INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Nanosponges As A Promising Nanocarrier Strategy For Dapagliflozin: Overcoming Solubility And Oral Bioavailability In Type 2 Diabetes Mellitus - A Comprehensive Review

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ARTICLE INFO

Published: 24 Aug. 2026

Keywords:
Dapagliflozin; Nanosponges; SGLT2 Inhibitor; Type 2 Diabetes Mellitus; Oral Bioavailability; Solubility Enhancement; BCS Class II; Nanocarrier; Antidiabetic Drug Delivery.

DOI:
10.5281/zenodo.22082146

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder affecting millions worldwide, characterized by insulin resistance, progressive β-cell dysfunction, and chronic hyperglycemia leading to severe macro- and microvascular complications. Sodium-glucose cotransporter-2 (SGLT2) inhibitors have revolutionized T2DM pharmacotherapy through their insulin-independent mechanism of promoting urinary glucose excretion. Dapagliflozin, a highly selective SGLT2 inhibitor, has demonstrated significant clinical benefits including glycemic control, cardiovascular protection, and renoprotection. However, its classification as a BCS Class III drug characterized by poor aqueous solubility (~0.17 mg/mL) and dissolution-rate-limited absorption it poses significant biopharmaceutical challenges that restrict its optimal oral bioavailability and therapeutic performance. To address these limitations, nanosponges have gained considerable attention as an innovative porous nanocarrier platform capable of encapsulating poorly soluble drugs through inclusion and non-inclusion complexation, converting crystalline drug into an amorphous state , thereby enhancing solubility, dissolution rate, intestinal permeability, and oral bioavailability. This review comprehensively discusses the pathophysiology of T2DM, the pharmacological and biopharmaceutical profile of dapagliflozin, the principles and preparation of nanosponges, their characterization, and their potential as an advanced nanocarrier strategy for dapagliflozin delivery. The review also highlights future perspectives in nanosponge-based antidiabetic drug delivery, establishing nanosponges as a promising and rational approach to overcome the solubility and bioavailability barriers of dapagliflozin in T2DM management.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent non-communicable diseases worldwide and represents a major public health challenge due to its rapidly increasing incidence, chronic nature, and associated complications. The disease is characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Long-term uncontrolled diabetes can lead to severe microvascular complications such as retinopathy, nephropathy, and neuropathy, as well as macrovascular complications including coronary artery disease, stroke, and peripheral vascular disorders. These Difficulties substantially reduce quality of life and contribute substantially to global morbidity and mortality. Recent epidemiological reports indicate that diabetes continues to rise at an at a rapidly increasing rate, fueled by urbanization and sedentary lifestyles, unhealthy dietary habits, obesity, and population aging. Consequently, diabetes has become one of the leading causes of disability-adjusted life years and healthcare expenditure worldwide. [1]

According to recent estimates from the International Diabetes Federation (IDF), the global burden of diabetes has increased dramatically over the past three decades. By 2024, approximately 800–830 million individuals were living with diabetes, representing nearly 11% of the adult population worldwide. Significantly, a substantial proportion of affected individuals remain undiagnosed, particularly in low- and middle-income countries where healthcare access and disease awareness remain limited. Projections suggest that the number of the prevalence of diabetes is projected to increase progressively in the coming years, potentially reaching 1.3 billion cases by 2050. This growing prevalence underscores the urgent need for more effective therapeutic strategies and innovative drug delivery systems capable of improving treatment outcomes and reducing disease-associated complications.[2]

Among the various forms of diabetes, Type 2 Diabetes Mellitus (T2DM) accounts for nearly 90–95% of all diagnosed cases. T2DM is a complex metabolic disorder characterized by insulin resistance in peripheral tissues combined with progressive pancreatic β-cell dysfunction. Initially, pancreatic β-cells compensate for insulin resistance by increasing insulin secretion; However, prolonged metabolic stress eventually leads to the failure of this compensatory mechanism, leading to chronic hyperglycemia. The development of T2DM is a complex process influenced by genetic predisposition, obesity, chronic inflammation, oxidative stress, dysregulated lipid metabolism, and various environmental factors. Continuous rise of blood glucose levels causes metabolic disturbances that damage multiple organ systems, thereby increasing the risk of cardiovascular disease, chronic kidney disease, and other diabetes-related complications.[3-4]

The management of T2DM primarily relies on lifestyle changes and drug therapy Conventional oral antidiabetic agents such as metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and SGLT2 inhibitors have significantly improved glycemic control and patient outcomes. While these therapies are clinically effective , many of these drugs suffer from formulation-related limitations including poor aqueous solubility, low permeability, limited oral bioavailability, rapid metabolism, and frequent dosing requirements. Such drawbacks can reduce therapeutic efficacy, increase variability in drug response, and compromise patient compliance. Consequently, the development of innovative drug delivery systems has become increasingly important that can overcome these

biopharmaceutical limitations has become a major focus of pharmaceutical research.Low oral bioavailability: Many agents show absorption below 20%.Frequent dosing requirement: Short biological half-lives necessitate repeated administration.Gastrointestinal side effects: Includes nausea, diarrhea, and abdominal discomfort.Poor stability in GI tract: Enzymatic degradation reduces drug effectiveness [3].

