REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Polymeric cyclodextrin nanosponge drug delivery systems: A review

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Received on: 10. 03. 2022

Revised on: 25. 03. 2022

Accepted on: 29. 03. 2022

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Abstract

Testicular Nanotechnology is redefining healthcare methods, and it is projected to have a significant impact in the next years, resulting in improved healthcare facilities. It has paved the way for therapeutic medication delivery and diagnostics. Medical nanoparticles are materials in the nanoscale (from 1 to 100 nm) employed in the development, production, control, and use of medicinal drugs or devices employed in developing, producing, controlling, and using medicinal drugs or devices. Aside from gene therapy, nano-based medicine delivery systems benefit cancer, diabetes, infectious diseases, neurological diseases, blood diseases, and orthopaedic-related maladies. Furthermore, the development of multifunctional nanotherapeutics is potentially needed to contribute to the present therapeutic area positively. Nanomedicines are preferable to conventional therapeutic approaches in cancer as they can transmit the drug efficiently to the damaged tissues, decreasing drug toxicity. Nanotechnology-based medicines and diagnostics are more effective while posing little or no side effects. Micelles of polymeric paclitaxel and polymeric asparaginase conjugates have been advocated for treating several tumours in this vein. Nanotechnology advancements have prepared nanorobotics to be applied in various healthcare applications. As a result, this review thoroughly highlights the potential of polymeric nanoparticles, Nano-emulsions, solid lipid nanoparticles, nanostructured lipid carriers, self-micellizing anticancer lipids, dendrimer, nanocapsule, and nanosponges approaches in cancer, as well as the potentialities of various nanocarriers and nanomedicines for a variety of applications in diagnostics and drug delivery. This article reviews the most recent literature on nanotechnology, particularly cyclodextrin-based polymers, in medicinal applications. Nanosponges have shown great potential in nanotechnology and targeted medicine delivery. Because they can be employed to solubilize poorly water-soluble medicines, boost stability, extend release, and improve bioavailability, these nano-sized structures with colloidal diameters and nano-sized voids can answer various questions formulation difficulties. This review focuses on nanosponge manufacturing procedures and characterization, factors affecting drug loading and release kinetics, and their use in the pharmaceutical industry.

Keywords: Testicular damage, cadmium, oxidative stress, inflammation.

1. Introduction

Cyclodextrins (CDs) and derivatives are the brightest prospects and versatile tools for developing novel drug delivery systems. Smart nanosystems with specialized physicochemical features and improved key variables such as controlled drug release and bioavailability of loaded medications for various ailments have resulted from their combined use with various nanomaterials.

The discovery and development of methods that improve the conveyance of pharmaceutical molecules to their target areas to increase efficacy, safety, and patient compliance, are among the goals of drug delivery research. Spatio-temporal control of release and increased bioavailability can be achieved by modifying the pharmacological properties of medications with various excipients, transporters, and medical devices. CDs and their supramolecular variants have been one of the most widely employed techniques for this aim (Bertrand et al., 2014; Brigger et al., 2002; Duncan & Gaspar, 2011; Gidwani & Vyas, 2015; Juliano, 2013; Venditto & Szoka, 2013; Zhang et al., 2006).

CDs are cyclic oligosaccharides with a distinctive truncated cone form of D-glucopyranose units linked by 1-4 glycosidic linkages obtained naturally. The three most prevalent CD kinds are α-, β-, and γ -CDs, which have six, seven, and eight units, respectively, and differ in solubility, melting points, and diameters. The hydroxyl groups face outward from a structural standpoint, while the hydrogen and glycosidic oxygen linkages face inside, giving the cone a hydrophilic outside surface and a hydrophobic internal cavity. As a result, this macromolecule works as a host, engaging with molecules with a lipophilic area and appropriate diameter via weak bonds while remaining soluble in an aqueous media; this behaviour is known as inclusion complex formation (Bonnet et al., 2015; Trotta, Zanetti, et al., 2012).

CDs are widely and successfully utilized as an effective tool to alter numerous aspects impacting medication performance and therapeutic profiles, particularly in the pharmaceutical field. CDs improve the perceived water solubility of poorly water-soluble medicines, minimizing undesirable effects, including gastrointestinal or cardiovascular problems eye inflammation. They Increase biological membranes permeability, decrease evaporation, and stabilize flavours in formulations to enhance taste, usability, and chemical stability.(Cavalli et al., 2006; Li & Ma, 2000). Some publications (Cavalli et al., 2010; S. Torne et al. , 2013) present a list of CD-based dosage forms that have been licensed by the regulatory authority in the US, Japan, and the EU. CDs have been frequently used to increase the solubility of poor aqueous solubility class II and IV drugs and treat cancer and parasitic problems. Present a list of CD-based dosage forms that have been licensed by the regulatory authority in the US, Japan, and the EU. CDs have been frequently used to increase the solubility of poor aqueous solubility class II and IV drugs and treat cancer and parasitic problems.(Lembo et al., 2013; Swaminathan, Pastero, et al., 2010; Swaminathan et al., 2013). However, since CDs have been employed to boost stability and disguise smells and odours, among other things, there have been reports of a complex development for class I and III medications (Ahmed et al., 2013; Swaminathan et al., 2007; S. Torne et al., 2013; S. J. Torne et al., 2010).

The lack of control over drug release during transport, which is dependent on host-guest interactions and the pH of the biological environment in the location, has slowed their use as a drug carrier (Mura, 2020; Vyas et al., 2008). As a result, research into CD derivatives has progressed tremendously, with chemical alterations improving and offering new features. The focus of this new phase was on CDs altered with functional groups, particularly hydroxypropyl-cyclodextrin (HP CD), which was used for improved solubility and entrapment characteristics, as well as amino-cyclodextrins and sulfo- cyclodextrins, which permit the expansion of their functions through binding, reactions, or grafting onto other materials.

All forms of nano-sized particles and can thus gain new features and characteristics are called nanomaterials. Nanomaterials have been used to improve the property of biopharmaceutical of medications using tactics such as nanoencapsulation, bioaccumulation, and site targeting (Bolaños et al., 2019; Novio, 2020). Nanomaterials, for example, can be used in therapy, diagnostics, and imaging, particularly for disorders involving inflammation and tumours, if they are appropriately developed. CDs and cyclodextrin derivatives, when paired with nanomaterials, have greatly improved both characteristics and applications, particularly in medication delivery (Mura, 2020; Otero-Espinar et al., 2010; Tian et al., 2020, 2021). The increased permeability and retention (EPR) effect occurs when The blood artery wall's endothelial lining becomes more porous than normal tissue, permitting nanoparticles or nanocarriers to

accumulate selectively (J. Guo et al., 2017; Mrówczyński et al., 2018; Pham et al., 2020; Rincón-López et al., 2021).
As a result, using multiple materials that demonstrate outstanding performance in combination is important to design a viable drug delivery system (Bolaños et al., 2021). Biocompatible polymers have made a significant contribution in this regard. These are often utilized in pharmaceutical applications with nanomaterials as they enhance drug loading, increase nanosystem stability and bioavailability, and offer new capabilities, such as controlled release by stimuli. These benefits include reducing doses, cheaper prices, and lower adverse effects. Administration of drugs through non-invasive routes such as the intranasal, oral, ophthalmic, and pulmonary use polymers. (Feczkó, 2021; Liu et al., 2015).

Achieving accurate Spatio-temporal control of medication release is another important factor to consider when creating an effective drug delivery system. Targeting agents are used to this, bringing the system directly to the active site and optimizing the process.
Another essential element is introducing stimuli-sensitive species or materials, such as pH, laser irradiation, or magnetic field, among others (Inostroza-Riquelme et al., 2018; Vetterlein et al., 2018). It is feasible to release a pharmacological component on demand by producing the stimulus.

