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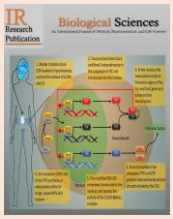

Nanosponges- An emerging trend in drug delivery

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ABSTRACT

Advancements in pharmaceutical research have led to the discovery of nanosized drug delivery systems that act as a means to deliver drugs at the target site. The nanosized carriers are studied for the diagnosis (biomarkers), prevention (prophylactic therapy), and treatment of the diseases. Nanosponges an offshoot of nanotechnology have gained upstream because of their unique structural properties. It is a tiny sponge made up of either organic or inorganic material with wide cavities between them. Gases, micromolecules, and macromolecules of both hydrophobic and hydrophilic in nature can be entrapped in the structure. Progress in the research has led to the development of four generations of nanosponges namely, plain nanosponges, modified nanosponges, stimuli-activated nanosponges, and molecularly imprinted nanosponges. They offer the advantages of a sustained-release profile, better bioavailability, and negligible toxicity. The present review provides brief information on the structural features, different generations, methods of preparation, characterization techniques and application of nanosponge formulation

Introduction

Nanotechnology, a forthcoming and integrated part of the science and technology field has numerous applications in the field of medicine and healthcare system. Nanomedicine an upshot of nanotechnology includes the physical study, chemical interactions, and biological activity of the drugs involved in the nanometric scale for the early detection and prevention of ailments. Various drug delivery forms include nanoparticles (1), nanoemulsion (2), niosomes (3), nanomicelles (4), nanodendrimers, and nanosponges (5). Target oriented delivery of therapeutic agents with improved therapeutic efficacy, optimized dosage regimen, and reduced adverse effect is the new interest in the area of drug delivery systems. Targeted delivery infers to the efficient and selective localization of therapeutic agents at the predefined site of action in threshold concentration without affecting non-targeted cells, thus minimizing the toxic effects. Effective targeted drug delivery system is the key obstacle faced by the researchers recently. Invention of new complex colloidal carrier, namely nanosponges, has the significant potential to overcome these obstacle.

Nanosponges are colloidal structures made of cross-linked polymers and its distinctive structural features include minute particles along with cavities in the nanomeric range (6,7). They are porous, non-toxic,

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List of abbreviation: *MIPS: Molecularly imprinted polymers; DMF: Di-methylformamide; DMS: Dimethylsulfoxide; PVA: Polyvinyl alcohol; PDI: Polydispersity index; UV: Ultraviolet; HPLC: High performance liquid chromatography; DTA: Differential Thermal Analysis; DSC: Differential Scanning Calorimetry; FTIR: Fourier Transform infrared; BCS: Biopharmaceutical classification system; BSA: Bovine serum albumin; MCF-7: Michigan Cancer Foundation-7.*

biocompatible, solid, and roughly spherical in shape with three-dimensional networks and tiny cavities that have the ability to encapsulate a wide range of therapeutic agents. Nanosponges have gained considerable attention because of their unique structure and numerous advantages that include their incredible ability to be able to improve solubility and deliver both hydrophobic and hydrophilic drugs as well as proteins, antibodies, vaccines, enzymes, and, biocatalysts (8). These nanosized sponges have the cavity to encapsulate the therapeutic agents and special chemical "linkers" to covalently bond with the targeted cells. They circulate in the body till target cells are not encountered, where they either adsorb or seep into the cell and release therapeutic agents in a predictable and controlled manner. Both organic and inorganic compounds are used for its synthesis and this delivery form gains superiority over others because of its remarkable absorption properties although its structure consists of high porosity (9). The complex structure of nanosponges is basically the build-up of polymers that are covalently bonded with cross-linkers to form tiny mesh-like structures. The nature of polymers used in nanosponge preparation may influence the cross-linking and hence the performance of nanosponges. Alteration in the proportion of the cross-linker to the polymer can be used to control the particle size of nanosponges (10). The list of cross-linker and polymers used in the synthesis of nanosponges is summarized in Table 1. Nanosponges are encapsulating nanoparticles that can be administered through oral, topical, parenteral, and inhalation routes. The oral dose can be the dispersion of nanosponges in the matrix of suitable diluents, excipients, and lubricants used in the fabrication of capsules or tablets whereas, the parenteral dose may be the simple mixture of nanosponges in saline or sterile aqueous solutions. Popularly developed nanosponges are titanium nanosponges (11), silicon, polystyrene (12,13), cyclodextrin (14–16), etc. The most common of all the types are cyclodextrin nanosponges (17). Structurally they are oligosaccharides with a hydrophobic core. Glucopyranose units are arranged in a cyclic structure capable of forming complexes with the guest moieties.