Recent advances in nanotechnology have opened new opportunities for improving the delivery and therapeutic performance of antidiabetic drugs. Nanocarrier-based systems including liposomes, solid lipid nanoparticles, nanoemulsions, polymeric nanoparticles, and nanosponges have demonstrated considerable potential for enhancing drug solubility, stability, permeability, and bioavailability. Among these novel carriers, nanosponges have attracted significant attention because of their highly porous three-dimensional architecture, large surface area, excellent drug-loading capacity, and ability to provide controlled and sustained drug release. These unique characteristics make nanosponges particularly suitable for the delivery of poorly soluble drugs and offer a promising platform for improving the therapeutic effectiveness of antidiabetic agents.[1]

The growing interest in nanosponge-based drug delivery systems has encouraged extensive research into their application for oral antidiabetic therapy. Through their ability to improve dissolution characteristics, enhance gastrointestinal absorption, protect drugs from degradation, and provide controlled drug release, nanosponges offer an effective approach for addressing the shortcomings of traditional drug delivery methods. Their potential to improve the clinical performance of modern antidiabetic agents, particularly sodium-glucose cotransporter-2 (SGLT2) inhibitors, has positioned them as an important area of investigation in contemporary pharmaceutical research.[4]

SGLT2 Inhibitors

Sodium–glucose co-transporter SGLT2 inhibitors are an important category of oral antihyperglycemic medications employed for the management of type 2 diabetes mellitus. Their therapeutic effect is achieved through inhibition of glucose reabsorption in the kidneys, leading to increased urinary elimination of glucose. This mechanism operates independently of insulin secretion and action, contributing to effective glycemic regulation with a lower incidence of hypoglycemia.In addition to their antidiabetic effects, SGLT2 inhibitors provide significant cardiovascular and renal benefits, including reductions in body weight, blood pressure, hospitalization due to heart failure, and progression of chronic kidney disease. Commonly used agents include Dapagliflozin, Empagliflozin, Canagliflozin, and Ertugliflozin.

Dapagliflozin is classified as a BCS Class III drug, exhibiting high aqueous solubility and low intestinal permeability. Despite its favorable solubility profile, its permeability-limited absorption can affect oral bioavailability, making it well suited for the development of innovative drug delivery platforms to overcome its biopharmaceutical limitations.

Despite their therapeutic advantages, SGLT2 inhibitors may cause adverse effects such as genital infections, urinary tract infections, volume depletion, and, rarely, diabetic ketoacidosis. Overall, they represent an important advancement in diabetes therapy due to their combined glucose-lowering, cardioprotective, and renoprotective properties.[5]

Dapagliflozin - Drug Profile

1. Chemical Identity & Physicochemical Properties

Dapagliflozin is chemically designated as (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl) phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol. It carries a molecular formula of $C_{21}H_{25}ClO_6$ and a molecular weight of 408.875 g/mol. Dapagliflozin is a white crystalline compound that exhibits good solubility in several organic solvents, including dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and ethanol. It possesses a melting range of approximately 55–60°C. The compound is identified by the Chemical Abstracts Service (CAS) number 461432-26-8, PubChem CID 9887712, and DrugBank accession number DB06292. Commercially, dapagliflozin is available under the trade names Farxiga in the United States and Forxiga in European countries. Despite its therapeutic importance, the drug exhibits limited physical stability when exposed to elevated temperature and humidity. Under unfavorable storage conditions, it may undergo a phase transition from its crystalline form to a liquid state, creating challenges during processing, handling, and formulation development. These stability-related concerns emphasize the need for suitable formulation strategies to ensure product quality, efficacy, and long-term storage stability.[6]

2. Mechanism Of Action

SGLT2 is the primary transporter that mediates renal glucose reabsorption and is mostly expressed in the S1 region of the kidney's proximal tubule. By decreasing renal glucose reabsorption and causing urine glucose excretion (glucuresis), the oral active, highly selective SGLT2 inhibitor dapagliflozin improves glycemic management in type 2 diabetes. Dapagliflozin differs from traditional antidiabetic medications that rely on insulin secretion or sensitivity pathways due to its insulin-independent action.[7]

3. Pharmacokinetics (ADME)

Dapagliflozin is quickly absorbed after oral treatment, reaching peak plasma concentrations after two hours. With an absolute oral bioavailability of around 78%, dose-proportional systemic exposure is seen throughout a broad range of 0.1–500 mg. It is widely distributed extravascularly, having an average distribution volume of 118 L. The primary inactive metabolite dapagliflozin 3-O-glucuronide is produced via metabolism, which mostly takes place in the liver and kidneys via UGT1A9. Less than 2% of the dose is excreted via the kidneys, but around 61% of the dose is retrieved as the glucuronide metabolite in urine. Due to its extended half-life of 12.9 hours, dapagliflozin can be taken orally once daily at doses of 5–10 mg.[8]

