Journal of Food and Drug Analysis

Volume 33 | Issue 3 Article 3

Targeted nanosponge-based treatment for pulmonary hypertension: A novel approach

Targeted nanosponge-based treatment for pulmonary hypertension: A novel approach

Jashanpreet Kaur*, Gursimran Kaur, Chamanpreet Kaur, Sandeep Kumar

Department of Pharmaceutics, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab, 140111, India

Abstract

Pulmonary Hypertension (PH) is a progressive and potentially fatal condition marked by high pulmonary artery pressure, resulting in heart failure and reduced oxygenation. Despite advancements in treatments, therapeutic options for PH remain limited, particularly in cases resistant to conventional therapies. In biomedical research, nanotechnology has become a potential area of study, presenting novel approaches to drug delivery and tissue targeting. Nanosponges, a class of nanoparticles with porous structures, have gained attention for their ability to encapsulate therapeutic agents, enhance drug stability, and provide controlled release. Nanosponges can be engineered to deliver vasodilators, anti-inflammatory drugs, and gene therapies directly to the pulmonary vasculature, minimizing systemic side effects and improving drug efficacy. Additionally, their unique surface properties allow for targeted delivery to specific cells or tissues involved in PH, such as the pulmonary arteries' smooth muscle and endothelial cells. This review explores the potential role of nanosponges in pulmonary hypertension, highlighting recent advances in their design and functionalization. The integration of nanosponges into PH therapy could revolutionize the treatment landscape, offering more effective and individualized treatment plans.

Keywords: Drug delivery, Endothelial cells, Nanosponges, Pulmonary hypertension, Targeted therapy

1. Introduction

1.1. Hypertension

Hypertension is now defined as having a systolic blood pressure (SBP) of 130 mmHg or higher and/or a diastolic blood pressure (DBP) of more than 80 mmHg. Among the most prevalent Hypertension's great prevalence and substantial clinical impact make it a leading cause of cardiovascular disease and death [1–4].

The following denotes the several stages of hypertension, under the most recent U.S. national guideline [5] (Table 1).

1.2. Pulmonary hypertension

A diverse collection of clinical conditions marked by elevated pulmonary artery pressure are together referred to as pulmonary hypertension (PH). By definition, PH is present in patients whose average pulmonary arterial pressure (mPAP), as ascertained by right heart catheterization (RHC), is greater than or equal to 25 mmHg [6]. About 10% of people over 65, at least 50% of heart failure (HF) patients, and 1% of the world's population suffer from hypertension of the lungs [7].

1.2.1. Categorization of hypertension in the lungs

There are five clinical subgroups of PH as stated by the World Health Organization [8,9] as shown in Fig. 1, 2.

1.2.2. Diagnosis

Angina, syncope, exhaustion, and dyspnea are common signs of PH. The primary cause of the symptoms is increasing right ventricular (RV) failure. A wide range of laboratory indicators have been examined as possible biomarkers for PH diagnosis

Received 5 May 2025; accepted 29 May 2025.
Available online 18 September 2025

* Corresponding author at: Department of Pharmaceutics, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab, 140111, India.
E-mail address: jpreetkaur42@gmail.com (J. Kaur).

https://doi.org/10.38212/2224-6614.3550

Table 1. Stages of hypertension.

Ranges	Systolic tension	Diastolic tension
Ordinary	90–119	60–79
Prior to blood pressure	120–139	80–89
• Phase 1 (Slight)	140–159	90–99
• Phase 2 (Moderate)	160–179	100–109
• Phase 3 (Harsh)	>180	>109
Isolated systolic hypertension	>140	<90

and surveillance. For many years, pro-BNP and brain natriuretic peptide (BNP) have been employed as stand-ins for mortality risk [10]. Although blood uric acid levels have been discovered to be inversely related to PVR, it is unknown what this association means clinically [11].

1.2.3. Evaluation

1. **ECG:** PH can still be diagnosed with a normal ECG. However, if QRS and QTc are extended, an irregular ECG may be a sign of serious illness [12–15].
2. **Chest Radiography:** The x-ray may show reticular opacifications, diaphragmatic flattening, hyperlucency, or volume loss in patients with lung illness. PH cannot be ruled out by a normal chest X-ray [16,17].
3. **Ultrasonography of the abdomen:** An abdominal ultrasound is mostly performed to look for kidney damage, portal hypertension, and liver abnormalities that could result from chronic PH. The degree of collateral damage to these organs can be evaluated with the use of ultrasonography [18].
4. **Cardiac Magnetic Resonance Imaging:** The test does not accurately predict pulmonary artery pressures, although it is sensitive for identifying early PH. The availability and expense of cMRI are also significant obstacles [19].

1.2.4. Comprehensive pulmonary hypertension management

The general supervision of PH is primarily symptomatic and is contingent upon the patient's needs as well as the nature and severity of the illness. Patients with persistent thromboembolic PH and those with comorbidities for which anticoagulation is appropriate are the only ones who are currently advised to utilize anticoagulation [20]. Chronic thromboembolic PH is best treated by pulmonary artery thromboendarterectomy [21]. Since pulmonary thromboendarterectomy has the potential to be curative, it is the preferred treatment for CTEPH. Most patients experience significant symptom alleviation as well as improvements in hemodynamics and RVF [22].

2. Nanosponges

Targeting drug delivery mechanisms has long been a goal in order to get the desired outcome. Nanosponges are tiny structures that resemble meshes and can encapsulate a wide range of materials, including drug compounds [23,24]. The lengthy polyester backbone is combined with tiny molecules known as crosslinkers, which function as tiny

