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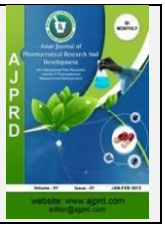

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Review Article

# Polymeric Nanosponges: A Promising Platform for Improving Roflumilast Solubility

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## A B S T R A C T

The drug roflumilast, a selective phosphodiesterase-4 enzyme inhibitor that can be used to treat persistent obstructive lung disease (COPD), has limited therapeutic potential due to its poor solubility and bioavailability. The aim of this literature review is to provide an overview of polymeric nanosponges as a novel drug delivery mechanism to enhance the solubility/bioavailability of roflumilast in vivo/vitro. Nanosponges are a type of nanocarrier that can be used to deliver poorly soluble drugs by encapsulating (i.e. solubilizing) these drugs—enhancing drug stability and providing zero order-controlled release. This review examines the fundamental properties of nanosponges including the different types of nanosponges, the preparation methods used to create them, and characterization methods. The role of nanosponges in improving the solubility of roflumilast by increasing surface area, molecular dispersion, and amorphous nature will also be discussed. Several formulation strategies and factors influencing the performance of nanosponges will also be covered. Finally, examples of in vitro and in vivo experiments that show improved solubility/bioavailability of roflumilast using nanosponges will also be presented in this review. In addition, advances in research related to targeted delivery, responsive to stimuli, and environmentally friendly synthesis of nanosponges will be discussed. Although there are barriers to the scale-up production of nanospounges and translational use in the clinic, the potential of polymeric nanosponges as a practical and versatile tool for advancing the therapeutic effectiveness of poorly soluble drugs like roflumilast is considerable.

**Keywords:** Roflumilast, Polymeric nanosponges , Solubility enhancement, Drug delivery system , COPD therapy ,Bioavailability

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## INTRODUCTIONS

The development of effective pharmaceutical formulations for poorly water-soluble drugs remains one of the biggest challenges today for drug delivery systems. A significant number of new drug molecules that are discovered fall under the Biopharmaceutics Classification System (BCS) Class II, which have low aqueous solubility and high permeability, resulting in low and variable oral bioavailability (1,2). Roflumilast is a selective phosphodiesterase-4 (PDE-4) inhibitor used for treating chronic obstructive pulmonary disease (COPD), but due to its hydrophilic property and slow dissolving rate in the gastrointestinal tract, it exemplifies these limitations with respect to its therapeutic effects compared to its potential toxicities; in addition to the fact that due to a lack of solubility, therapeutic efficacy will be limited, and higher doses will be needed to achieve adequate responses, therefore increasing the risk of adverse drug effects. Therefore, it has now become a priority for the industry to improve the solubility and dissolution characteristics of these types of drugs. (1,3)

Numerous traditional and modern approaches have been explored to develop pharmaceutical formulations for overcoming solubility difficulties. Some of these include creating salts of the drug, creating solid dispersions of the drug in another material, complexing drugs with other agents, micronizing drug particles into smaller sizes, and formulating lipid-based dosage forms. However, the above approaches have challenges including, but not limited to: physical stability (e.g., drug is in the crystalline state and may undergo recrystallization), limitations on the amount of drug that can be contained in a container (e.g., low drug loading), and problems that arise when attempting to scale up

the manufacturing of drug products using the above approaches. More recently, the use of nanotechnology for drug delivery has emerged as a promising new area for enhancing the solubility and bioavailability of hydrophobic drug compounds. Uses of nanoparticles, liposomes, nanoemulsions, and nanocrystals are all examples of nanotechnology-based processes that enhance the solubility of compounds by decreasing the size of drug particles (to increase their surface area) or modifying the drug's crystalline structure (to an amorphous form). Nanocarrier systems have advantages when compared to the above processes in terms of controlling the release rate of drugs, targeting specific tissues, and improving drug pharmacokinetics (3,4,5).

