MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Cyclodextrin-Based Nanosponges as Novel Approach for Drug Delivery

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Abstract

Over the last two decades, the drug delivery market has witnessed the advent of nanotechnology. Nanotechnology involves developing and applying chemical, physical, and biological systems characterized by structures ranging from single atoms or molecules to submicron dimensions. It also consists of the integration of resulting nanostructures into larger systems. Medical nanotechnology has shown a growing inclination toward reducing costs and improving the efficacy of existing medications, diagnostic tools, implants, prosthetics, patient monitors, and personal healthcare. The primary objective has been to develop intelligent drug delivery systems to maximize activity and minimize side effects. This review focuses on nanostructured materials, a significant category of advanced nanotechnology-based carriers. Nanostructured materials include polymeric-based and lipid-based nano systems. The review provides an overview of recent variations in this classification, particularly emphasizing cyclodextrin nanosponges. Cyclodextrins are remarkable molecules owing to their unique amphiphilic structure, they are natural oligosaccharides that hold promise in more targeted and controlled drug delivery release.

Keywords: Nanoscience, nanoparticles drug delivery system, lipid-based nanoparticles, polymeric nanoparticles, cyclodextrin-based nanosponges.

1. Introduction

1. Oral dosage forms:

The oral route is the most prevalent and favored method for administering drugs. Approximately 60% of available drug products are designed for oral consumption. Furthermore, oral formulations account for roughly 90% of the worldwide market share in pharmaceutical formulations meant for human use, with nearly 84% of the highest-selling

pharmaceutical products being delivered through oral administration (Prasad et al., 2017).

The oral route is favored for several reasons, including its non-invasive nature, excellent patient adherence, ease of drug administration and storage, cost-effectiveness, lack of stringent sterility requirements, and the ability to mass-produce oral medications (Alqahtani et al., 2021). Additionally, the human intestine offers a vast surface area exceeding 300 m2, rich in enterocytes across various regions, making it an attractive option (Homayun B, 2019).

Despite the numerous advantages of the oral route, it presents several challenges (Alqahtani et al., 2021). Multiple factors influence the absorption of orally administered drugs, encompassing physiological aspects of the body and the physicochemical characteristics of the drug (SongN-N, 2004). To traverse from the gastrointestinal tract (GIT) lumen to the epithelium, mucosa, and the walls of blood or lymph capillaries for absorption, a drug encounters several barriers, including gastric juices, the pericellular matrix, and a layer rich in mucus. Another critical biological challenge pertains to the pH levels within the GIT, as it can affect the drug's stability and dissolution rate before absorption. In contrast to the stomach, the duodenum offers a highly permeable intestine region with a neutral pH. The transit time through the gastric region is also a biological obstacle, impacting drug bioavailability and resulting in unpredictable drug plasma levels (Alqahtani et al., 2021).

Moreover, first-pass metabolism leads to significant drug loss before absorption, involving intestinal efflux mechanisms, metabolism along the gut wall, and degradation within the gut lumen (SongN-N, 2004). The drug's solubility and intestinal permeability are widely recognised as crucial physicochemical parameters that influence the rate and extent of oral absorption (SongN-N, 2004). Solubility, the initial step determining a drug's availability for membrane permeability, is often considered a limiting factor in oral drug absorption. After achieving solubility, the drug must cross the intestinal membrane, which consists of a phospholipid bilayer with cell blocks and aqueous pores at tight junctions between cells. According to this membrane structure, lipophilic active compounds can pass through cells via the transcellular route, while hydrophilic small drugs can move through tight junctions via the paracellular route. Some molecules necessitate specific carriers for transportation across the membrane (carrier-mediated transport). Consequently, intestinal membrane permeation primarily hinges on the drug's lipophilicity, hydrophilicity, and molecular size (SongN-N, 2004).

2. Nanotechnology or nanoscience:

In the past decade, the prefix 'nano' has seen widespread use across various fields of knowledge. Terms like nanoscience, nanotechnology, nanomaterials, and nanochemistry have become increasingly common in scientific literature, popular books, and even mainstream newspapers, making them accessible to a broad audience, including non-experts. The origin of this prefix can be traced back to the ancient Greek word 'νᾶνος,' which means dwarf and, by extension, something very small. Within the framework of the International System of Units (SI), it signifies a reduction factor of 109 times (Devalapally et al., 2007; Jarai et al., 2020; Kakkar & Pal Kaur, 2013). Consequently, the nano-sized realm is typically measured in nanometers, with 1 nanometer corresponding to 10^{-9} meters. This range encompasses systems larger than molecular dimensions yet smaller than macroscopic ones, generally between 1 and 100 nm.

Nanotechnology is essentially the science of extremely tiny particles. It entails utilising and manipulating substances on a microscopic scale where the behaviour of atoms and molecules takes on distinctive characteristics, leading to various remarkable and captivating applications. Over recent years, nanotechnology and nanoscience have rapidly evolved across multiple fields. They offer exciting prospects for developing materials, including those intended for medical purposes, where conventional methods may encounter limitations. Recognising that nanotechnology is not limited to a single technique that impacts only specific areas is crucial. While frequently referred to as the 'science of the minuscule,' nanotechnology doesn't merely involve creating very minute structures and products. Nanoscale features are commonly integrated into more extensive materials and surfaces. In essence, nanotechnology encompasses the design, production, and application of materials at atomic, molecular, and

macromolecular scales, creating innovative nanosized materials.

Pharmaceutical nanoparticles, for instance, are solid carriers for drugs that are submicron in size and may or may not biodegrade. These nanoparticles, often 10 nm to 1,000 nm in diameter, are colloidal drug delivery systems fashioned from natural, synthetic, or semi-synthetic polymers. They exhibit diverse inner structures.

2.1. Advantages of nanotechnology:

Numerous studies have been conducted to discover and enhance novel medications for more precise disease targeting. Nanotechnology provides a means to overcome limitations by facilitating the delivery of therapeutic agents to specific disease sites. Many drugs encounter challenges related to their administration routes due to issues like poor solubility, permeability, and bioavailability, which ultimately lead to suboptimal pharmacokinetics (Halwani, 2022). Consequently, the objective is to create a dosage form with an effective pharmacokinetic delivery system. Nanoparticles can serve as drug carriers, deliver therapeutic agents to specific body regions, or function as therapeutic agents themselves (Khan et al., 2022). Utilising nanoparticle-based drugs offers a promising approach to tailor drug-specific properties by manipulating the biopharmaceutical and pharmacokinetic characteristics of the molecule (Singh et al., 2019). The primary advantages of employing nanotechnology to enhance disease targeting with therapeutic agents include mitigating undesirable toxicity from nonspecific distribution, improving patient adherence, and yielding favourable clinical outcomes, thereby indirectly alleviating the burden on healthcare systems (Devalapally et al., 2007). Overall, the drive to develop new medicines and therapies centred on nanotechnology stems from the desire to create treatments that are not only less toxic but also more cost-effective compared to conventional approaches (Lu et al., 2021).

Nanoparticles offer several benefits, including straightforward preparation, heightened bioavailability, prolonged residence within the body, and precise drug delivery targeting (Khosa et al., 2018).

Recent attention has been directed toward vesicular drug delivery systems, which can encapsulate hydrophilic drugs within aqueous cores and hydrophobic drugs within bilayer membranes. This encapsulation shields the drug from the biological environment and enables sustained release over time (Nsairat et al., 2022).