CD derivatives and other nanomaterials are excellent methods for increasing a medicinal formulation's bioavailability. As a result, the number of disorders for which it can be used is growing all the time. Oral, ocular, intranasal, and intravenous delivery routes have all been investigated. Also, CD's impact is underlined in its potential to boost the solubility and permeability of the drugs, as previously stated. Nanomaterials have a wider range of applications; for example, they can be employed to improve site targeting, increase water solubility, stability, and dissolution rate, or attain either a rapid and complete absorption profile or a delayed and protracted absorption profile.
As a result, CDs derived products and nanomaterials offer new therapeutic alternatives for APIs that are unsuccessful in conventional systems due to inadequate drug bioavailability or stability.
These nanosystems enable the development of vehicles for smart drug delivery for specific ailments and individualized therapy.

1.1 Classification of Cyclodextrin Nanomaterials

1.1.1 Lipid-Based Nanocarriers

Lipid-based nanocarriers are among the most often employed nanostructured materials combined with CDs derivatives, and they are pioneers in the design of innovative medication delivery systems. These systems are made up of biocompatible and biodegradable components that are adaptable and offer benefits such as drug loading, stability, and controlled drug release
Lipid-based nanocarriers can be utilized for targeted distribution, given via various routes, and even carry lipophilic and hydrophilic medicines (Valetti et al., 2013). Furthermore, they have demonstrated enhanced pharmacokinetics, effectiveness, and safety of many medicines (Dang et al., 2014; Vinaud et al., 2020).
However, significant concerns should be made about these systems' loading capacity and passive release, which may be seen in systems designed to transport hydrophilic molecules (Ghasemiyeh & Mohammadi-Samani, 2018).

1.1.2 Liposomes

Liposomes are artificial vesicles with a spherical shape consisting of one or more lipid bilayers surrounding an aqueous interior space (Hasan et al., 2014; Puri et al., 2009). They are mostly amphipathic phospholipids with a lipophilic tail and hydrophilic head. This liposomal formulation has a favourable pharmacokinetic profile and accumulates preferentially in tumours. Liposomes and CDs have been combined in a number of ways, including the incorporation of complexes within the aqueous cavity of liposomes, this method known as "drug-in CD-in liposome systems." The administration of a Pin1 inhibitor encapsulated in cyclodextrin and pegylated liposomes loaded was used by Russo Spena et al. to develop a novel treatment for late stages ovarian cancer (Russo Spena et al., 2018).
The liposomes efficiently reduced ovarian tumour growth in vivo by altering Pin1 cancer-driving pathways by promoting a proteasome-dependent degradation of Pin1.
Nanoliposomes (NLs), which are naturally present in cell plasma, have been found as possible biocompatible drug carriers, increasing bioactive medicines' effectiveness by increasing their

solubility and bioavailability in vitro. Furthermore, the successful deployment of NLs as drug carriers will play a critical role in pharmaceutical applications due to their special and unique physicochemical and biological features and their ease of size manipulation (Hasan et al., 2019). Souri et al. recently incorporated a cyclodextrin-vitamin E complex into sodium caseinate coated nanoliposomes. The coated LPs had a more controlled release profile in the simulated gastrointestinal state. The systems demonstrated promising benefits and possible uses in the nutraceutical and medical industries (Souri et al., 2021).

1.1.3 Nanoemulsions

Nanoemulsions are O/W or W/O systems that are transparent. The size range of the droplets is from 50 to 200 nm and are known for their outstanding suspension stability due to their nano- size and droplet steric stability. Similarly, nanoemulsions as a template produced several lipid nanocarriers (D. A. Real et al., 2021; Vinaud et al., 2020). Hou et al. recently developed a cinnamon essential oil nanoemulsion co-emulsified with HP-cyclodextrin and polysorbate-80 to protect the components and extend the release to have longer antimicrobial action (Hou et al., 2021). The findings revealed that essential oils might be incorporated into the hydrophobic cavity, forming inclusion complexes limiting aggregation and reducing nanoemulsion particle size. The inclusion of HP-cyclodextrin reduced essential oil loss, release rate , and increased stability. Antibacterial activity was observed against E. coli and S.aureus.

1.1.4 Solid-Lipid Nanoparticles

Solid-lipid nanoparticles (SLNs) are systems with colloidal particles with 50 - 1000 nm diameters. They have similar benefits to liposomes and nanoemulsions, but they are more successful in protecting drugs from chemical degradation and controlling drug release (Puri et al., 2009). SLNs have a solid lipid core with a surfactant monolayer coating. Fatty acids, saturated fatty acids (e.g., stearic acid), triglycerides (e.g., tristearin), glyceride mixes (e.g., Imwitor), or waxes may make up their hydrophobic lipid core (e.g., cetyl palmitate). Drugs can be dissolved or dispersed in them (Anderluzzi et al., n.d.; Kushwaha et al., 2013; Mehnert & Mäder, 2012). At both room and human body temperatures, they are solid. The main disadvantages of these formulations include expulsion of drug particles with time and unwanted particle development due to aggregation or coagulation, which can damage the nanosystems' stability and cause problems with dose administration.

1.1.5 Lipid Micelles

Lipid Micelles are dispersions with a lipophilic core and a lipophobic shell are lipid micelles. They develop from amphiphilic molecules or surfactant agents (Valetti et al., 2013). Su et al. (Su et al., 2021) produced an astaxanthin HP-cyclodextrin inclusion complex in an aqueous solution that self-assembled into micelles and accomplished solid-phase loading of the medication. The researchers increased the micelle's aggregation properties by adding glyceryl monostearate, a tiny flexible molecule that improves the drug's solubility and antioxidant action. According to the findings, The inclusion complex increased free radical scavenging activity and API solubility. According to tissue distribution investigations, the medication bioavailability was raised fourfold in pharmacokinetics trials, and the system targeted the liver to exercise its antioxidant effects.

1.1.6 Polymeric Nanocarriers

Polymers can assist boost bioavailability, control release, and target delivery of the drug because of their structural properties and adaptability. Numerous biocompatible polymers on the market can be customized for practically any medicinal use.

The following summarizes the most recent scientific research utilizing natural or synthetic polymers mixed with CDs or CDs derivatives for medicinal nanocarriers.

1.1.6.1 Natural Polymer-Based

cellulose, chitosan, and hyaluronic acid are natural polymers in nanoparticles combined with CDs. The most common natural polymer is cellulose.

In the pharmaceutical business, cellulose derivatives are commonly utilized and exceedingly beneficial, serving as controlled release coat and improving the solubility and bioavailability of low water-soluble medicines (Arca et al., 2018; Priotti et al., 2017). The production of nanocrystals made of cellulose loaded with β-CD has been investigated, and good findings have been obtained. Ndong-Ntoutoume and colleagues

reported the complexation of negatively charged cellulose nanocrystals with cationic β-CD in 2016 (Ndong Ntoutoume et al., 2016). The researchers discovered that curcumin-CD/cellulose nanocrystals were more effective than curcumin alone or curcumin-CD complex by 3-4 folds, suggesting that cellulose, a natural polymer, increased cellular absorption.

Chitosan is a biocompatible and biodegradable polymer made from chitin from crab and shrimp shell debris, commonly utilized in drug delivery nanoparticles(D. Real et al., 2018).

The structure of chitosan has groups that can be changed to create a polymer with various uses (Bakshi et al., 2020; D. A. Real et al., 2013). Crosslinking positively charged chitosan with negatively charged tripolyphosphate is an attractive method in medicinal nanosystems based on CDs and chitosan (negatively charged). Chitosan, which is incorporated in a nonionic CD and immersed in a polymeric network, acts as a polymer for the continuous release of the medication in these nanoparticles. Tang and colleagues combined salazosulfapyridine, a medication used to treat rheumatoid and inflammatory bowel illnesses, with dimethyl- CD in a CD inclusion complex, which resulted in a considerable increase in drug loading efficiency (Tang et al., 2017).

Nanogels based on chitosan can be used for delivery and control the drug release at different pH levels by modifying the chemical composition. Song et al. created nanogels based on chitosan derivatives and HP CD, coated with the red blood cell membrane and co-encapsulated a lipophilic medication, paclitaxel, to achieve anticancer activities (Song et al., 2017). To improve paclitaxel entrapment and manage its release, HP CD-acrylate was added to the nanogel.