Advancement in the research has led to the classification of cyclodextrin nanosponges into four generations. The foremost generation is plain nanosponges. They are further divided into four based on the linking group between the cyclodextrin molecule and the cross-linker. They are the urethane group, carbonate group, ester group, and ether group. The next generation is the "modified nanosponges" which exhibit special properties such as fluorescence, and carboxylation by reacting with an organic cyclic anhydride or by exhibiting electrical charge. Stimuli-activated nanosponges are the next generation which responds according to external stimuli such as a change in pH behaviour or temperature-activated nanosponges. The last generation is the "MIPS- molecularly imprinted polymers" which are specifically targeted to certain molecules (9).

Table 1. List of chemicals used in the synthesis of nanosponges.

Polymers	Cyclodextrins and their derivatives such as β Cyclodextrins, alkyloxycarbonyl Cyclodextrins, hyper cross-linked polystyrenes,
Co-polymers	Ethylcellulose, polyvinyl acetate, and poly (valerolactoneallylvalerolactone)
Cross-linkers	Diaryl carbonates, diphenyl carbonates, pyromellitic anhydride, epichloridine, glutarldehyde, carboxylic acid dianhydrides, dichloromethane and carbonyldiimidazoles
Apolar solvents	Dimethylformamide, dimethylacetamide and ethanol

Advantages of Nanosponges (18,19)

1. Entrapment of a wide range of therapeutics, both hydrophilic and hydrophobic drugs and reduced adverse effects.
2. Mask the unpleasant flavors and convert liquid dosage form into solid dosage form by incorporating immiscible liquids.
3. Encapsulation of therapeutic agents into the cavity of the nanosponge prevents it from environmental damage and degradation.

4. Improved stability and solubility of poorly water-soluble drugs.
5. Site-specific targeted delivery of the therapeutic agents in a controlled and predictable manner.
6. Non-irritating, non-allergic, non-toxic, and non-allergic.
7. Cost-effective and improved tolerance leads to better patient compliance.
8. Extended-release of drugs up to 12 hours.
9. Better physical, thermal (temperature up to 130℃), and chemical stability.
10. Self-sterilizing nature as bacteria cannot penetrate inside due to micron size pores (0.25µm).

Preparation of nanosponges

Solvent method

The polymer is mixed in a polar (greater dipole moment) aprotic solvent such as DMF (dimethylformamide) or DMS (dimethylsulfoxide). This is added to an excessive cross-linker solution. The molar ratio of the cross-linker and the polymer should be in the ratio of 4-16, preferably the reaction is carried up to 48 hours at a temperature ranging from 100 ℃ to the reflux temperature of the solvent (fig. 1). Commonly used cross-linkers are dimethyl carbonate and carbonyl di imidazole. At the end of the reaction, the mixture is cooled to room temperature and then the product is retrieved by vacuum filtration and later by soxhlet purification. Afterward, the product is vacuum-dried and ground in the mill to get homogenous powder (20).

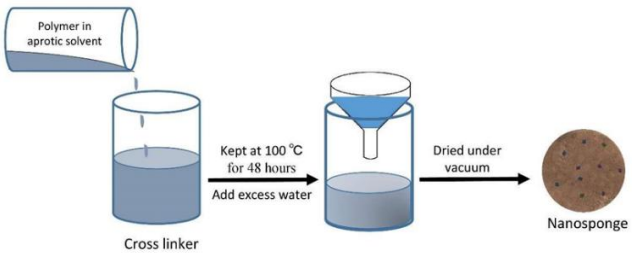

Figure 1. Nanosponge preparation by solvent method.

Emulsion-solvent diffusion method

Different ratios of ethyl cellulose and polyvinyl alcohol (PVA) are employed to improve the release of the drug for a prolonged time. A definite quantity of 100 polyvinyl alcohol is added to the aqueous external phase. The drug and the polymer are dissolved in 20ml of dichloromethane, this is slowly added to the former solution with the help of a magnetic stirrer at a rate of 10001500 rpm. the product is then dried in a hot air oven at around 40 ℃ and then stored in an airtight container as shown in Fig. 2 (21).

