powerful bacteriocin, in cancer treatment. Researchers investigated its ability to inhibit tumor growth, particularly in melanoma, by encapsulating it in cyclodextrin-based nanosponges (CDNS). Findings revealed that nisin-loaded nanosponges significantly increased bioavailability, enhanced cellular uptake, and effectively suppressed tumor growth in animal models. These results highlight CDNS as a promising nanocarrier for targeted anticancer drug delivery, improving therapeutic efficacy while maintaining stability and controlled release [37].

Two CD-NS formulations were developed to enhance QCT's aqueous solubility and biological effects, including anti-proliferative and anti-SARS-CoV-2 activity. QCT-loaded CD-NS showed high encapsulation efficiency (94.17–99.31%) and improved solubilization. The 2-HPβCD-based formulation demonstrated superior drug release and efficacy. Findings highlight the potential of nanosized CD-NS for enhanced lung cancer and SARS-CoV-2 treatment, paving the way for further studies on parenteral or oral administration [38]. CD nanosponges expand the potential of CD-based drug delivery systems for mTHPC. They efficiently encapsulate and solubilize mTHPC, enhancing its penetration in 3D tumor spheroids. The study confirms their ability to modulate biodistribution by adjusting CD type and concentration. With low toxicity and improved plasma retention, CD nanosponges hold promise as an advanced, smart system for mTHPC delivery in future preclinical studies [39].

Nanosponges (NSs) have significantly improved the effectiveness of anticancer drugs while minimizing side effects. Polymer-based NSs, particularly β-CD-based formulations, enhance drug solubility, protect against degradation, and regulate long-term release. Their versatility allows integration into various dosage forms and delivery routes. NSs also show promise for advanced therapies, such as microneedles for skin and breast cancer treatment. Despite their potential, NS research remains at the preclinical stage, urging further investigation for cancer therapy advancements [40].

Budesonide-loaded nanosponges were successfully developed using microwave irradiation, offering industrial potential due to rapid processing. Cyclodextrin-based nanosponges encapsulate both hydrophilic and lipophilic drugs, ensuring controlled release at targeted sites. QbD optimization of the BCD:DPC ratio (1:6) and 20-minute microwave reaction enhanced drug yield, release, and efficiency. The optimal formulation (F-9) demonstrated improved bioavailability, highlighting QbD's role in refining nanosponge-based drug delivery systems [41].

Method of Preparation of Nanosponges:

Table.1: Commonly used method of preparation to formulate nanosponges

Sr. No	MethodofPreparation	Procedure(55-57)
1	Emulsionsolvent diffusionmethod	The process begins by dissolving a polymer in a solvent, then dispersing it in water with the help of a stabilizer. A second solvent then used to quickly extract the first one, triggering the polymer to form nanosponges.
2	Solvent Method	n the solvent method for making nanosponges, a polar aprotic solve (such as DMSO) is used to dissolve a polymer. A cross-linker is the added to form a structured 3D network. Once the solvent is remove the nanosponges naturally self-assemble into their final structure
3	QuasiEmulsionsolvent diffusi method	The process starts by using ultrasonication to dissolve a polymer an rug mixture, known as the inner phase. This mixture is then combin with an outer water solution containing polyvinyl alcohol (PVA). Th blend is continuously stirred for an hour, then filtered to remove an unwanted particles, and finally dried at a low temperature to comple the formation process.
		Nanosponges are formed by first dissolving polymers and drugs in

4	Emulsion Solvent Evaporatio method	solvent, then blending the mixture with a stabilizer solution in wate s the solvent rapidly evaporates, the polymer naturally self-assemb nto nanosponge structures. The final product is then filtered to remo impurities and dried to complete the process

Table.2: Evolving challenges for nanosponges in current drug development

Method of Preparatio	Excipients	Result	Challenges	Reference
Emulsion Solvent diffusion method	Ethyl cellulose, PolyvinylAlcohol, Dichloromethane, Millipore water	Less yield (> 1gm), high particle size (1 micron) because of no homogenization c formulation, less stirring sped (2 hrs) on magnetic stirrer	Filtration was done using whatman filter paper and tray dried a 40°Cwhich and high particle size because c improve polymer ratic	(58)
Quasi Emulsion solve diffusion method	Beta– cyclodextrin, Ethyl cellulose, PolyvinylAlcohol, Millipore water	Less yield (> 1gm), high particle size (1 micron) because of no homogenization c formulation, less stirring speed (2 hrs on magnetic stirrer	Beta– cyclodextrin, was slightly insoluble in water which caused lumps in final produc was tray dried at 40°Cfor 15 minutes. There was more moistur entrapment and less yield	(59)
Emulsion solvent evaporation method	Ethyl cellulose, PolyvinylAlcohol, Dimethyl carbonate, Millipore water	Less yield (> 1gm), high particle size (1 micron) because of no homogenization c formulation	Stirring speed was 3 hours on a magnetic stirrer. Filtration was done using Whatman filterpaper, andthe tray driedat40°Cfor15 minutes.	(60)

Evolving Challenges:

Nanosponges offer high porosity, cost-effectiveness, and easy functionalization, making them ideal for removing pollutants like dyes, pharmaceuticals, and heavy metals from water. Cyclodextrin-based nanosponges provide excellent biocompatibility and adsorption capabilities. However, further studies are

needed to refine adsorption mechanisms, optimize functionalization, and address biosafety concerns for improved pollutant removal efficiency. Material type, dosage, and interaction dynamics also require deeper investigation to enhance performance [42].Nanosponge-based systems are highly porous, cost-effective, and eco-friendly, making them excellent drug delivery substitutes. Cyclodextrin nanosponges, known for their biocompatibility and low toxicity, enhance drug solubility and stability. They have diverse applications, including targeting, photoprotection, and blood purification.