2.2. Nanoparticle drug delivery system (NDDS):

Drug delivery methods based on nanotechnology usually come in countless forms. Ligands are fundamental in these methods and can take many forms, including peptides, aptamers, antibodies, sugars, nucleic acids, and small molecules. Achieving targeted drug delivery involves considerations of factors such as nanoparticle size, surface characteristics (e.g., hydrophobicity), and the use of specific ligands. Additionally, the physical properties of nanoparticles play a significant role in determining their ability to bind to and be absorbed by the target site. Carriers of nanoparticles are typically composed of materials like iron oxides, dendrimers, biodegradable polymers, gold (Gardouh et al., 2022), lipid-based carriers (90) such as micelles and liposomes, and viral nanoparticles.

2.3. Types of Nanoparticles

2.3.1. Lipid-based nanocarriers:

2.3.1.1. Solid lipid nanoparticles (SLNs):

Solid Lipid Nanoparticles (SLNs) are lipid-based structures that maintain their solid state at room temperature. Their particle size typically falls within the range of 50 nm to 1,000 nm. SLNs consist of a stable hydrophobic core enveloped by a single coating layer composed of phospholipids. Stabilisation of SLNs is achieved through the use of various surfactants for emulsification. These nanoparticles offer several advantages, including increased biodegradability, enhanced bioavailability, and the potential for targeted drug delivery to the brain.

Various forms of lipids are employed in the formulation of SLNs. These lipids encompass:

a) Cholesterol.

b) Triglycerides, including tri-palmitin, tri-laurin,

and tri-myristin.

c) Fatty acids, such as behenic acid, decanoic acid, and palmitic acid.

d) Partial glycerides like glyceryl mono-stearate and glyceryl behenate.

e) Waxes such as cetyl palmitate.

Different surfactant types are used to stabilise lipid dispersions, including lecithin, phosphatidylcholine, sodium cholate, sodium glycolcholate, and poloxamer 188. SLNs have extensive applications in cancer research, where they can accumulate within tumours and facilitate the targeted delivery of anticancer drugs to the brain.

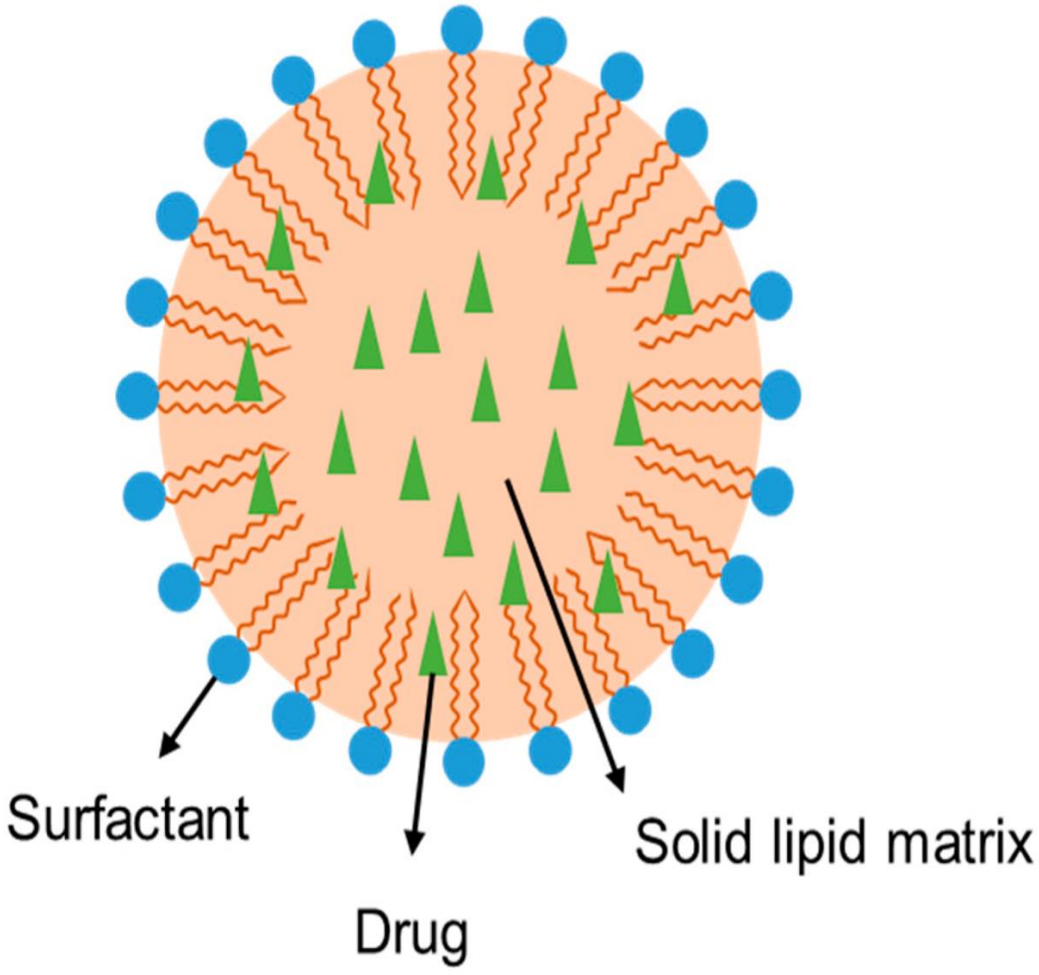

Fig. 1 Structure of solid lipid nanoparticles (SLNs) (Nguyen & Van-An, 2022)

2.3.1.2. Liposomes:

Liposomes are shaped as spherical vesicles surrounded by a bilayer structure composed of phospholipids and cholesterol, with particle sizes falling within the nanometer range. These lipids possess amphiphilic characteristics, featuring a hydrophilic core surrounded by a hydrophobic lipid bilayer. Liposomes find utility in drug delivery systems due to their ability to encapsulate hydrophilic and hydrophobic drugs. Various factors influence liposome properties, including their composition, particle size, surface charge, and formulation method.

Nano-liposomes primarily carry various substances, including antibacterial agents, antiviral drugs, insulin, anticancer medications, and plasmid DNA

(Hallaj Nezhadi & Hassan, 2015). However, liposomes often face challenges related to opsonisation, a process that eliminates liposomes from the bloodstream and leads to their degradation. Following administration, liposomes are typically identified by phagocytic cells and rapidly removed from the blood circulation.

To overcome this hurdle, surface modification of liposomes is performed, involving the camouflaging of liposomes with PEG, a technique known as PEGylation (Zaky et al., 2023). This process yields modified liposomes referred to as PEGylated liposomes or stealth liposomes.