Cross-linked polymeric networks are novel nanoscale polymeric nanocarriers composed of a three-dimensional porous network capable of compartmentalizing lipophilic drug molecules. These nanoscale carriers have several unique benefits, including increased drug capacity, enhanced stability, controlled delivery rates and improved dissolution of the drug. In particular, by physically entrapping drug molecules in their porous matrix, nanosponges can significantly boost the apparent solubility and dissolution rates of poorly soluble drugs (e.g. Roflumilast). Their tunable properties also enable improvement in drug delivery performance through variation of the polymer type and the degree of cross-linking. A growing body of research indicates that polymeric nanosponges may be an effective means of overcoming solubility challenges and enhancing the therapeutic efficacy of hydrophobic pharmaceuticals. (5,4).

## Roflumilast: Physicochemical and Biopharmaceutical Profile

Roflumilast is a selective phosphodiesterase-4 inhibitor, which is very effective in the reduction of inflammation. It is primarily used in the treatment of chronic obstructive pulmonary disease (COPD). It is lipophilic in nature, has a complex aromatic ring, and contains fluoro and methoxy groups, which make it very difficult to dissolve in water. It has high permeability but very low solubility in water, which indicates that the compound falls under the BCS Class II drugs. The physicochemical properties of the compound, which include high lipophilicity (log P) and crystalline nature, play an important role in the solubility and bioavailability of the compound. The compound can be said to be suitable for formulation techniques in which the solubility of the compound has to be improved so that it can be dissolved quickly.(6,7)

One of the major problems associated with roflumilast was that it did not dissolve well in water, which meant that it would take a long time to dissolve in the stomach, thus limiting how well it could be absorbed through the mouth. The solubility problem, therefore, implies that there would be a variation in the bioavailability of this drug, and higher doses would be required to achieve therapeutic plasma concentrations. From a biopharmaceutical perspective, roflumilast was metabolized in the liver extensively, mainly by cytochrome P450 enzymes, including CYP3A4 and CYP1A2. This led to an active metabolite, roflumilast N-oxide, which was a major component of its pharmacological activity. The drug has moderate oral bioavailability, a relatively long half-life, which enables once-daily dosing. Variations in how well it was absorbed and how rapidly it was metabolized could alter its pharmacokinetic profile(8,9)

Hydrophobicity, poor wettability, and crystalline form of roflumilast are considered to be the main causes of its formulation problems. Apart from its pharmacological limitations, dose-dependent side effects can occur due to changes in plasma concentrations during treatment, such as gastrointestinal disturbances and weight loss. In this case, it may be necessary to develop innovative drug delivery systems for this drug, which can enhance its solubility, release rates, and therapeutic activity. One possible approach would be to apply nanotechnology, such as "polymer nanosponges," to enhance drug dispersion and dissolution rates. (8,10).

## Overview of Nano sponge

Nanosponges are advanced drug delivery systems that are nano-sized and have the ability to encapsulate a wide variety of drug molecules. Nanosponges are formed through the cross-linking of polymers or cyclodextrins, giving them the characteristic sponge-like structure with many cavities. The high porosity enables the entrapment of hydrophobic drugs, shielding them from degradation and increasing their solubility. The nanoscale nature and high surface area of nanosponges increase the solubility and interaction of the drug with the biological membranes, hence increasing the bioavailability. The ability of nanosponges to carry hydrophobic as well as hydrophilic drugs makes them an important drug delivery system (11).

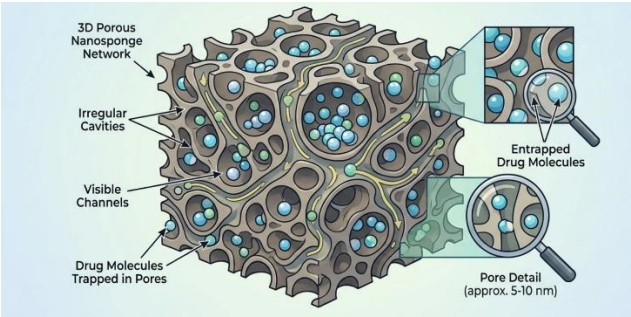


**Figure 1:** 3D porous structure of Nanosponge

Nanosponges can be classified into different types based on composition and method of preparation. Polymeric nanosponges are prepared from synthetic or natural polymers, such as polyesters, ethyl cellulose, and Eudragit, to ensure controlled release and structural integrity. Cyclodextrin-based nanosponges are prepared through cross-

linking cyclodextrin, a compound that includes a hydrophobic cavity and is capable of forming inclusion complexes with the drug, hence improving solubility and stability. Furthermore, hybrid nanosponges are a mixture of both polymeric and cyclodextrin-based nanosponges, hence improving functionality such as targeting and increased capacity for the drug. The type of nanosponge is often based on the physicochemical properties of the drug and the release pattern required (12).

