International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 1, 2024

Review Article

NANOSPONGE FOR ENHANCING SOLUBILITY AND BIOAVAILABILITY OF ORAL DRUGS: REVIEW

ISHAK E. KERILOS[1], HOSSAM S. EL-SAWY[1*], SHERIF K. ABU ELYAZID[2], MAGDY IBRAHIM[3]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Egyptian Russian University, Badr City-11829, Cairo, Egypt. [2]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Cairo-11651, Egypt. [3]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo-11562, Egypt
***Corresponding author: Hossam S. El-Sawy; *Email: hossam-elsawy@eru.edu.eg**

Received: 26 Sep 2023, Revised and Accepted: 25 Oct 2023

ABSTRACT

New developments in nanoparticle-based oral medicine have resulted in a profusion of studies to improve the solubility, permeability, and chemical stability of various medications. Nanosponges (NSs) are one type of carriers utilized in this many carrier systems. NSs are nanosized carriers with a sponge-like shape. They have hydrophilic cavities and hydrophobic branches, which aid in the loading of both hydrophilic and hydrophobic medicines. Nano-sponges have a 3-dimensional network and a nanometric cavity size. NSs are very porous, with the capacity to entrap active moieties and the advantage of controlled release. These tiny sponges circulate in the body to reach a specific place and release the medicine in a controlled and predictable manner, assisting in the resolution of numerous issues such as drug toxicity and low bioavailability. One of their significant impacts is the ability to enhance oral absorption and bioavailability. The primary goal of this review is to provide brief updates on NSs for increasing medicine oral absorption as well as their evolutions in loading drugs for enhancing their oral deliverability and treatment of a variety of diseases.

Kyewords: Nanosponge-based delivery systems, Methods of preparations, Cyclodextrins, Cross-linking agents, Systemic delivery, Enhanced oral absorption

DOI: https://dx.doi.org/10.22159/ijap.2024v16i1.49490 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Oral administration is clearly proposed as the most convenient drug administration method, with various advantages over alternative delivery channels, including lack of discomfort sensation, ease of self-administration, and great patient compliance. The great majority of marketed medications are frequently delivered orally around the world. The efficacy of these medications is determined by their oral absorbability, which is determined primarily by drug-based characteristics and the physiology of the gut [1, 2]. Some medications' undesirable properties, such as poor hydrophobicity, low permeability, chemical instability, and excessive first-pass metabolism, have a deleterious impact on drug transit through the gastrointestinal (GI) barriers [3]. The GI tract has physical, chemical, enzymatic, and biological membrane barriers that affect the transit and effectiveness of poorly absorbed medicines [4, 5].

Nanosponges (NSs) are tiny mesh-like structures (fig. 1) that may carry a wide range of substances [6, 7]. They have a revealed spherical colloidal nature and have been found to possess a very high solubilization capacity for poorly soluble medicines due to their inclusion and non-inclusion behavior [8]. NSs have recently been produced and proposed for drug delivery. NSs can also solubilize poorly water-soluble medicines [9], providing extended release and enhancing drugs bioavailability [7, 10].

In this review, brief discuss of benefits and problems of using drugs via oral route as well as detailed different approaches and types of NS-based delivery systems with a focus on their applications as an oral-formulations with enhanced absorption, have been illustrated.

It is important to note that the Egyptian Knowledge Bank (EKB) platform was used to acquire data for this review from Innovare Academic Sciences (IAS) journals and other sources and publishers. In order to gather information from research articles and review articles that have been published in the last 20 y and are related to the chosen keywords, search criteria have been undertaken using the keywords (Nanosponge-based delivery systems, Methods of preparations, Cyclodextrins, Cross-linking agents, Systemic delivery, and Enhanced oral absorption). The results of data collecting from the aforementioned sources have been thoroughly acquired, examined, summarized, and appropriately cited in this review.

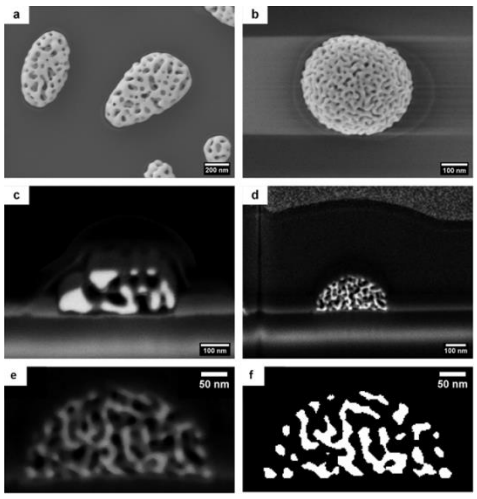

Fig. 1: SEM images of nanosponges [11]

