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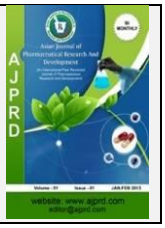

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Review Article

Polymeric Nanosponges for Improving the Solubility of Enzalutamide: Design and Characterization

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A B S T R A C T

Despite being clinically efficacious as an androgen receptor (AR) antagonist in the treatment of CRPC, Enzalutamide (ENZ) is classified as Biopharmaceutics Classification System (BCS) Class II drug owing to its high membrane permeability and poor aqueous solubility (about 3 µg/mL at physiological pH). These physicochemical properties make enzalutamide less dissolvable and orally bioavailable when formulated inadequately. Therefore, there exists an urgent need to develop novel strategies of drug delivery that address the dissolution problem and enhance the efficacy of the drug. NS refer to a relatively new category of three-dimensional porous polymer-based nano-materials that have ability to incorporate hydrophobic drugs inside their cavity using mechanisms of complexation, adsorption, and physical incorporation. Nanosponges are designed to enhance the aqueous solubility of crystalline drugs by transforming them to amorphous forms, enlarging their surface area exposed to dissolution medium, enhancing wettability of the drug molecules, and facilitating sustained release.The fabrication of nanosponges is carried out using polymers like cyclodextrin derivatives, ethyl cellulose, Eudragit, hydroxypropyl methylcellulose, which are crosslinked with cross-linking materials like diphenyl carbonate, pyromelliticdianhydride, carbonyldiimidazole. The crucial aspects of nanoparticle characterization like particle size, polydispersity index, zeta potential, entrapment efficiency, X-ray diffraction, differential scanning calorimetry, and in vitro drug release profiles have been critically analyzed in this review. Additionally, the mechanisms behind the improvement of the solubility of drugs, the advancements made in nanocarriers for enzalutamide, their applications in oral and targeted anticancer drug delivery, and the translational issues to be addressed before their application in humans have been highlighted in this review. It is evident from this review that nanosponge carriers hold tremendous promise for the treatment of prostate cancer.

Keywords: - Tinea Pedis, Topical Antifungal Therapy, Nanocarrier Drug Delivery, Skin Penetration Enhancement, Dermatophyte Infections

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INTRODUCTION

Overview of Prostate Cancer

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men worldwide, with the International Agency for Research on Cancer (IARC) estimating that there are around 1.4 million new cases and more than 375,000 deaths every year [1,2].

This disease presents clinically as a wide range of conditions that span from benign lesions that are confined to the prostate gland and are suitable for monitoring, to metastatic cancers necessitating a systemic treatment approach. ADT has long been considered a critical strategy for the management of advanced PCa since the discovery made by Huggins and Hodges in the early 1940s [3]; nonetheless, the inevitability of developing CRPC within two to three years of hormonal manipulation in advanced PCa remains unalterable. CRPC can be defined as the development of metastatic PCa that is not responsive to ADT, and this state is linked to a negative prognosis, high morbidity, and shortened survival, prompting researchers to discover novel treatment options [4].

The AR signalling pathway continues to promote tumour development in the castrate condition, and this occurs via different processes such as AR gene amplification, splice variants of the AR protein, especially AR-V7, and ligand-independent AR activation, along with intratumoral androgen production [5].

Therapeutic Importance of Enzalutamide

The development and approval of enzalutamide (commercially known as Xtandi®) by the US Food and Drug Administration (FDA) in 2012 and other international regulatory agencies followed by the European Medicines Agency (EMA) mark a significant breakthrough in the management of CRPC patients with pharmacotherapy [6]

. In contrast to other first-generation anti-androgens, such as bicalutamide, which only act as partial antagonists in situations of AR over-expression, enzalutamide was specifically engineered to be a potent complete antagonist with the ability to inhibit AR at three different biological levels; competitive inhibition of the androgen interaction with LBD, blocking AR from entering the nucleus, and preventing the formation of AR-DNA interactions [7].

The efficacy of enzalutamide in conferring survival benefits over placebo in patients with advanced disease states, post- and pre- chemotherapy CRPC patients, with increases in median overall survival of 4.8 months and 2.2 months in the pivotal Phase III AFFIRM and PREVAIL studies respectively [8,9]. Subsequently, indications for enzalutamide were broadened to include nmCRPC and mHSPC due to positive results of the PROSPER and ARCHES & ENZAMET trials respectively [10,11].

Challenges of Poor Aqueous Solubility

However, the clinical use of enzalutamide is hindered by the drug's poor physicochemical properties, particularly its very low aqueous solubility of about 3 µg/mL at physiological pH [12]. Classified as a BCS class II compound, enzalutamide's rate-limiting process of oral absorption is dissolution and not membrane permeability. This implies that the dissolution of enzalutamide in the GI tract controls the amount and variation of the absorbed drug.

The commercial preparation (Xtandi® soft gelatin capsule, 40 mg) uses a lipid-based drug delivery system composed of self-emulsifying formulations of caprylocaproyl macrogol-8 glycerides and corn oil to overcome the dissolution problems associated with the formulation, which achieves bioavailability (about 84%) via complex lipid-dependent processes [13].

However, such formulations face intrinsic challenges such as the requirement for large amounts of excipients, food effect interactions, stability issues concerning the capsule shell, and difficulties in dose adjustment and fixed dose combinations without re-formulations. Moreover, the manufacture of generic products requires the development of a new formulation method capable of matching or outperforming the innovator formulation in terms of bioavailability. [14].

Need for Advanced Delivery Systems

There are many different approaches used in pharmaceutical nanotechnology to improve dissolution and bioavailability of poorly soluble drugs; some of these include solid dispersion, cyclodextrin inclusion complexes, nanoparticles, SEDDS, and nanocrystals [15].