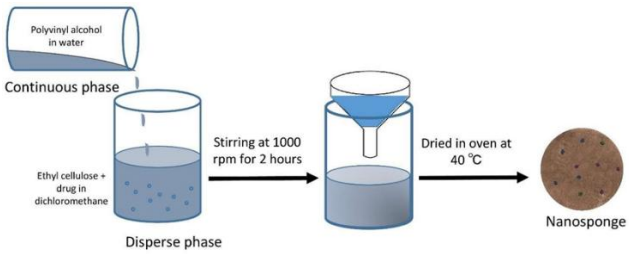

Figure 2. Nanosponge preparation by emulsion solvent diffusion method.

Ultrasound-Assisted synthesis

Polymers are directly made to react with the cross-linking agent. No solvent is involved, the solution is sonicated at 90℃ for 5 hours. The product obtained is cooled, and washed after removing the excess of the polymer (fig.3). Further purified by soxhlet extraction, dried under vacuum, and stored at room temperature (22).

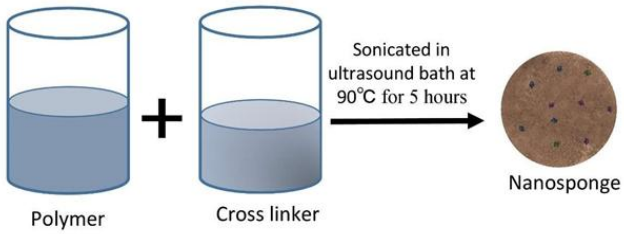

Figure 3. Nanosponge preparation by sonication method.

Quasi-emulsion solvent diffusion

It consists of two phases the outer and the inner phase. Eudragit RS100 is dissolved in an appropriate solvent and then the drug is mixed by ultrasonication at 35 ℃. This inner phase is added to the outer phase which consists of polyvinyl alcohol solution in water with constant stirring for about an hour. The final product is filtered, and dried in a hot air oven at 40 ℃ for almost 12 hours (23,24).

From hyper cross-linked β-cyclodextrin

Three-dimensional networks of roughly spherical structures are formed by reacting cyclodextrin with cross-linkers such as di-isocyanates, diaryl carbonates, dimethyl carbonate, and carbonyl diimidazole. They are about the size of proteins containing pores and channels in their structure (fig. 4). The pore size of the cavities can be controlled along with the size of the nanosponges. Highly hydrophobic drugs can be incorporated into these moieties. Fast drug release can be achieved by decreasing the cross-linking of nanosponges

(5,25,26). β-cyclodextrin nanosponges can be prepared by reacting completely dissolved β-cyclodextrin in the dimethyl formamide with carbonyl di-imidazole cross-linked for 4 hours at 100℃. A transparent cluster of hyper cross-linked cyclodextrin obtained at the end of the condensation polymerization reaction is roughly grounded and washed with deionized water to remove dimethyl formamide. Soxhlet extraction of the byproducts with ethanol is done to completely remove the unreacted reagents. Further drying of extracted powder is done overnight in the oven at 60℃ to obtain fine spherical shape powder. It is then dispersed in deionized water. The suspended colloidal part is recovered and lyophilized to get sub-micron spherical nanosponges (27,28).

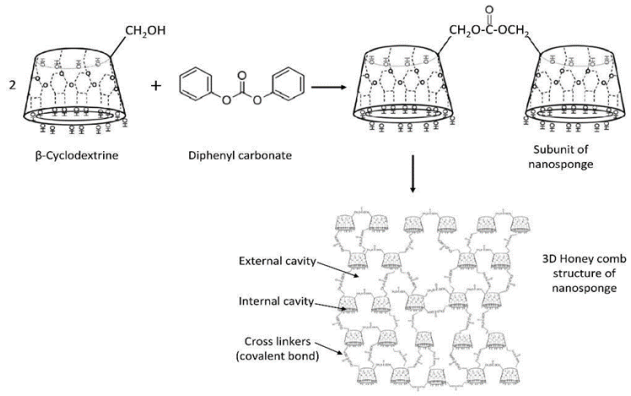

Figure 4. Nanosponge preparation by hyper cross-linked cyclodextrin.