Benefits and problems of using drugs via oral route

Among the several techniques for administration, the oral drug delivery system is the most effective and secures one [12, 13]. The market's oral formulations are easier to administer and produce adequate therapeutic concentrations *in vivo*, making the per-oral (PO) delivery route the best option [14]. The oral administration technique has several advantages over parenteral approaches, including as preventing cannula-related infections caused by probable iatrogenic dissemination of bacteria through the patient's inserted cannula [15]. Patient inconvenience is also decreased especially with dangerous infections that could be treated at lower risk and often in a short-term hospitalization or without hospital admission at all [16]. Furthermore, oral drug formulations are less expensive on the market than parenteral medications. The latter typically necessitates sterile and isotonic diluents, needles, syringes, and nursing time, which may result in a financial burden for the patient [17, 18]. For the long-term treatment of chronic cardiovascular and cerebrovascular disorders, oral administration is preferred due to higher patient compliance, due to no pain and cost-effectiveness [19]. Although the oral therapy has not been very frequently used in cancer chemotherapy, new cytotoxic drugs of oral formulations undergoing preclinical and clinical trials could be seen during the last decade [20].

However, there are influential hurdles confronting the delivery of drug by oral route. Oral delivery is significantly affected by the physicochemical properties of the drugs. Some drugs or active ingredients show poor aqueous solubility and low permeability that negatively influence the GI absorption. Drugs are potentially degraded in the GI tract due to the high acid content of the stomach, enzymes present in the lumen of the intestine, e. g., insulin [21] or interacted with endogenous components such as bile, which alter their absorption. Low bioavailability of drugs is also caused by an extreme hepatic first-pass effect and rapid drug metabolism., e. g. ezetimibe [22]. Efflux mechanisms have the potential to restrict drug absorption as well. The low and variable bioavailability of various agents is caused by the drug transmembrane efflux proteins, such as P-glycoprotein, which are abundant in the epithelial cell membrane, e. g. lumefantrine [23] and darunavir [24]. Therefore, it is crucial for new drug delivery systems to develop in order to overcome these limitations.

Nanosponges

Because of their interior hydrophobic cavities and exterior hydrophilic branching (fig. 2), NSs may load both hydrophilic and hydrophobic therapeutic molecules, providing remarkable versatility [8]. NSs mimic a three-dimensional scaffold or network more so. The backbone is a lengthy piece of polyester that dissolves with molecules known as cross-linkers, which function as tiny grappling hooks to connect various polymer components (fig. 2) [25]. The end result is spherically shaped particles with cavities where drug molecules can be housed [8].

By reacting cyclodextrin (CD) with a suitable crosslinker, which produces nano-sized materials with hyper-crosslinked CD known as NSs (fig. 2), these formulations can be used to cover up an unpleasant drug flavor. This helps turn liquid substances into solids, which achieves the desired taste-masking effect to the oral drug formulations [26]. To optimize drug loading and obtain a customized release profile, the cross-linking-to-cyclodextrin ratio can be adjusted during production [27]. Depending on the compound used as a crosslinker, NSs can be created as neutral or acidic NSs that can swell [28]. Their highly porous nanomeric nature enables drug molecules to orient themselves in NS's inclusion as well as interact in a non-inclusion fashion, which offers higher drug loading compared with the parent cyclodextrin molecules [27].

The higher degree of entrapment efficiency (EE), which enables NSs to operate as a pool for different medicinal compounds, is one of the benefits associated with the use of NSs [29]. They assist in preventing molecules from degrading as well. The preparation process is rather simple and has a high degree of regeneration. They can also easily incorporate liquids into their three-dimensional structure [30]. One of the drawbacks of this kind of formulation is that it can entrap small molecules with the required efficiency over large ones, especially those with masses under 500 Dalton (Da). Drug loading is also affected by crystallization level [31]. Additionally, there is a chance of dose dumping, which can be reduced by using polymer blends that help encapsulate substances with greater molecular masses [32]. They have been shown to be secure for both invasive and oral routes, making them a potential drug delivery vehicle [26, 33]. For oral administration, the complexes may be dispersed in a matrix of excipients, diluents, lubricants and anti-caking agents suitable for the preparation of capsules or tablets [34, 35]. NSs are encapsulating type of nanoparticles, which encapsulate the drug molecules within its core [36].