Nanosponges have several advantages, and they are most suitable for drug delivery systems. First, nanosponges improve solubility, especially for poorly water-soluble drugs, by incorporating them into a porous structure and converting them into an amorphous or molecularly dispersed form. Second, nanosponges enable controlled and sustained release, thus maintaining therapeutic levels of a drug for a longer period. Third, nanosponges improve drug stability by shielding the incorporated drug from environmental degradation, such as exposure to heat, light, and oxidation. Lastly, nanosponges reduce the toxicity associated with a drug, especially when a controlled release mechanism minimizes peak plasma concentrations and side effects (13)

Despite the advantages, nanosponges have some limitations that need to be overcome to make them clinically relevant. The first major limitation is the scale-up problem, as the reproducibility and uniformity may not be easily achieved. The use of organic solvents in the preparation methods is also a major limitation, as the toxicity of the solvents is a major problem, and hence the need for the purification process. The cost factor is also an important limitation, as the cost may be high because of the use of special polymers and cross-linkers, as well as the techniques used (14,15).

## Polymeric Nanosponges

Nanosponges are a new form of nanosized drug delivery systems that are described as highly porous three-dimensional networks that are capable of encapsulating a broad range of active agents. Nanosponges are generally produced through cross-linking polymers or cyclodextrins, resulting in a structure that resembles a sponge and is comprised of nano-sized cavities. The highly porous nature of nanosponges is such that these systems are capable of encapsulating both lipophilic and hydrophilic compounds, and this is one major reason why nanosponges are used to improve the solubility of poorly soluble compounds. The nano-sized nature of nanosponges, coupled with a high surface area, is such that these systems are capable of improving the solubility and interaction of poorly soluble compounds, hence improving the bioavailability of these compounds(16,17)

From a structural point of view, nanosponges have been described as an interconnected matrix of polymers with cavities and channels where drugs can be trapped through non-covalent interactions like van der Waals forces, hydrogen bonding, and hydrophobic interactions. The structural advantages of nanosponges allow for efficient encapsulation of drugs and protect the API from environmental degradation, such as light, heat, and oxidation. In addition, nanosponges can be used for sustained release of drugs through the slow diffusive release of encapsulated drugs. These advantages of nanosponges make it a highly promising tool in advanced drug delivery systems, especially for hydrophobic drugs like roflumilast. (18,19,20)

## Preparation Methods Polymeric Nanosponges

### Solvent Method

The solvent method is one of the most commonly used techniques in the preparation of polymeric nanosponges, which is based on the principle of cross-linking the polymer in an organic solvent medium. In the solvent method, the polymer is first dissolved in an appropriate organic solvent, such as dimethylformamide or dichloromethane, followed by the addition of an appropriate cross-linking agent under appropriate temperatures with constant stirring. This results in the formation of a three-dimensional porous nanosponge network. Finally, the product is purified, and the nanosponges are dried. The advantages of the solvent method include simplicity, control of the particles, and high efficiency in the loading of the drugs. The limitations of the solvent method include the use of toxic organic solvents, the need to purify the product, and the toxicity of the solvents, which may pose challenges in the future in the field of pharmacy. (21)

### Emulsion Solvent Diffusion Method

The emulsion solvent diffusion method is based on the principle of the diffusion of an organic solvent into an aqueous phase, and as a result, nanosponges are formed. In the emulsion solvent diffusion method, the organic solvent, along with the polymer and drug, is taken and emulsified into an aqueous phase, usually containing a stabilizer, using high-speed stirring. During the process, the organic solvent diffuses into the aqueous phase, and the polymer forms nanosponge particles. The nanosponge particles are collected, washed, and dried. The emulsion solvent diffusion method offers the advantage of better control over the particle size, distribution, and high entrapment efficiency. However, optimization of the parameters is important, and the presence of surfactants requires additional purification. In addition, the process is complex, making the scale-up difficult. (22,23)