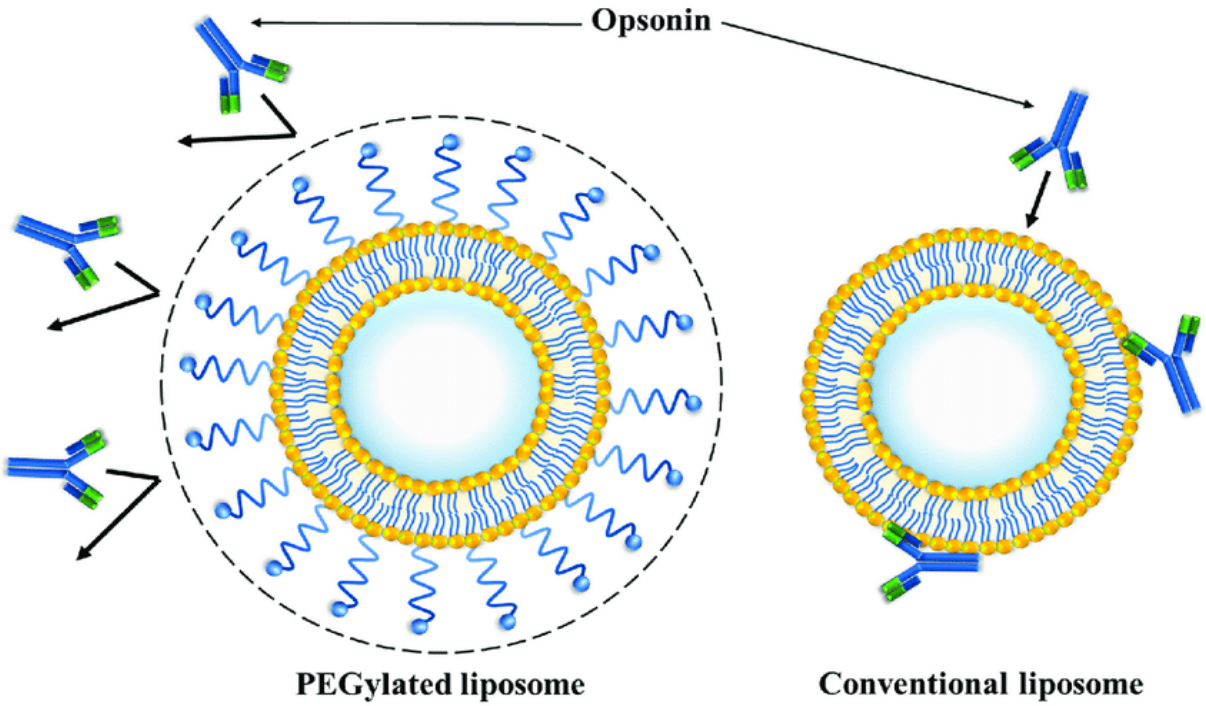

Fig. 2 Comparison between conventional liposomes and PEGlyated liposomes structures (Le et al., 2019).

2.3.1.3. Niosomes:

Niosomes, known as non-ionic surfactant-based vesicles, have emerged as liposome alternatives. These structures are created from non-ionic surfactants in aqueous solutions, forming enclosed bilayer configurations (Masjedi & Montahaei, 2021; Mukherjee et al., 2022). Niosomes are generated through the self-assembly of nonionic surfactants in aqueous environments, and when heat or physical agitation is applied, they develop into closed bilayer structures.

Interestingly, in the 1970s and 1980s, L'Oréal pioneered and patented niosomes, with the initial product including "niosome," Lancôme, introduced by L'Oréal in 1987 (US Patent 4830857, 1989). Niosomes have gained attention in the cosmetics industry due to their ability to enhance skin penetration, stabilise encapsulated drugs, and improve the bioavailability of poorly absorbed substances. They are particularly well-suited for topical delivery, as they extend the residence time of active constituents in the stratum corneum and epidermis while minimising systemic absorption.

Compared to phospholipid-based vesicles like liposomes, niosomes offer advantages such as excellent chemical stability, reduced costs, and a comprehensive range of available surfactant classes. However, it's worth noting that niosomes have certain drawbacks, such as the absence of (GRAS) generally recognised as safe components found in liposomes, and they are known to be somewhat more irritating to the skin.

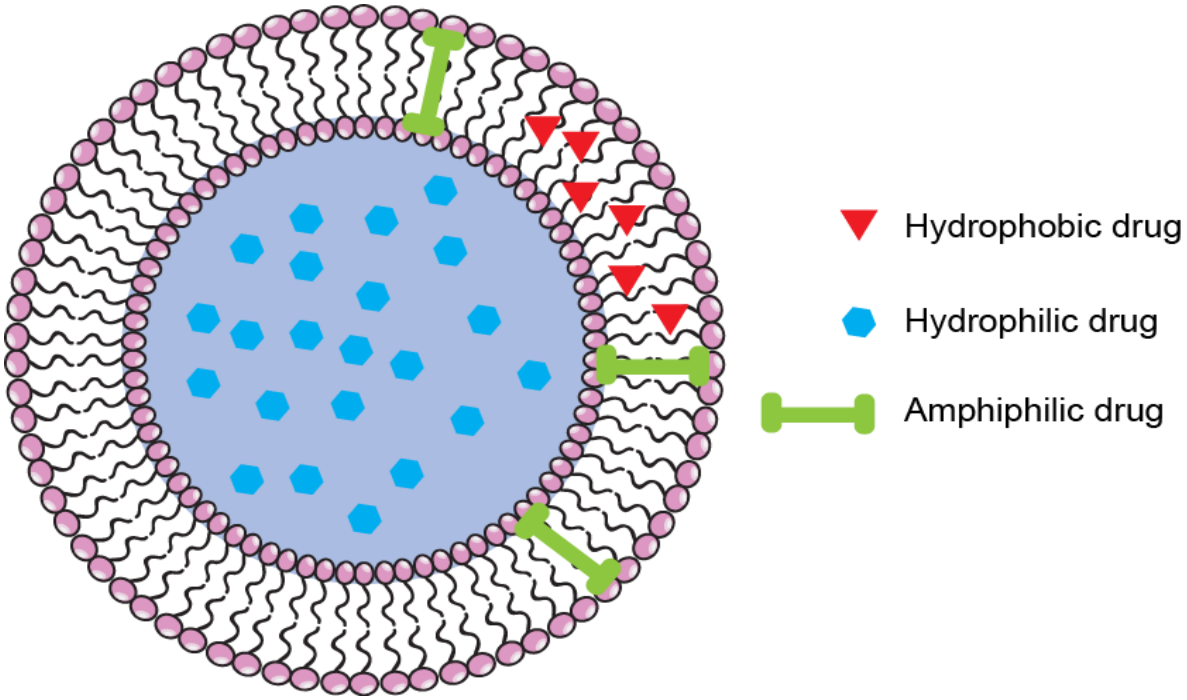

Fig. 3 Structure of niosomes (Girigoswami et al., 2020).

2.3.1.4. Transferosomes

Deformable liposomes, known as transfersomes, represent a type of elastic nanovesicle constructed primarily from phospholipids. Typically, transfersomes contain 10-25% edge activators (EAs), agents like Tween 80, Span 80, and sodium cholate, known to soften the membrane. This EA content contributes to the remarkable deformable nature of transfersomes. When these vesicles encounter skin pores, they can adapt their membrane flexibility, allowing them to pass through the pores without external assistance, a phenomenon known as self-optimizing deformability. Transfersomes exhibit exceptional deformability, enabling them to traverse even the narrowest pores effectively. Several formulations based on transfersomes are presently being assessed in various clinical trial stages. For example, there is ongoing research into the safety and efficacy of ketoprofen-loaded transfersomes (marketed as Diractin®) for treating knee osteoarthritis. Notably, transfersomes are susceptible to chemical instability due to their tendency to undergo oxidative degradation. It is essential to prepare them in degassed and inert gas-purged aqueous media, such as nitrogen or argon, to mitigate oxidation. Storage at low temperatures and protection from light also help prevent oxidation. Additionally, post-preparation techniques like freeze-drying and spray-drying can enhance the storage stability of transfersomes. Natural phospholipids often lack the required purity, making synthetic phospholipids suitable alternatives. The cost-effectiveness of transfersomal formulations is influenced by the raw materials used in lipid excipients and the expensive equipment needed for manufacturing. Consequently, phosphatidylcholine, a relatively cost-effective lipid component, is widely used.