Chemicals used to produce nanosponges

Polymers

Hyper-cross-linked polystyrene, cyclodextrins, alkyloxy carbonyl cyclodextrins, 2-hydroxy propyl cyclodextrins, and copolymers of poly (Valero lactone-allylvalero lactone) and poly (Valero lactone-allyl Valero lactone oxepanedione) are among the polymers used to make NSs (table 1) [8, 38].

Crosslinkers

Diphenyl carbonate, diarylcarbonates, dicyandiamides, diisocyanates, pyrrolidine, carbonyldiimidazoles, glutaraldehyde, carboxylic acid dianhydrides, 2,2-bis(acrylamido)acetic acid, and dichloromethane are crosslinkers used to create NSs (table 1) [8, 38].

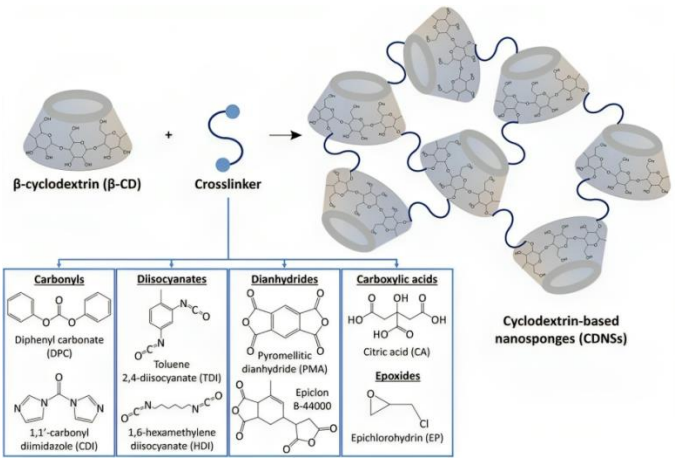

Fig. 2: Synthesis of CD-NSs through the reaction between β-cyclodextrin and a crosslinker such as carbonyls, diisocyanates, dianhydrides, carboxylic acids and epoxides [37]

Table 1: Examples of components used in the preparation of NSs

Composition of nanosponges	Examples	References
Polymers	Hyper Crosslinked Polystyrene Cyclodextrin (alkoxy carbonyl cyclodextrins)	[10, 39]
	2-hydroxypropyl-Methyl-β-cyclodextrin	[40]
	Methyl-β-cyclodextrin	[39, 40]
	Hydroxy propyl β-cyclodextrin	[38, 39]
	Hyper crosslinked polystyrene	[40]
	Poly-Valero-lactone	[39]
	Eudragit RS100	[39]
	Acrylic Polymer	[39]
Crosslinkers	Diphenyl carbonate	[40, 41]
	Carbonyl diimidazole	[39-41]
	Pyromellitic anhydride	[39-41]
	Di-isocyanates	[39-41]

Types of nanosponges

NS can be designed and formulated into a variety of different types according to the polymer added, its concentration, and the appropriate preparation technique. Beta CD-based NS is one of the most frequently prepared and widely utilized types of NS. Beta-CD NS formulation is a relatively straightforward process, and there are several possible modifications (fig. 3) [42, 43].

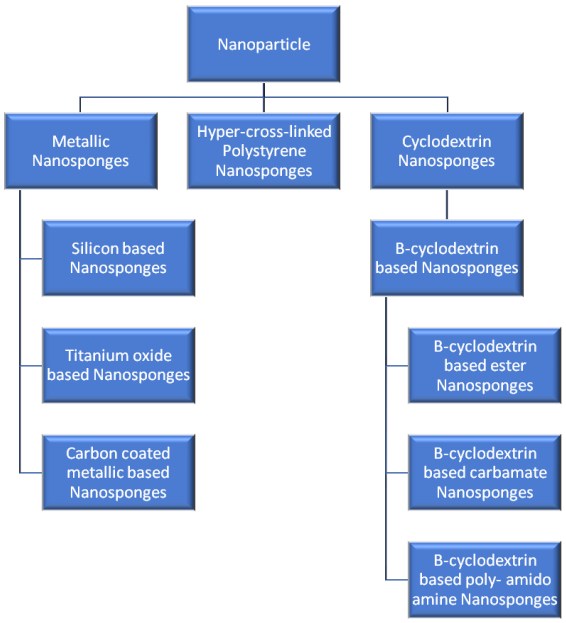

Fig. 3: Types of nanosponges based on composition [43]

Methods of preparation of nanosponges

Solvent method

In the process, suitable solvents such as dimethylformamide and dimethyl sulfoxide, which are polar aprotic solvents, were used.