4. Renal Outcome

Dapagliflozin showed considerable protective effects on renal function with chronic kidney disease (CKD). It reduced the risk of a sustained decline in kidney function (≥50% decrease in eGFR), progression to end-stage kidney disease (ESKD), and death from renal or cardiovascular causes. Overall, dapagliflozin reduced the risk of the primary renal composite outcome by approximately 39% compared with placebo. The benefits were consistent across all KDIGO CKD risk categories and were observed in patients both with and without type 2 diabetes. Prolonged therapy was associated with a reduced rate of eGFR decline, helping to preserve kidney function and delay CKD progression.[9]

5. Approved Indications & Dosing

Dapagliflozin holds regulatory approval for Type 2 Diabetes Mellitus, Heart Failure with Reduced Ejection Fraction (HFrEF), and chronic kidney disease (CKD). It is approved in both the USA and EU for treatment of adults with symptomatic heart failure with reduced ejection fraction. A once-daily oral dose of 10 mg is the standard therapeutic regimen for adults across all approved clinical indications. Furthermore, dapagliflozin holds a unique position among SGLT2 inhibitors as the only agent authorized for use in children and adolescents aged 10 years and above with T2DM. Its use in type 1 diabetes was formally withdrawn due to an unacceptable risk of diabetic ketoacidosis.[10]

6. Safety Profile

The safety profile of dapagliflozin remains largely consistent across different clinical applications, and the drug is generally well tolerated by most patients. However, the occurrence of specific adverse events warrants careful monitoring during treatment. Real-world pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS) database from 2012 to 2023 confirmed its capacity to treat a wide range of diseases while highlighting adverse events that warrant ongoing surveillance. Regulatory-mandated warnings include genitourinary infections, hypotension, volume depletion, and diabetic ketoacidosis, particularly in susceptible populations.[11]

Nanotechnology-Based Drug Delivery Systems

To address these challenges, nanotechnology-based delivery systems have been extensively explored to improve solubility, stability, and bioavailability .[12]Among these, nanosponges have gained significant interest due to their porous architecture and ability to encapsulate both hydrophilic and lipophilic compounds .[13]

Nanosponges are cross-linked polymeric nanostructures containing interconnected pores that allow efficient drug encapsulation and controlled release. Incorporating SGLT2 inhibitors into nanosponges provides an effective strategy to overcome their physicochemical limitations. [14]

Their high surface area and porous matrix enhance drug loading and dissolution behavior . Additionally, they protect active molecules from chemical and enzymatic degradation. Studies have shown that nanosponge formulations significantly improve bioavailability by enhancing solubility and membrane permeation.[15]

They also enable sustained drug release, resulting in improved therapeutic outcomes and reduced dosing frequency.[16] Recent research further indicates prolonged drug action and improved deposition in antidiabetic therapy.[17] Advanced multilayer nanosponge systems have demonstrated even higher entrapment efficiency and enhanced bioavailability.

The primary objective of this review is to explore nanosponge-based delivery systems and their role in enhancing the therapeutic performance of SGLT2 inhibitors in diabetes management.[18]

Concept And Definition Of Nanosponges

Nanosponges are nanoscale porous carriers designed to encapsulate drug molecules and release them in a controlled manner.[19]

Cyclodextrin-based nanosponges are formed through cross-linked polymer networks that generate nano-sized cavities for drug incorporation. Their sponge-like structure enables encapsulation of both hydrophilic and hydrophobic molecules while protecting them from degradation.[20]

These systems are classified as hyper-crosslinked polymers with nanosized pores that act as reservoirs for drug storage and release.[21,22]

Structural Characteristics

- Nanosponges possess a three-dimensional porous framework with nanochannels formed through cyclodextrin cross-linking.[23]
- Their high surface area facilitates increased drug loading capacity.[24]
- They are generally spherical particles with nanoscale pores that enable efficient drug diffusion.[25]
- Their amphiphilic nature allows interaction with both water-soluble and lipid-soluble drugs.[26]

Advantages Of Nanosponges

- Enhance solubility of poorly water-soluble drugs. [27]
- Provide controlled and sustained drug release. [28]
- Improve therapeutic efficacy and reduce dosing frequency. [29]
- Exhibit good biocompatibility and safety for pharmaceutical use. [30]

Types Of Nanosponges

Cyclodextrin-Based Nanosponges

Cyclodextrin nanosponges are among the most extensively researched systems in drug delivery.These structures are formed by cross-linking cyclodextrin molecules using agents such as epichlorohydrin or carbonyldiimidazole, resulting in a three-dimensional porous network capable of drug encapsulation.The nanochannels created between cross-linked cyclodextrin units facilitate the incorporation of both hydrophilic and hydrophobic drugs. Their amphiphilic nature enhances drug solubility and stability by forming inclusion as well as non-inclusion complexes.β-cyclodextrin is commonly used due to its suitable cavity size, excellent biocompatibility, and strong complex-forming ability with various drugs.Cyclodextrin nanosponges have demonstrated effectiveness in improving dissolution rates and bioavailability of poorly soluble drugs such as nicardipine by enhancing drug entrapment and release characteristics.