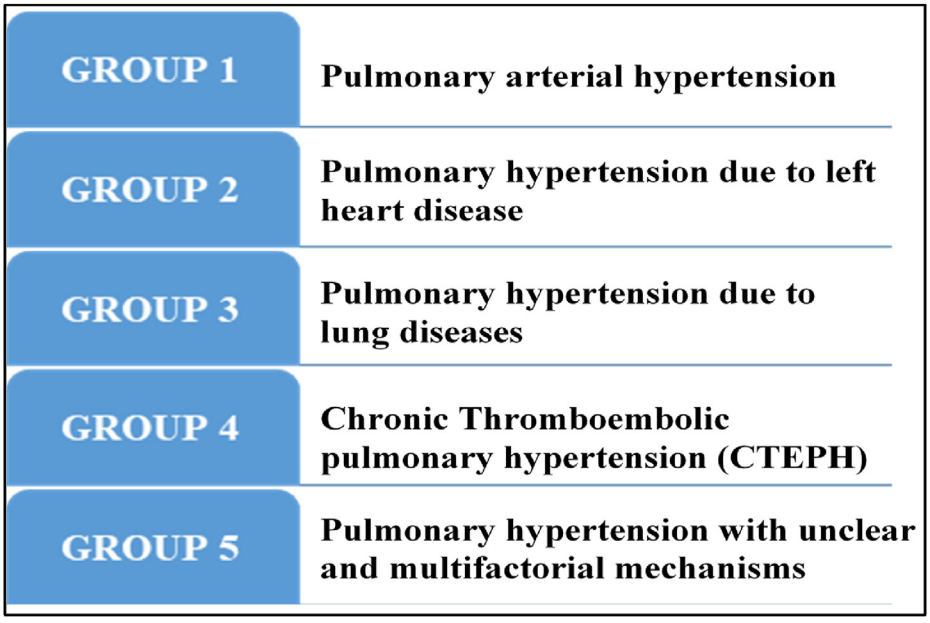

Fig. 1. Classification of pulmonary hypertension.

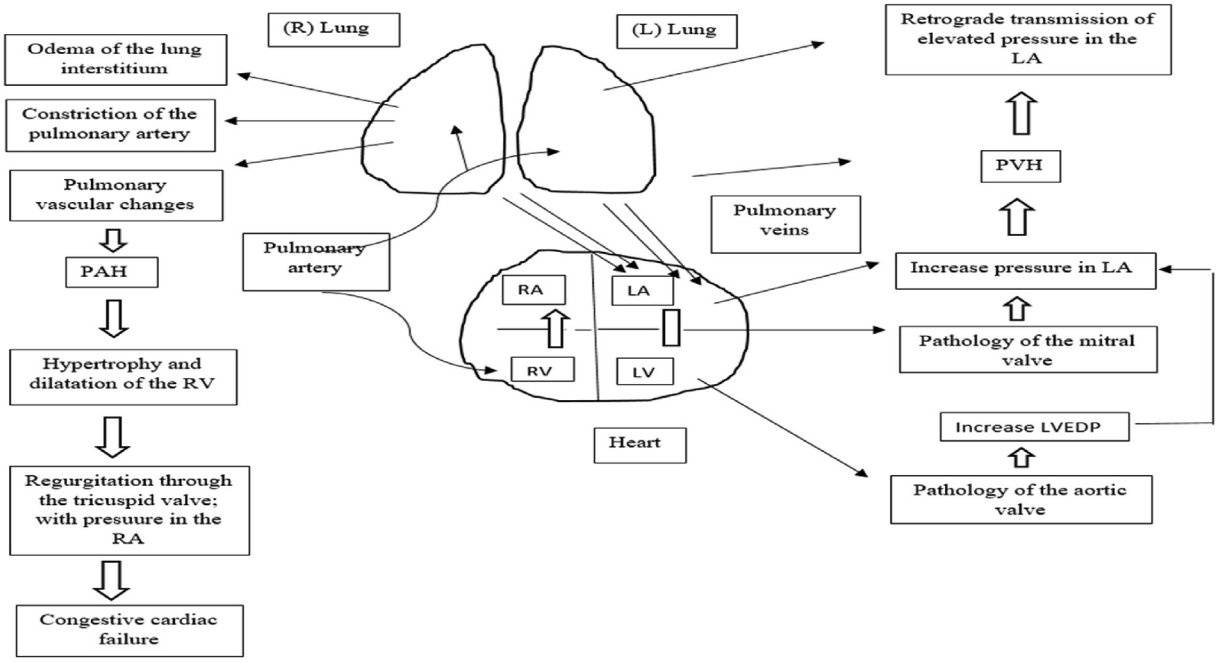

Fig. 2. Pathophysiology of pulmonary arterial hypertension.

grappling hooks to hold the various components of the polymer together. Because nanosponges are an encapsulating class of nanomaterials, they can include and encapsulate a wide range of medications because they are made up of tiny particles with voids that are just a few nanometers in diameter [25]. By encapsulating hydrophilic as well as lipophilic moieties, these materials assist improve the solubility of molecules [26]. They also have a spherical colloidal structure and improve the solubilization ability of both lipid-soluble and water-soluble medications [27]. They improve the bioavailability of medications with extended release [28]. They don't result in any toxicity, allergic reactions, irritations, or mutations [29]. Because of its solid structure, nanosponges can be safely administered through alternative methods [30].

Nanosponges have already been used in a variety of applicable domains, including the pharmaceutical and cosmetic industries [31]. Because of their small size, nanosponges can be delivered both venous and pulmonary. The medication molecules are housed inside the center of nanosponges, which are encasing nanoparticles [32]. Additionally, they have no trouble integrating liquids into their 3D structure [33] as shown in Fig. 3.

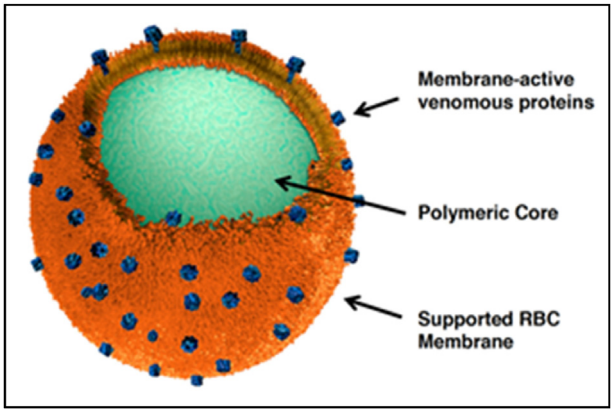

Fig. 3. Structure of nanosponge.

2.1. Key characteristics of nanosponges

Nanosponges are made of particles of a certain size, and by varying the ratios of crosslinking agents and polymers, their polarity can be changed. The diameters of nanosponges with changeable void polarity are 1 μm or less [34]. This kind of encapsulating nanoparticle can retain the medication molecule in its center [35]. The crosslinker's functional groups and concentration have an impact on the nanosponges porosity and provide adjustable polarity [36]. They are shown to be stable at temperatures up to 130 °C and pH values between 1 and 11. They are discovered to be non-toxic, biodegradable, and permeable [37]. When creating a topical formulation with nanosponges, the nanosponges are combined with hydrogel applied topically; for parenteral compositions, they are combined using aqueous solution, saline, or sterile

water [38]. Because of their high aqueous solubility, weakly water-soluble medications can be administered with them [39]. They produce transparent, colloidal with a milky colour combinations in water, and they possess the further advantage of being easily redeveloped using solvent extraction, microwaves, and the thermal desorption process.