Hyaluronic acid is a biopolymer found in connective, epithelial, and neural tissues and is a linear anionic biopolymer. Functional groups in hyaluronic acid can be functionalized for stimuli-response. The negative surface charge of nanosystems coated with hyaluronic acid hinders clearance by the reticuloendothelial system (Kim et al., 2019). Yang et al. produced biodegradable nanoparticles for cancer treatment in 2016 (Yang et al., 2016).

1.1.6.2 Synthetic Polymer-Based

In the last three decades, the field of synthetic materials for biological applications has exploded. Synthetic polymers are the most common, owing to many commercially available monomers and the ease of functionalizing them. Indeed, biocompatible polymers with the appropriate characteristics can be synthesized (Luo et al., 2020; Sponchioni et al., 2019). Dash and coworkers, For example, researchers looked into using synthetic and commercially available polymers like polyvinyl alcohol (PVA) and Pluronics® as stabilizing agents to increase the entrapment efficacy of encapsulated curcumin nanoparticles in HP CD from 1–5% (no polymer) to around 60% (polymer) (with polymer) (Dash & Konkimalla, 2017). When the solvent evaporates, the polymer prevents curcumin from aggregating and leaving the CD cavity. Finally, researchers discovered that curcumin nanoparticles in combination with PEGylated liposomal doxorubicin could be used as a co-treatment in cancer treatment.

Nanoparticle suspensions were created by Maged and associates (Maged et al., 2016) utilizing CDs and polymers to enhance econazole solubility and bioavailability for ophthalmic delivery as a Candida albicans and tinea pedis antifungal treatment. HP CD and Tween 80 were the most effective method for enhancing medication release and reducing econazole nitrate agglomeration has been demonstrated. In vitro tests examined two β-CD derivatives coupled with stabilizer polymers. After one-year storage hence they were chosen for bioavailability tests in rabbits.

Covalent and supramolecular binding are the two most frequent ways to use CD to change synthetic polymers. The nanopolymer created by Han et al., in which CDs were connected to a polymer chain (Han et al., 2020), is an example of the first. Polyethene glycol derivate was used as the main polymer in this work, attached to various amino-CDs. Pyrene encapsulated ferulic acid as an API, and the loading properties were investigated. Furthermore, in an in vitro release investigation, a low pH environment increased drug release (pH triggering). After intravenous injection, Nano-sized micelles concentrations increased in the rat liver, showing a possible utility in liver cancer treatment.

1.1.6.3 Polymeric Cyclodextrins Nanosystems

In the 1980s, Cyclodextrins-based polymer for medicinal applications was developed (Petitjean et al., 2021). These were made up of CDs, which served as the system's unit, and a crosslinking agent, referred to as nanosponges if they were nanometer-sized. The β-CD has become the most often used unit in recent years, with

epichlorohydrin and diphenyl carbonate serving as the most popular crosslinking agents. A wide range of polymeric CD derivatives for drug delivery have been investigated (Challa et al., 2005; Tian et al., 2020). Their primary goal is to improve the solubility of poorly water-soluble medicines and increase their bioavailability by improving their release profile (Gadade & Pekamwar, 2020; Yao et al., 2019).

CD-based polymers crosslinked with epichlorohydrin is commercially available through businesses like Cyclolab®. Yakavets and colleagues, Temoporfin loaded CD nanosponges, found that the association constant was larger than the monomer in both cases (Yakavets et al., 2020). The major purpose was to investigate the penetration of DNA into tumour structure for cancer therapy. According to the authors, the nanosponges had an extended-release than the plain β-CD with a more efficient temoporfin diffusion and penetration profile in all tumour cells. Similarly, Giglio and colleagues evaluated the loading of sorafenib on a βCD-based polymer, finding that drug-loaded polymer had a two-fold higher affinity to cancer cells (Giglio et al., 2018).

Cordaro and colleagues developed a fluorescently labelled CD-based nano polymer loaded with the diclofenac to treat inflammation in osteoarticular disorders and as a potential theranostic probe (Cordaro et al., 2020).

Probe loading did not affect diclofenac loading, resulting in a 1% loading capacity and a loading efficiency of 92%. Also, the extended-release profile was discovered, with no probe remains, making it suitable for syringeable formulations, especially given its physicochemical features. Furthermore, there were no negative impacts on cell proliferation or viability, and the cells were cleared quickly.

Another notable benefit of these systems is synergistic therapy or medicinal or diagnostic substances co-loading. Prof. Greg's group investigated the loading of Ethionamide and a pharmacological booster onto β-CD nanopolymer (Costa-Gouveia et al., 2017; Salzano et al., 2017). The polymers boosted drug solubility by a factor of ten when compared to β-CD. In another research, the drug efficacy was tested in M. tuberculosis-infected cells. In addition, in vivo experiments in mouse lungs indicated that the system was more effective than the plain drug, even with no booster or nanocarriers, indicating that it may be used to treat tuberculosis.

The investigation of polymeric cyclodextrin derivatives shows innovative crosslinking agents, and new derivatives have also been examined. That part and coworkers (Thatiparti et al., 2017) developed an innovative synthesis employing diglycidyl ether as a crosslinker and HP CD. The addition of the antibiotics novobiocin and vancomycin in these pseudo polyrotaxane CDs derivatives was investigated. Polymers produced with varied chain length crosslinkers had better features, such as enhanced stability compared to other similar systems and a higher loading capacity. The polymers with shorter chain crosslinkers had the best loading capacity. In CD-based carrier systems, both medicines had a delayed release profile than in non-specific polymers and increased antibacterial efficacy and cell adherence.

Nanosponges for drug delivery, on the other hand, have made substantial progress in recent years. They improve CD's characteristics and increase the number of approaches for their application. They are typically manufactured using diphenyl-carbonate and related materials. Moin and colleagues, for example, for the prospective therapeutic and pain treatment by co-loading paracetamol, aceclofenac, and caffeine, into CD-based nanosponges with Diphenyl carbonate. (Moin et al., 2020). The system had an extended and steady release profile, suggesting that it could be used in pain therapy.

Surprisingly, Using a nanocarrier enhances the drug bioavailability by boosting its solubility and stability due to supramolecular inclusion, also decreasing the time needed by the drug to be removed from the bloodstream.

Shringirishi and colleagues, for example, investigated the bioavailability and released a profile of nifedipine/βCD-based nanosponges in 2017 for treatment of angina pectoris and hypertension (Shringirishi et al., 2017). In simulated stomach fluid, drug release showed a burst release for the first four hours, then shifted to a regular release for the next 24 hours. The nanosystem's loading efficiency was 78 %, and its size was 430 nm. Its oral bioavailability was 3.6 times higher than the control formulation in vivo tests, and it had appropriate stability for six months.

In 2018, Zidan et al. investigated the release of atorvastatin calcium loaded on CD-based nanosponges and their effect on cholesterol and triglyceride levels (Zidan et al., 2018). Carbonyldiimidazole was used to make the polymers in various ratios. With a size of 420 nm,

the sponges had a maximum drug-loading capacity of 34%. The in vitro release analysis revealed a biphasic pattern, with a quick release of 58 % after 1 hour and then a protracted release of 6 hours, which was better than the drug's dissolution rate of 43 %. In vivo release showed enhanced pharmacokinetic and pharmacodynamic characteristics, a 2.13-fold increase in drug bioavailability, and enhancement in therapeutic efficacy in animals with fatty livers. Amin and colleagues (Amin et al., 2020) investigated the bioavailability and released characteristics of Febuxostat/β-CD nanosponges to treat gout in 2019. For nanosponges with varying diphenyl carbonate ratios and diameters ranging from 220 to 300 nm, loading efficiency range 88 - 100 %.

The drug-loaded nanosponge-based tablets had acceptable qualities, with a controlled release profile that allowed 30% release within 1 hour and 75% after 6 hours. It had a relative bioavailability of 217 %, according to in vivo testing.