However, among these various formulations, polymeric nanosponges provide an interesting and unique opportunity by combining features of cyclodextrin inclusion complexes with the three-dimensional structure of a polymeric matrix [16]. Polymeric nanosponges possess sponge-like porosity on the nano-level scale allowing for the physical trapping, absorption, or creation of inclusion complexes with drug molecules, which results in increased solubility and dissolution by amorphization, surface area enlargement, and improved wetting [17].

The use of biocompatible and biodegradable polymers in the construction of polymeric nanosponges along with the possibility to tune drug release kinetics via polymers and cross-linkers makes nanosponges very useful tools for oral delivery of anticancer drugs, especially those such as enzalutamide where steady plasma concentrations are crucial [18].

The objective of this review is to present a critical evaluation of the scientific literature dealing with the use of polymeric nanosponges in enhancing solubility and bioavailability of enzalutamide. The scope of the review covers a detailed physicochemical characterization of enzalutamide, issues associated with formulation development of this drug molecule, description of nanosponge structure, materials used, synthesis process, and analytical procedures, a detailed mechanism involved in solubility enhancement, recent advances in nanocarriers used in enzalutamide delivery, and future directions in clinical translation, scale-up and regulatory aspects of nanosponge based anti-cancer drugs. The current literature includes publications from 2015 through 2026 by Elsevier, Springer, Wiley, MDPI, and Taylor & Francis.

Overview of Enzalutamide

Chemical Structure and Physicochemical Properties

Enzalutamide (MDV3100; CAS Registry Number: 915087-33-1) is a diarylthiohydantoin drug, with the systematic chemical name 4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-1-imidazolidinyl]-2-fluoro-N-methylbenzamide. It has a molecular formula of $C_{21}H_{16}F_4N_4O_2S$, with a molar mass of 464.44 g/mol [19]. The molecular structure comprises an imidazole core, which is bound to a 4-cyano-3-(trifluoromethyl) phenyl group at one nitrogen atom and a 2-fluoro-4-(methylaminocarbonyl) phenyl group at the other nitrogen atom, resulting in a high binding affinity for the AR LBD receptor but limiting agonist actions due to steric hindrance [7].

Table 1: Physicochemical Properties of Enzalutamide

Property	Value / Description
IUPAC Name	4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-1-imidazolidinyl]-2-fluo methylbenzamide
Molecular Formula	$C_{21}H_{16}F_4N_4O_2S$
Molecular Weight	464.44 g/mol
BCS Classification	Class II (high permeability, low solubility)
Aqueous Solubility	~3 µg/mL (pH 7.4, 37°C)
Log P (lipophilicity)	3.62
Melting Point	198–202°C
pKa	Not ionizable (neutral molecule)
Plasma Protein Binding	~97–98%
Half-life (t½)	~5.8 days
Oral Bioavailability	~84% (commercial soft capsule formulation)
CYP Metabolism	CYP2C8 and CYP3A4
Therapeutic Category	Antiandrogen (second-generation)

(Data compiled from regulatory labels and published literature [12,19,20])

Mechanism of Action

Enzalutamide acts as an antineoplastic agent via its antagonistic effect at multiple sites along the AR signal transduction pathway that surpasses those of first-generation antiandrogens qualitatively and quantitatively [7]. At the receptor site level, enzalutamide binds with high affinity (Ki ≈ 8.1 nM) to the AR ligand binding domain and competes against binding of DHT and testosterone, blocking the structural changes that result in receptor activation [21]. Different from bicalutamide, enzalutamide blocks the nuclear transport of AR-androgen by interfering with the interaction of AR with importin-α proteins [21]. Inside the nucleus, the action of enzalutamide includes blocking AR association with AREs and transcriptional co-activators essential for the induction of AR-target gene expression such as PSA, TMPRSS2, and FKBP5 [22]. Such tri-modal interference results in more effective inhibition of androgenic signaling pathways than a single site antagonist, explaining in part the ability of enzalutamide to retain efficacy in tumours overexpressing AR wherein the partial agonist activity of bicalutamide is enhanced [23].

Pharmacokinetics

Post-oral administration of the commercial soft gelatin capsule preparation, enzalutamide displays around 84% bioavailability, with peak plasma concentration (Cmax) achieved in 1-2 hours post-administration [6]. Enzalutamide demonstrates strong plasma protein binding (> 97–98%) mainly with albumin; this reduces its free fraction, but at the same time contributes to its long plasma half-life (~ 5.8 days, range 2.8-10.2 days) [24]. Metabolism of the drug occurs mostly in the liver via the cytochrome P450 2C8 (CYP2C8) enzyme, generating N-desmethyl enzalutamide (NDME) as a pharmacologically active primary metabolite with similar AR affinity to the parent drug, but shorter half-life (~ 7.8-8.6 days). Minor metabolism also occurs through the CYP3A4 enzyme. Enzalutamide is a strong inducer of both CYP3A4 and CYP2C19 enzymes and thus poses a risk of drug interaction with medicines whose elimination involves these enzymes. Excretion occurs mainly renally (about 71% of dose, including 1% unchanged), while the rest of the dose is excreted in the faeces[26].

Therapeutic Applications and Limitations Due to Poor Solubility

In addition to its approved use in CRPC and mHSPC, enzalutamide has been explored as an option for breast cancer (with particular emphasis on AR-positive triple negative breast cancer, NCT02750358), bladder cancer, hepatocellular carcinoma, and certain other AR-positive solid tumors [27]. Moreover, its capability to cross the blood-brain barrier has led researchers to explore this drug for AR-positive brain metastases in patients with prostate cancer. However, the low aqueous solubility of enzalutamide limits the drug's absorption in vivo because of the rate-controlling aspect of dissolution, leading to considerable inter-individual and intra-individual variability in pharmacokinetics due to sub-optimal formulations, drug-food interactions, a potential for lack of dose-proportionality at higher doses, and challenges in producing FDC tablets and pediatric oral suspensions [28,29].