Polymer was added and thoroughly blended into these solvents. The above mixture was ideally mixed with a crosslinker/polymer ratio of 8:2. The resulting mixture was then allowed to react for 48 h at temperatures ranging from 10 °C to the solvent's reflux temperature. After the reaction was completed, the solution was cooled to room temperature. To obtain the product from the above-cooled solution, an excess amount of bi-distilled water was added, and the product was recovered using vacuum filtration [7].

Ultrasound-assisted method

The polymer ultrasonic junction is used in the ultrasound-assisted method of synthesis. Crosslinking occurs without the use of a solvent, and polymer crosslinking occurs as a result of ultrasonic waves.

Polymer and crosslinker were combined in a flask at a reasonable molar ratio. The flask was placed in an ultrasound bath at a temperature of 90 °C for 5 h during the ultrasonication process. After sonication, the temperature of the collected mixture was reduced, and the product was harshly split and cleaned to extract unreacted polymer and reagents with an excess volume of water [44]. Soxhlet extraction was used to purify the washed solid with ethyl alcohol. The filtered NSs were vacuum-dried and properly processed before further drug loading [45].

Melt method

During the melting process, the cross-linker and polymer are melted together. All of the ingredients were thoroughly combined. NSs were collected by repeatedly washing the product with a suitable liquid. Cleaning the product, extracting the waste polymer and unreacted reagents, and dividing the product into NSs [46]. Such blank NSs were then subjected to narcotic encapsulation.

Bubble electrospinning

A typical electrospinning configuration consists primarily of a syringe, a syringe pump, as defined in many literatures, a high-voltage power, and a grounded collector. However, one of the major limitations limiting their applications is the amount of output of nanofibers.
Polyvinyl alcohol is another polymer that can be used in bubble electrospinning. The solution of polymer (10%) was organized by

adding distilled water to it, and it was then moved in 80-90 ℃ for 2 h to obtain a one-phase mixture. It was then allowed to achieve at room temperature with the polymer solution before being used to prepare nano-porous fibers [47].

Synthesis by the use of microwave radiation

This is a simple microwave irradiation synthesis of CD NSs that significantly reduces reaction time. These NSs have higher levels of crystallinity. Microwave radiation synthesis of NSs produced a fourfold reduction in reaction time compared to traditional heating methods, as well as a homogeneous particle size distribution with uniform crystallinity.

Singireddy *et al.* [49] conducted an experiment to determine the benefits of microwave-assisted heating over conventional heating during the synthesis of CD-based NSs. According to the findings of the study, NSs synthesized using microwave-assisted synthesis doubled the drug holding capacity of the model drug. High-resolution transmission electron microscopy (HR TEM) results revealed that the NSs produced by microwave synthesis were highly crystalline, with an increased degree of complexity and a narrow size distribution. Under microwave-assisted heating conditions, the reaction time was greatly reduced for all reactions, and the reaction products improved significantly [48]. The advantage of synthesis using microwave irradiation is that it produces direct energy to the targeted molecules, allowing energy to be delivered precisely. The energy is not lost from heating the container walls or the liquid adjacent to the reactant molecules, so the full effect is seen as the reaction progresses to completion [49]. Microwave synthesizer was used to prepare-CD in Para-crystalline form, and diphenyl carbonate (DPC) was used for crosslinking [50].

Preparation of NSs from hyper-crosslinked β-cyclodextrin

Their function as drug transporters is carried out as nano-sporous materials arranged from CDs. They are framed by this 3-D structure, which could be a typically circular assembly about the size of a protein with directs and openings in the inner portion.

Di-isocyanates, diaryl-carbonates, carbonyl di-imidazoles, and other compounds, for example, react to CD as a crosslinker [51]. The measurement of wipes is determined by porosity, surface thickness, and charge for the relationship to various atoms. In an impartial or acidic structure, NSs are mixed depending on the crosslinker used. They are composed of solid particles that have been modified in their crystalline structure. The ability of NSs to demonstrate the tranquility and dissolvability of distinct structures is limited [6].

Emulsion solvent diffusion method

This method involves two steps to change the amount of natural and aqueous material (ethyl cellulose and polyvinyl alcohol). The dispersed stage with ethyl cellulose and moiety is dissolved in 150 ml of fluid continuous process when dichloromethane (20 ml) and a clear amount of polyvinyl liquor are added [52]. The mixture is now thoroughly blended for two hours at 1000 revolutions per minute. The required NSs were filtered out and held for 24 h in an oven set at 40 °C for drying. Desiccators have been used to store dried NSs, and solvent evacuation is guaranteed [53].