As a result of changes in their properties, such as enhanced solubility, stability, and acceptable mechanical qualities in pharmaceutical formulations such as tablets, CD-based covalent polymerics have become widely used in the recent five years. Furthermore, crosslinking facilitates the creation of inclusion and non-inclusion compounds, which increases the quantity of medication delivered and makes them more efficient hosts (Salazar et al., 2021). Furthermore, investigations on in vivo models have demonstrated improving medication bioavailability. The drug's release from the formulation, on the other hand, is always studied in vitro, in biological media or cells, using a gradient. In vivo research should be used to investigate this point, especially given the high constants of stability CD–guest often reported, which would make it difficult to release at a precise spot. Combining these systems with other therapeutic drugs to modulate stimuli release is an intriguing method (Silva et al., 2018). The work of Asela et al. (Asela et al., 2021)is an example. They describe loading phenylethylamine and 2-amino-4-(4-chlorophenyl)-thiazole on nanosponges with 90 % and 150 % loading capacity, respectively, resulting in an eight-fold increase in the number of pharmaceuticals that these nanosystems can carry. Furthermore, the simultaneous loading of gold nanospheres as a second therapeutic agent in each nanosystem is possible thanks to the exposure of the drug functional groups, which has an efficiency of 85 %. This method can potentially transform nanosystems into stimuli-responsive smart systems for regulated medication release, such as antidepressants and antimicrobials (Tao et al., 2020). Among the different types of nanosponges are Titanium-based nanosponges(L. Guo et al., 2008), Silicon nanosponges(Farrell et al., n.d.), Polystyrene nanosponges (Davankov et al., 1996), and Cyclodextrin based nanosponges (Swaminathan, Pastero, et al., 2010).

Cyclodextrin (CD) is a truncated conical-shaped oligosaccharide with a hydrophobic cavity and hydrophilic external surface built up from D-(+)-glucopyranosyl units linked by a-1,4-glycosidic bonds. CD family has three main derivatives α, β and γ CD, constituting six, seven, and eight glucose units, respectively(Rousseau, n.d.)

Due to its great capacity of complex formation, low cost, acceptable cavity size for a wide range of medicines, and safety for oral administration, β -cyclodextrin is the most frequent type of cyclodextrin employed in nanosponges manufacturing (Diniz et al., 2018). However, due to nephrotoxicity and low water solubility, its application via parenteral administration is restricted (*Cyclodextrins in Pharmaceutics, Cosmetics, and Biomedicine*, 2011). Although α and γ cyclodextrins have a higher water solubility, α-CD has insufficient cavity size for the inclusion of many drugs, and γ-CD is expensive to use (*Cyclodextrins in Pharmaceutics, Cosmetics, and Biomedicine*, 2011). Hydroxyl groups oriented towards both sides of the conical-shaped structure away from the cavity are responsible for external hydrophilicity. (Rousseau, n.d.) the internal hydrophobicity results from hydrogens H-3 and H-5 pointing into the cavity. This unique 3D structure of CD with hydrophobic cavity and hydrophilic surface (figure 1) can totally or partially encapsulate hydrophobic molecules in aqueous media or solid-state by the formation of reversible complexation process (Del Valle, 2004). Reactive hydroxyl groups on the outer side of CDs can be crosslinked with bi or polyfunctional materials such as active carbonyl compounds, dianhydrides, diisocyanates, etc., to form insoluble 3D covalent networks called cyclodextrin based nanosponges. (Trotta, SHENDE, et al., 2012). Cyclodextrin NS is a non-irritant, biodegradable carrier for many molecules of different molecular weights as proteins, vaccines, anticancer drugs, and enzymes. Also suitable for extended-release drug delivery (Vishwakarma et al., n.d.). Unlike most carriers, the NS system can maintain the molecular form, size, and shape of the loaded agents without the need for surfactants (Mognetti et al., 2012).

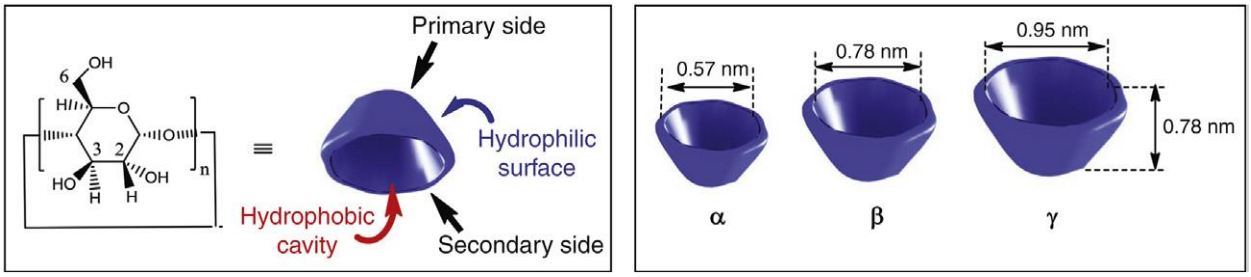

Figure 1: 3D structures with geometric dimensions of α, β and γ CD. (Rousseau, n.d.)

2. Advantages and disadvantages of crosslinked CD (Nanosponges) based drug delivery systems:

- Reduce side effects while maintaining the efficacy of the entrapped drug (Couvreur & Vauthier, 2006; Minelli et al., 2012)
- NS provides controlled release up to 24 hrs of the entrapped drug and protects the drug against in-vivo conditions maintaining the bioactivity of the drug; this is due to the surrounding polymer network that hinders the diffusion of the entrapped drug, thus supporting slower release kinetics. (Caldera et al., 2017)
- Drug delivery across various body barriers like a blood-brain barrier. (Garcia-Garcia et al., 2005)
- Masking unpleasant flavours (Indira, 2012)
- The disadvantage of nanosponges is their ability to include only small molecules.

3. Characteristics of nanosponges:

- A specific size can synthesize nanosponges by changing the crosslinker to polymer ratio. (Trotta et al., 2006)
- Non-toxic, porous insoluble in most organic solvents and stable at high temperatures up to 300 °C(S et al., 2012)
- NSs based formulations are stable over the pH range of 1 to 11 (Patel & Oswal, 2012)
- They are insoluble, form clear and opalescent suspensions in water, and easily regenerate with solvents through thermal desorption or extraction. (Setijadi et al., 2009)
- Chemical linkers enable nanosponges to bind to a specific target site. (Swaminathan, Cavalli, et al., 2010)

4. Preparation methods of Nanosponge:

CD-based NS may be prepared by the solvent method, melt method, or ultrasonication technique

4.1. Melt method:

In this method, CD and crosslinker are homogenized and melted along with each other with continuous stirring at 100 C for 3-5 Hrs. The mixer was cooled to room temperature, and the obtained product was broken and washed repeatedly with a suitable solvent to remove the reaction byproducts.

4.2. Solvent method:

In this method, CD and the crosslinker are solubilized in apolar aprotic solvents like dimethyl sulfoxide or dimethylformamide. The reaction started by applying heat ranging from 10 C to reflux temperature for 1 to 48 hrs. Once the polymerization process was completed, cool the solution to room temperature and add the cooled solution to excess water. The product was recovered by filtration or centrifugation and purified by extended Soxhlet extraction(Lala et al., 2011; Trotta et al., 2009).

The result is the development of solid nanoparticles with a spherical morphology with high solubilizing effectiveness for poorly water-soluble compounds, either through inclusion or non-inclusion complex formation. The transparent block of hyper-crosslinked cyclodextrins can be incubated with medication for loading when condensation polymerization is complete. Using a high-pressure homogenization technique, the size reduction procedure can be translated to synthesized nanosponges. An aqueous suspension of nanosponges is homogenized for 10 minutes using an Ultra Turrax at a preset speed (rpm). Subsequently, this homogenized suspension undergoes numerous homogenization cycles in a

high-pressure homogenizer. Swaminathan et al., for example, used an Ultra Turrax at 24,000 rpm for 10 minutes to homogenize a 2 % m/V aqueous suspension of swellable-cyclodextrin-poly amidoamines-nanosponges. This homogenized suspension was then placed in a high-pressure homogenizer and subjected to 12 homogenization cycles in a recirculation mode, with five cycles at 7000 psi, five cycles at 5000 psi, and two cycles at 5000 psi. The aqueous nanosuspensions of polyamidoamines-nanosponges were employed for characterization and protein complexation experiments. This approach can produce nanosponges with a limited size distribution, and the resulting product can be safely stored in the refrigerator at 4 °C without aggregation (Swaminathan et al., 2010).