### Ultrasound-Assisted Synthesis

Ultrasound-assisted synthesis is a technique where ultrasonic energy is employed to aid in the formation of polymeric nanosponges. In this technique, ultrasonic energy is utilized for efficient mixing and cross-linking of nanosponges. The mechanism of this technique involves the creation of cavitation bubbles, which generate high Temperature 'and pressure conditions for efficient nanosponge formation. In this technique, a mixture of monomer and cross-linking agent is subjected to ultrasonic energy for a particular time interval. The nanosponges thus formed are collected and dried. The advantages of this technique include reduced reaction time, formation of smaller-sized nanosponges, and minimal thermal degradation of drugs. However, some disadvantages of this technique include equipment requirements, degradation of some polymers due to high-intensity ultrasonic energy, and scalability issues for industrial applications.. (24).

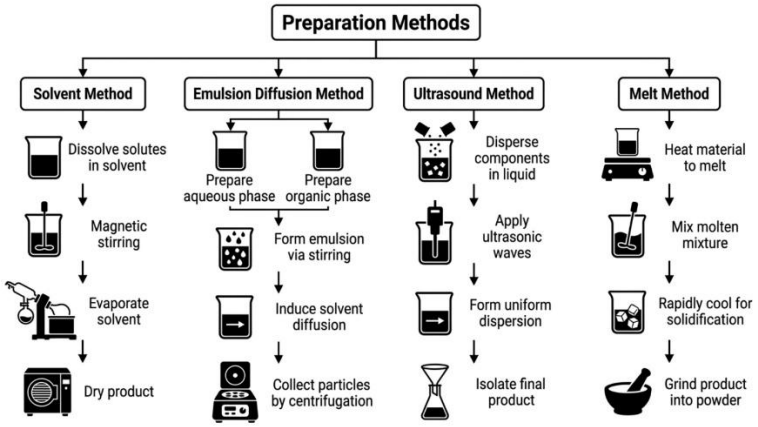


**Figure 2:** Preparation Methods

## Melt Method

The melt method is a solvent-free method that is based on the principle of the thermal cross-linking reaction of the polymer. In this method, the polymer and the cross-linking agent are mixed and heated above the melting point, and the reaction is allowed to take place. The mixture is then cooled and solidified, and the nanosponge is ground and sieved. The advantages of this method are that it is an environmentally friendly method as the organic solvents are avoided, and the chances of toxicity are reduced. Moreover, the method is simple and cost-effective. However, the major limitation is that the method may not be applicable to thermolabile drugs and polymers, as they degrade at high temperatures. Moreover, the method may not be easy in controlling the particle sizes and making them uniform compared to other methods.25)

## Characterization Techniques of Polymeric Nanosponges

Physicochemical characterization of polymeric nanosponges is a significant factor in the assessment of the potential of the polymeric nanosponges as a carrier of drugs. Particle size and size distribution are of significant importance in the assessment of the release of the drug, solubility enhancement, and bioavailability of the drug. Particle size and size distribution are generally assessed using a technique called dynamic light scattering (DLS). During this technique, the smaller the size of the particles, the greater the surface area of the particles exposed to the solvent system, which increases the dissolution rates of the particles. Zeta potential is another significant factor in the assessment of the stability of the nanosponge suspensions. The greater the absolute value of the zeta potential of the nanosponge suspensions, the greater the stability of the suspensions (26,27)

Morphological characterization is done using scanning electron microscopy and transmission electron microscopy. These techniques give an idea about the surface morphology and internal architecture of nanosponges. Scanning electron microscopy is used to study the surface morphology of nanosponges. Transmission electron microscopy is used to study the internal architecture of nanosponges. Fourier Transform InfraRed Spectroscopy is used to study the drug polymer compatibility. This is done by observing the characteristic peaks. If peaks are observed, it indicates that the drug and polymer are chemically incompatible. Since no peak is observed, the drug and polymer are chemically compatible. (28,29)