Naproxen sodium NSs were created by Ilyas *et al.* [54] using the solvent diffusion method and it was discovered that some formulations had a diffusion rate close to 89% and a drug loading efficiency close to 98%. Additionally, they looked at stability studies, zeta potential, viscosity, and particle size. The Fourier Transform Infrared Spectroscopy (FTIR) results showed no evidence of a drug-excipient interaction. High drug loading efficacy and an exceptional drug release profile were also specified by the results [54].

Quasi emulsion solvent method

The polymer was used to arrange the NSs in various sums. The inner stage is prepared and added to a fair dissolvable stage using Eudragit RS 100. Under ultrasonication, the drug built a response and broke down at 35 °C. This internal process used in the polyvinyl alcohol-containing outside phase goes around as an emulsifying operator. The blend is blended at room temperature for 3 h at 1000-2000 rpm and dried for 12 h in an air-warmed oven at 40 °C [39].

Methods to load drugs in nanosponges

The particle size, which should be less than 500 nm, is the most important factor in drug delivery into NSs. The NSs are suspended in water and then sonicated to prevent aggregation. The dispersion is then centrifuged to produce a colloidal solution, which separates into supernatant and NSs upon freeze drying. The drug is then dispersed in excess and constantly stirred for a specified period of time, allowing the process of complexation to occur and thus aiding in the formation of NSs in an aqueous suspension. The un-complexed drug is separated after complexation by repeating the centrifugation process [55]. Finally, the NSs were obtained through solvent evaporation or freeze-drying solid crystals. The complexation of the crystal structure of the NSs with the drug is a major target. The loading capacities of para-crystalline NSs are greater than those of crystalline NSs. In crystalline forms, drug loading occurs as an inclusion complex, whereas in poorly crystalline NSs, drug loading occurs as a mechanical mixture [56].

Drug release mechanism via nanosponges

The NSs have multiple openings in their structures available in their core, which allow free passage of the drug molecule through and the liquid has reached the state of saturation for the drug molecule. When the end result is applied to the skin or taken internally, the encapsulated moiety has the freedom to move into the vehicle and thus be taken in by the skin [57], which contributes to the reduction of the drug concentration in the vehicle, causing unsaturation and thus disrupting the balance. This process is repeated until the entire medication has been absorbed by the body. The process described above aids in the selection of vehicles suitable for the NS preparation. As the liquid is being prepared, the drug molecule's solubility rises, decreasing the benefit of its gradual release and making the drug moiety behave as though it had been added in its free form rather than its trapped form [30].

Progress of nanosponges in improving oral absorption of drugs

Progress of NSs in improving oral absorption of drugs Parallel to the great development in nanomedicine, NSs for active ingredient delivery has also emerged rapidly due to their relatively small size, NSs have colloidal sizes with a mean diameter of less than 1 μm and narrow size distribution and form opalescent suspensions on dispersion in water. The zeta potential of carbonate NSs is about −25 mV, which is sufficiently high to produce stable water suspensions that do not undergo aggregation over time [6], and thus also bypass the physiological barriers more freely. It is noteworthy that the decrease in particle size lead to a significant increase in the surface area of insoluble drug particles, which subsequently results in enhanced absorption via monolayer cells of the GI tract [58].

β-Cyclodextrin NS has been widely used as a candidate to improve oral bioavailability of many drugs; some researches proved that β-CD modulates P-glycoprotein (P-gp) activity, modulatory mechanisms of are complicated, which mainly contain changing the fluidity of the cellular membrane, inhibiting P-gp ATPase activity, reducing P-gp expression and changing cholesterol levels [59]. Some of the advantages seen with the use of NSs is the higher degree of entrapment efficiency (EE), which help in making NSs act as a pool for various pharmaceutical substances [29], which help in protecting molecules from degrading. The encapsulated drug is protected from the first-pass metabolism because of the use of crosslinkers and other materials which are used in NS formulation [60]. NSs are prepared by encapsulating gamma-oryzanol possess antioxidant activity and provides strong protection from photodegradation [61]. NSs are appreciated for a category of versatile drug delivery strategy that have been applied for the treatment of several diseases (table 2).

Anti-cancer drugs

NS is a promising nanocarrier to enhance anti-cancer drugs because oral medications sometimes have low bioavailability in addition to low selectivity to the target tumor in cancer patients. Paclitaxel-loaded NSs were administered to rats by oral gavage using commercially available TAXOL® as the control. The oral bioavailability of the drug was increased about 3-fold after the administration of paclitaxel-loaded NSs, in comparison to the control [62].