4.3. Ultrasonication technique:

This method is executed in the absence of solvents by applying sonication. In brief, CD and crosslinker are mixed in a flask, placed in a water-filled ultrasound bath, heated to 90°C, and sonicate for 5 hrs. The washing and purification processes were similar to those applied to the previous methods.
The advantages of this method are a solvent-free method, and the produced particles are spherical with uniform particle size. (Trotta et al., 2006).
The manufacture, crystallization, and purification of the acquired product proceeded the same manner as the melt or solvent technique. Due to the absence of organic solvents, probe sonication, a high-energy input procedure, can be used as a substitute for ultrasonication. Trotta et al. used ultrasound probes to create ultrasound-assisted nanosponges (Trotta et al. 2007). Anandam et al. investigated the effects of two alternative heating methods for nanosponges preparation (microwave and conventional) on crystallinity, shape, and size distribution of the resulting nanosponges in a recent study (Anandam et al. 2016). The nanosponges made using two different methods showed significant structural differences. Nanosponges manufactured using the microwave approach were reported to have a restricted size distribution, greater crystallinity, and drug loading (by 2-fold) than their traditional counterparts. Overall, researchers' extensive structural characterization and other experiments confirmed the microwave method's preferred and distinct promising effects.

4.4. *Factors affecting Nanosponges formulation*

Based on the previously reported data by the authors (Ahmed et al., 2013; Trotta, Zanetti, et al., 2012) :

4.4.1. Type of crosslinkers and polymers
The type of polymers and crosslinkers used in nanosponges preparation affect the type and behaviors of nanosponges. By changing the molar ratio of the crosslinker, which affects the crosslinking degree, we can control and modify the drug loading and release.
4.4.2. Type of drug:
The encapsulated drug should have a low molecular weight between 100 to 400 gm /mole with not more than five condensed rings, have a water solubility of less than 10 mg/ml,
and melting point below 250^0C as high melting points compounds do not have a high stability loading process may be affected by the rigidity of the compounds with high melting temperatures. (Tejashri et al., 2013)
4.4.3. Interaction medium:
hydrophilic medium will lead the organic molecules into hydrophobic cavities, while
an organic solvent tends to release the organic molecules trapped in nanosponges cavities.
4.4.5. Complexation temperature:
Increased temperature is inversely correlated to the stability constant of the complex. So, temperature control should be maintained throughout the reaction.
4.4.6. Degree of substitution.
The degree of crosslinking increases with the higher the number of substituents,
Nanosponges with high porosity will produce due to more interaction between polymer molecules.

4.5. Drug loading into nanosponges

The prepared nanosponges are suspended in water with a dispersed amount of the drug-loaded. Maintain the suspension under stirring for the specific time required for the complexation process. The uncomplexed drug is separated by centrifugation, then dry the solid crystals of loaded nanosponges by freeze-drying or solvent evaporation technique. (Tejashri et al., 2013)

4.6. Characterization of nanosponges

4.6.1. Particle size and polydispersity indices:
By dispersing the sample in water or any other convenient solvent, this measurement is usually done by particle size analyzers applying dynamic light scattering (DLS).

4.6.2. Zeta potential:

Zeta potential is the measurement of surface charge. It is the potential difference between the fixed fluid layer to dispersion medium and dispersed particles (Kutscher et al., 2010). The zeta potential can be used to forecast the sign of the NS's surface charge and its colloidal stability after dispersion. To ensure stable nanosponges suspension, the charge should be sufficiently high. The pharmacokinetics of the nanoformulation, as well as cell-targeting behavior, might be affected by surface charge. (Sahay et al., 2010)

4.6.3. Fourier transform-infrared spectroscopy (FT-IR):

FT-IR is a critical tool to determine the appearance of functional groups' peaks in the FT-IR spectrum and the formation of bonds between monomers and indicates the polymer formation(Brittain et al., 1991). By combining sample powder with potassium bromide and compressing the matrix into a thin disc, the measurement is performed on a dried sample in the range of 600-4000 Cm-1 (Ahmed et al., 2013). The peak range of 1700 to 1750 cm-1 in crude nanosponges demonstrates the establishment of a carbonate bond. The main nanosponges (-CD) units show no identifiable peaks in the FTIR spectrum in the same range(Anandam & Selvamuthukumar, 2014b).

The fundamental advantage of FTIR is its excellent selectivity and sensitivity, in addition to its inexpensive cost. However, there is a drawback in the possibility of crosslinker bands hiding the characteristic peaks (Bragagni et al., 2010). Much research used FTIR for nanosponges characterization for Telmisartan(M. Rao et al., 2013), Camptothecin (Swaminathan, Pastero, et al., 2010), and Quercetin (Anandam & Selvamuthukumar, 2014a). Figure. 2. Show the FTIR spectra of camptothecin, crude NS, and NS formulations of Camptothecin loaded NS.

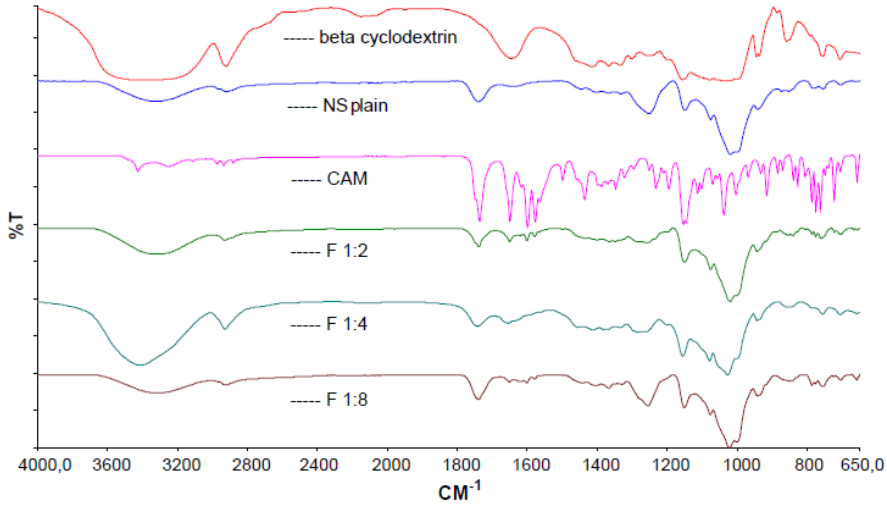

Fig. 2. FTIR spectra of CAM, NS, and NS formulations. (Swaminathan, Pastero, et al., 2010)

4.6.4. Raman spectroscopy

Based on the light scattering concept, Raman spectra are created by irradiating a substance with laser light. The pattern of wavelength changes is important for identifying a chemical fingerprint corresponding to a molecular structure. (Franzen & Windbergs, 2015). This molecular methodology provides a useful analytical method for identifying and investigating molecules' vibrational modes and detecting molecular bond changes. Compared to FTIR spectroscopy, this method has certain distinct advantages, such as no or little sample creation and insensitivity to water absorption bands (Mura, 2015). Raman spectroscopy can be used in conjugation with FTIR to understand drug-NS interaction better.

(Swaminathan et al., 2013) The typical peaks of dexamethasone in Raman spectroscopy were disappeared or veiled, demonstrating dexamethasone-NS interaction.

4.6.5. Differential scanning calorimetry (DSC).
DSC is a thermo-analytical method that determines the change in drug substances as a heat function. Loss of drug melting peak indicates molecular dispersion of the drug within the polymer structure.(Hombreiro-Pérez et al., 2003; Jeong et al., 2002). The DSC method can quantify the heat of transitions and reactions. It distinguishes between first-order thermodynamic differences like fusion and second-order thermodynamic variations like Tg (glass transition temperature). (Encyclopedia of Analytical Chemistry, 2001). The disappearance of the drug melting peak in the DSC thermogram of NS confirms the drug interaction due to the drug's transformation from crystalline to amorphous state. (Bettinetti et al., 2002). Many researchers used DSC for NS characterization for reservatrol (Ansari et al., 2011), Telmisartan (M. Rao et al., 2013), and camptothecin (Swaminathan, Pastero, et al., 2010).Figure 3. Show the DSC thermogram of Telmisartan drug, which showed a sharp peak at 269 C, while the thermogram of crude CD, NS, and formulations of loaded drugs-NS showed the absence of this peak, indicating crosslinking of NS.