Differential Scanning Calorimetry (DSC) is employed to evaluate the physical state of the drug in the nanosponge matrix. DSC can be utilized to confirm if the drug is in the crystalline state or has been converted into an amorphous state, which is commonly linked to solubility enhancement. Moreover, the drug loading capacity and entrapment efficiency are two other parameters that are very important in defining the amount of the drug that has been successfully entrapped in the nanosponges. In most cases, these two parameters are evaluated using techniques such as UV spectroscopy or HPLC after separating the free drugs from those entrapped in the nanosponges. The high values of these parameters are desirable in the formulation of nanosponges, which can be effective in the treatment of diseases while using the least amount of the drugs in the formulation.(30)

## Solubility Enhancement Mechanism

Polymeric nanosponges have been found to increase the solubility and the rate of dissolution of poorly soluble drugs through multiple mechanisms, namely increased surface area, amorphization, and improved wettability. The nanosponge drug carriers have the advantage of possessing an extremely large surface area, as the nanoscale dimension provides an extremely large surface area-volume ratio, thereby facilitating the interaction between the drug and the dissolution medium, and hence accelerating the rate of drug dissolution as per the Noyes-Whitney equation. Moreover, the drug is present in an amorphous state as opposed to the crystalline state, as the drug is dispersed in the nanosponge matrix. The amorphous form is characterized by high energy and the absence of a crystalline lattice, and hence the solubility and rate of dissolution are increased as compared to the crystalline form. The transition from the crystalline to the amorphous form is the major factor responsible for the improved drug release profile(31-35)

In addition, the wettability and dispersibility of hydrophobic drugs are improved by the interaction with hydrophilic polymeric networks, thus creating an opportunity for interaction with biological fluids. The drug is released faster because the penetration of the dissolution medium is facilitated by the porous nature of the nanosponge, hence faster drug diffusion. The interaction between the drug and the polymer, through the formation of hydrogen bonds and

van der Waals forces, helps in the solubilization of the drug, thus preventing its aggregation and recrystallization. All these mechanisms play an important role in the improvement of the solubility and bioavailability of drugs, hence the importance of the use of polymeric nanosponges as an innovative approach to the solubility improvement of drugs, especially roflumilast, in the management of COPD. (61-64)

## Application of Polymeric Nanosponges for Roflumilast

The development of roflumilast-loaded polymeric nanosponge formulations is largely dependent on the selection of appropriate polymers and optimization of the parameters involved in the process. Ethyl cellulose, poly(lactic-co-glycolic acid) (PLGA), and Eudragit are some of the most commonly used polymers, as they are biocompatible and have the potential to form cross-linked networks. The type of polymer is found to affect the particle size, drug loading capacity, and release profile of the drug. Moreover, the selection of an appropriate cross-linking agent and method, such as the emulsion solvent diffusion method, is found to play an important role in the development of nanosponge formulations. Optimization of the drug/polymer ratio is considered to be an important factor, as the ratio is found to affect the drug release profile. Increasing the polymer concentration is found to enhance the entrapment efficiency, but the drug release is slowed down, and the particle size is increased, hence requiring optimization. (38).

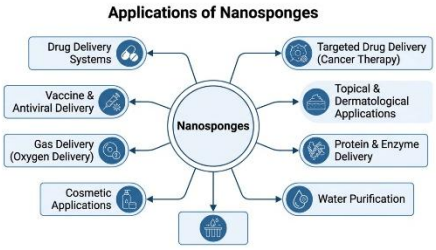


**Figure 3:** Applications of Nanosponges

Polymeric nanosponges are found to increase the solubility of roflumilast through several mechanisms. The large surface area offered by the nanoscale particles is found to increase the solubility of the drug by maximizing the interaction with the dissolution medium. The drug is also found to be in the molecularly dispersed state, thus avoiding the problem of poor wettability and aggregation of the drug crystallites. The second mechanism is amorphization, in which the drug is converted from the crystalline form to the amorphous form, thus increasing the solubility and the rate of dissolution. The combined effect is the significant increase in the solubility and the rate of dissolution of the drug. (39,40)