2.3.1.5. Ethosomes:

Ethosomes are elastic nanovesicles primarily composed of phospholipids and feature a substantial ethanol content ranging from 20% to 45%. Ethanol is an effective permeation enhancer when incorporated into vesicular systems to create these elastic nanovesicles (Chauhan et al., 2022).
The mechanism behind ethanol's function involves interacting with the lipid molecules' polar head group region. This interaction lowers the melting point of the stratum corneum (SC) lipids, enhancing lipid fluidity and increasing cell membrane permeability. The high flexibility of the vesicular membranes, attributed to the presence of ethanol, enables ethosomes to navigate through pores considerably smaller than their actual diameters

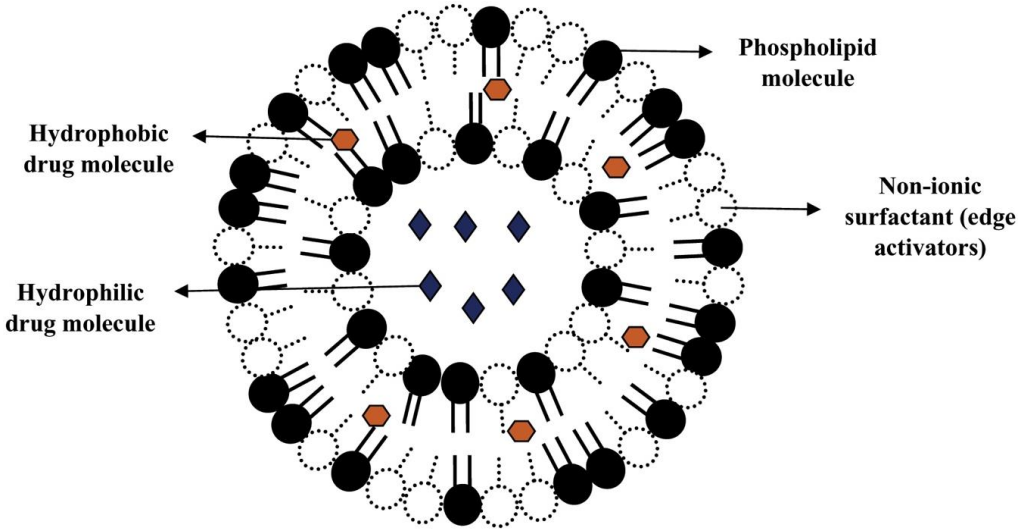

Fig. 4 Transferosomes structure (Ritika. & Amrish., 2021).

(Paiva-Santos et al., 2021).

Compared to conventional liposomes or hydroalcoholic solutions, ethosomal systems exhibit significantly improved delivery capabilities in quantity and depth when delivering substances to the skin. Nonetheless, it's worth noting that ethosomes may encounter challenges related to variable phospholipid purity and the higher cost associated with their use (Chauhan et al., 2022).

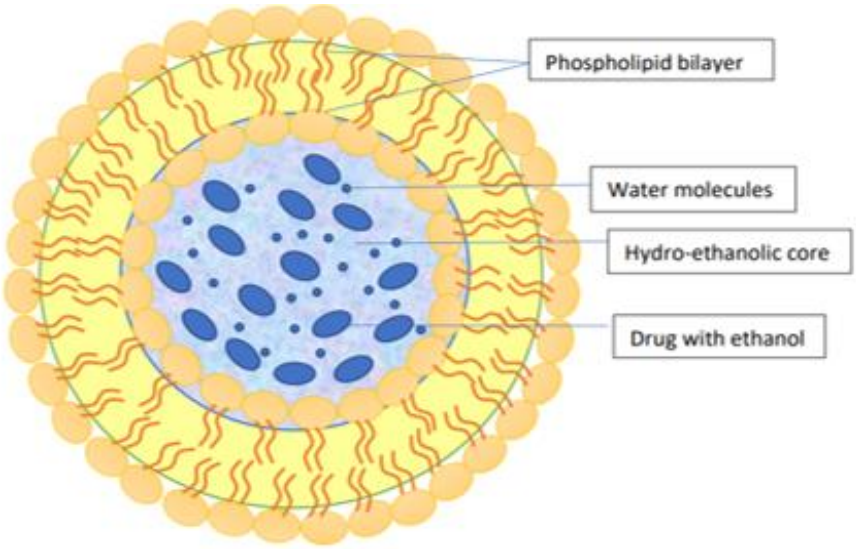

Fig. 5 Ethosomes structure (Khanam. et al., 2022).

2.3.1.6. Spanlastics:

Recently, a novel elastic nano vesicular system known as 'nano plastics' has emerged, initially developed by Kakkar and Kaur in 2011. These vesicles consist of Span 60 as non-ionic surfactants and an edge activator at the nanoscale (Alaaeldin et al., 2021).

The edge activator comprises additional hydrophilic surfactant components that impart flexibility to the lipid bilayer membranes of these nano-spanlastic vesicles. This flexibilisation leads to the formation of pores and the destabilisation of lipid bilayers, ultimately enhancing the vesicles' deformability (Sallam et al., 2021).

These vesicles exhibit elasticity and are applicable in enhancing corneal permeability and delivering anti-fungal drugs to the skin.

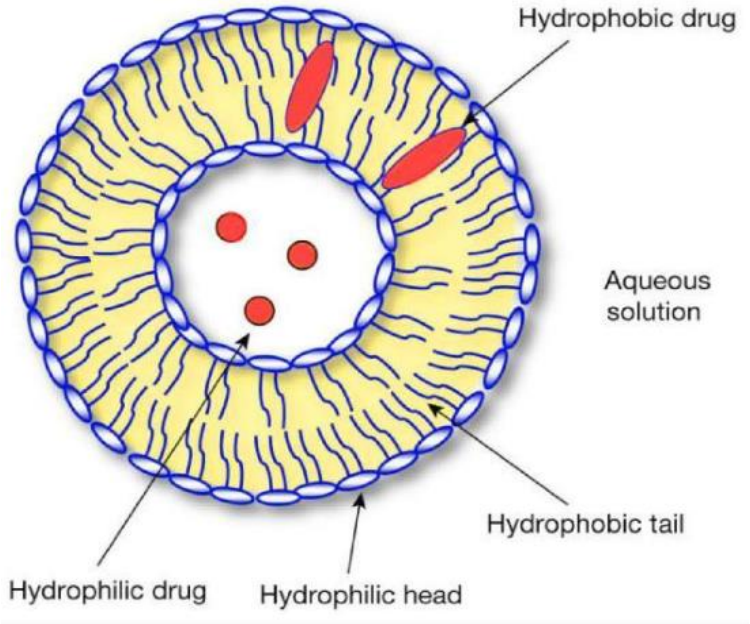

Fig. 6 Spanlastics nano vescicles (Chauhan & Verma, 2017).

2.3.2. Polymeric nanoparticles:

In recent years, there has been significant interest in polymeric nanoparticles (NPs) because of their unique properties resulting from their tiny size. These polymeric NPs offer several advantages as drug carriers, including their potential for controlled drug release, shielding drugs and other biologically active molecules from environmental factors, and enhancing their bioavailability and therapeutic effectiveness (Jarai et al., 2020). Two recognised types of polymeric NPs are reservoir systems, known as nanocapsules, and matrix systems, referred to as nanospheres (Zielińska et al., 2020). Furthermore, these polymeric particles have demonstrated their effectiveness in stabilising and safeguarding drug molecules such as proteins, peptides, or DNA from various environmental factors that could lead to degradation. Consequently, these polymers hold promise for multiple applications in protein and gene delivery (Bennet et al., 2014).