2.2. Materials needed to prepare nanosponges

Depending on the kind of nanosponges that are desired and the level of crosslinking that is needed, a variety of chemicals have shown encouraging results and can be used to create them. The quantity of crosslinking, which depends on the concentration of the crosslinker, is an essential part of nanosponges since it affects the way that the medicine is encapsulated and released.

The following discusses many ingredients required to make nanosponges [40].

2.2.1. Polymers

Nanosponges development and performance are influenced by the kind of polymer used in their formation. Additionally, the type of medicine to be entrapped and the intended release profile determine which polymer is best [41]. Commonly used polymers are methyl β-Cyclodextrin, poly-Valerolactone, hydroxy propyl β-cyclodextrin, Eudragit RS 100 and acrylic Polymer.

2.2.2. Crosslinking agent

The structure of the polymer and the medication whose nanosponges are to be made determine the kind of crosslinker that should be used. Furthermore, various crosslinking agents have the ability to drastically change important characteristics, such as the polymer's ability to swell and its hydrophilicity or hydrophobicity [42]. For instances carbonyl diimidazole, carboxylic acid dianhydrides, glutaraldehyde, dichloromethane and diarylcarbonates.

2.2.3. Copolymers

Utilize in combination with polymers to enhance their properties. For examples ethyl cellulose, Polyvinyl alcohol, Poly (Valerolactone allyl Valerolactone).

2.2.4. Polar solvents

Commonly used are ethanol, Dimethyl-acetamide and Dimethyl-formamide.

2.3. Methodology for nanoparticle preparation

The following sections discuss the various methods for producing nanosponges:

2.3.1. Solvent technique

This method involved combining the polymer with a suitable solvent, namely a polar aprotic solvent. This mixture was added in excess of the crosslinker, preferably in a 4:16 crosslinker/polymer molar ratio. For one to 48 h, the reaction was conducted at temperatures between 10 °C and the reflux temperature of the solvent. After the response was finished, the mixture was allowed to reach room temperature. After that, the product was mixed with a sizable volume of additional bidistilled water, collected by vacuum filtration, and purified using ethanol and a drawn-out Soxhlet extraction procedure. The substance was ground into a uniform powder in a mechanical mill after being vacuum-dried [43] as shown in Fig. 4.

2.3.2. Melt technique

The crosslinker and the polymer melt together during the melting process. Every component was thoroughly mixed. By frequently washing the purchased item with an appropriate substance, nanosponges were gathered. After cleaning, the product is separated into nanosponges by removing the waste polymer and unreacted reagents [44]. The

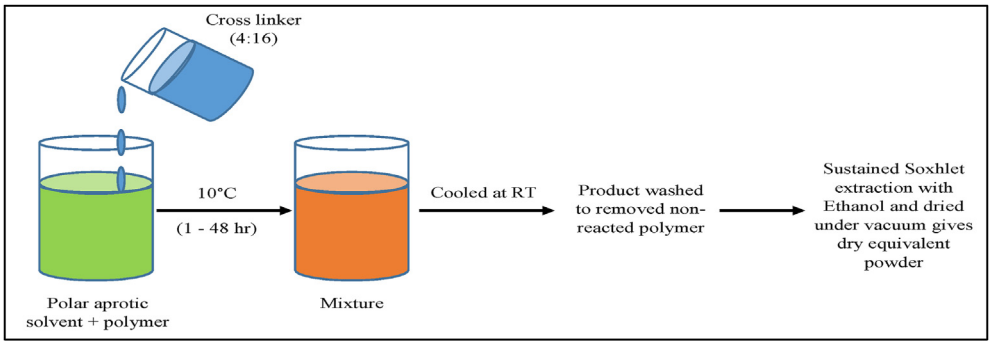

Fig. 4. Pictorial representation of solvent method.

encapsulation of drugs was further subjected to such blank nanosponges as shown in Fig. 5.

2.3.3. Solvent diffusion method

2.3.3.1. Emulsion solvent diffusion technique. This method uses two different levels of aqueous and organic phases. Drugs and polymers are combined in the organic phase, whereas polyvinyl alcohol (PVA) is utilized in the phase of water [45]. After dissolving the medication and polymer in the proper organic solvent, this stage is gradually combined with the watery phase and agitated for two or more hours at 1000 rpm using a magnetic stirrer. After that, the completed nanosponges are filtered, cleaned, and allowed to air dry at ambient temperature or in a vacuum oven set at 40 °C for 24 h [46] as shown in Fig. 6.

2.3.3.2. Solvent technique for quasi-emulsions. In this method, the inner stage is made with Eudragit RS 100 and added to a reasonable dissolvable stage. When subjected to ultrasonication, at 35 °C, the medication produced a reaction and broke down [47]. The exterior phase that contains polyvinyl alcohol uses this internal process as an operator for emulsification. After 3 h of stirring at 1000–2000 rpm at room temperature, the mixture is dried in an air-warmed oven for 12 h at 40 °C as shown in Fig. 7.

2.3.3.3. Technique with ultrasound assistance. This method involves sonicating a reaction between polymers and crosslinkers without the need of a solvent to create the nanosponges. This technique creates spherical, homogeneous nanosponges. This process involves adding crosslinkers like pyromellic anhydride or di-phenyl carbonate to the polymer in the flask at a predetermined molar ratio. Once the flask's mixture had cooled, it was heated to 90 °C in an ultrasonic bath loaded with water. A water wash is performed on the mixture to eliminate any surplus non-reacted polymer. Using ethanol and a lengthy Soxhlet extraction procedure, the mixture is refined [48,49] as shown in Figs. 8, 9.

2.4. Factors influencing the development of nanosponges

2.4.1. The properties of the polymer and crosslinker employed

Crosslinkers help build an nanosponges three-dimensional configuration. The quantity of crosslinker employed helps determine drug entrapment [50]. The nanosponges solubility in water or any other solvent depends on the kind of crosslinker

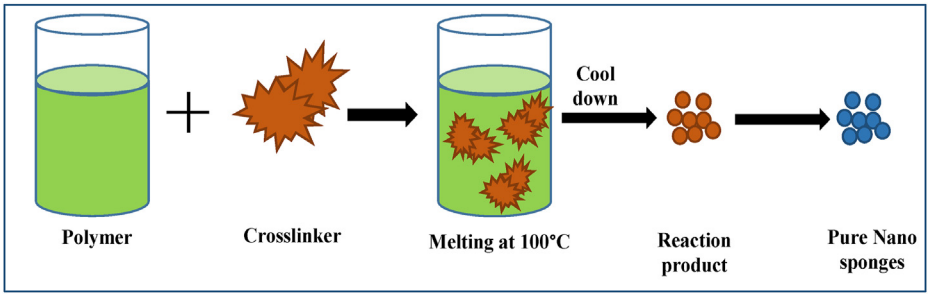

Fig. 5. Pictorial representation of Melt method.