Tamoxifen-loaded NS of appropriate particle size were prepared by conventional inclusion complexation technique. Marked enhancement in pharmacokinetic parameters of Tamoxifen with Tamoxifen-loaded NS formulation as compared to Tamoxifen citrate. The plasma concentrations of Tamoxifen by the oral NS formulation were significantly higher (P<0.01) than the Tamoxifen citrate at the same dose (1.44 fold and 1.38 fold higher than plain drug) [63].

Table 2: Examples of oral drugs complexed by using NSs

Drug class		Examples
Antineoplastic		Paclitaxel [62], Tamoxifen [63]
Analgesics and anti-inflammatory drugs		Acetylsalicylic acid [64], Meloxicam [65], Piroxicam [66]
	Antihypertensives	Telmisartan [67]
CVS drugs	Antiarrhythmic agents	Amiodarone hydrochloride [39]
	Anticoagulants	Warfarin [39]
	Antihyperlipidemic drugs	Atorvastatin [68], and fenofibrate [58]
	Cardiac drugs	Carvedilol [69], Digoxin, and Talinolol [39]
	Antianxiety drugs	Lorazepam [39]
CNS drugs	Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Primidone [39]
	Antiepileptic	Phenytoin [39]
Antidiabetics		Glibenclamide [70], Glipizide [53], Nateglinide [39]
Antimicrobials and anti-infectives	Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethoxazole, Trimethoprim, Cephalexin [39,71]
	Antivirals	Acyclovir [72], Nelfinavir [73], Indinavir, Ritonavir, and Saquinavir [39]
	Antifungals	Griseofulvin [74]
	Anthelmintics	Albendazole, Mebendazole, and Praziquantel [39]
Antihistamines		Terfenadine [39]
Anti-oxidants		Resveratrol [56]
Peptides and proteins		Insulin [75]
Hormonal therapy		Progesterone [39]
Immunosuppressants		Cyclosporine, Sirolimus, and Tacrolimus[39]

Analgesics and anti-inflammatory drugs

The non-steroidal anti-inflammatory drug acetylsalicylic acid (ASA), which is a member of BCS class III, was created into pyromellitic dianhydride cross-linked B-cyclodextrin NSs [64]. According to TEM studies, the average diameter of the particles in ASA-loaded NSs ranges from 40 to 60 nm, and they have a consistent spherical shape. A stable colloidal formulation could be made because the zeta potential was high enough. Studies conducted both *in vitro* and *in vivo* revealed that pyromellitic cross-linked-cyclodextrin NSs released ASA slowly and continuously over a 24-hour period. When used in a NS formulation by oral gavage to treat carrageenan-induced rat paw edema, ASA significantly (P<0.01 and P<0.05) reduced inflammation compared to plain ASA and the control group, respectively. According to these findings, the ASA NS. These results indicate that the ASA NS formulation may be used for oral delivery of the drug [64]. Meloxicam, an oral Cox-2 inhibitor and an effective anti-inflammatory drug, is used to treat osteoarthritis. Because of its limited solubility and stability, it has low oral absorption. Shende *et al.* [65] investigated the use of NS to solve these disadvantages. They combined meloxicam medicines in 1:8 molar ratios in NS produced with-CD Crosslinker pyromellitic dianhydride (PMDA). The synthesized-CD-Meloxicam NS demonstrated enhanced aqueous solubility. Piroxicam (PXM) is a highly effective nonsteroidal anti-inflammatory drug. PXM possesses analgesic and anti-inflammatory properties. It is commonly used to treat osteoarthritis, rheumatoid arthritis, acute pain, joint inflammation, and pre and post-surgery pain. PXM is classified as a Class II medication because of its low solubility and high permeability. Because of PXM limited solubility, it has a low bioavailability after oral administration. The formation of inclusion complexes with-CD improves the analgesic response to PXM in mice and increases the relative bioavailability of PXM-NS by 1.42 fold when compared to commercial tablets [66].

Cardiovascular drugs

Telmisartan, an antihypertensive BCS class II drug, was studied to see how carbonate NSs affected it. Telmisartan has a low bioavailability and an estimated solubility in water of only 9.9 g/ml. Telmisartan's ability to dissolve more quickly was observed when it formed a ternary complex with NSs and NaHCO3 [67].