Key features include:

- Formation of a three-dimensional porous structure through polymerization with cross-linkers
- Presence of hydrophobic internal cavities and hydrophilic outer surfaces
- High drug loading capacity due to interconnected nanochannels
- Amphiphilic properties enabling encapsulation of diverse drug types
- Wide applicability in oral, topical, and targeted drug delivery due to stability and biocompatibility. [31]

Polymeric Nanosponges

Polymeric nanosponges are specialized 3D, cross-linked nanostructures designed to trap pharmaceutical compounds within their internal cavities. These systems possess a large surface area and a narrow particle size distribution, enabling efficient drug encapsulation and enhanced drug-loading capacity.

By acting as a protective shield, the polymer matrix safeguards enclosed drugs from both enzymatic breakdown and chemical instability, ensuring better overall durability. Moreover, nanosponges effectively enhance the solubility of poorly water-soluble lipophilic drugs by

entrapping them within their highly porous three-dimensional structure.

The delivery of medications from these carriers is typically gradual and regulated, utilizing processes like diffusion, matrix swelling, and surface erosion. Their excellent biocompatibility and biodegradability render them highly suitable for a wide range of pharmaceutical and biomedical applications.

By facilitating improved absorption and sustained presence in the bloodstream, these nanocarriers contribute to enhanced therapeutic performance and prolonged pharmacological activity. Surface modification techniques enable these nanocarriers to achieve site-specific drug delivery, making them promising systems for targeted and localized cancer therapy.

The distinctive porous structure of nanosponges enables the co-encapsulation and simultaneous delivery of multiple therapeutic agents, making them highly suitable for combination therapy. Their architecture facilitates controlled diffusion and sustained drug release over extended periods. Various preparation techniques have been employed for nanosponge fabrication, including ultrasonic-assisted synthesis, emulsion-based methods, and solvent evaporation techniques. [32,33]

Metal–Organic Framework (MOF) Nanosponges

MOF Nanosponges

Metal-organic framework (MOF) nanosponges are a sophisticated category of porous nanostructures created by the coordination of metal ions with organic ligands, resulting in precisely organized 3D architectures. The tunable pore size and exceptionally large surface area of these systems make them highly efficient carriers for the encapsulation of therapeutic agents.

As a class of hybrid nanomaterials, MOF nanosponges are synthesized through the coordination-driven assembly of metal centers and organic linkers, producing crystalline structures with sponge-like porosity. Their pore sizes generally fall within the microporous range (<2 nm); however, these dimensions can be engineered by modifying fabrication parameters according to therapeutic requirements.

MOF nanosponges exhibit outstanding physicochemical properties, such as high specific surface area, exceptional porosity, and customizable surface functionality. Moreover, the inherent susceptibility of their coordination bonds to degradation enhances their biocompatibility and biodegradability. These advantages contribute to efficient drug encapsulation and controlled release performance.[34,35]

Ethyl Cellulose Nanosponges

Ethyl cellulose nanosponges are advanced polymeric drug delivery systems fabricated using ethyl cellulose to create a highly porous three-dimensional nanostructure. This architecture enables efficient encapsulation of therapeutic agents and supports their controlled release. Due to their versatility, these nanosponges are widely employed in oral, topical, and targeted drug delivery applications.

These nanocarriers generally possess particle sizes between 100 and 800 nm and are characterized by a large surface area and substantial internal porosity. Their structural features enable efficient encapsulation of both hydrophilic and lipophilic therapeutic agents. In addition, the incorporation of ethyl cellulose imparts excellent

biocompatibility and non-irritant properties, contributing to their favorable safety profile.

Mechanism Of Drug Delivery

Drug molecules are encapsulated within the porous nanosponge matrix and released in a controlled manner through diffusion, enabling sustained drug delivery. Upon administration, nanosponges act as localized drug reservoirs, enhancing drug retention at the target site while reducing systemic exposure and associated adverse effects.

Applications Of Nanosponges

The versatility of these nanocarriers has led to their exploration across a wide spectrum of medical and cosmetic fields, such as:

- Oncology: Targeted cancer treatments.
- Dermatology: Management of skin disorders.
- Infection Control: Antifungal and antimicrobial therapies.
- Tissue Repair: Accelerated wound healing.
- Inflammation: Anti-inflammatory drug delivery.
- Cosmetics: Advanced cosmeceutical formulations.

A notable example of their efficacy is seen in simvastatin-loaded nanosponges, which achieved a wound recovery rate of over 90% in just 11 days.[36]

Microporous Hyper-Crosslinked Polystyrene Nanosponges

Microporous hyper-crosslinked nanosponges are highly porous polymeric materials synthesized through extensive cross-linking of polystyrene. These systems form rigid three-dimensional networks with permanent nanoscale porosity, making them suitable for adsorption and drug delivery applications.They are considered advanced hyper-crosslinked polymers (HCPs) with well-defined nanoscale architecture.

Structural Features And Properties

Key characteristics include:

- Very high surface area (approximately 1000–2000 m^2/g)
- Microporous structure with pore sizes below 2 nm
- High thermal and chemical stability
- Insolubility in most solvents
- Tunable pore size and functional groups

The dense cross-linked network creates permanent cavities that function as reservoirs for drug molecules or gases.