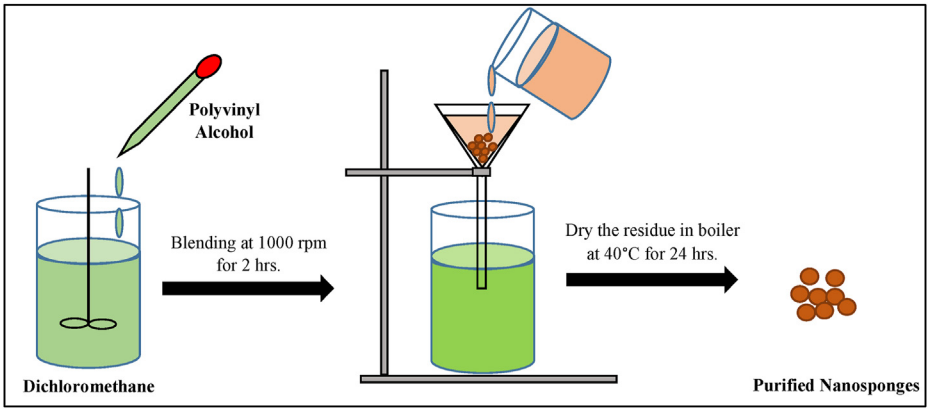

Fig. 6. Pictorial representation of the diffusion technique for emulsion solvents.

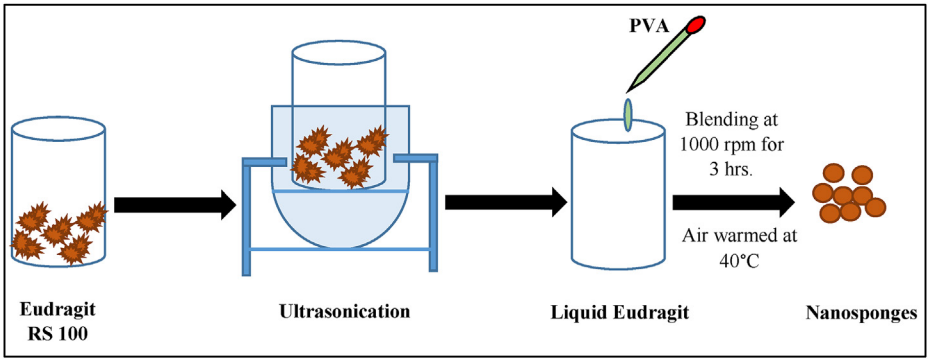

Fig. 7. Pictorial representation of Solvent technique for quasi-emulsions.

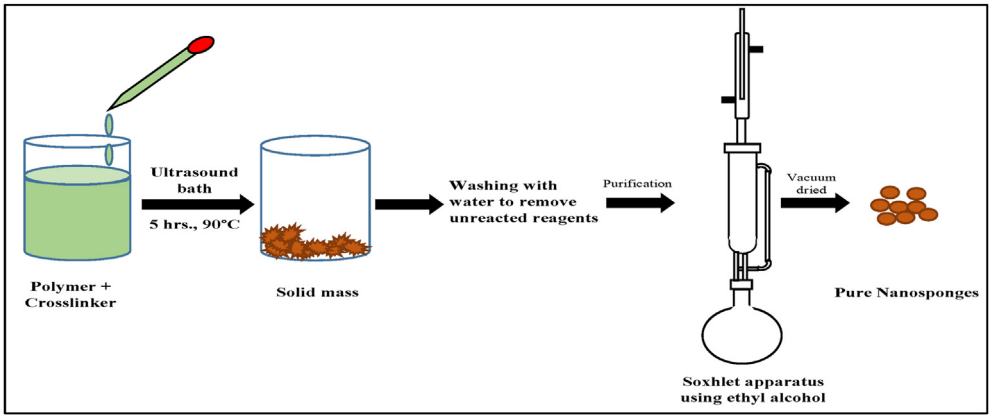

Fig. 8. Pictorial representation of Ultrasound-assisted method.

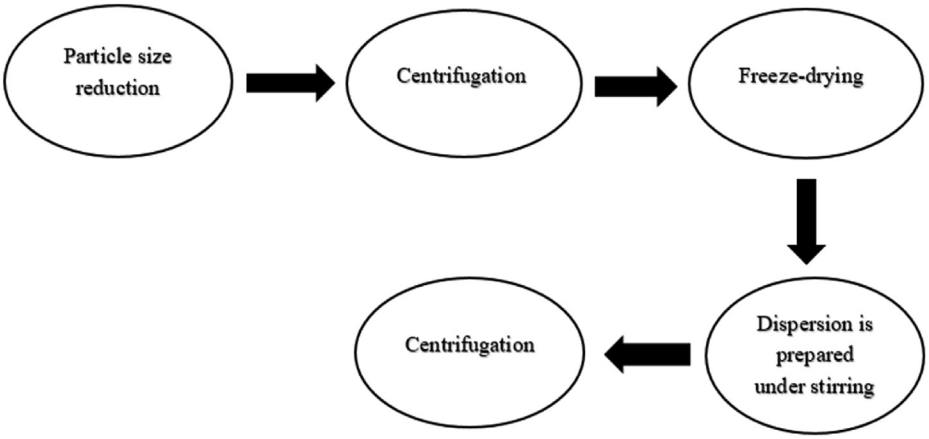

Fig. 9. Loading of drug into the nanosponges.

that is utilized [51]. Hydrophilic nanosponges are employed for enhancing drug absorption and serving as a practical drug transporter to provide formulations with swift release [52,53]. Hydrophobic nanosponges are employed as a continuous release drug delivery technology for water-loving medications, including as proteins and peptides [54].

2.4.2. Medium for demonstrating pharmacological properties and interactions

A molecule must possess specific qualities that make it appropriate for encapsulation in order to be chosen for incorporation into nanosponges [55]. The organic drug molecule becomes trapped in the hydrophobic cavities of nanosponges if the medium is

hydrophilic, and organic molecules are released from the nanosponges if the medium is an organic solvent [56].

2.4.3. Temperature

A drug or nanosponges complex's stability constant usually drops with temperature, possibly as a result of weakened contact forces such van der Waals and hydrophobic forces [57,58].