2.3.2.1. Nanocapsules:

Nanocapsules are considered one of the most promising nanoparticle types. Typically, nanocapsules are nanoscale vesicular delivery systems with an oil core enclosed by a sturdy shell. The inner oily core primarily functions as a reservoir for hydrophobic drugs. At the same time, the surrounding shell serves as a protective barrier, providing nanocapsules with stealth properties, often achieved by including polyethene glycol (PEG) moieties. In terms of composition, nanocapsules share similarities with micelles, which feature an enlarged lipid core; liposomes, which are vesicular structures formed by hydrating phospholipids in an aqueous environment, or polymeric nanoparticles that have a clear distinction between their core and coat (Nasr & Abdel-Hamid, 2015)

Nanocapsules offer numerous advantages as drug delivery systems, owing to their distinctive interfacial properties and straightforward formulation techniques. They can also be modified on their surface with functional groups, enabling targeted drug delivery (Nasr & Abdel-Hamid, 2015). Furthermore, they exhibit high drug-loading efficiency, and their outer shell acts as a protective barrier, isolating the encapsulated payload from the surrounding tissue. This isolation prevents drug degradation or sudden release caused by factors like pH, temperature, enzymes, or other environmental conditions (Deng et al., 2020).

2.3.2.2. Nanosphere:

Nanospheres are spherical structures with a polymeric matrix, typically ranging in diameter from 10 to 200 nm. These nanospheres are commonly constructed using biodegradable, biocompatible, and synthetic polymers. The drug can be dissolved, entrapped, encapsulated, or affixed to the polymer matrix. Nanospheres can be

either amorphous or crystalline, which can effectively shield the drug from chemical and enzymatic degradation. Within this polymer matrix, the drug is evenly distributed and uniformly dispersed.

One notable feature of nanospheres is their ability to release the encapsulated drug gradually and continuously. Drug release occurs primarily through diffusion, with the release rate influenced by the polymer matrix's composition and its capacity to absorb fluids. Additionally, nanospheres can avoid rapid clearance by phagocytes, resulting in an extended circulation duration in the bloodstream. Nanospheres can penetrate tissues and gaps between cells to reach target organs. Furthermore, attaching ligands to their surfaces facilitates site-specific targeting. Their non-toxic nature, or reduced toxicity, makes them highly desirable for drug delivery purposes.

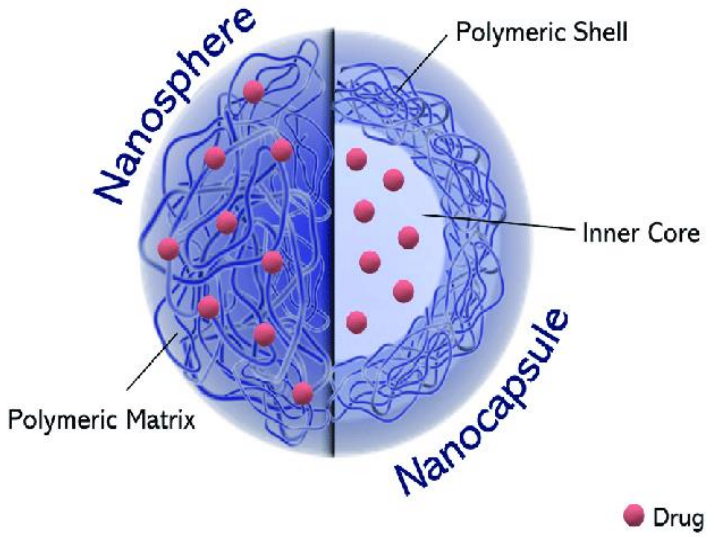

Fig. 7 Structure of nanocapsules and nanospheres as types of polymeric particles (Gagliardi et al., 2021).

2.3.2.3. Nanosponges:

Targeted drug delivery systems have been a longstanding objective for achieving specific therapeutic goals. Initially, the Nanosponge drug delivery system was primarily employed for topical applications. However, in the 21st century, Nanosponges have expanded their applicability to oral and intravenous (IV) administration routes (Elbahwy et al., 2017).

Nanosponges represent a contemporary class of materials consisting of minuscule particles characterised by narrow cavities measuring just a few nanometers in size. These tiny particles possess a unique capability to encapsulate lipophilic and hydrophilic substances, thereby enhancing the stability and bioavailability of poorly water-soluble drugs (Abd Elbary et al., 2011).

Nanosponges are a 3D mesh or network composed of biodegradable polymers. These polymers are combined with a crosslinker in a solution to produce nanosponges. Typically, the polymers are biodegradable, gradually breaking down within the body. Once the nanosponge scaffold degrades, it releases the loaded drug molecules in a controlled manner.

- **Nanosponges for drug delivery:**

Nanosponges possess a small porous structure that allows them to accommodate water-insoluble drugs. The formation of complexes between nanosponges and medicines significantly enhances dissolution rates, solubility, and drug permeability. It has been reported that nanosponges based on β-cyclodextrin

are three to five times more effective in delivering drugs to their intended targets. Nanosponges are typically in a solid form and can be formulated for various routes of administration, including oral, parenteral, topical, and inhalation dosage forms. For oral administration, such as tablet or capsule preparations, nanosponges are dissolved in proper excipients like diluents, anti-caking agents, and lubricants (Khafagy et al., 2022).

- **Cyclodextrin:**

Cyclodextrins (CDs) are remarkable molecules owing to their unique amphiphilic structure. These natural oligosaccharides consist of α-(1,4)-linked glucopyranose units, with the first three members labelled as α-, β-, or γ-cyclodextrin, containing 6, 7, or 8 glucopyranose units, respectively. Due to the conformation of the glucopyranose units, CDs take on the shape of a truncated cone or torus featuring a hydrophobic cavity (Periasamy, 2020). CDs possess Lewis base properties, allowing them to form host−guest supramolecular structures (Usacheva et al., 2020; Wang et al., 2021). Thanks to hydroxyl groups at both ends of the cavity, their hydrophilic outer surface makes them water-soluble. It enables interactions with polar compounds through hydrogen bonds or the hydrophobic effect (Suárez & Díaz, 2022).

It's worth noting that using cyclodextrin nanosponges (CDNSs) is still in its early stages. CDNSs leverage cyclodextrin's porosity and amphiphilic characteristics, allowing them to load and solubilise both lipophilic and hydrophilic molecules, thereby enhancing drug solubility, stability and bioavailability. However, it's essential to consider the relatively low association constants characterising cyclodextrin-guest complexes (D'Aria et al., 2022). When drugs and cyclodextrins are physically mixed, there's often no or limited improvement in bioavailability after oral administration. Conversely, enhanced bioavailability is achieved when drugs are complexed with cyclodextrins, resulting in AUC enhancement ratios ranging from 1.1 to 46-fold compared to control formulations like crystalline or lyophilised drugs (Brewster & Loftsson, 2007).

This property opens doors for encapsulating, releasing, and permeating active constituents (Mane et al., 2021; Pushpalatha et al., 2019). Various types of CDs can be used, including natural (α-CD, β-CD, and γ-CD) and chemically modified derivatives like carboxymethyl-βCD (Yakavets et al., 2020), sulfobutylether-βCD (Olteanu et al., 2014), halide-βCD (Utzeri et al., 2022), tosylated-βCD (Sadjadi et al., 2019), or 2-hydroxypropyl-βCD (Argenziano et al., 2019),. Among these, βCD forms are preferred for constructing cyclodextrin nanosponges (CDNSs) due to their cavity size, which imparts higher complexation ability, more encapsulation sites, stability, cost-effectiveness, and higher production rates (Guineo-Alvarado et al., 2021).