Atorvastatin is a poorly water-soluble drug, it was complexed with B-cyclodextrin-based NSs, Atorvastatin when complexed with b-CD NS it displayed a biphasic release pattern with an increase in the dissolution, also increase bioavailability about 2.13-folds as compared to the plain drug. Pharmacodynamic studies in rats with fatty liver revealed significant reduction (P <0.05) in total cholesterol, triglyceride, LDL and increased level of beneficial HDL-C along with improvement in the associated liver steatosis as confirmed through photomicrographs of liver sections [68].

A non-selective third-generation beta-blocker called Carvedilol (CRV) is used to treat angina pectoris, congestive heart failure, and hypertension. The extensive first-pass metabolism of CRV may account for its low bioavailability (25%), which was observed after oral administration. The CRV bilosomes were prepared, optimized and characterized for particle size, surface morphology, encapsulation efficiency and ex-vivo permeation studies. Then, the optimized formula was incorporated into a carboxymethyl cellulose/hydroxypropyl cellulose (CMC/HPC) composite mixture to obtain buccal NSs enriched with CRV bilosomes. An improved swelling was discovered by morphological analysis of the prepared NSs, which had a porosity of 67.58%. Rats were tested *in vivo*, and the results showed that CRV-loaded NSs effectively enhanced systolic and diastolic blood pressure, decreased elevated oxidative stress, improved lipid profile, and demonstrated a potent cardio-protective effect [69].

Central nervous system drugs

Carbamazepine is a member of BCS class II and has low solubility and high permeability. To improve the drug's solubility and rate of dissolution, carbamazepine NSs were made using the emulsion solvent diffusion method. For the NSs formulation, solubility and an increase in dissolution rate when compared to the plain drug were also shown. The preparation of the Carbamazepine NSs tablets was successful, and the formulation was determined to be stable [39].

Antidiabetic drugs

Gliclazide is a class II BCS anti-diabetic medication. Different drug-polymer ratios were used in the emulsion solvent diffusion method to create the gliclazide NSs using Eudragit S100 as a polymer, and that improves the bioavailability of the drug [53].

Another oral anti-diabetic medication is Glibenclamide, which is virtually insoluble in water and has a 45 percent oral bioavailability due to its complexation with NSs. When compared to pure

Glibenclamide, a regulated increase in the percentage of drug release is seen in the case of Glibenclamide NSs generated by the emulsion solvent diffusion method using a high-speed homogenizer [70]. Additionally, Nateglinide is a BCS Class II medication with limited solubility. To boost Nateglinide's solubility, it was effectively synthesized into NSs utilizing ethyl cellulose as a polymer and dichloromethane as a cross-linker [76].

Antimicrobial agents and anti-infectives

Bacterial infection

An antibiotic called trimethoprim is mostly used to treat urinary tract infections and bladder infections. Poor oral bioavailability is caused by low water solubility. We created Trimethoprim loaded NSs with extended-release tablets to improve its solubility and delay the drug's release to the urinary system. The preparation of trimethoprim NSs included the use of ethyl cellulose as an entrapping agent and dichloromethane as a cross-linking agent in varying ratios. The NSs were then tested for their ability to flow powder, yield percentage, entrapment efficiency, morphology, zeta potential, particle size, and *in vitro* drug release characteristics. According to the findings, highest drug release for all formulations was 98.43 0.1%. From this investigation, we deduced that trimethoprim-loaded NSs extended release tablets show delayed drug release up to 10 h with improved solubility and dissolution [71].

Viral infection

Due to its effectiveness in treating herpes simplex virus infections, acyclovir-a synthetic nucleoside analogue produced from guanosine-is a commonly used antiviral drug (O'Brien and Campoli Richards, 1989). However, neither parenteral nor oral administration of the Acyclovir formulations currently on the market can result in the medication reaching target locations in sufficient concentrations. Due to acyclovir's sluggish and inadequate absorption in the digestive system, its pharmacokinetics after oral administration are highly variable, and its oral bioavailability is only 10 to 30%. Current therapies necessitate the administration of substantial doses, up to 1.2 g/day, because, on average, about 80% of the prescribed amount is not absorbed. carboxylated CD-based NSs (Carb-CD-NSs) carrying carboxylic groups within their structure were purposely designed as novel Acyclovir carriers. Carb-NS showed enhanced drug loading and more prolonged release kinetics in comparison with NS. Moreover, enhanced *in vitro* antiviral efficacy was observed when Acyclovir was encapsulated within Carb-CD-NS [72].