In vitro studies have shown that roflumilast-loaded nanosponges have a higher rate of dissolution compared to pure drug and other formulations. The porous nature and hydrophilicity of the nanosponges ensure rapid drug release in simulated gastrointestinal fluids. (46, 47) The in vivo studies have also shown that nanosponge formulations of roflumilast have better oral bioavailability, and this has been attributed to better absorption. The pharmacokinetic parameters, such as Cmax and AUC, have been shown to be significantly increased. Moreover, better pharmacodynamic effects, including reduced airway inflammation and reduced frequency of exacerbations, have been observed after using roflumilast, which has been attributed to the controlled release of the drug. (48,49,50)

Polymeric nanosponges also have a number of advantages when compared to other nanocarrier formulations such as liposomes, solid lipid nanoparticles, and nanocrystals. For instance, liposomes are biocompatible and can effectively encapsulate a drug, but they also present a problem related to stability, such as leakage and shelf life. On the other hand, solid lipid nanoparticles are able to effectively control the release and improve stability, but they may also present problems such as limitations in drug loading and expulsion during storage. Lastly, nanocrystals are able to improve solubility through a reduction in size, but they are not able to control the release and protect the drug from degradation. However, polymeric nanosponges are able to effectively improve solubility, stability, control release, and protect the drug from degradation, making them a more efficient nanocarrier system for hydrophobic drugs such as roflumilast (52-55)

## Factors Affecting Nanosponge Performance

The efficiency of polymeric nanosponges is affected by several factors, especially with regard to the drug release and efficiency. The nature of the polymer used is one of the important factors that define the integrity of the nanosponge drug delivery system. Polymers used in nanosponges, such as ethyl cellulose, PLGA, and Eudragit, have different physicochemical properties. These properties have been shown to influence the efficiency of drug release. Moreover, the density of cross-linking is also an important factor that affects the internal architecture of the nanosponges. High-density cross-linking is known to produce more compact nanosponges with small pore sizes, thus slowing down the rate of drug release. (41,42,)

Another crucial aspect is the concept of drug loading, which refers to the amount of the drug entrapped in the nanosponge matrix. The optimal amount of the drug is essential to ensure efficient delivery while avoiding instability, including leakage of the drug from the nanosponge matrix. (43) The method of preparation is another aspect affecting the nanosponge formulation, including the size, shape, and entrapment efficiency, as the method of preparation, including the solvent method or emulsion diffusion, allows varying control over the parameters. Particle size is another critical aspect affecting solubility enhancement and bioavailability, as smaller particles will provide a larger surface area, thus increasing the rate of solubility and

absorption. However, smaller particles may cause aggregation, which must be addressed appropriately. Hence, optimization of these parameters is critical to develop an efficient, stable, and reproducible nanosponge-based drug delivery system (44,45).

**Table 1:** Factors influencing the performance of polymeric nanosponges

| Factor | Description | Impact on Nanosponge Performance |
|---|---|---|
| **Polymer Type** | Nature and properties of polymer used (e.g., ethyl cellulose, β-cyclodextrin) | Influences drug compatibility, encapsulation efficiency, and release behavior |
| **Cross-linking Density** | Degree of cross-linking between polymer chains | Higher density reduces pore size and slows drug release; lower density increases release rate |
| **sDrug Loading** | Amount of drug incorporated into nanosponges | Affects entrapment efficiency and release profile; excessive loading may cause drug leakage |
| **Preparation Method** | Technique used (solvent method, emulsion diffusion, etc.) | Determines particle size, morphology, and uniformity |
| **Particle Size** | Size of nanosponge particles | Smaller size increases surface area, enhancing solubility and dissolution rate |
| **Solvent Type** | Organic solvent used during preparation | Affects polymer solubility and formation of nanosponge structure |

## Recent Advances and Research Trends

Recent developments in nanosponge technology have focused on improving functionality, specificity, and sustainability of drug delivery systems. One of the key advancements is the design of stimuli-responsive nanosponges, which can release the encapsulated drug in response to specific triggers such as pH, temperature, enzymes, or redox conditions. These smart systems enable site-specific and controlled drug release, thereby enhancing therapeutic efficacy while minimizing systemic side effects. For instance, pH-sensitive nanosponges can selectively release drugs in acidic environments such as inflamed tissues or tumor sites, making them highly promising for precision medicine applications. (16,33,).