Applications

1. **Drug Delivery:** Encapsulation of poorly soluble drugs, Sustained and controlled drug release, Protection from degradation, enhancing stability and bioavailability
2. **Gas Storage and Separation:** Efficient adsorption of gases such as CO_2 and H_2
3. **Water Treatment:** Removal of pollutants, dyes, and heavy metals
4. **Catalysis:** Functionalization with metals (e.g., palladium, iron) for catalytic applications
5. **Functionalized Systems:** Incorporation of magnetic particles or nanofillers for targeted delivery and easy recovery.[37]

Mechanism Of Drug Sequestration And Liberation In Nanosponges

Drug Loading And Entrapment Principles

Nanosponges are engineered as 3D, cross-linked polymeric frameworks featuring internal nano-cavities. These voids function as specialized

molecular reservoirs designed to house and protect therapeutic agents.[38]

The Encapsulation Process

The transformation of empty nanosponges into drug-loaded systems typically follows a systematic protocol:

1. Synthesis: Establishing the network via cross-linking chemical reactions.
2. Homogenization: Using sonication to disperse the nanocarriers uniformly within a specific medium. [39]
3. Saturation: Introducing a surplus of the drug into the prepared dispersion.
4. Complexation: Utilizing persistent agitation to facilitate the migration of drug molecules into the structural cavities.
5. Purification: Employing centrifugation to isolate the nanosponges from any non-sequestered drug particles.
6. Solidification: Utilizing techniques like lyophilization (freeze-drying) to yield the final stable product. [41]

Modes Of Drug Integration

The interaction between the drug and the nanosponge can occur in several distinct ways:

- Inclusion Complexation: The drug resides within internal voids, held by van der Waals forces, hydrogen bonds, or hydrophobic interactions. This primarily helps in boosting the solubility of the compound. [40]
- Adsorption on the Surface: Active molecules bind to the exterior interface or superficial pores, which often results in a rapid initial release phase
- Matrix Entrapment: Medications are physically held within the interstices of the polymer scaffold; the efficiency of this method is largely dictated by the density of the cross-linking
- Chemical or Electrostatic Bonding: In tailored delivery systems, drugs may be tethered through ionic attractions or covalent bonds. [40]

Factors Affecting Drug Entrapment

- Physicochemical properties of the drug (e.g., molecular weight, solubility)
- Nature of polymer and cross-linking agent
- Degree of cross-linking
- Temperature conditions
- Crystallinity of the nanosponge structure. [41]

Drug Release Mechanism

Mechanisms Governing Drug Liberation From Nanosponges

The Diffusion-Equilibrium Model

Unlike traditional delivery systems, nanosponges feature an interconnected porous architecture devoid of an external membrane. Consequently, the movement of the drug into the systemic circulation is primarily dictated by concentration gradients and shifts in chemical equilibrium.

Sequential Release Dynamics

The process of drug delivery typically unfolds through the following stages:

The drug release mechanism of nanosponges is primarily governed by diffusion and concentration-gradient-driven transport. Initially, drug molecules exist in a dynamic equilibrium between the internal porous cavities and the external environment. Following administration, absorption of the free drug from the surrounding medium lowers the local drug concentration, creating a state of unsaturation. This concentration imbalance generates a diffusion gradient that

promotes the release of entrapped drug molecules from the nanosponge matrix. The liberated drug subsequently diffuses through the surrounding medium and penetrates the target tissues. Continuous restoration of equilibrium results in a sustained and controlled release pattern, thereby maintaining therapeutic drug concentrations for prolonged periods and enhancing treatment efficacy. [41,42]

Classification Of Drug Release Mechanisms

Drug release from nanosponges can be categorized into several mechanisms based on the mode of drug transport and carrier characteristics:

- **Diffusion-Controlled Release:** This mechanism involves the gradual migration of drug molecules through the interconnected porous network of the nanosponge matrix, resulting in sustained and controlled drug delivery.
- **Desorption-Controlled Release:** In this type of release, drug molecules adsorbed onto the surface of the nanocarrier are rapidly detached and released into the surrounding medium, often producing an initial burst effect.
- **Degradation-Controlled Release:** This mechanism is observed in biodegradable nanosponge systems, where the progressive degradation of the polymeric framework facilitates the release of the encapsulated drug. [35]

Factors Influencing Drug Release Kinetics

The rate and extent of drug release from nanosponges are governed by several formulation and environmental parameters:

- **Degree of Cross-Linking:** Increased cross-linking density produces a tighter polymeric network, restricting drug diffusion and consequently reducing the release rate.
- **Polymer Characteristics:** The hydrophilic or hydrophobic nature of the polymer significantly influences drug–polymer interactions, swelling behavior, and drug release patterns.
- **Drug–Polymer Interactions:** The strength of physical adsorption, hydrogen bonding, or other intermolecular interactions between the drug and polymer matrix affects the ease with which the drug is released.
- **Environmental Conditions:** External factors such as pH, temperature, ionic strength, and the composition of the surrounding biological medium can alter the release behavior and overall performance of the nanosponge system. [36]

Methods Of Preparation Of Nanosponges (2020–2026)