2.4.4. The extent of replacement of crosslinking

The level of crosslinking and number of substituents are directly correlated; a higher number of substituents can result in a higher degree of crosslinking, that produces extremely permeable nanosponges with an interior structure that resembles a mesh [59]. The final value of the nanosponges which is based on the purity of the resource and the product processing, determines how important degree of polymer substitution is [60].

2.4.5. The nature of complexity

When the temperature rises, the medication and the mixture created with the nanosponges consistency constant falls, reducing the contact forces, such as the water-hating and van der Waal forces [61].

2.5. Evaluation of nanosponges

2.5.1. Size of particles and polydispersity

Utilizing MAS OPTION and 90 Plus particle size reequipped particle sizing software, the particle size can be ascertained by dynamic light scattering [62].

2.5.2. Zeta potential

The average of all measurements was used to determine the particles' average hydrodynamic diameter and polydispersity index [63].

2.5.3. Fourier transform infrared spectroscopy

The detection ranges for pharmaceuticals, polymer compounds of drugs, bare nanosponges, medication-loaded nanosponges [64]. Nanosponges bands slightly alter during complicated formation [65].

2.5.4. Porosity

Helium pycnometers are used to study porosity since the gas may pass through and between the channel media found in nanosponges. The substance's true volume is calculated using helium displacement [66].

Porosity percentage is equal to (bulk volume - actual volume/bulk volume) times 100.

2.5.5. Dissolution test

Using a customized basket constructed from five meters of stainless steel wire and rotating at 150 rpm, the USP XXIII dissolution equipment can be used to examine the dissolution profile of nanosponges. When examining the solubility of active chemicals, the chosen dissolve medium guarantees that sink conditions are maintained. The finished samples undergo analysis using the available analytical methods [67].

2.5.6. Test for resilience

The rate of release is gradually slowed by an increase in crosslinking. Thus, the resilience of sponges can be examined and adjusted as necessary by taking into account the release pattern as a time-dependent function of crosslinking [68].

2.6. Applications of nanosponges

Nanosponges' versatility and biocompatibility make them useful in a variety of medical applications. In the manufacturing of topical dosage forms, tablets, capsules, pellets, granules, suspensions, and solid dispersions, they can be employed as excipients [69].

2.6.1. Drug delivery

Drug solubility, stability, and rate of dissolution can all be enhanced with nanosponges. They can also be used to transform liquids into solids and cover up disagreeable tastes [70]. It may be possible to distribute complexes in a blend of anticoagulants, excipients, thinners, and lubricants in tablets and capsules with the proper formulation for oral administration [71].

2.6.2. Immobilization of enzymes

Lipases are especially affected by the problem of enzyme immobilization since it increases their consistency and changes characteristics such as reaction rates and enantio selectivity [72].

2.6.3. Prevents photodegradation

Gamma-oryzanol is encapsulated with robust protection against photodegradation to create nanosponges [73].

2.6.4. Autoimmune disorders

The creation of biomimetic nanoparticles, which take inspiration from nature and enhance the interaction of synthetic materials with biological systems, has garnered significant interest in the realm of nanomedicine lately [74–77]. By employing a function-based strategy to accomplish broad-

spectrum neutralization, the nanosponge platform distinguishes itself from traditional nanomaterial-based methods that work via complementary structures [78].

2.6.5. Cancer treatment

The administration of anticancer drugs is one of the most difficult tasks in the pharmaceutical industry these days due to their poor solubility. According to one report, the compound of nanosponge is three times more effective than direct injection at slowing the growth of tumors [79].

2.6.6. Sustained release drug delivery

Acyclovir is a popular antiviral medication because it effectively treats herpes simplex virus infections. Both formulations had no early burst effect, demonstrating that the medication was not poorly adsorbed onto the surfaces of the nanosponge [80].

2.7. Nanosponges in pulmonary hypertension

Pulmonary hypertension (PH), a dangerous illness marked by high blood pressure in the pulmonary arteries, is being treated with nanosponges, a novel therapeutic method. Their potential as tailored medication delivery systems is among the most exciting uses of nanosponges in this area. Nanosponges have the potential to increase the efficiency of therapeutic agents while reducing systemic side effects by encapsulating drugs that are specifically made to lower pulmonary artery pressure and delivering them directly to the lungs.

Long-term, regulated medication release is made possible by the special porosity structure of nanosponges. This continuous release helps maintain therapeutic drug levels in the bloodstream, which is especially helpful in the management of long-term conditions such as pulmonary hypertension. Nanosponges may improve the adherence of patients to their therapy plans along with enhance overall therapy outcomes by delivering a consistent supply of medication. The possible decrease in toxicity is another important benefit of employing nanosponges in pulmonary hypertension treatment. Because they are systemic in nature, traditional treatments for PH frequently have a variety of adverse effects. The danger of side effects can be decreased by using nanosponges to carry drugs only to the lungs, limiting the exposure of other organs to these drugs. This focused strategy not only improves the treatment's safety profile but also makes it possible to employ larger dosages of drugs when needed.

2.8. Conclusion

The use of nanosponges has become a viable therapeutic strategy for the treatment of pulmonary hypertension (PH), a complicated and frequently lethal illness marked by high lung blood pressure. These nanostructures are engineered to target specific molecular pathways involved in the disease, offering potential advantages over traditional treatments. Nanosponges can be designed to deliver drugs directly to the pulmonary vasculature, improving the bioavailability and reducing side effects by localizing treatment. Moreover, their unique features, including a high surface area and biocompatibility, facilitate enhanced interaction with cellular targets, leading to improved drug efficacy. Recent studies suggest that nanosponges can help modulate inflammation and endothelial dysfunction-key factors in PH pathogenesis. Despite encouraging initial findings, more study is required to maximize the long-term efficacy, stability, and safety of nanosponges in therapeutic settings. Overall, the use of nanosponges represents a novel and exciting avenue for PH therapy, potentially transforming the landscape of treatment for this challenging disease.

Ethics statement

This review is based solely on published previous research and no new experiments involving either human or animal subjects were conducted. All cited studies needed to adhere to ethical guidelines and obtain proper institutional approvals.

Data access statement

All data used in this review are publicly accessible from cited publications. No new data sets were created, and all sources have been duly credited according to FAIR and ALLEA guidelines.

Author contributions

Jashanpreet Kaur: Concept, Literature Review, Manuscript Writing

Gursimran Kaur: Review, Editing

Ms. Chamanpreet Kaur: Supervision, Review, Manuscript Writing

Dr. Sandeep Kumar: Supervision, Review

Funding

This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The author declares no conflict of interest regarding this manuscript.