While promising for drug delivery, cancer, and COVID-19, further research is needed to ensure safety, scalability, and regulatory compliance. Nanosponges also hold potential for environmental and industrial applications [43].

Nanotechnology has revolutionized formulation development at the nanoscale, enabling more advanced drug delivery systems. By optimizing crosslinking and utilizing software-driven formulation improvements, nanosponges effectively overcome issues like burst release, stability concerns, and drug loading challenges. These versatile carriers enhance drug targeting, absorption, and sustained release while also finding applications in cosmetics and purification. Future research aims to reduce costs and minimize polymer-related side effects for large-scale production [44].NS serve as versatile drug carriers, delivering both hydrophilic and hydrophobic drugs via inclusion and non-inclusion complexes. Cyclodextrin-based NSs enhance solubility, bioavailability, and oral absorption for various diseases, including cancer and diabetes. Their advantages include controlled release, site-specific targeting, and minimal side effects. However, further research is needed to develop non-toxic NSs with well-defined metabolic pathways for safe in vivo applications [45]. cross-linked cyclodextrin nanosponges using DPC and PMDA to enhance Irbesartan's solubility. The optimized PMDA-CDNS formulation significantly improved solubility and drug release compared to DPC-CDNS. In vitro studies confirmed faster dissolution, while molecular docking validated the stability of PMDA-CDNS. Characterization techniques further verified the formation of inclusion complexes, demonstrating its potential as an effective nanocarrier for Irbesartan delivery [46].

The study developed IBR-loaded, CDI-crosslinked HPβCD nanosponges to enhance sustained drug release and bioavailability in cancer therapy. The optimized formulation showed improved physicochemical properties, prolonged drug release, and higher bioavailability than conventional formulations. Its porous nanostructure boosted therapeutic efficacy while reducing dosing frequency and side effects. Future research will focus on stability, efficacy across cancer types, and toxicity evaluations for clinical applications [47].

A risk-based approach was used to develop a nanosponge-loaded topical gel of FDN for rheumatoid arthritis treatment. The formulation's characteristics were influenced by ethyl cellulose and PVA ratios, affecting drug release and particle properties. The gel demonstrated improved skin permeation, prolonged drug release, and minimal irritation, making it a promising candidate for reducing dosing frequency and enhancing therapeutic efficacy. Future studies will explore stability and patient-focused applications [48].

Nanosponge technology was developed to improve extended drug release in topical formulations, addressing challenges like drug toxicity, low bioavailability, and unpredictable release. These biocompatible cross-linked polymers efficiently encapsulate hydrophilic and hydrophobic drugs, enhancing stability and minimizing side effects. Beyond drug delivery, nanosponges have applications in cosmetics, biomedicine, and environmental remediation. Further research is needed to optimize formulations and confirm their safety through clinical studies for pharmaceutical advancements [49].This study developed silymarin-loaded

nanosponges using the melt technique for skin cancer treatment. The optimized batch showed improved solubility, encapsulation, and delayed release. Encapsulation enhanced anti-inflammatory, antioxidant, and anti-cancer properties, strengthening its effectiveness against melanoma. Cell studies confirmed increased potency and apoptosis in cancer cells. Further research on topical formulations and in vivo evaluations is needed to maximize its therapeutic potential [50].

Ribociclib-loaded ethylcellulose-based nanosponges as a promising breast cancer treatment. Optimized for particle size, PDI, zeta potential, entrapment efficiency, and drug loading, these nanosponges improved drug release while enhancing cytotoxicity and apoptotic cell death in MDAMB-231 and MCF-7 cancer cells. The findings suggest nanosponge encapsulation as an effective strategy for repurposing ribociclib in breast cancer therapy [51]. Raloxifene-loaded nanosponges, significantly improving drug solubility and dissolution. Encapsulation in cyclodextrin nanosponges enhanced cytotoxicity against MCF-7 breast cancer cells compared to free RLX powder. The formulation's improved solubility may reduce side effects while boosting anticancer activity. Further research is needed to fully assess its therapeutic potential and safety for clinical applications [52]. The combination of γ-CD-MOF and β-CDNS as a composite carrier significantly enhances CUR's drug loading capacity and solubility, improving local absorption. CURγ-CD-MOFβ-CDNS forms a bioadhesive gel when applied to exudative wounds, providing protection, drug release, and exudate absorption. Its low hygroscopicity makes it superior to hydrogels, and its additive-free composition ensures excellent biocompatibility for effective topical drug delivery [53].

Nanosponges are advanced drug carriers synthesized using polymers, metals, and metal oxides. They are produced through various methods, including melt, emulsion, and sol-gel techniques. Researchers optimize their formulation based on drug loading, particle size, and encapsulation efficiency. Functionalized nanosponges improve drug delivery to tumors but may pose toxicity risks. Studies suggest safety, though further research is needed to minimize adverse effects [54].

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