Sl. No.	Method	Procedure (Short)	Key Features
1	Solvent Method	Polymer dissolved in DMSO/DMF and reacted with cross-linker under reflux, followed by purification	High drug loading; rigid structure [43]
2	Solvent Emulsification	Drug-polymer solution in DCM added to PVA	Uniform particles; controlled size [44]

		solution under stirring for solvent evaporation	
3	Ultrasound-Assisted	Polymer and cross-linker reacted using ultrasound at ~90°C without solvent	Green method; narrow size distribution[45]
4	Melt Method	Polymer and cross-linker melted, mixed, cooled, and purified	Simple; solvent-free; scalable [46]
5	Hyper-Crosslinking	Cyclodextrins cross-linked using agents like PMDA to form porous network	High porosity; stimuli-responsive[47]
6	Freeze Drying	Nanosponge dispersion centrifuged and lyophilized to obtain dry powder	Stable; preserves structure [48]

Characterization Of Nanosponges

The evaluation of nanosponges involves comprehensive characterization to understand their structural, physicochemical, thermal, and drug delivery attributes, all of which play a crucial role in determining drug loading capacity and release performance.

Particle Size, Polydispersity Index (PDI), And Zeta Potential

Particle size characterization of nanosponges is typically carried out using Dynamic Light Scattering (DLS), a widely employed technique for determining particle size distribution. Particle size plays a crucial role in influencing drug dissolution, absorption, and bioavailability. Smaller particles possess a larger surface area-to-volume ratio, which enhances drug solubility and promotes faster drug release. The Polydispersity Index (PDI) is used to evaluate the uniformity of particle size distribution within the formulation, with lower PDI values indicating a more homogeneous and stable nanosystem. In addition, zeta potential analysis provides information regarding the surface charge of nanoparticles and serves as an important indicator of colloidal stability. Higher absolute zeta potential values generally reflect stronger electrostatic repulsion between particles, thereby reducing aggregation and improving dispersion stability. [49]

Morphological Analysis (SEM And TEM)

Surface morphology and structural characteristics of nanosponges are commonly evaluated using Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). SEM images generally demonstrate a porous, sponge-like surface that contributes to high drug-loading capacity and sustained release behavior. TEM offers high-resolution visualization of the internal architecture, enabling detailed assessment of particle shape, size, and pore distribution. The interconnected porous network observed through these imaging techniques serves as evidence of successful nanosponge formation and supports their application as efficient drug delivery carriers. [50]

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy is employed to identify functional groups and evaluate interactions between the drug and polymer matrix. Changes in characteristic absorption bands suggest the successful formation of inclusion complexes within the nanosponge matrix.This technique also helps determine compatibility between the drug and excipients, confirming the absence of undesirable chemical interactions or degradation. [51]

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is widely employed to evaluate the thermal characteristics of drug-loaded nanosponges, including melting transitions, crystallinity, and polymorphic changes. Changes in thermograms reveal whether the drug remains crystalline or is transformed into an amorphous state after encapsulation.The reduction or disappearance of the drug's melting peak indicates successful incorporation into the nanosponge matrix and improved stability. Variations in enthalpy further confirm uniform molecular dispersion within the polymer network. [52]

X-Ray Diffraction (XRD)

XRD analysis is applied to determine the crystalline characteristics of both the drug and nanosponge system. A decrease or absence of distinct crystalline peaks suggests conversion of the drug into an amorphous form, which contributes to enhanced solubility and bioavailability. [53]

Surface Area And Porosity Analysis (BET Method)

Brunauer–Emmett–Teller (BET) analysis is used to evaluate surface area and pore size distribution. [54] Increased surface area and porosity are key factors that improve drug loading capacity and adsorption efficiency within nanosponges. [55]

Drug Entrapment Efficiency

Entrapment efficiency is to determine the amount of drug effectively entrapped within the nanosponge matrix. Greater drug entrapment suggests efficient drug–polymer association and supports the overall effectiveness of the nanosponge formulation. [56]

In Vitro Drug Release Studies

Standard in vitro dissolution studies are performed to investigate the drug release pattern and release kinetics. The porous structure of nanosponges facilitates prolonged and regulated drug release. In most cases, drug molecules are released through a diffusion-driven process, gradually moving from the internal nanosponge matrix into the external medium and thereby maintaining drug availability over an extended period. The release rate is influenced by factors such as pore size, degree of cross-linking, and drug polymer interactions. The Higuchi and Korsmeyer–Peppas models are commonly used to analyze drug release kinetics and identify the predominant mechanism, including Fickian diffusion and non-Fickian or anomalous transport. [57]

Swelling And Porosity Studies

Swelling behavior and porosity analysis provide valuable insights into the functional characteristics of nanosponges. Swelling behavior reflects the capacity of the polymeric network to absorb surrounding fluids and undergo volumetric expansion, thereby influencing drug diffusion and release kinetics. Porosity refers to the internal void

spaces present within the nanosponge structure and plays a significant role in determining drug-loading capacity and release characteristics. A higher degree of porosity generally provides greater accessible surface area and pore volume, facilitating efficient drug encapsulation and contributing to controlled and sustained drug release.These parameters are evaluated by using solvent uptake and gravimetric techniques. [58]

Chemical And Structural Analysis (NMR)