This study introduces an emerging approach to creating multifunctional cyclodextrin derivatives by crosslinking cyclodextrin polymers.

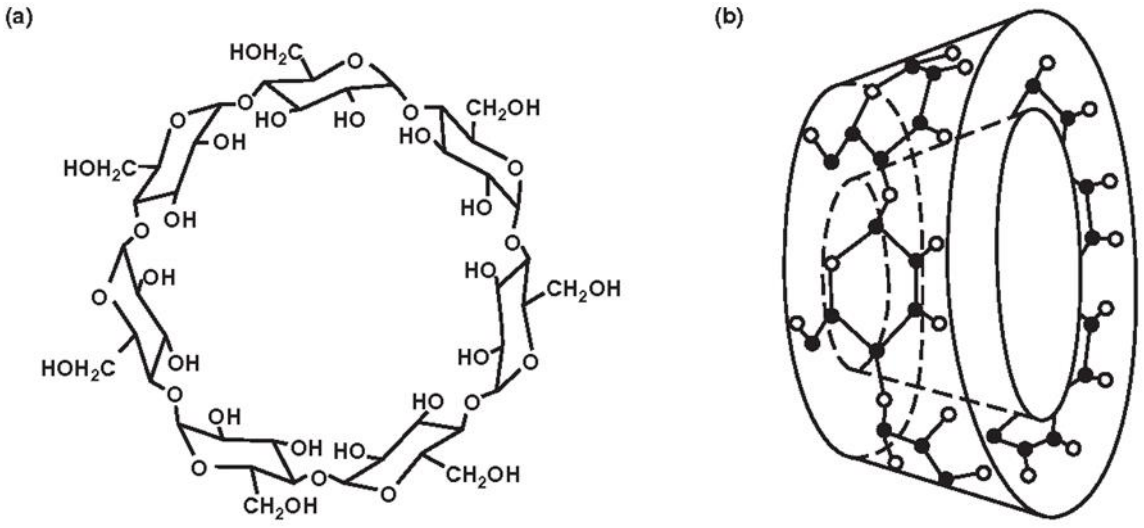

Fig. 8 Cyclodextrin structure (a) and the toroidal shape (b) of the b-cyclodextrin molecule (Jambhekar & Breen, 2016).

➢ Cyclodextrin-based nanosponges

De Quan Li and Min Ma initially coined the term' cyclodextrin nanosponges' in 1998. They used it to describe a structure involving β-cyclodextrin crosslinked with diisocyanates. Under microscopic examination, this structure exhibited a porous nature and displayed a notably high affinity for various organic pollutants (Li & Ma, 2000). Cyclodextrin-based nanosponges are minute mesh-like formations resembling microscopic 'sponges,' with diameters ranging from 200 to 500 nm. These structures can encapsulate a wide range of drugs. Cyclodextrin-based nanosponges are essentially hypercrosslinked polymers derived from cyclodextrins. They are created by crosslinking native α-, β-, and γ-cyclodextrins with suitable crosslinking agents. Various crosslinkers can be employed for this purpose, including active carbonyl compounds like carbonyl imidazole, diphenyl carbonate, or organic dianhydrides (Trotta et al., 2012). The extent of crosslinking can be adjusted to meet specific drug release rate requirements. It has been observed that increased crosslinking results in slower drug release, while reduced crosslinking leads to faster release. Consequently, by fine-tuning the degree of crosslinking, drug release can be controlled in a predictable manner (Kumar & Rao, 2019).

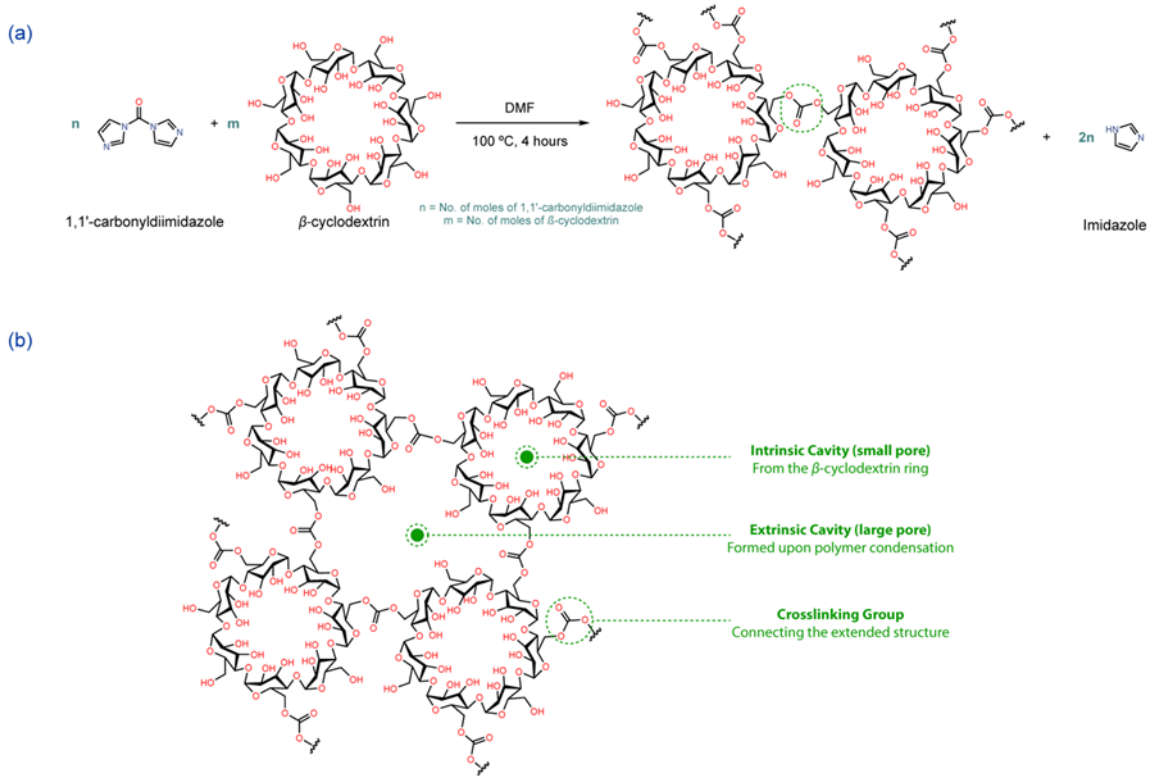

Fig. 9 The chain-growth polycondensation reaction between β-CD and CDI.

➢ Properties of cyclodextrin nanosponges (CDNS)

CDNSs are colloidal systems with an average diameter size typically less than 1μm and a narrow size distribution, indicated by a polydispersity index (PDI) of less than 0.7, which is a characteristic of monodispersed particles (Kumar et al., 2021). These particles possess a high ζ-potential (usually around ±30 mV), often exhibiting a negatively charged surface. This property allows them to disperse quickly in water, forming stable suspensions, and they tend to repel each other electrostatically rather than acting as surfactants, as they do not aggregate (Suvarna et al., 2021; Trotta et al., 2012).