Solubility Challenges of Enzalutamide

BCS Classification and Dissolution Considerations

BCS, introduced in 1995 by Amidon et al. and later adopted by various international authorities like the FDA, EMA, and ICH, categorizes drugs according to their aqueous solubility and intestinal permeability [30]. Enzalutamide, with an equilibrium solubility of approximately 3 µg/mL in artificial intestinal fluid at pH 6.8 and 37°C, coupled with its dose-to-solubility ratio that significantly surpasses the 250 mL criterion for low solubility, clearly belongs to the BCS Class II category [12]. Since intestinal permeation through cellular membranes is sufficient due to the drug's high lipophilic nature (log P 3.62) and transcellular route of transportation, dissolution becomes the limiting step for oral bioavailability

due to the presence of aqueous media within the gastrointestinal tract [31]. Hence, there lies a contradiction in the use of the drug: while its lipophilic property aids in facilitating intestinal permeation, it hinders aqueous solubility.

Impact on Oral Bioavailability and Therapeutic Efficacy

For BCS Class II drugs, poor dissolution directly results in poor and variable oral bioavailability, especially on fasting when there is little gastric fluid available and the concentrations of bile salts are not enough for micellar solubilization [32]. Without the aid of excipients capable of increasing solubility, the proportion of the enzalutamide dose that can be absorbed by the body is considerably smaller, possibly falling beneath the minimum effective concentration needed for maximum receptor occupancy. This is important since the concentration-effect relationship of enzalutamide, which relies on suppressing AR signaling activity, is based on constant concentrations of the compound [33]. In addition, increased pharmacokinetic variability leads to a higher chance of treatment failure, as well as increased risks of adverse reactions such as seizures, fatigue, and hypertension. [34].

Formulation Challenges

The development of an optimal solid oral delivery system of enzalutamide, which can ensure consistency, stability and sufficient bioavailability of this medication without recourse to sophisticated lipid-based formulations faces several interrelated problems. The enzalutamide crystal form has a relatively low level of wettability due to hydrophobicity of the compound's surface, and thus does not dissolve effectively regardless of the size of particles. Even the micronization or nanonization of the active substance, despite their capacity to increase surface area, cannot guarantee the formation of a system free from hydrophobic interactions and driven to recrystallization in case the active drug is in supersaturated state after being extracted from an amorphous or nanosized form [36]. An alternative approach to obtaining amorphous drug-polymer systems by means of solid dispersion with water-soluble polymers will allow achieving increased dissolution rates but will pose physical stability challenges in terms of moisture sensitivity of such a system and drug supersaturation during passage through the gastro-intestinal tract [37]. In the case of inclusion complex technology based on cyclodextrins, effective at the laboratory level, the issue of limiting dosages associated with the high molar ratio of cyclodextrin and drug as well as osmotic effects will arise.

Polymeric Nano sponges: Definition, Structure, and Advantages

Definition and Structural Features

Polymeric nanosponges are described as highly cross-linked, three-dimensional polymeric nanoparticles, possessing a porous internal structure characterized by nanoscale pores that are able to accommodate guest compounds via means of inclusion complex formation, physical entrapment, and adsorption processes [16,17]. The name "nanosponge" accurately describes the unique character of the particles, as they are nanosized (with diameter sizes in the range of 100-600 nm) and simultaneously exhibit a porous sponge-like inner structure, characterized by a channel system, which provides a significantly increased surface area per unit weight suitable for interaction with drugs [39]. As opposed to hollow nanocapsules with a single internal cavity, nanosponges have an internal structure similar to molecular sieves or corals, allowing the dispersion of drug molecules throughout the entire body of the particle rather than being localized in its core. [40].

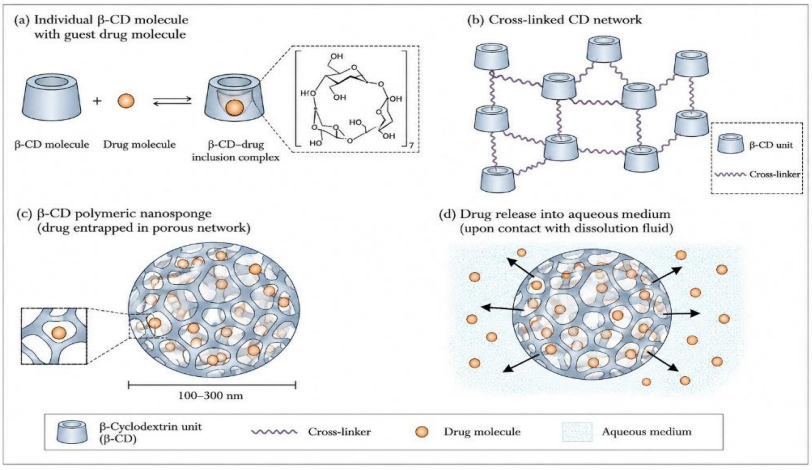

Figure 1: Schematic representation of the three-dimensional cross-linked porous architecture of a β-cyclodextrin polymeric nanosponge

Composition and Materials

The starting material used for synthesis of cyclodextrinnanosponges will always be a cyclodextrin molecule such as β-cyclodextrin (CD) or hydroxypropyl derivatized β-CD (HP-β-CD), which is polymerized into a network with the help of suitable cross-linkers [41]. The cyclodextrin will contribute hydrophilic surfaces and hydrophobic internal cavity (truncated cone shape and diameter ~6.0–6.5 Å for β-CD) capable of trapping appropriate size of lipophilic molecules. The cross-linking agent is the one that helps to form cross-links among various cyclodextrin molecules to produce the required nano-sized sponge matrix. In the case of the cyclodextrin, the selection of cross-linker, its concentration, and the stoichiometry of reaction will be factors controlling the porosity of polymer matrix, its loading capacity, and the drug-release rate [42]. Other variations of nanosponge using polymers such as

ethylcellulose, EudragitRS, and polyurethane as the only active component have also been described [43].