Fungal infection

The antifungal agent griseofulvin (GRI) is obtained from the mold Penicillium Griseofulvin. It is used orally and is used to treat dermatophyte and ringworm infections. It is typically prescribed for infections of the scalp, hair, nails, and skin that do not respond to topical therapies. GRI has a water solubility of 8.64 mg/l and a log P (octanol/water) of 2.15. GRI is classified as a class II medication by the Biopharmaceutics Classification System (BCS), with dissolution rate being the key limiting factor in absorption. Furthermore, one of the probable side effects of this medicine is an unpleasant taste. Liquid formulations are typically advised for pediatric patients since they are easy to administer. However, the production of such formulations may be limited by the drug solubility. Comparing the formulation of NS-loaded GRI to plain GRI, the dissolving efficiency % increased by 3.19 folds, the C_{max} and AUC_{0-48} increased by 2.13 and 3.78 folds, and the dissolution efficiency % increased by 3.19 folds. The capacity of GRI NSs to totally cover the bitter taste of GRI was proven by a taste masking evaluation [74].

Anti-oxidants

Resveratrol is an antioxidant found in high concentrations, both free and conjugated, in grape juice, peanuts, and mulberries, as well as other plant extracts. It has been used in medicine for decades to treat many diseases, such as inflammation, cardiovascular disease, dermatitis, gonorrhea, fever, and hyperlipidemia. It is also responsible for the cardiovascular benefits associated with moderate red wine consumption. Resveratrol has been demonstrated to have health-promoting properties such as cancer chemoprevention [56]. Furthermore, it has been discovered that resveratrol has antibacterial and antifungal properties, which are important etiological agents in human skin infections. Because of its hydrophobicity, dissolution is a rate-limiting stage in *in vivo* absorption, posing a severe barrier for oral bioavailability. However, when Resveratrol was combined with CD-NSs, *in vitro* release and stability were improved as compared to the plain medication. On HCPC-I cells, cytotoxic experiments revealed that resveratrol NS formulations were more cytotoxic than pure resveratrol. According to the permeation research, the resveratrol NS formulation had good penetration in pigskin. The accumulation research in rabbit mucosa revealed that the resveratrol NS formulation accumulated better than the basic substance [56].

Osteoporosis drugs

Bisphosphonates (risedronate), which are classified as Biopharmaceutics Classification System class III (freely soluble and low permeability), have been utilized to treat osteoporosis due to their strong binding affinity to bones. Risedronate has poor and erratic absorption. NSs were statistically developed by full 32 factorial design using Design of Experiment software, with concentration of polymer and stabilizer as independent variables and particle size and entrapment efficiency as experimental responses by utilizing the modified quasi-emulsion solvent diffusion technique [77].

Peptides and proteins

Insulin's physicochemical properties, such as its partially hydrophilic nature, presence of charge, and high molecular weight, make transporting insulin through membranes problematic. Furthermore, it is vulnerable to chemical and physical degradation mechanisms, as well as numerous proteases found at potential delivery sites. Because of the controlled release properties provided by the crosslinker to the CD NS, it is protected from degradation in the stomach and promotes intestinal absorption. Following the synthesis of CD NS, researchers created pH-sensitive cyclodextrin NSs as a potential nanotechnological approach to protein delivery by oral administration, using insulin as a case study [75]. The chosen NS was not only capable of incorporating bovine insulin, but also of releasing it in a continuous and pH-dependent manner. Crosslinking-cyclodextrins with pyromellitic dianhydride yielded NS, which was then formed using a top-down technique. The *in vitro* release of insulin was minor at a gastric pH (below 2%), but sustained at an intestinal pH, demonstrating the NS's pH-sensitive behavior. After duodenal and oral administrations, the *in vivo* experiments verified the presence of insulin in rat plasma and a significant hypoglycemic impact in diabetic rats. These preliminary findings are intriguing, and the researchers plan to continue researching this CD-NSs technology for the oral administration of insulin, as well as apply it to other proteins of medicinal interest [75].

CONCLUSION

NSs are a versatile drug carrier system because they can carry both hydrophilic and hydrophobic drugs through inclusion and non-inclusion complexes. Cyclodextrin-based NSs are widely used to improve the solubility and bioavailability of drugs for different kinds of diseases, including cancer, diabetes… etc. Many developments in NS formulations have long been shown to improve oral absorption due to their inherent advantages, such as improve solubility, improved stability, enhanced permeability and absorption, controlled drug release, prolonged release, site-specific targeting, and low side effects. On the other hand, it is important to carefully consider the expected toxicity from NSs (in light of the formulation constituents chosen and their makeup). It is anticipated that more study shall be done on the creation of non-toxic NSs with established metabolic processes *in vivo*.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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