Nuclear Magnetic Resonance (NMR) spectroscopy provides extensive molecular-level information about nanosponge structures and confirms the formation of inclusion complexes.Shifts observed in proton signals in ^{1}H NMR spectra indicate interactions between drug molecules and the polymer matrix, indicating successful drug incorporation. Additionally, NMR helps verify cross-linking and structural integrity of the nanosponge network, ensuring formulation stability. [59]

SGLT2 Inhibitor Delivery Using Nanosponges

Increase Solubility

The porous architecture of nanosponges promotes the incorporation of poorly water-soluble SGLT2 inhibitors, thereby enhancing their apparent solubility, dispersion, and dissolution within the gastrointestinal tract. [60]

Dissolution Profiles With Acceleration

The porous framework's large surface area makes it possible for poorly soluble substances, like dapagliflozin, to dissolve more quickly. [61]

Oral Bioavailability Optimization

Higher systemic availability is the outcome of better absorption through the intestinal wall made possible by the concurrent improvement in solubility and membrane permeability. [62]

Extended And Regulated Release

The diffusion-controlled release characteristics of these nanocarriers allow for prolonged maintenance of therapeutic drug levels, thereby offering the potential to reduce dosing frequency and enhance treatment convenience. [63]

Protection Against Gastric Deterioration

Active drugs are rotected from gastric acid-induced degradation and enzymatic breakdown and intestines by being encapsulated within the nanosponge matrix. [64]

Accuracy In Targeting

Medication can be targeted to specific biological sites through surface functionalization of nanosponges, which increases therapeutic efficacy while reducing off-target systemic effects. [65]

Enhanced Stability Of Molecules

By providing a stable microenvironment, Nanosponges protect the encapsulated drug from chemical degradation and environmental stress. [66]

Enhanced Transport Of Membranes

These approaches facilitate the transport of drugs across biological barriers, which directly encourages more effective medication absorption. [67]

Adaptability In Dosage Forms

Because of its great versatility, nanosponges can be included into a variety of pharmaceutical forms, such as gels, capsules, and tablets, to meet the demands of patients. [68]

Increased Loading Effectiveness

The sponges' vast internal volume and complex three-dimensional structure enable the high-capacity encapsulation of medicinal compounds. [69]

Improved Pharmacokinetic Characteristics

Nanosponges increase the overall therapeutic effect by delaying the drug's clearance and extending its duration in the bloodstream. [70]

Enhanced Compliance With Treatment

Patients find it simpler to adhere to long-term treatment plans when there are fewer daily dosages needed and fewer adverse effects. [71]

Drug Recrystallization Inhibition

High solubility levels are maintained by keeping medicines in an amorphous condition inside the nanocarrier, which stops them from crystallizing. [72]

Optimal Therapeutic Outcomes

A more successful therapeutic outcome results from the combination of enhanced absorption, steady release, and increased bioavailability. [73]

Specific Pharmacological Action

The precision of the treatment can be improved by engineering modified nanosponges that exclusively release drugs at the targeted location of action. [74]

Co-encapsulation Of Multiple Drugs

Nanosponges structural adaptability enables the simultaneous delivery of several therapeutic drugs, supporting intricate combination treatment regimens. [75]

Recent Research On SGLT2 Inhibitors (2020–2026)

Sl.no	SGLT2 Inhibitor	Formulation / Nanocarrier System	Particle Size (nm)	Research Focus & Key Findings
01	Empagliflozin (EMPA)	Nanoemulsion optimized via Box–Behnken experimental design (BBD)	~50 nm to 150 nm *(Optimized globule range)*	Neuroprotection in Alzheimer's: Leverages the drug's potent anti-inflammatory and antioxidant properties to manage neuroinflammation. Keeping the globule size under 150 nm is essential for exploiting endocytic pathways to cross the blood-brain barrier (BBB).[76]
02	Canagliflozin (CFZ)	Nanosuspension	Sub-micron range *(Typically < 500 nm)*	Solubility Enhancement: Specifically engineered to dramatically increase the effective surface area of poorly water-soluble Canagliflozin, significantly accelerating its dissolution profile.[77]
03	Canagliflozin (CFZ)	Nanocrystals (processed via fluid bed	~200 nm to 400 nm *(Before*	Drying Method Optimization: Investigated turning wet nanosuspensions into dry, stable

		granulation vs. spray-drying)	*drying/upon redispersion)*	solid nanocrystals. Evaluated how fluid bed granulation and spray-drying affect physical stability and redispersibility for solid tablet manufacturing.[78]
04	Dapagliflozin (DAPA)	Solid Lipid Nanoparticles (SLNs)	~100 nm to 250 nm	Controlled Oral Delivery: Developed a controlled-release lipid matrix optimized through statistical design. Maximizes oral absorption and extends the therapeutic window to effectively manage hyperglycemia in type 2 diabetes.[79]
05	Dapagliflozin (DAPA)	Cardiac homing peptide functionalized mesoporous silica nanoparticles (MSN)	~100 nm *(Monodispersed core)*	Targeted Heart Repair: Designed a biocompatible, targeted delivery vehicle that routes DAPA directly to damaged cardiac tissues. Designed to treat heart failure and mitigate adverse ventricular remodeling after a myocardial infarction.[80]