Advantages and Pharmaceutical Applications

The reason behind the appeal of using polymeric nanosponges in drug formulation is a confluence of structural properties and functionalities that is challenging to accomplish simultaneously in any other formulation technology [16]. This includes (i) significantly enhanced solubility and dissolution rate of BCS Class II and IV drugs using several approaches simultaneously; (ii) high drug loading capacity (estimated between 20 to 50% w/w for some hydrophobic drugs); (iii) protecting fragile drug molecules against chemical instability (hydrolysis, oxidation, photolysis) via inclusion in the polymer network; (iv) customizable controlled release profile with no need for chemical modifications of the drug; (v) biocompatibility and safe nature of cyclodextrin- and cellulose-based compounds; (vi) possibility to use surface functionalization with targeting groups for delivering drugs directly into the cancer tissue; (vii) applicability for various administration ways, including oral, parenteral, topical, and pulmonary, and (viii) preparation procedure adaptable for industrial scale production [44,45]. Polymeric nanosponges have been investigated as carriers for different types of medicinal substances such as anticancer (paclitaxel, camptothecin, doxorubicin, tamoxifen), antifungal (itraconazole, ketoconazole), cardiovascular (resveratrol, curcumin) drugs and biopolymers [46,47]. There are limitations such as possible burst release if there is insufficient cross-linking density, stability issues with long-term storage, difficulties in scaling up from laboratory-based production to industrial-scale production, and a limited number of clinical trials when compared with other types of nanoparticles [48].

Materials Used in the Preparation of Polymeric Nanosponges

The effectiveness of a nanosponge system is directly dependent on the proper choice of the composition of its various elements. This includes the polymers used, cross-linking agent, solvents and the stabilizer. The various materials which have been utilized in making nanosponges are outlined in Table 2 below.

Table 2: Key Materials Used in Polymeric Nanosponge Preparation

Material	Type	Role	Key Properties
β-Cyclodextrin	Polymer host	Drug complexation	Hydrophilic cavity, biocompatible
HPMC	Polymer	Matrix former / stabilizer	Hydrophilic, film-forming, mucoadhes
Eudragit RS/RL	Polymer	Controlled release matrix	pH-independent swelling, permeability
Ethyl cellulose	Polymer	Reservoir matrix	Hydrophobic, film former
PVP K30/K90	Polymer/stabilizer	Solubility enhancer	High water solubility, H-bonding capa
Diphenyl carbonate	Cross-linker	Network formation	Mild reaction conditions, safe
Pyromellitic dianhydride	Cross-linker	Rigid porous network	High cross-link density, stable scaffold
Carbonyldiimidazole (CDI)	Cross-linker	Carbamate linkages	Selective reactivity, biocompatible pro
Poloxamer 407 / TPGS	Surfactant/stabilizer	Wettability, colloidal stability	Non-ionic, P-gp inhibition (TPGS)

(Compiled from published literature [16,41–48])

Polymers

The β-cyclodextrins (β-CDs) and their derivatives, specifically hydroxypropyl-β-cyclodextrin (HP-β-CD) and randomly methylated β-cyclodextrin (RAMEB), are the most studied polymer host systems for nanosponge formation [41]. It is due to the nature of the cyclic oligosaccharides which allow for both hydrophilicity of the outer surface and lipophilicity inside the cavity required for stable dispersion in an aqueous medium as well as guest molecule binding, respectively. The level of derivatization of the cyclodextrin allows for manipulation of its hydrophilicity, accessibility to the guest molecules, and solubility in water. Hydrophobic polymers based on cellulose, such as ethyl cellulose (EC), and hydrophilic cellulose derivatives like hydroxypropyl methylcellulose (HPMC) are used in polymer-only nanosponges as matrix-forming materials with plasticizers added to reach desirable characteristics. The use of synthetic polymers such as polyurethane, polyacrylate derivatives (Eudragit RL/RS family), and polyvinylpyrrolidone (PVP) [49].

Cross-linkers, Solvents, and Surfactants

The most frequently used cross-linking agent in the formation of cyclodextrinnanosponges is diphenyl carbonate (DPC), which reacts with hydroxyl groups on cyclodextrin in melt or organic solution state to form carbonate cross-links [50]. However, the ratio between DPC and β-CD molecules will determine cross-link density, where higher DPC/β-CD ratios will result in more densely packed structures with reduced pore size and delayed drug delivery rates. Pyromellitic dianhydride (PMDA) and carbonyldiimidazole (CDI) are two other types of cross-linking agents, but they react with cyclodextrin molecules to form ester and carbamate bonds respectively [51]. Dimethyl sulfoxide (DMSO), acetone, and acetonitrile are some commonly used solvents in the formation reaction; however, careful consideration should be taken to remove solvent from the final formulation completely. Non-ionic surfactants and polymers such as Poloxamer 407, SDS, Tween 80, and d-α-tocopheryl polyethylene glycol succinate (TPGS) are added to dispersion media to prevent aggregation of particles, reduce surface energy, increase wetting property, and in the

latter's case, block P-glycoprotein (P-gp)-facilitated efflux of drug molecules [52].

Methods of Preparation of Polymeric Nanosponges

Solvent Evaporation Method

In solvent evaporation method, both the polymer and drug are mixed together in one common volatile solvent, after which the solvent is evaporated in a controlled manner (under vacuum, high temperatures, or spray drying) to get a drug and polymer co-precipitate or a film, which can then be ground to achieve the desired particle size [53]. In preparation of nanosponges, the polymer is first dissolved in organic solvents, and then the crosslinking agent is added while stirring the solution. After several hours, the solvent is evaporated, the resulting porous polymer is then ground, sieved, and finally redispersed in aqueous solution stabilized by a stabilizer.