However, NSs can undergo swelling when they absorb water, forming a gel-like structure similar to hydrogels. Although the degree of swelling in CDNSs is not directly related to their uptake capacity, PMA and CA CDNSs exhibit more significant swelling at lower crosslinker quantities than carbonate and carbamate-based ones. This swelling decreases as the crosslinker-to-CD ratio increases due to stronger crosslinking and reduced structural elasticity (Hoti et al., 2021; Rubin Pedrazzo et al., 2022; Trotta, 2011). Polyamidoamine CDNSs exhibit substantial swelling in aqueous media and contain both acidic and basic groups (Swaminathan et al., 2010). Additionally, PMA and CA linkers may introduce branching and carboxylic acid groups, causing fluctuations in ζ-potential due to pH sensitivity. This enables them to host cations and organic molecules simultaneously (Varan et al., 2020).

Using an EPI linker leads to NSs that are more hydrophilic than those obtained with carbonyl, dianhydride, or diisocyanate linkers.

The characteristics of NSs, including their size, surface area (SBET), porous network, charge, and ζ-potential, influence their interaction with analytes. As listed in Table 2, these properties are significantly affected by the CDNS structure, which depends on the choice of the linker and CD form, the CD-to-crosslinker ratio, solvent, catalyst, and synthetic conditions. All these parameters play a vital role in CDNS properties regarding loading capacity and efficiency (typically higher in crystalline CDNSs and native CDs), release profiles, and solubility. Crosslinked cyclodextrin polymers are often insoluble in water and organic solvents (Sherje et al., 2017; Venuti et al., 2017).

The amount of crosslinker used influences the surface area and porosity of CDNSs. Increasing the proportion of crosslinkers about CD generally results in smaller pore diameters. A higher degree of crosslinking leads to a more excellent SBET value, indicating superior polymeric interconnection and greater porosity. This is evident in βCD: Epiclon NSs, where the degree of crosslinking increases from 61% to 94% with higher crosslinker amounts (from 1:2 to 1:8 M ratios) (Gholibegloo et al., 2019).

NSs are thermally stable structures up to 300°C and are resistant to organic solvents. Their formation can be monitored using infrared spectroscopy, which reveals bands that do not exist in the original CDs. For example, carbonate CDNSs exhibit an elongation of the C=O bond of the carbonate linkage at 1720–1780 cm−1, while carbamate CDNSs show characteristic peaks at 1700, 1630, and 1550 cm−1 due to amide-like carbonyl stretching and N−H bending. Ester CDNSs display a 1720–1735 cm−1 band corresponding to C=O ester bonds.

CDNSs have a wide range of applications due to their ability to encapsulate various molecules. They are valuable for enhancing solubility, cytotoxicity, and bioavailability of drugs, drug delivery, protecting and transporting unstable molecules, catalysis, environmental remediation, chemical and biological sensing (critical in disease diagnosis), gas transport, and enzyme, protein, vaccine, and antibody release as a form of treatment. Their safety, biodegradability, non-toxicity, and biocompatibility make them promising materials for these applications.

Compared to activated carbon (with SBET = 600–700 m2 g−1), CDNSs have a lower surface area but similar interaction capacities for lipophilic molecules. This means these molecules are adsorbed on the surface and transported into the bulk of the NSs during inclusion complex formation or internal diffusion. This results in higher apparent stability constants than free CDs (non-bonded), which cannot host hydrophilic or high-molecular-mass analytes. Although inclusion compound formation is highly favoured in water, it is reversible in organic solvents like ethanol, making CDNSs easily recoverable and reusable without the need for hazardous combustion techniques used with activated carbon (Trotta, 2011).

- **Advantages of nanosponges**

- Due to their amphiphilic properties, nanosponges have the unique capability to simultaneously accommodate both hydrophobic and hydrophilic molecules. Hydrophobic drugs can be incorporated into the nanosponge structure, effectively enhancing their solubility.

- Nanosponges can release drug molecules in a controlled and predictable manner.

- A notable advantage is the straightforward chemical process of creating these particles.

- Cyclodextrins (CD) can be cross-linked to create nanopores, and these nanopores act as locations for loading drugs.

- The exceptional characteristics of nanosponges are linked to their capability to manipulate particle structure and regulate the characteristics and dimensions of openings. This can be achieved by adjusting the ratio of cross-linker to polymer, which allows for the control of cross-linking extent, thereby influencing drug loading and release.

- Due to their minuscule pore size (0.25 µm), nanosponges prevent bacterial penetration, effectively acting as self-sterilizers.

- The nanosponge drug delivery system is non-toxic, non-irritating, and non-mutagenic.

- Nanosponges aid in the removal of toxic and venomous substances from the body.

- The nanosponge drug delivery system minimises the occurrence of side effects.

- Enhance the stability of formulations and provide greater formulation flexibility.

- Nanosponges can be coupled with specialised linkers to target diseased cells, resulting in enhanced effectiveness, reduced side effects, lower dosage requirements, reduced dosing frequency, and improved patient adherence.

Nanosponge complexes exhibit stability across a wide pH range (1 to 11) and at temperatures up to 130°C.

➢ **Disadvantages of nanosponges**

- Nanosponges can effectively encapsulate small molecules but may not be suitable for larger ones.

- There is a potential risk of dose dumping in certain situations.

➢ **Methods of preparations**

Solvent method

This approach entails dissolving cyclodextrin and a crosslinker in a suitable solvent, typically polar aprotic solvents like DMSO, DMF, pyridine, or butanone (Anandam & Selvamuthukumar, 2014). Alternatively, environmentally friendly solvents, such as water or aqueous solutions, can be used to promote sustainability (Jafari Nasab et al., 2018; Swaminathan et al., 2010), and even deep natural eutectic solvents (NADES) have been employed (Cecone et al., 2020). A catalyst is sometimes added to accelerate the reaction (Demasi et al., 2021). Usually, an excess amount of the cross-linker is utilised, with CD: crosslinker molar ratios ranging from 1:2 to 1:16 (Jain et al., 2020).

Following the condensation polymerisation reaction, the extraction of nanosponges (NSs) often involves precipitation using solvents like water, ethyl acetate (Cecone et al., 2018; Matencio et al., 2020; Youssef et al., 2015), or acetone (Khajeh Dangolani et al., 2019), among other potential solvents (Appell et al., 2018; Ferro et al., 2014; Garrido et al., 2019; Lo Meo et al., 2020; Pawar & Shende, 2021).

For reactions involving dianhydride linkers alone or with 2-hydroxyethyl disulphide, the addition of triethylamine (Et_3N) as a primary catalyst is necessary, and the exothermic reaction occurs rapidly at room temperature (Nazerdeylami et al., 2021; Suvarna et al., 2021; Yazdani et al., 2022). With other linkers like MDI (Khajeh Dangolani et al., 2019), HDI (Yazdani et al., 2022), DPC (Singh et al., 2018) and DMC, Et_3N can also be used to accelerate the reaction, either with or without an elevated temperature.

Ultra-sound assisted synthesis

In this technique, nanosponges are generated by subjecting polymers and cross-linkers to sonication without a solvent. The process involves mixing the polymer with the cross-linker in a specific molar ratio within a conical flask. This flask is then immersed in an ultrasound bath filled with water and heated to 90°C. The mixture is sonicated for 5 hrs and left to cool at room temperature, producing a roughly ground product. The product is then rinsed with deionised water to eliminate any unreacted polymer. Subsequently, it undergoes a purification step through extended soxhlet extraction using ethanol. The final product obtained is dried under

vacuum conditions and stored at 25°C until it's ready for further utilisation (Trotta & Tumiatti, 2005).