Acknowledgement

"I sincerely thank my friend and guide for their unwavering support and encouragement."

Specific Contribution of Each Author.

References

[1] Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation 2016;134:441–50. https://pubmed.ncbi.nlm.nih.gov/27502908/

[2] Verdecchia P, Reboldi G, Angeli F, Trimarco B, Mancia G, Pogue J, et al. Systolic and diastolic blood pressure changes in relation with myocardial infarction and stroke in patients with coronary artery disease. Hypertension (Dallas, Tex, 1979) 2015;65:108–14. https://pubmed.ncbi.nlm.nih.gov/25331850/

[3] Reboldi G, Angeli F, De Simone G, Staessen JA, Verdecchia P. Tight versus standard blood pressure control in patients with hypertension with and without cardiovascular disease. Hypertension (Dallas, Tex, 1979) 2014;63:475–82. https://pubmed.ncbi.nlm.nih.gov/24343119/

[4] Angeli F, Reboldi G, Verdecchia P. Hypertension, inflammation and atrial fibrillation. J Hypertens 2014;32:480–3. https://journals.lww.com/jhypertension/fulltext/2014/03000/hypertension,_inflammation_and_atrial_fibrillation.7.aspx

[5] Haynes WG, Webb DJ. Endothelin as a regulator of cardiovascular function in health and disease. J Hypertens 1998;16:1081–98. https://pubmed.ncbi.nlm.nih.gov/9794709/

[6] Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62:D42–50. https://pubmed.ncbi.nlm.nih.gov/24355641/

[7] Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al. A global view of pulmonary hypertension. Lancet Respir Med 2016;4:306–22. https://pubmed.ncbi.nlm.nih.gov/26975810/

[8] Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913. https://pubmed.ncbi.nlm.nih.gov/30545968/

[9] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119. https://pubmed.ncbi.nlm.nih.gov/26320113/

[10] Voelkel MA, Wynne KM, Badesch DB, Groves BM, Voelkel NF. Hyperuricemia in severe pulmonary hypertension. Chest 2000;117:19–24. https://pubmed.ncbi.nlm.nih.gov/10631193/

[11] Foris V, Kovacs G, Tscherner M, Olschewski A, Olschewski H. Biomarkers in pulmonary hypertension: what do we know? Chest 2013;144:274–83. https://pubmed.ncbi.nlm.nih.gov/23880678/

[12] Rich JD, Thenappan T, Freed B, Patel AR, Thisted RA, Childers R, et al. QTc prolongation is associated with impaired right ventricular function and predicts mortality in pulmonary hypertension. Int J Cardiol 2013;167:669–76. https://pubmed.ncbi.nlm.nih.gov/22459397/

[13] Watanabe R, Hori K, Ishihara K, Tsujikawa S, Hino H, Matsuura T, et al. Possible role of QRS duration in the right ventricle as a perioperative monitoring parameter for right ventricular function: a prospective cohort analysis in robotic mitral valve surgery. Front Cardiovasc Med 2024;11:1418251

[14] Henkens IR, Gan CTJ, Van Wolferen SA, Hew M, Boonstra A, Twisk JWR, et al. ECG monitoring of treatment response in pulmonary arterial hypertension patients. Chest 2008;134:1250–7. https://pubmed.ncbi.nlm.nih.gov/18641107/

[15] Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, et al. The prognostic role of the ECG in primary pulmonary hypertension. Chest 2002;121:513–8. https://pubmed.ncbi.nlm.nih.gov/11834666/

[16] Ascha M, Renapurkar RD, Tonelli AR. A review of imaging modalities in pulmonary hypertension. Ann Thorac Med 2017;12:61–73. https://pubmed.ncbi.nlm.nih.gov/28469715/

[17] Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216–23. https://pubmed.ncbi.nlm.nih.gov/3605900/

[18] Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoeper MM. Systemic consequences of pulmonary hypertension and right-sided heart failure. Circulation 2020;141:678–93. https://pubmed.ncbi.nlm.nih.gov/32091921/

[19] Swift AJ, Lu H, Uthoff J, Garg P, Cogliano M, Taylor J, et al. A machine learning cardiac magnetic resonance approach to extract disease features and automate pulmonary arterial hypertension diagnosis. Eur Hear journal Cardiovasc Imaging 2021;22:236–45. https://pubmed.ncbi.nlm.nih.gov/31998956/.

[20] Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, et al. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation 2014;129:57–65. https://pubmed.ncbi.nlm.nih.gov/24081973/

[21] Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53:1801915. https://pubmed.ncbi.nlm.nih.gov/30545969/

[22] Raza F, Vaidya A, Lachariteroberge AS, Lakhter V, Al-Maluli H, Ahsan I, et al. Initial clinical and hemodynamic results of a regional pulmonary thromboendarterectomy program. J Cardiovasc Surg (Torino) 2018;59:428–37

[23] Swaminathan S, Vavia PR, Trotta F, Cavalli R, Tumbiolo S, Bertinetti L, et al. Structural evidence of differential forms of nanosponges of beta-cyclodextrin and its effect on solubilization of a model drug. J Inclusion Phenom Macrocycl Chem 2013;76:201–11. https://link.springer.com/article/10.1007/s10847-012-0192-y

[24] Bolmal UB, Manvi FV, Kotha R, Palla SS, Paladugu A, Reddy KR. Recent advances in nanosponges as drug delivery system. Int J Pharm Sci Nanotechnology(IJPSN) 2013;6:1934–44. https://www.ijpsnonline.com/index.php/ijpsn/article/view/604

[25] Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-Torres LS, et al. Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnol 2018;16:71. https://pubmed.ncbi.nlm.nih.gov/30231877/

[26] Galbis E, de-Paz MV, Iglesias N, Lacroix B, Alcudia A, Galbis JA. Core cross-linked nanoparticles from self-assembling polyfma-based micelles. Encapsulation of lipophilic molecules. Eur Polym J 2017;89:406–18

[27] Swaminathan S, Cavalli R, Trotta F, Ferruti P, Ranucci E, Gerges I, et al. In vitro release modulation and conformational stabilization of a model protein using swellable polyamidoamine nanosponges of β-cyclodextrin. J Inclusion Phenom Macrocycl Chem 2010;68:183–91. https://link.springer.com/article/10.1007/s10847-010-9765-9

[28] Patel E, Oswal R. Nanosponge and micro sponges: a novel drug delivery system. 2012

[29] Damasco JA, Ravi S, Perez JD, Hagaman DE, Melancon MP. Understanding nanoparticle toxicity to direct a safe-by-design approach in cancer nanomedicine. Nanomater (Basel, Switzerland) 2020;10:1–41. https://pubmed.ncbi.nlm.nih.gov/33147800/