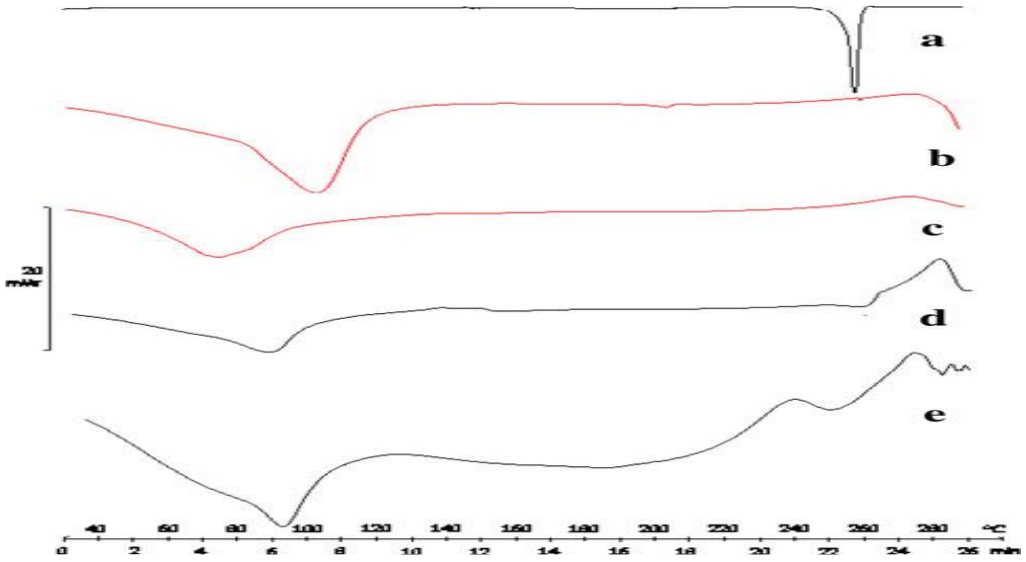

Fig.3 DSC spectra of (a) TEL, (b) b-CD, (c) NS, (d) IC2, (e) IC6 (M. Rao et al., 2013)

4.6.6. X-ray diffraction (XRD):
Characterization and identification of crystalline formations. It provides comprehensive information on texture, phases, structures, and other structural factors such as crystallinity, average grain size, crystal defects, and molecular strain. It is based on monochromatic X-rays being constructively blocked by a crystalline material. The dispersion of atoms in the sample's lattice planes is used to estimate the X-ray diffraction peak intensities. As a result, X-ray diffraction is a fingerprint of periodic atomic systems in the sample under investigation. (Aa et al., 2015). By identifying changes in 2θ values compared to physical mixtures, pure drug, and NS, this approach can confirm these nanosystems' crystalline and amorphous characteristics. Furthermore, changes in the intensity of diffractogram peaks provide information about the crystalline size of NS. Figure 4. Show the X-ray diffraction patterns of plain b-CD and camptothecin drugs.

4.6.7. Drug loading:
Nanosponges water dispersion was incubated with an excess of drug and shaking for 24 hrs at room temperature, nanosponges aliquots were separated and freeze-dried. (Cavalli et al., 2006).

4.6.8. Microscopy studies:
Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) evaluate particle shape and size. (E et al., 2004). The topographical changes caused by the medication, polymer, and cross-linker interaction are evaluated using this analytical technique. Different forms of NS, such as rosuvastatin, have also been studied using SEM (Gabr et al., 2018).

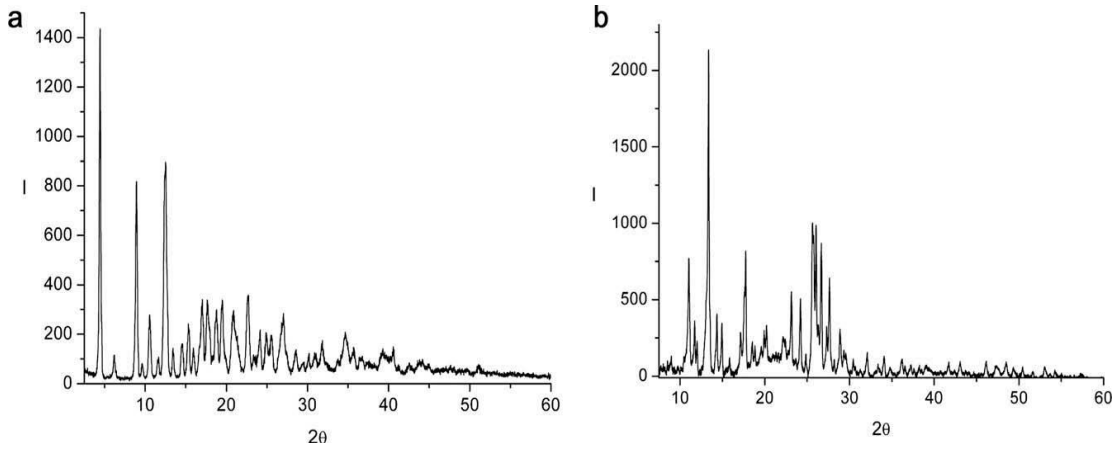

Fig. 4. XRPD pattern of (a) the plain β -CD; (b) XRPD pattern of CAM drug. (Swaminathan, Pastero, et al., 2010)

A high-voltage electron beam is delivered through the material to create a picture via the TEM technique. There are two sources for producing electron beams: field-emission and thermionic. Tungsten needles serve as field emitters, whereas lanthanum hexaboride crystals and tungsten filaments serve as thermionic emitters (Williams & Carter, 2009). Topography through TEM has also been carried out for various types of NS like rosuvastatin (Gabr et al., 2018).

4.6.9. In-vitro release kinetics:

Using a multi-compartment rotating cell. An aqueous dispersion of drug-loaded nanosponges is placed in the dialysis membrane, and the receptor compartment is filled with phosphate buffer pH 7.4 or pH 1.2. the buffer is withdrawn and analyzed at fixed time intervals and replaced with fresh buffer (Trotta et al., 2009).

4.7. **Applications of nanosponges in pharmaceuticals**:

4.7.1. Solubility and bioavailability enhancer

Enhancing medication bioavailability would result in a lower necessary dose to achieve pharmacological concentrations, which would result in better treatments, fewer side effects, and better patient compliance.

Complexation or solid dispersion of the drug in cyclodextrin cavities improves drug solubility of poorly water-soluble drugs due to reduced drug crystallinity; the hydrophobic cavity hides the drug while hydrophilic hydroxyl groups are exposed to the aqueous environment resulting in a water-soluble complex (Challa et al., 2005).

Nanosponges have been reported to enhance the solubility of many poorly soluble drugs like Quercetin and Itraconazole (Anandam & Selvamuthukumar, 2014a; Swaminathan et al., 2007).

The paclitaxel and IL-2-loaded nanogels produced with HP CD-acrylate and chitosan derivatives for cancer treatment was investigated by Song et al. After IV administration, plasma paclitaxel and IL-2 concentrations were measured. Nanogels had 2.2-fold paclitaxel and 2.6-fold IL-2 concentration at 0.5 h compared to free paclitaxel + IL-2, and the IL-2 circulation time was similarly prolonged. Compared to free paclitaxel + IL-2, non-coated nanogels showed a 4.6-fold increase (AUC0t). (Song et al., 2017).