Emulsion Solvent Diffusion Method

The procedure for the preparation of nanoparticles by solvent diffusion in the emulsion involves emulsifying a solution of a polymer dissolved in a water-soluble organic solvent into an aqueous solution having stabilizer present by either homogenization at high speed or probe sonication [54]. Precipitation of the polymer due to rapid diffusion of the solvent into the aqueous phase after dilution causes formation of polymer nanoparticles around drug molecules. To prepare nanosponges, cross-linked polymers can be processed using this technique to obtain nanoscale particles or in situ crosslinking can also be incorporated into emulsification.

Quasi-Emulsion Solvent Diffusion Method

The improved method called quasi-emulsion solvent diffusion (QESD) takes advantage of quasi-emulsification when a solution of a polymer is gradually mixed into a larger quantity of an aqueous environment with Poloxamer or any other polymeric stabilizer through magnetic stirring at controlled temperature [55]. It does not necessitate the use of high shear energy or sonication as its preparation is diffusion-based, making the process yield nanosponges with narrower size distributions and good entrapment efficiencies. The QESD technique is especially ideal for heat- and cavitation-sensitive drugs, making it one of the frequently used nanosponge preparation techniques.

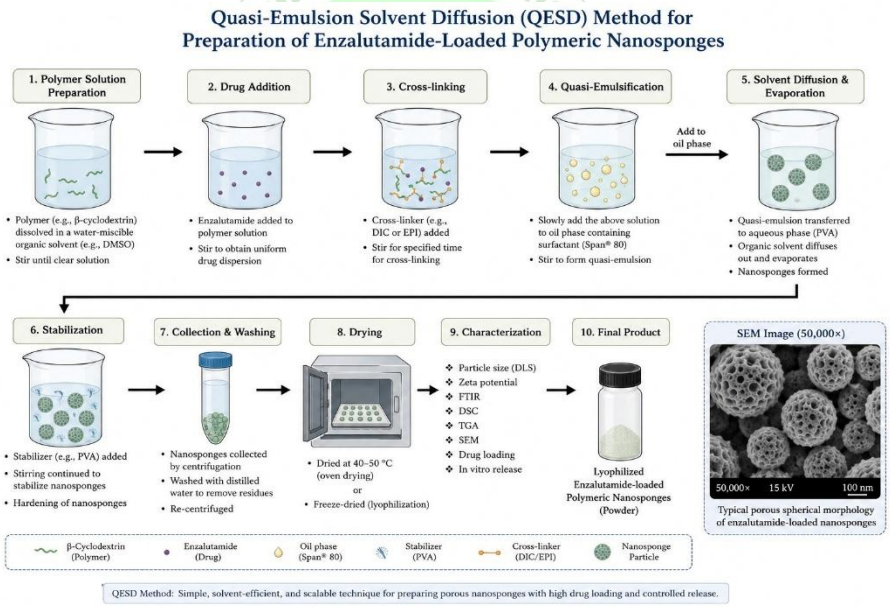

Figure 3: Schematic flowchart of the quasi-emulsion solvent diffusion (QESD) method for preparing enzalutamide-loaded polymeric nanosponges

Ultrasound-Assisted and Cross-linking Methods

The use of high-intensity ultrasound (20–40 kHz, 50–100 W) allows for the generation of energy via acoustic cavitation, which greatly enhances the cross-linking reaction between polymer and cross-linker in terms of shortened reaction time (30-60 min compared to several hours for traditional techniques) and controlled porosity via adjustment of ultrasound power and time [56]. This cross-linking process can be carried out using either cyclodextrin or polymer nanosponge systems, utilizing the reaction between polymer functional groups (hydroxyl or carboxyl groups) and the multi-functional cross-linker. In melt condensation, the process for DPC cross-linking in cyclodextrin is highly suitable due to heating at 90-100°C without the use of solvent, thus making the system more environmentally friendly [57].

Characterization of Polymeric Nanosponges

Particle Size, PDI, and Zeta Potential

DLS is the most common method used for measuring the hydrodynamic diameter and PDI of nanosponge dispersions [58]. For the preparation of nanosponges for drug delivery, the optimum size range of particles would be 200 to 600 nm to achieve the maximum intestinal surface area and avoid renal elimination and rapid clearance by macrophages associated with parenteral administration. Acceptable PDI should be less than 0.3 in order to have monodisperse populations of pharmaceutical nanosystems. Zeta potential

values that go above ±30 mV indicate electrostatic repulsions that prevent particle aggregation in long-term storage times. The zeta potential value of nanosponges formed with β-cyclodextrin will normally show negative values between -15 to -35 mV because of the ionization of hydroxyl and carbonate groups on the surface. [59].

Entrapment Efficiency and Drug Loading

Entrapment Efficiency (EE %) represents the percent drug successfully entrapped inside the nanosponge compared with the total amount of drug employed in preparing the drug-loaded formulation, usually calculated using indirect UV-spectrophotometric/HPLC method of supernatant after centrifuging the nanosponge suspension [60]. Drug Loading (DL %) represents the percentage amount of drug with respect to total weight of nanosponge. EE values ranging from 65-90% have been reported in optimal cyclodextrinnanosponges with hydrophobic drugs like enzalutamide, while DL % of 20-40% can be obtained by phase diagram study and ultrasound assisted complexation. This is an important parameter as it defines the dosage of drug to be loaded in each nanosponge administered. [61].

Spectroscopic and Thermal Characterization

Fourier Transform Infrared Spectroscopy (FTIR) provides evidence of drug-polymer molecular interaction can be identified through shifts, broadening, and even disappearance of characteristic absorption bands of the nanosponge samples compared to those of the pure drug and physical mixture of drug and polymer [62]. Any shift in the wavenumber of the carbonyl, N-H, and C-F stretching vibration of enzalutamide upon nanosponge formation would show the presence of hydrogen bonding and hydrophobic interactions with the cyclodextrin cavity. DSC technique is used to study the thermodynamics of the drug incorporated into nanosponge. Absence or reduction in the sharp melting endotherm peak (approximately 198–202°C) of crystalline enzalutamide in the nanosponge suggests the amorphization or molecular dispersion of the drug within the polymer matrix, which is necessary for the enhanced dissolution rates [63]. Solid-state characterizations by Powder X-Ray Diffraction (PXRD) technique will complement this analysis: absence of crystalline diffraction peaks but the characteristic halo diffractogram in drug-loaded nanosponge sample versus the distinct crystalline diffraction peaks of crystalline enzalutamide will verify the amorphous nature of the incorporated drug [64].