[30] Praveen K, Balamurugan K. Targeted drug delivery through nanosponges and its approach. Res J Pharm Technol 2020;13:3524–9. https://rjptonline.org/AbstractView.aspx?PID=2020-13-7-84

[31] Liang L, Liu DP, Liang CC. Optimizing the delivery systems of chimeric RNA.DNA oligonucleotides. Eur J Biochem 2002;269:5753–8. https://pubmed.ncbi.nlm.nih.gov/12444962/

[32] Cavalli R, Trotta F, Tumiatti W. Cyclodextrin-based nanosponges for drug delivery. J Inclusion Phenom Macrocycl Chem 2006;56:209–13

[33] Jagtap SR, Bhusnure OG, Mujewar IN, Gholve SB, Panchabai VB. Nanosponges: a novel trend for targeted drug delivery. J Drug Deliv Therapeut 2019;9:931–8. https://www.researchgate.net/publication/333943344_Nanosponges_A_Novel_Trend_for_Targeted_Drug_Delivery

[34] Swaminathan S, Vavia PR, Trotta F, Torne S. Formulation of betacyclodextrin based nanosponges of itraconazole. J Inclusion Phenom Macrocycl Chem 2007;57:89–94. https://link.springer.com/article/10.1007/s10847-006-9216-9

[35] Roy D. Nanosponges: AN overview of the emerging novel class of drug delivery system. World J Pharmaceut Res 2019;8:957–73. https://www.academia.edu/41503039/Nanosponges_AN_OVERVIEW_OF_THE_EMERGING_NOVEL_CLASS_OF_DRUG_DELIVERY_SYSTEM

[36] Hayiyana Z, Choonara Y, Makgotloe A, Toit L, Kumar P, Pillay V. Ester-based hydrophilic cyclodextrin nanosponges for topical ocular drug delivery. Curr Pharm Des 2016;22:6988–97. https://pubmed.ncbi.nlm.nih.gov/27981908/

[37] Setijadi E, Tao L, Liu J, Jia Z, Boyer C, Davis TP. Biodegradable star polymers functionalized with beta-cyclodextrin inclusion complexes. Biomacromolecules 2009;10:2699–707. https://pubmed.ncbi.nlm.nih.gov/19663421/

[38] Elmataeeshy ME, Sokar MS, Bahey-El-Din M, Shaker DS. Enhanced transdermal permeability of Terbinafine through novel nanoemulgel formulation; Development, in vitro and in vivo characterization. Futur J Pharm Sci 2018;4:18–28

[39] Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, et al. Strategies to address low drug solubility in discovery and development. Pharmacol Rev 2013;65:315–499. https://pubmed.ncbi.nlm.nih.gov/23383426/

[40] Tiwari K, Bhattacharya S. The ascension of nanosponges as a drug delivery carrier: preparation, characterization, and applications. J Mater Sci Mater Med 2022;33:28. https://pubmed.ncbi.nlm.nih.gov/35244808/

[41] Pathan M. Nanosponges: a novel approach for targeted drug delivery. Gupta Publ; 2018. https://www.academia.edu/38201990/Nanosponges_A_Novel_Approach_for_Targeted_Drug_Delivery

[42] Jain A, Prajapati SK, Kumari A, Mody N, Bajpai M. Engineered nanosponges as versatile biodegradable carriers: an insight. J Drug Deliv Sci Technol 2020;57:101643. https://www.researchgate.net/publication/339676182_Engineered_nanosponges_as_versatile_biodegradable_carriers_An_insight

[43] Rita L, Amit T, Chandrashekhar G, Kundnani PKM. Current trends in β-Cyclodextrin based drug delivery systems. 2011

[44] Rao MRP, Bhingole RC. Nanosponge-based pediatric-controlled release dry suspension of Gabapentin for reconstitution. Drug Dev Ind Pharm 2015;41:2029–36. https://pubmed.ncbi.nlm.nih.gov/26006328/

[45] Sharma R, Walker RB, Pathak K. Evaluation of the kinetics and mechanism of drug release from econazole nitrate nanosponge loaded carbapol hydrogel. Indian J Pharm Res Educ. 2011;45

[46] Bachkar BA, Gadhe L, Battase P, Mahajan N, Wagh R. Nanosponges: a potential nanocarrier for targeted drug delivery. 2015

[47] Eldose A, Twinkle P, Honey S, Twinkle Z, Jain H, Umesh U. Nanosponge: a novel nano drug carrier. J Adv Res Pharm Biol Sci 2015;1 (ISSN 2208-2360). 01–7.

[48] Farsana P, Sivakumar R, Haribabu Y. Hydrogel based Nanosponges drug delivery for topical applications – a updated review. Res J Pharm Technol 2021;14:527–30. https://rjptonline.org/AbstractView.aspx?PID=2021-14-1-96

[49] Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. Nanosponges: a novel class of drug delivery system - review. J Pharm Pharmaceut Sci 2012;15:103–11

[50] Sherje AP, Dravyakar BR, Kadam D, Jadhav M. Cyclodextrin-based nanosponges: a critical review. Carbohydr Polym 2017;173:37–49. https://pubmed.ncbi.nlm.nih.gov/28732878/

[51] Arshad K, Khan A, Bhargav E, Rajesh Reddy K, Sowmya C. Nanosponges: a new approach for drug targetting. IJPPR 2016;7:381–96. www.ijppr.humanjournals.com

[52] Trotta F, Cavalli R. Characterization and applications of new hyper-cross-linked cyclodextrins. Compos Interfaces 2009;16:39–48. https://www.tandfonline.com/doi/abs/10.1163/156855408X379388

[53] Gidwani B, Vyas A. A comprehensive review on cyclodextrin-based carriers for delivery of chemotherapeutic cytotoxic anticancer drugs. BioMed Res Int 2015;2015:198268. https://pubmed.ncbi.nlm.nih.gov/26582104/

[54] Tejashri G, Amrita B, Darshana J. Cyclodextrin based nanosponges for pharmaceutical use: a review. Acta Pharm 2013;63:335–58. https://pubmed.ncbi.nlm.nih.gov/24152895/

[55] Swaminathan S, Vavia PR, Trotta F, Cavalli R. Nanosponges encapsulating dexamethasone for ocular delivery: formulation design, physicochemical characterization, safety and corneal permeability assessment. J Biomed Nanotechnol 2013;9:998–1007. https://pubmed.ncbi.nlm.nih.gov/23858964/