Due to its lack of corneal permeability, dexamethasone has poor aqueous solubility and limited clinical uses in ocular conditions. Swaminathan et al. used a diphenyl carbonate crosslinker to produce dexamethasone nanosponges for ocular administration. Hyper-branched polymeric colloidal systems with exceptionally high encapsulation efficiency were stated to be synthesized nanosponges. The study's goal was to create dexamethasone complexes with three different types of -cyclodextrin nanosponges (all with different cross-linking ratios) for ocular applications. The incubation-lyophilization procedure was used to nano-encapsulate several nanosponges formulations. To confirm the interactions and encapsulation of dexamethasone with nanosponges, XRPD, DSC, and FTIR-ATR investigations were used. In vitro release tests showed that dexamethasone was released in a

regulated manner for about 5 hours. With low polydispersity indices, particle sizes of loaded nanosponges formulations were marked between 350 and 660 nm, and zeta potentials were high enough (between 20 and 27 mV) to generate a stable colloidal nanosuspension. The spherical colloidal nature of nanosponges was further confirmed by transmission electron microscopy (TEM) and atomic force microscopy (AFM) studies. Furthermore, no adverse reactions have been recorded in an ex vivo safety assessment research on the bovine cornea, validating the system's safety. On excised bovine cornea in corneal holders, the permeability of dexamethasone from improved nanosponge formulations was tested; the results showed greater permeability than the marketed formulation (Swaminathan et al. 2013).

4.7.2. Stability enhancer:

Some compounds including volatile oils, BCS class-II, and class IV drugs can be encapsulated into nanosponges, thereby capitalizing on the solubility, dissolution, and stability of such drug moieties

B-CD units increase the stability of the complexed drug (Girek & Ciesielski, 2011). Bovine serum albumin (BSA) proteins are not stable in solution form and need to be stored in a lyophilized form which could not maintain their native protein structure. BSA encapsulated in Cyclodextrin-based polyamidoamine nanosponges shows increased stability(Swaminathan, Cavalli, et al., 2010).

Resveratrol was encapsulated in nanosponges, and this incorporation led to a marked increase in the solubility and stability of the drug. In vitro studies on porcine skin and on rabbit buccal mucosa showed enhanced drug permeation from resveratrol-loaded nanosponges permeation (Ansari et al., 2011)

Recent advances in genetic engineering have propelled the industrial applications of enzymes by increasing the stability, economy, and specificity of enzymes. Some enzymes that have found increasing applicability in the industry include alpha-amylase, trypsin, cellulose, pectinase (clarification process in fruit juice), ligninase (to break down lignin), and lipase. This catalytic activity of enzymes is attributed to the exact orientation of the active site (Osmani et al., 2015b; Vyas et al., 2008).

Vaidya et al. have developed surface-active nanosponges by lysozyme impregnation to uphold lysozyme's conformational stability, to shatter bacterial cell wall via 1,4-β-linkages hydrolysis between N-acetylmuramic acid and N-acetyl-d-glucosamine residues occurring in peptidoglycan layer, and to control calcium release in hypocalcemia (Vaidya et al., 2001)

4.7.3. Drug release modulating:

Loaded drugs into nanosponges systems are retained and slowly released over time, evading the drawbacks of frequent administration of the most commercially available products. Hydrophilic nanosponges can enhance the absorption of the drug through biological barriers. Hydrophobic nanosponges can be used as sustained-release carriers for highly water-soluble drugs such as proteins (Vyas et al., 2008).

Lippia organizes essential oil was encapsulated in HP CD inclusion complexes and incorporated in NLC, as proven by Pires et al. (Pires et al., 2019). The developed follicular accumulation mechanism, according to the findings, produced a depot for regulated distribution with a six-day shelf life.

Curcumin was found in plasma for at least 12 hours (up to 72 hours) following intraperitoneal distribution of nanocrystals, although free curcumin was not detectable after 8 hours. This exceptional rise in bioavailability is reflected in the increased efficacy seen in a large number of in vivo studies on Charcot-Marie-Tooth-1A transgenic rats (Caillaud et al., 2020).

Linalool (a liquid component of many essential oils with a boiling point of 198 °C) was encapsulated in various nanosponges as a liquid oil model for preserving and extending the release of volatile molecules such as essential oils (Cavalli et al. 2006b). Linalool can be integrated into the β-cyclodextrin nanosponges matrix at a concentration of around 8% w/w. DSC analysis confirmed the entrapment. The linalool β-cyclodextrin combination was used to conduct in vitro release investigations. Linalool release from nanosponges was half that of the -cyclodextrin complex after 2 hours, indicating that the molecule was stabilized within the nanosponge structure. In a published study, Torne et al. developed nelfinavir mesylate (a protease inhibitor with low bioavailability) loaded nanosponges to improve nelfinavir mesylate solubility. The release of drugs from nanosponges was shown to be slower than the release of drugs from the -cyclodextrin complex (S. J. Torne et al., 2007), implying that nanosponges can prolong drug release over time and achieve sustained release when administered orally.

Shende et al. used a polymer condensation process to create cyclodextrin-based calcium carbonate (CaCO3) nanosponges as new carriers for regulated

calcium delivery in the treatment of hyperphosphatemia (Shende et al. 2013). The nanosponge encapsulation of $CaCO_3$ was confirmed by FT-IR and DSC studies, and SEM analysis revealed a roughly spherical shape of nanosponges with porous nature and a mean particle size of about 400 nm. The moisture content and Ca encapsulation of produced nanosponges were 81–95 % and 0.1–0.7 %, respectively. The optimized formulation was said to provide regulated enteric release, which could be useful in managing and treating hyperphosphatemia.

Shende et al. produced meloxicam inclusion complexes and nanosponges using -cyclodextrin to improve meloxicam solubility stability and extend meloxicam release overtime in another study (Shende et al., 2015). Different approaches were suggested, including kneading, manual mixing, and sonication. The zeta potential, particle size, encapsulation effectiveness, stability, and in vitro and in vivo drug release of the nanosponges were all measured. FT-IR spectroscopy and DSC were used to confirm the interaction of meloxicam with nanosponges, which resulted in an amorphous meloxicam state, as shown by PXRD data. According to SEM micrographs, Nanosponges had particle sizes ranging from 350 to 765 nm. The observed zeta potential was high enough to achieve improved stability. Furthermore, in vitro and in vivo experiments revealed that nanosponges released meloxicam for up to 24 hours, as expected. As a result, researchers proposed using nanosponges-based devices for the regulated delivery of analgesic and anti-inflammatory medicines.

To achieve controlled release, better bioavailability, and taste masking, Rao and Bhingole developed an oral dry solution of gabapentin, a bitter medication with low bioavailability (60 %) and a short half-life (5–7 hours) (M. R. P. Rao & Bhingole, 2015). The traditional melt procedure was used to make cyclodextrin nanosponges, then loaded with drugs. FT-IR, DSC, and PXRD tests were used to evaluate gabapentin nanosponges complexes, as well as saturation solubility and taste analysis. Using the suspension layering approach, complexes were coated with ethyl cellulose and Eudragit RS-100. The resulting dry gabapentin suspension was tested for dispersibility, taste, sedimentation, leaching, dissolution, and pharmacokinetics. The study's findings revealed maximum drug trapping by nanosponges complexes, controlled release for up to 12 hours (due to polymer coating), minimal leaching, and good flavour masking. In addition, in vivo studies demonstrated that gabapentin had a 24 % higher bioavailability than ordinary gabapentin.

4.7.4. Effective delivery carriers:

As anticancer drug delivery: camptothecin is a potent anticancer agent with strong activity against colorectal cancer(Bamigbola, 2012); due to its intrinsic toxicity, poor stability, and low water solubility, it has limited therapeutic use(Minelli et al., 2012; Swaminathan, Pastero, et al., 2010). By incorporating camptothecin into cyclodextrin NS, stability and solubility issues were resolved, and the complex also demonstrated low hemolytic action while exhibiting strong cytotoxicity against cancer cells. (Swaminathan, Pastero, et al., 2010).

Paclitaxel is used to treat head and neck(Wall et al., 1966), lung and bladder cancer; due to its poor water solubility and extensive metabolism in the liver, it has low bioavailability through the oral route. Therefore, due to its low bioavailability, it is administrated through the IV route by dissolving the drug in a toxic solvent (Cremophor EL) which may cause anaphylactic shock(S. J. Torne et al., 2010). Cremophore EL free Paclitaxel-NS complex was developed to overcome the drawbacks and showed an ability to solubilize and effectively deliver the drug into cancer cells (Mognetti et al., 2012).