Emulsion solvent diffusion method

This procedure relies on the emulsification phenomenon involving two phases that do not mix: internal and external (Abd-Elal et al., 2020). The internal phase is created by slowly adding the crosslinker, under continuous magnetic stirring, to a solution containing cyclodextrin (CD) and an analyte for inclusion in a polar aprotic solvent, typically dimethylformamide (DMF). The external phase is an aqueous solution, and the internal phase is slowly added drop by drop into it, with vigorous stirring, at room temperature. The resulting suspension undergoes lyophilisation, and the cyclodextrin nanosponges (CDNSs) are subsequently dried (Gangadharappa et al., 2017).

Microwave-Assisted Synthesis

Traditional heating methods and ultrasound heating often result in uneven transformations due to temperature variations, leading to longer reaction times and difficulty scaling up the process. In contrast, microwave irradiation accelerates reactions four times faster than the melting method. Moreover, microwave synthesis offers better reproducibility and scalability due to its ability to provide consistent and controlled heating.

This method can produce highly crystalline cyclodextrin nanosponges (CDNSs) characterised by a small particle size distribution (Aleksandra Ciesielska (DSNS) et al., 2020). This is achieved by reacting cyclodextrin with a suitable crosslinker, typically diphenyl carbonate (DPC), using polar aprotic solvents like DMF (Anandam & Selvamuthukumar, 2014; Sharma et al., 2022; Zainuddin et al., 2017). Solvent condensation synthesis can also be conducted using microwave irradiation. For instance, Vasconcelos et al. (Vasconcelos et al., 2016) utilised a tin octanoate catalyst to facilitate the reaction between β-cyclodextrin and HDI crosslinker in DMF solvent, employing a microwave system at 80°C for 30 minutes.

Mechanochemical Synthesis

The CD-crosslinker reaction can also be initiated through mechanochemistry, which involves directly absorbing mechanical energy to activate chemical bonds (Jicsinszky & Cravotto, 2021). Typically, this form of activation takes place between solid materials or solidified reactants within ball mills. This approach minimizes or eliminates the need for solvents, which is in contrast to conventional methods that often rely on significant quantities of solvents, many of which are derived from fossil fuels. Consequently, mechanochemistry is regarded as a more sustainable method, as it ensures mass transport and energy dispersion through efficient grinding in the solid state.

While solvents like ethanol and acetone are still employed in the purification of CDNSs, they are relatively volatile compared to polar aprotic solvents with high boiling point like DMF or DMSO, which involve complex recycling processes. Ball mills have some disadvantages, including challenges with limited temperature control (though temperatures typically do not exceed 72°C during CDNS synthesis), scalability, and the use of tightly closed containers, which cause difficulties to remove water during batch processes and prolonging the polycondensation reactions.

These limitations can be solved by utilizing twin-screw extruder reactors, which provide precise temperature control and enable more scalable processes by transitioning from batch operations to continuous processing. In general, mechanochemistry offers a straightforward, cost-effective, and faster approach to obtaining CDNSs. Two examples of this are: 1) the use of ball mills to produce CDNSs with CDI as the cross-linker in just 3 hours; and 2) the use of an extruder for CDNS preparation, employing βCD, CA crosslinker, and sodium hypophosphite monohydrate as a catalyst. In the latter case, the equipment is preheated to a temperature between 120 and 180°C, and the solid mixture is gradually introduced, with the process taking between 5 and 25 minutes. This is in contrast to the conventional approach, which involves vacuum conditions for minimum 4 hours and uses water as a solvent (Rubin Pedrazzo et al., 2022; Tannous et al., 2021).

- **Factors affecting the formulation of nanosponges**

Nature of polymer

The choice of polymer in nanosponge preparation can impact its formation and pre-formulation. It

should be noted that the nanosponge's cavity size must be sufficiently large to accommodate a drug molecule of a specific size for complexation.

Drug

For a drug molecule to form a complex with nanosponges, it should possess certain specific characteristicslike:

- The drug molecule's molecular weight should fall within the range of 100-400 Daltons.
- The drug molecule's structure should not comprise more than 5 condensed rings.
- The drug should exhibit low solubility in water, ideally less than 10 mg/ml.
- The drug's melting point should be below 250°C.

Temperature

Temperature fluctuations can have an impact on the interaction between drugs and nanosponges. Typically, as temperature rises, the drug-nanosponge complex's stability tends to decrease. This reduction can be attributed to a decrease in interaction forces, including Van der Waal forces and hydrophobic forces, between the drug and nanosponges as temperature increases.

Degree of substitution

The ability of nanosponges to form complexes can be significantly influenced by the parent molecule's substituents, including their number, position, and type.

Method of preparation

The process used to load drugs into nanosponges can impact the interaction between the nanosponges and the drug. While the effectiveness of a method is primarily influenced by the drug and polymer's properties, there are instances where processes like freeze-drying can alter the complex formation between the drug and nanosponge

- **Characterization of nanosponges**

Below are the methods used to characterize the drug-nanosponge complexes:

Solubility studies

Inclusion complexes are a valuable method for assessing drug solubility and bioavailability. This technique is commonly used to analyze nanosponge-drug inclusion complexes. The degree of inclusion can be determined through phase solubility plots. Solubility studies are carried out to understand the drug's pH sensitivity, solubilization pattern, and factors influencing drug solubility.

Microscopic study

Microscopic examinations of nanosponge-drug interactions can be performed using SEM (scanning electron microscopy) and TEM (transmission electron microscopy). The formation of inclusion complexes can be observed by noting differences in crystalline structure when viewed under an electron microscope.

Zeta potential determination

Zeta potential refers to the electric potential difference between two layers of fluid, specifically the dispersion medium and an immobile layer, which is associated with dispersed particles. Zeta potential serves as a crucial indicator of colloidal dispersion stability. It can be measured by adding an additional electrode to particle size equipment or a zeta sizer. A higher zeta potential value in a colloidal dispersion signifies greater stability.

Particle size and polydispersity

The particle size is assessed using dynamic light scattering (DLS) through 90Plus particle size analysis software. Dynamic light scattering is a method employed to determine the size distribution of nanoparticles. Ultimately, this process provides the final particle diameter and the polydispersity index (PDI).

Thermodynamical method

If there are alterations in drug molecules or particle transformations occurring prior to the thermal degradation of nanosponges, these can be detected through thermo-chemical analysis. Such alteration in drug particles might involve processes like melting, evaporation, oxidation, decomposition, and

alterations in the polymer structure. These modifications in the drug molecules are indicative of the formation of a robust complex.

Infrared spectroscopy

Infrared spectroscopy can be employed to examine the interaction between the drug and nanosponges in their solid state. During the formation of complexes, there may be slight shifts in the nanosponge bands. In cases where guest molecules comprise less than 25% of the complex, the drug's spectrum can become

$$\mathbf{LE} = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} \text{ X } 100$$

somewhat concealed by that of the nanosponges. Consequently, this technique might not be the most suitable for distinguishing inclusion complexes compared to other methods.

Loading efficiency

The loading efficiency of a nanosponge particle can be assessed by measuring the amount of drug incorporated into the nanosponge through UV spectrophotometry and using HPLC (high-performance liquid chromatography) for the nanosponges. The loading efficiency of nanosponges can be computed using the following equation:

Conclusion

The enthusiasm for nanotechnology, especially employing nanostructure-based systems for drug delivery through different pathways, has experienced a substantial upsurge in recent decades. Among the carriers that have been studied extensively, cyclodextrin nanosponges have emerged as the most auspicious choice for drug delivery. Many methods have been dev(Zaky et al., 2023)eloped for the preparation of nanosponges loaded with drugs. Nanosponges offer a versatile array of solutions for delivering hydrophobic drugs characterized by weak aqueous solubility and low bioavailability. These solutions are both safe and cost-effective, presenting a positive outlook for the field.

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