[56] Omar SM, Ibrahim F, Ismail A. Formulation and evaluation of cyclodextrin-based nanosponges of griseofulvin as pediatric oral liquid dosage form for enhancing bioavailability and masking bitter taste. Saudi Pharm J SPJ Off Publ Saudi Pharm Soc 2020;28:349–61. https://pubmed.ncbi.nlm.nih.gov/32194337/

[57] Bhowmik H, Venkatesh DN, Kuila A, Kumar KH. Nanosponges: a review. Int J Appl Pharm 2018;10:1–5

[58] Challa R, Ahuja A, Ali J, Khar RK. Cyclodextrins in drug delivery: an updated review. AAPS PharmSciTech 2005;6:E329–57. https://pubmed.ncbi.nlm.nih.gov/16353992/

[59] Kamble M, Zaheer Z, Mokale S, Zainuddin R. Formulation optimization and biopharmaceutical evaluation of imatinib mesylate loaded β-cyclodextrin nanosponges. Pharm Nanotechnol 2019;7:343–61. https://pubmed.ncbi.nlm.nih.gov/31549599/

[60] Bhattacharjee S. Polymeric nanoparticles. Princ Nanomedicine. 2019:195–240

[61] Ravi SC, Krishnakumar K, Nair SK. Nano sponges: a targeted drug delivery system and its applications. GSC Biol Pharm Sci 2019;7. https://gsconlinepress.com/journals/index.php/gscbps/article/view/340

[62] Swaminathan S, Pastero L, Serpe L, Trotta F, Vavia P, Aquilano D, et al. Cyclodextrin-based nanosponges encapsulating camptothecin: physicochemical characterization, stability and cytotoxicity. Eur J Pharm Biopharm 2010;74:193–201. https://pubmed.ncbi.nlm.nih.gov/19900544/

[63] Shringirishi M, Prajapati SK, Mahor A, Alok S, Yadav P, Verma A. Nanosponges: a potential nanocarrier for novel drug delivery-a review. Asian Pacific J Trop Dis 2014;4:S519–26. https://www.researchgate.net/publication/280290136_Nanosponges_A_potential_nanocarrier_for_novel_drug_delivery-a_review

[64] Krabicová I, Appleton SL, Tannous M, Hoti G, Caldera F, Pedrazzo AR, et al. History of cyclodextrin nanosponges. Polymers (Basel) 2020;12:1122. https://pubmed.ncbi.nlm.nih.gov/32423091/

[65] Yaşayan G, Şatōroğlu Sert B, Tatar E, Küçükgüzel İ. Fabrication and characterisation studies of cyclodextrin-based

nanosponges for sulfamethoxazole delivery. J Inclusion Phenom Macrocycl Chem 2020;97:175–86

[66] Donato ID, Lazzara G. Porosity determination with helium pycnometry as a method to characterize waterlogged woods and the efficacy of the conservation treatments. Archaeometry 2012;54:906–15. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1475-4754.2011.00657.x

[67] Devi LL. Formulation and development of losartan nanosponge capsules. Asian J Res Biol Pharm Sci;8:24–38. https://doi.org/10.36673/AJRBPS.2020.v08.i01.A05

[68] Salunke A, Upamanyu DN, Pandey AK, Rawat PK. Nanosponges: a recent technology for Nanomedicine. Pharm Innov 2019;8:703–9. https://www.thepharmajournal.com/archives/?year=2019&vol=8&issue=5&ArticleId=3496

[69] Moya-Ortega MD, Alvarez-Lorenzo C, Concheiro A, Loftsson T. Cyclodextrin-based nanogels for pharmaceutical and biomedical applications. Int J Pharm 2012;428:152–63. https://pubmed.ncbi.nlm.nih.gov/22388054/

[70] Alongi J, Poskovic M, Frache A, Trotta F. Role of β-cyclodextrin nanosponges in polypropylene photooxidation. Carbohydr Polym 2011;86:127–35

[71] Cavalli R, Trotta F, Tumiatti W. Cyclodextrin-based nanosponges for drug delivery. J Inclusion Phenom Macrocycl Chem 2006;56:209–13. https://link.springer.com/article/10.1007/s10847-006-9085-2

[72] Mateo C, Palomo JM, Fernandez-Lorente G, Guisan JM, Fernandez-Lafuente R. Improvement of enzyme activity, stability and selectivity via immobilization techniques. Enzym Microb Technol 2007;40:1451–63. https://www.researchgate.net/publication/222340597_Improvement_of_enzyme_activity_stability_and_selectivity_via_immobilization_techniques

[73] Sapino S, Carlotti ME, Cavalli R, Ugazio E, Berlier G, Gastaldi L, et al. Photochemical and antioxidant properties of gamma-oryzanol in beta-cyclodextrin-based nanosponges. J Inclusion Phenom Macrocycl Chem 2013;75:69–76. https://link.springer.com/article/10.1007/s10847-012-0147-3

[74] Kroll AV, Fang RH, Zhang L. Biointerfacing and applications of cell membrane-coated nanoparticles. Bioconjug Chem 2017;28:23–32. https://pubmed.ncbi.nlm.nih.gov/27798829/

[75] Yoo JW, Irvine DJ, Discher DE, Mitragotri S. Bio-inspired, bioengineered and biomimetic drug delivery carriers. Nat Rev Drug Discov 2011;10:521–35. https://pubmed.ncbi.nlm.nih.gov/21720407/

[76] Peppas NA. Intelligent therapeutics: biomimetic systems and nanotechnology in drug delivery. Adv Drug Deliv Rev 2004;56:1529–31. https://pubmed.ncbi.nlm.nih.gov/15350286/

[77] Fang RH, Jiang Y, Fang JC, Zhang L. Cell membrane-derived nanomaterials for biomedical applications. Biomaterials 2017;128:69–83. https://pubmed.ncbi.nlm.nih.gov/28292726/

[78] Sellergren B, Allender CJ. Molecularly imprinted polymers: a bridge to advanced drug delivery. Adv Drug Deliv Rev 2005;57:1733–41. https://pubmed.ncbi.nlm.nih.gov/16253386/

[79] Silpa JN, Nissankararao S, Bhimavarapu R, Siddhartha S. Nanosponges: a versatile drug delivery system. 2013

[80] Lembo D, Swaminathan S, Donalisio M, Civra A, Pastero L, Aquilano D, et al. Encapsulation of Acyclovir in new carboxylated cyclodextrin-based nanosponges improves the agent's antiviral efficacy. Int J Pharm 2013;443:262–72. https://pubmed.ncbi.nlm.nih.gov/23279938/