**Table 2:** Recent Advances and Research Trends in Polymeric Nanosponges

| Trend | Description | Impact on Drug Delivery |
|---|---|---|
| **Stimuli-Responsive Nanos** | Designed to release drug in response to triggers such as pH, temperature, enzymes, or redox conditions | Enables site-specific and controlled drug release, improving therapeutic efficacy and reducing side effects |
| **Targeted Drug Delivery** | Surface functionalization with ligands (antibodies, peptides, folic acid, etc.) for specific tissue targeting | Enhances drug accumulation at target site and minimizes off-target toxicity |
| **Green Synthesis Methods** | Use of eco-friendly solvents, biodegradable polymers, and solvent-free techniques | Reduces environmental impact and improves safety and regulatory acceptance |
| **Combination Therapy** | Co-encapsulation of multiple drugs within nanosponges | Provides synergistic therapeutic effects, especially in chronic diseases |
| **Hybrid Nanosponges** | Integration with other nanocarriers (lipid-based, metallic nanoparticles) | Improves multifunctionality and delivery efficiency |

Another significant trend involves the concept of drug delivery systems, where nanosponges are functionalized with drug-delivery moieties like antibodies or peptides to specifically target diseased tissues or cells. Such drug delivery systems have been reported to enhance drug accumulation at the site of action. In another significant trend, researchers have been exploring green synthesis approaches for nanosponges, where materials and techniques are being developed to reduce the use of hazardous chemicals and energy consumption during synthesis. These approaches have been reported to be more environmentally friendly, thus aligning with regulatory requirements. In another interesting trend, combination therapy approaches have been proposed for nanosponges, where multiple drugs with synergistic properties can be delivered to combat complex diseases. These findings clearly indicate the potential of polymeric nanosponges for drug delivery systems. (47-49)

## Future prospectives

The future of polymeric nanosponges in drug delivery largely relies on the successful scale-up and commercialization of such formulations. Although studies carried out on nanosponges in a laboratory setting have shown promising results, for such formulations to be scaled up and commercialized, several challenges associated with reproducibility, cost-effectiveness, and optimization of processes during large-scale production are likely to be addressed. Furthermore, the development of standardized protocols and quality control measures would be important in ensuring batch uniformity and stability of nanosponge formulations. (51)

Another area where nanosponges are finding increased attention is in personalized medicine, where drug delivery systems can be designed according to individual patient needs, disease conditions, and genetic information. In this regard, it can be stated that various properties of polymeric nanosponges can be adjusted according to individual patient needs. Despite all these advantages, there are various clinical translation

challenges associated with nanosponges, such as a lack of in vivo data, possible toxicity issues, and strict regulatory guidelines for nanomedicines. In conclusion, it can be stated that overcoming all these challenges will be crucial for the clinical application of polymeric nanosponges and further transformation of nanosponges into commercially viable drug delivery systems. (56-57)

## CONCLUSION

In this context, polymeric nanosponges have been recognized as a highly promising and versatile approach in drug delivery technology to overcome the problems associated with poorly water-soluble drugs, including roflumilast. The porous structure, high surface area, and ability of polymeric nanosponges to encapsulate hydrophobic drugs enhance solubility, dissolution rate, and bioavailability. The molecular dispersion and amorphization capabilities of polymeric nanosponges effectively overcome one of the major limitations of roflumilast, thereby enhancing its therapeutic performance. Moreover, the versatility of polymeric nanosponges in terms of polymers, cross-linking density, and formulation techniques enables precise control over drug targeting and release profiles. The superiority of polymeric nanosponges has been demonstrated in comparison with conventional drug delivery systems, including liposomes, solid lipid nanoparticles, and nanocrystals, in terms of stability, controlled drug release, and reduced toxicity. Despite the advantages, several issues remain to be addressed.In essence, the inclusion of nanosponges in the drug delivery system of roflumilast is an important breakthrough in the application of nanotechnology in the field of pharmaceuticals. With continued studies and investigations into the development of novel methods of synthesizing nanosponges, the potential for the application of nanosponges in the development of drug delivery systems is high, especially in the management of COPD.

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