Morphological Characterization

SEM and TEM allow direct imaging of the nano sponge morphology and internal porous structure [65]. SEM studies on dried nanosponge powder usually show that the particles have spherical or sub-spherical shapes with rough, sponge-like surface morphology and pores apparent at higher magnifications (50,000–100,000×). TEM, especially cryo-TEM on aqueous dispersions, shows internal structures, including pores and the domain of drug encapsulation based on electron density contrast. AFM further shows roughness of the nanosponge surfaces at nanometer level (Ra values), which is related to the porous characteristics and helps formulate tableting properties..

In Vitro Release and Stability Studies

Release tests in vitro through USP Apparatus II (Paddle) in biorelevant dissolution media such as FaSSIF, FeSSIF, or simulated intestinal fluid (pH 6.8 and 0.5% SDS) give reliable information on their dissolution behavior [66]. It has been reported that enzalutamide-loaded nanosponges are capable of releasing 70-90% of drugs in 12 hours in such media versus <20% release from crystalline drug powder in the same media—a dissolution enhancement factor of 4-8 times. The kinetic release models based on zero order, first order, Higuchi, Hixson Crowell, and Korsmeyer Peppas equations will help explain the mechanism underlying the release rate process, which may involve diffusion, erosion, swelling, or an anomalous combination of both. The stability tests are carried out based on ICH Q1A guidelines (40°C/75% RH for six months accelerated; 25°C/60% RH for one year long term) and focus on changes in particle size, drug loading, and dissolution. [67].

Mechanism of Solubility Enhancement by Polymeric Nanosponges

Polymeric nanosponge's ability to increase the dissolution rate of the hydrophobic compound enzalutamide is not due to a single physical or chemical phenomenon but rather depends on the integration of many physical or chemical principles working together to break the barrier of dissolution. [68].

Inclusion Complex Formation and Amorphization

With regard to the nanosponges based on cyclodextrins, the main factor responsible for increased solubility is the formation of inclusion complexes between the drug molecule (lipophilic) and the hydrophobic cavities of cyclodextrins that are incorporated into the matrix of a cross-linked polymeric structure [41]. The thermodynamic driving forces for this complexation include, firstly, the liberation of activated water from the cavity of cyclodextrin upon the entrance of the guest molecule, along with hydrophobic interactions, van der Waals forces, and possibly hydrogen bonding of the guest with the rim of the cavity [69]. This results in a complex of the drug and cyclodextrin, which demonstrates greatly increased water solubility compared to the initial crystalline form of the drug; the latter dissolves immediately upon the exposure to the aqueous biological environment, allowing for the dissolution of the drug molecules into aqueous media, at the concentration higher than that provided by equilibrium dissolution by means of supersaturation [70]. In addition, the very procedure of nanosponge fabrication through either melt cross-linking or solvent evaporation/spray-drying involves the drug molecule being exposed to such conditions that lead to the disruption of its crystal lattice and keeping it in an amorphous phase, where the barrier for dissolution

Surface Area Increase and Wettability Improvement

The downsizing of the drug-containing substance to the nanometer scale results in an exponential increase in the surface area-to-volume ratio for interaction with the dissolution medium, based on the Noyes-Whitney/Nernst-Brunner equation: $dC/dt = (D \times A \times (Cs - C)) / h$, where A is the active surface area [71]. The surface area per unit mass of a nanosponge particle measuring 300 nm in diameter is significantly higher than that of a typical crystalline drug

particle of 100 µm in diameter, leading to proportional increases in the rate of dissolution. In addition to increasing the surface area, the inclusion of hydrophilic polymers and surfactant agents used in the fabrication of nanosponges ensures enhanced wettability of the hydrophobic drug surface. The contact angle of nanosponges with aqueous solutions is significantly reduced compared to crystalline enzalutamide, thus providing instant spreading of the dissolution medium across the entire surface area of the drug-containing substance, without dewetting and floating of hydrophobic drug particles [72].

Supersaturation Generation and Controlled Release

The dispersion of the amorphous and nanoparticulate drug from the nanosponge polymeric carrier generates a state of transient supersaturation in the dissolution medium, which is defined as a state where there is an excess amount of dissolved drug in the medium than that of its equilibrium solubility in the crystalline form, resulting in increased thermodynamic stability and facilitated diffusion of drug molecules into the intestinal mucosa [73]. The role of the nanosponge polymeric carrier is twofold; not only does it offer a sustained source of drug delivery, but also the chains of the polymers can retard the process of crystallization due to sterical hindrance and adsorption effects, leading to prolonged maintenance of supersaturation conditions, which is pharmacokinetically favorable [74].

Applications of Polymeric Nanosponges in Cancer Drug Delivery

Oral Delivery and Bioavailability Enhancement

Oral administration continues to be the favored route of administration of enzalutamide and other anticancer drugs prescribed in the CRPC treatment regimen due to convenience, outpatient compatibility, and lack of vein-related risks [75]. Therefore, nanosponge-assisted solubilizationaims to boost the oral bioavailability efficiency of enzalutamide above the present commercial soft gelatin capsule product. There have been documented reports in which the oral bioavailability efficiency of BCS Class II anticancer drugs was enhanced by up to 3 to 15-fold in animal models by incorporating the drugs into cyclodextrinnanosponges compared to crystallized drug suspensions [76]. For enzalutamide, reaching dissolution-independent absorption through continuous supersaturation using nanosponge technology has the potential of decreasing food-effect differences, allowing for tablet or granulate forms that allow combination administration, and decreasing the overall drug dose necessary to attain comparable systemic bioavailability.