Tamoxifen is a nonsteroidal antiestrogen drug; its oral absorption is inhibited by an acid efflux pump(S. Torne et al., 2013). Tamoxifen-NS protected the drug against the acid environment and showed enhanced anticancer activity with increased bioavailability(S. Torne et al., 2013). Xu et al. created and studied -cyclodextrin-based nanosponges carriers for molecular encapsulation of doxorubicin, a popular anticancer drug. The doxorubicin binding capability of the -naphthyl alanine residue connected to the major face of the -cyclodextrin derivative was high. The carrier-doxorubicin inclusion complex was shown to be highly stable in a wide range of acidic circumstances (pH 1–7); nevertheless, the encapsulated drug was slowly released under hyperthermic conditions (up to 50 °C). In cell culture tests, doxorubicin complexation with nanosponges significantly reduced doxorubicin toxicity while simultaneously protecting cell uptake. In vitro investigations validated the release of doxorubicin caused by heat and the increase in cellular absorption. According to the findings, the new -cyclodextrin derivative successfully encapsulates doxorubicin and the inclusion is thermally sensitive, allowing for effective

doxorubicin delivery in conjunction with hyperthermia therapy techniques (Xu et al. 2014).

Antifungal drug delivery: Itraconazole is an abroad spectrum antifungal agent with low bioavailability due to poor solubility. By loading itraconazole in NS, the solubility was increased by 50 folds (Swaminathan et al., 2007).

HP CD and Tween 80 together inhibited econazole nanosuspension agglomeration during storage and improved drug release from the nanosuspension. Based on the combination of HP CD and Tween 80, Maged et al. created an econazole formulation. The addition of chitosan-HCl to this antifungal nanoformulation increased drug release and ocular bioavailability, suggesting that polymer inclusion in this type of nanosystem makes a significant contribution (Maged et al., 2016).

Acyclovir is highly effective against the herpes simplex virus as antiviral drug delivery. Because of its lipophilicity, the drug is not completely absorbed from the GIT. So, high doses are needed, accompanied by increasing toxicity and side effects(Ghosh et al., 2006). Researchers encapsulated acyclovir in carboxylated CD NS. The release was 22% after 3 hrs; cellular uptake was increased compared to the plain drug(Lembo et al., 2013).

As antidiabetic drug delivery: Repaglinide promotes the insulin release from the pancreatic cells; as a lipophilic drug with low solubility, the drug solubility was assessed after incorporating two types of NS β-CDNS and sulfo butyl ether β-CDNS. The release with both NS types was higher than the plain drug (Olteanu et al., 2014). Although the solubilization was higher with β-CDNS and the loading was higher with sulfobutylether β-CDNS.

To improve the anaesthetic efficacy of transdermal Butamben, Mura et al. developed deformable liposomes carrying the medicine as a CD complex (Mura et al., 2021). Liposomal formulations significantly increased the intensity and duration of the drug anaesthetic effect in rabbits in vivo compared to its hydroalcoholic solution.

The use of nanosponges in topical gels and lotions is another medical use (Friedrich et al. 2015; Pando et al. 2015). Ansari et al. made one such attempt to demonstrate the topical applicability of nanosponges. Resveratrol, a polyphenolic phytoalexin with anti-oxidant characteristics found in various plant sources, is important in preventing various human ailments (Chauhan 2015; Rauf et al. 2016). Resveratrol was encapsulated in nanosponges, significantly improving the drug's solubility and stability. In vitro investigations on porcine skin and rabbit buccal mucosa revealed that resveratrol-loaded nanosponges improved medication penetration (Ansari et al. 2011b). In a separate study, researchers created and characterized a minoxidil-loaded nanosponges-based hydrogel system for topical application on the scalp to overcome the drawbacks of currently available minoxidil topical solutions. For the manufacture of nanosponges employing diphenyl carbonate as a crosslinker, a solvent evaporation approach was suggested. Solid dispersion was used to load minoxidil into the nanosponges. Fourier transform infrared (FT-IR), differential scanning calorimetry (DSC), and scanning electron microscopy were used to investigate the nanosponges and minoxidil-nanosponge complexes (SEM). In addition, drug-loaded nanosponges were mixed into hydrogel formulations, and their appearance, homogeneity, gelling, pH, viscosity, spreadability, drug content, and in vitro drug release were all examined. Compared to minoxidil topical solution, nanosponges-based hydrogel showed excellent outcomes (Ansari et al., 2014).

Glaucoma treatment as glaucoma is one of the most common irreversible causes of blindness globally. Galloway et al. have created a novel image-guidance system for the controlled distribution of neuroprotective medicines in the form of nanosponges in light of this fact. Animal models and ex vivo human tissue were used to characterize and analyze the created system's performance, yielding promising results (Galloway et al., 2014). Lambert et al. developed nanosponges encapsulating hypotensive medications such as Brimonidine, Travoprost, and Bimatoprost. They tested the efficiency of the nanosponges-based delivery system to reduce intraocular pressure in mice over a long period. Microbeads were administered into the anterior lobe of mice, followed by intravitreal injections of drug-loaded nanosponges to induce bilateral ocular hypertension. Confocal microscopy was used to look at retinal ganglion cell (RGC) uptake and retinal deposition after Neuro-DiO nanosponges were injected intravitreally. According to the findings, nanosponges encapsulating all three hypotensive drugs significantly reduced intraocular pressure with varying %ages and time durations, as follows: brimonidine (12–30 % intraocular pressure-lowering up to 6 days), travoprost (19–29 % intraocular pressure-lowering up to 4 days), and bimatoprost (400 nm size nanosponges, 24–33 %

intraocular pressure-lowering up to 17 days; 700 Furthermore, RGCs were observed to uptake Neuro-DiO released from nanosponges, and Neuro-DiO deposition in the retina increased with time. This study demonstrated the nanosponge carrier's potential for successful ocular delivery of hypotensive and other medicines. Furthermore, nanosponges-based devices can be used to target RGCs and neurons that degenerate in glaucoma (Lambert et al., 2015).

5. Conclusion

CDs are one of the most versatile supramolecular structures in delivery systems studies, particularly when incorporated into various nanomaterials, such as lipid and metal nanoparticles, and newly found nanomaterials such as metal-organic framework nanoparticles and carbon dots. Modified CDs will undoubtedly continue to increase due to their adaptability and synergy with nanomaterials in supramolecular chemistry and pharmaceutical sciences and nanotechnology applied to biomedicine. Cyclodextrin derivatives excel in improving pharmaceutical water solubility and stability. When mixed with nanomaterials, they can boost loading efficiency, increase colloidal stability. controlled medication release induced by a stimuli internal or external stimuli is conceivable. From a biological standpoint cyclodextrin derivatives have been shown to boost drug and nanosystem bioavailability, reduce cytotoxicity, and improve biosafety in various in vivo and in vitro experiments.

Cyclodextrin-based nanosponges are an unusual type of biocompatible delivery system that, because of flexible crosslinked polymers, provides for a smooth transition from conventional to versatile distribution and meets the requirements. The method encapsulates both hydrophilic and lipophilic medicines, allowing for controlled and predictable drug release at the target region, enhancing bioavailability and efficacy. Controlling the polymer to crosslinker ratio allows for the desired particle size and release rate. Furthermore, nanosponges-based delivery methods solve the solubility problem of newly created drug entities and preserve the active moieties from degradation. Advanced methods such as stimuli-sensitive nanosponges and tumour-targeting can also be used to overcome the negative effects associated with traditional formulations. Currently, a lot of effort is being put into developing faster and easier procedures for making nanosponges.

Furthermore, molecular imprinting of nanosponges with pharmaceuticals is a burgeoning topic of research these days; the drug can be intercalated into the nanosponges reticulate complex during manufacturing to induce slower drug release. Research is currently focused on synthesizing and characterizing PEGylated nanosponges, soluble nanosponges, and cationic nanosponges for various applications. To summarise, cyclodextrin-based nanosponges with a variety of favourable properties can be supported as an advanced carrier in the field of drug delivery and nanotherapeutics. They can contribute as a potential instrument for effective and efficient drug delivery.

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