Comparison Of Nanosponges With Other Nanocarriers

Parameter	Nanosponges	Liposomes	SLNs	Nanoemulsions	Polymeric NPs
Structure	3D porous network	Bilayer vesicles	Solid lipid core	Oil–water dispersion	Polymer matrix
Drug Type	Both types	Mostly lipophilic	Lipophilic	Lipophilic	Both
Stability	High	Moderate	Good	Low	Good
Release	Sustained	Leakage risk	Controlled	Rapid	Controlled
Toxicity	Low	Low	Moderate	Surfactant-based	Polymer-based
Advantage	High loading, improves solubility	Targeted delivery	Protects drugs	Easy formulation	Flexible design
Limitation	Scale-up issues[81]	Leakage, short shelf life[82]	Crystallization [83]	Instability[84]	Complex synthesis[85]

Challenges And Limitations Of Nanosponges

Limitations On Scale-Up

Due to the intricacy of fabrication methods such solvent-based synthesis, cross-linking reactions,

and ultrasound-assisted procedures, the transfer of nanosponge production from laboratory to industrial scale is still challenging. These methods necessitate stringent control over parameters such as temperature, cross-linker levels, and solvent composition, which could lead to batch-to-batch variability. Reproducibility and overall product quality are affected by the difficulty of achieving uniform porosity and constant particle size on a wide scale.

Toxicity Associated With Cross-Linkers And Polymers

Despite the widespread belief that nanosponges are friendly systems, some cross-linking agents, such as diphenyl carbonate and carbonyldiimidazole, may be harmful if residues are left over after purification. Particularly in oral and injectable formulations, the presence of unreacted monomers or leftover solvents can jeopardize safety. Therefore, using non-toxic cross-linkers and safe, biodegradable polymers is essential for medicinal applications.

Limited Clinical Evidence

Most nanosponge-based formulations are still under preclinical investigation, with only a few advancing to clinical evaluation. While experimental studies have demonstrated encouraging outcomes, there is a lack of sufficient human data to validate their safety and therapeutic effectiveness. This limitation hinders their progression toward commercialization.

Reproducibility Issues

Differences in formulation techniques, polymer selection, and cross-linking conditions can lead to inconsistencies in nanosponge characteristics such as particle size, porosity, and drug loading efficiency. Such variability affects reliability and poses challenges for large-scale manufacturing).

Prospects For Nanosponges In The Future

Targeted Administration Of Drugs

To achieve targeted drug delivery to specific tissues, future developments might concentrate on surface modification of nanosponges with targeting moieties like peptides or antibodies. This strategy may enhance therapeutic outcomes while minimizing systemic adverse effects, particularly in chronic conditions such as diabetes.

Customized Nanomedicine

Advances in nanotechnology and precision medicine may facilitate the development of patient-specific nanosponge delivery systems. These formulations could be customized according to specific needs, such as targeting strategies, release kinetics, and dose optimization.

CONCLUSION

The application of nanosponges as advanced drug delivery carriers has gained significant interest, especially for improving the solubility, dissolution, and therapeutic performance of poorly water-soluble SGLT2 inhibitors. Their highly porous structure promotes effectiveness of drug encapsulation, which improves solubility, bioavailability, and controlled drug release. They are quite beneficial for antidiabetic treatment because of these qualities.

The therapeutic value of dapagliflozin, a selective sodium-glucose co-transporter-2 inhibitor, to enhance glycemic ability to improve glycemic control while providing additional cardiovascular and renal benefits has established dapagliflozin as an important therapeutic option for the management of type 2 diabetes mellitus (T2DM).

Despite these benefits, its low water solubility and dissolution-rate-limited absorption make it a Biopharmaceutics Classification System (BCS) Class III medication, which poses serious formulation issues and may limit oral bioavailability and therapeutic efficacy.

Their sustained-release capability enables prolonged maintenance of therapeutic drug levels, which may reduce the need for frequent administration and enhance patient compliance. Furthermore, the protective nanosponge matrix helps shield the encapsulated drug from biological degradation, thereby improving its stability. However, before extensive clinical application is possible, a number of issues need to be resolved. Large-scale production issues, formulation component safety concerns, regulatory obstacles, and inadequate clinical validation are still major obstacles.

Future studies may increasingly investigate combination therapeutic approache, targeted delivery methods, and individualized treatment plans would increase the clinical potential of nanosponge-based systems. Extensive research and clinical evaluation will be essential for translating these potential carriers into practical therapeutic applications. Nanosponge-based delivery systems offer a promising approach for dapagliflozin by addressing limitations related to aqueous solubility, dissolution, oral bioavailability, drug stability, controlled release, patient compliance, and therapeutic efficacy. The development of next-generation dapagliflozin formulations. Ongoing research and successful clinical translation of nanosponge-based technology have the potential to optimize pharmacological performance, improve therapeutic outcomes, and ultimately enhance the quality of life of individuals with type 2 diabetes mellitus.

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HOW TO CITE: Harshitha V.*, G. Harini Kumari, Nanosponges As A Promising Nanocarrier Strategy For Dapagliflozin: Overcoming Solubility And Oral Bioavailability In Type 2 Diabetes Mellitus - A Comprehensive Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 8, 3951-3973. https://doi.org/10.5281/zenodo.22082146