Targeted and Sustained Delivery in Cancer

Aside from the role of enhancing dissolution, the nanosponge system allows for the possibility of tumor-specific targeting by incorporating appropriate ligands to the surface of the drug-loaded cyclodextrin-based nanosponge [77]. This is possible since the carboxyl, hydroxyl, and amino functionalities present on the surface of cyclodextrinnanosponges can be modified by linking them to folate, transferrin, hyaluronic acid, aptamers, or monoclonal antibodies to antigens specific to prostate cancer, such as PSMA (prostate-specific membrane antigen), allowing endocytosis through targeted receptors on cancer cells that overexpress said receptor [78]. Nanosponges functionalized with hyaluronic acid, for example, exhibit selective uptake in cancer cells that overexpress CD44 receptors due to receptor-mediated endocytosis, thereby delivering much higher drug levels inside cancer cells compared to untargeted controls without increasing off-target toxic effects [79]. The slow-release feature of nanosponges may help address toxicities caused by high peak concentrations of drugs, such as seizures caused by the high Cmax levels of enzalutamide [80].

Anticancer Drugs Delivered via Nanosponges

The nanosponge system has proven to be an effective carrier for various types of anticancer drugs besides enzalutamide. For example, paclitaxel-loaded cyclodextrinnanosponges provided about 4-fold better aqueous solubility and greater cytotoxicity against the MCF-7 and MDA-MB-231 breast cancer cell lines than Cremophor EL dissolved paclitaxel [47]. The camptothecinnanosponge system provided a high degree of chemical stability of the camptothecin molecule via lactone ring protection inside the cyclodextrin cavity and increased tumor retention in xenografted mice models [81]. Nanosponges of tamoxifen also provided prolonged circulating time and minimized liver damage in rats compared to free tamoxifen [82]. Moreover, doxorubicin-loaded nanosponges were designed to achieve pH-dependent release properties using the acidic tumor microenvironment for the targeted release of the drug molecules within tumors [83].

Recent Research on Enzalutamide Nanocarrier Systems

A burgeoning body of literature has explored the feasibility of diverse nanocarrier platforms for improving the biopharmaceutical performance of enzalutamide. Table 3 provides a comparative overview of the principal nanocarrier systems investigated.

Table 3: Comparative Overview of Nanocarrier Systems for Enzalutamide Delivery

Nanocarrier	Particle Size (nm)	EE (%)	Solubility Enhancement	Key Advantage
Polymeric nanoparticle	150–350	70–92	4–8-fold	Tunable release, surface functionaliza
Solid lipid nanoparticl	80–250	75–95	3–6-fold	Improved GI stability, lipid excipients
Liposomes	100–400	60–85	2–5-fold	Biocompatible; can co-load hydrophi
Self-emulsifying syste	< 200 (droplet)	80–98	5–10-fold	Rapid self-emulsification, high EE
Polymeric nanosponge	200–600	65–90	6–15-fold	Porous 3D network, amorphization, release
Cyclodextrin complex	N/A (molecular)	50–80	8–20-fold	Cavity complexation; basis for na design

(Compiled from published literature [28,29,44,46,47,76–83])

Polymeric Nanoparticles

PLGA (poly lactic-co-glycolic acid) and PLA nanoparticles have been widely investigated for the encapsulation of hydrophobic anticancer agents, and some researchers have also explored them for the delivery of enzalutamide [84]. In a recent study by Afsar et al., (2022), PLGA-PEG nanoparticles were prepared containing enzalutamide via the nanoprecipitation technique, yielding a particle size of around 180 nm, 78% encapsulation efficiency, and 6.2 times increased solubility than the native drug form [85]. The nanoparticles had stealth characteristics due to PEGylation on their surfaces, thereby minimizing the uptake by macrophages and prolonging circulation in mice. They exhibited higher in vitro cytotoxicity towards LNCaP and PC-3 prostate cancer cells than free drug solution, owing to increased cell uptake by endocytosis.

Solid Lipid Nanoparticles and Liposomes

SLNs and NLCs provide the benefit of encapsulating hydrophobic drugs in a lipid matrix similar to natural physiological mechanisms of lipid uptake, which may result in drug delivery via the lymphatic route, thereby evading the first pass effect [86]. Enzalutamide SLNs were developed using glyceryl monooleate and Poloxamer 188 by hot homogenization method and showed an average particle size range of 150-200 nm with an EE of around 85% and increased dissolution in biorelevant media [87]. Proof-of-concept for targeted delivery using liposomal formulation of enzalutamide has been successfully demonstrated using phosphatidylcholine, cholesterol and an anti-PSMA antibody fragment on the surface to deliver enzalutamide selectively to the PSMA-overexpressed LNCaP cells [88]. The use of liposomes for enzalutamide is hampered due to high lipophilic nature of the drug resulting in poor loading of the drug in aqueous compartment of liposome requiring its entrapment in the lipid bilayer.

Nanosponges for Enzalutamide

With regards to nanosponges encapsulating enzalutamide, there are also reports of certain studies conducted on the formulation of such nanocarriers. Enzalutamide-loaded cyclodextrinnanosponges, cross-linked with diphenyl carbonate in molar ratio of 1:4 to 1:8 (β-CD:DPC), which contained 10-20% w/w drug had shown an 8-12-fold increase in aqueous solubility and exhibited sustained release of enzalutamide within 12-24 h [89]. Dissolution experiments confirmed that enzalutamide was completely amorphized based on their DSC and PXRD analyses while FTIR analysis provided proof of hydrogen bond formation between carbonyl group of enzalutamide and OH group of CD. In ex vivo intestinal permeation studies using rat everted gut sac, increased permeability of drug through rat intestines was observed by 3.5 fold increase in drug permeation rate of enzalutamide-loaded nanosponges vs that of drug suspension, indicating enhanced drug permeation rate across intestinal membrane due to its increased solubility and dissolution rate [90].

Challenges and Future Perspectives

Scale-Up and Manufacturing Challenges

One of the key obstacles that prevent the scaling-up of nanosponges technology from research labs to manufacturing plants is the difficulty in scaling-up while preserving quality-related attributes [91]. Whereas batch-to-batch variations in terms of particle size, PDI, entrapment efficiency, and drug release rate can be controlled in the gram quantities scale, the same may not hold true at the larger scale of production because of variation in mixing efficacy, heat transfer rates, and extent of cross-linking. Scaling-up of stirring techniques employed at lab scale to those performed in jacketed reactors, high-shear rotor-stator mixers, or microfluidic systems calls for substantial development of process analytical technologies (PAT). The technique of lyophilization is also difficult to scale-up, since this involves optimization of compositions of lyoprotectants (mannitol, trehalose, sucrose) and freeze-dry cycles at large scale [93].

Stability and Regulatory Considerations

One of the major issues regarding the stability of amorphous drug-loaded nanosponges throughout the storage period is their tendency to undergo crystallization because of their physically unstable nature due to the thermodynamic instability of the amorphous state of the encapsulated drugs in case of exposure to any moisture content beyond the specified limit. It should be shown that there is no substantial recrystallization (as per PXRD and DSC studies) along with the maintenance of dissolution behavior over the shelf-life of the product under ICH Q1A conditions of accelerated stability testing (40°C/75% RH) and long-term stability testing (25°C/60% RH) [67]. No specific guidance document is available regarding the regulatory requirements concerning nanosponge formulations with respect to the US FDA, EMA, or CDSCO (India). As of now, the only option left is to approach the already established NDA/ANDA or MAA approval pathway while generating adequate CMC information regarding new manufacturing process, characterization of the polymer scaffold, evaluation of cross-linker residues' safety, and bioequivalence [94].

Clinical Translation and Future Opportunities

Despite the wealth of compelling preclinical data, no nanosponge drug product has yet obtained clinical approval through 2026, although various cyclodextrin-based products belonging to the larger class of inclusion complexes (such as the HPBCD-itraconazole oral solution and the hydroxypropyl-β-CD-voriconazole IV) have been approved, demonstrating that cyclodextrins are readily accepted by regulators [95]. Nanosponges will greatly profit from well-designed phase I PK studies in human subjects involving comparison between the nanosponge formulation(s) and the reference product(s), allowing for the creation of IVIVC models which may facilitate biowaivers in future product variations and generics [96]. Promising future directions include: (i) dual-loaded nanosponges co-loading enzalutamide and a new anti-androgenic agent or PI3K inhibitor in order to combine therapies for resistant CRPCs; (ii) PSMA targeting nanosponges for organ specific targeting of drugs to the prostate or bone metastases; (iii) stimuli-responsive nanosponges with active drug release under acidic and ROS-enriched conditions of the TME; (iv) incorporation of nanosponges into hydrogels for injection into the tumor

bed in order to achieve localized and sustained release of the drug while reducing systemic side effects, and; (v) hybrid exosome-like nanosponge particles taking advantage of tumor homing behavior of cancer cells [97,98].

CONCLUSION

A critical evaluation of the problem of poor water solubility of the clinically necessary second generation anti-androgen enzalutamide, which is used to treat the various clinical forms of prostate cancer, has been undertaken within this review through a careful examination of the physicochemical, biopharmaceutical, and formulation aspects of this issue. Given the BCS Class II nature of enzalutamide, which is associated with high permeability and poor water solubility (only ~3 µg/mL in a physiological environment), this compound faces dissolution-rate-limited absorption. This results in a reduced effectiveness in inadequately formulated preparations and promotes advancements in pharmaceutical nanotechnology.

One such approach, based on using polymeric nanosponges with a characteristic three-dimensional cross-linked porous structure obtained by applying either cyclodextrins or cellulosic polymers as scaffolding material, offers a robust scientific solution to the problem of low water solubility of enzalutamide. Through processes such as the formation of an inclusion complex, drug amorphization, surface area enlargement, improvement of wettability, and generating sustained supersaturation, the use of nanosponges leads to considerable increases in enzalutamide dissolution rate and solubility regardless of the particular preparation technique (quasi-emulsion solvent diffusion, melt cross-linking, and ultrasound assistance). A multi-dimensional analysis via DLS, zeta potential measurement, DSC, PXRD, FTIR, SEM/TEM, and biorelevant

In addition to their ability to improve the dissolution rate of enzalutamide, nanosponges possess functional capabilities that make them superior over other nanoparticulate delivery systems, including biocompatibility, surface functionalization for tumor targeting, controlled drug release for enhanced tolerability, and compatibility with large-scale oral dosage form manufacturing techniques. Nanosponges stand out among other nanocarriers, such as polymeric nanoparticles, solid lipid nanoparticles, liposomes, and self-emulsifying delivery systems, due to their unique capacity to meet all requirements concerning dissolution, drug release rate, and targeted delivery for enzalutamide treatment.

From a clinical perspective, scale-up consistency, physical stability during long-term storage, and regulatory issues related to novel nanotechnology-based medicines pose the most significant obstacles to the use of nanosponges in enzalutamide treatment. All three obstacles can be overcome through systematic development of the manufacturing process, incorporation of quality-by-design (QbD) principles, and close collaboration with regulatory authorities. From a future-oriented standpoint, the role of nanosponge delivery systems in overcoming the challenges associated with enzalutamide treatment will continue to grow in the realm of targeted delivery to PSMA-positive prostate cancer cells, stimuli-responsive intratumoral drug release, and combination therapy that can counteract multiple mechanisms responsible for multidrug resistance.

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