Polymerization

First, a monomer is formed by preparing a solution of the drug. The aqueous phase is prepared separately by mixing a surfactant and dispersant which aids in the formation of a suspension. Both phases are mixed and the process of polymerization is initiated either by catalysis or by increasing the temperature gradient (29).

Evaluation and characterizations of nanosponges

The complex form between carrier nanosponges and the encapsulated drug should be characterized and evaluated for the desired parameters. Characterizations and evaluation of nanosponges include determination of particle size, zeta potential, morphological structure, drug loading, solubility, etc.

Particle size and Polydispersity

The particle size of drug-loaded and unloaded nanosponges can be determined by dynamic light scattering laser light diffractometry or Malvern zeta sizer. They give the mean particle size and Polydispersity. Further, the cumulative graph can be plotted between particle size and time to study the effect of size on the drug release pattern. For nanosponges, particle sizes ranging from 10 to 25 m are preferred in the final optimized formulation as a size greater than 30 m imparts grittiness (30,31).

The Polydispersity index (PDI) can also be determined from the dynamic light scattering device. PDI gives the index of spread variation or width within the size distribution of particles. The lower value of PDI infers monodispersity whereas the higher value infers polydispersity and wider distribution of particle size (30,31).

Zeta potential

Zeta potential is the measurement of the charge on the surface of a particle. It can be easily measured by introducing an additional electrode to the Malvern zeta sizer instrument (32).

Loading efficacy

The loading efficacy of the nanosponge refers to the quantitative estimation of the amount of drug encapsulated in the nanosponge cavity. It can be determined by dissolving the nanosponge complexes in a suitable solvent and sonicating it to break the complex formation which is further diluted and analyzed by ultra-violet spectroscopy or high-performance liquid chromatography technique (33–35). The percentage loading efficacy of nanosponges can be calculated by the following equation:

Drug loading efficiency (%) = (Practical amount of drug-loaded/Theoretical amount of drug-loaded)x 100

Microscopy study

The microscopic aspects of the nanosponge and drug complexes can be studied by transmission electron microscopy and scanning electron microscopy. The formation of the inclusion complex is indicated by the difference in the crystallization state of drug-bounded and unbounded nanosponges. It also determines the morphological structure of the nanosponge formulation (27,36).

X-ray diffractometry

X-ray diffractometry of powder can be used to determine the solid stage inclusion complexation. For the liquid drugs, the difference in the diffraction pattern of complexed nanosponges and uncomplexed nanosponges indicates the complex formation, as liquids do not have a diffraction pattern

of their own. For solid drugs, a comparative evaluation of the diffraction pattern of complex nanosponges with that of a mixture of polymer-drug mixture is done. The diffraction pattern of the complex is used to detect the chemical decomposition and complex formation. Single crystal X-ray structure analysis can be used to detect the detailed geometrical structure of inclusion and interaction behavior of components (37).

Solubility studies

Higuchi and Connor's equation of phase solubility is used to study the effect of the solubility of an incorporated drug on the complex formation and therapeutic efficacy of the nanosponges (24).

Drug release kinetics

The drug release mechanism of nanosponges can be studied through a multi-compartment rotating cell approach with a dialysis membrane in a Franz diffusion cell. Drug drug-loaded nanosponge complex is introduced in the donor compartment and diffusion media in the receptor compartment. The sample was withdrawn at a predetermined time period and replaced with the same volume of diffusion media. The sample withdrawn was then analyzed by UV spectroscopy or HPLC. To identify the mechanism of drug release kinetics from the nanosponge, the data obtained was analyzed by zero order, first order, Hixon Crowell, Higuchi, Kopcha, Makoid-Banakar, and Korseemeyer-Peppas models (38,39).

Thermo-analytical methods

The thermo-analytical method is used to detect the changes in the drug moiety before the thermal degradation of the drug-loaded nanosponges complex. The drug may undergo oxidation, decomposition, evaporation, polymeric transition, or melting. Any kind of alteration in the drug moiety indicates the complex formation of nanosponges. It can be measured by observing the shifting, broadening, or emergence of new peaks on the thermogram obtained by DTA and DSC.

Alternation in weight loss also denotes the inclusion of complex formation (40).

Fourier Transform Infrared (FTIR) analysis

Infrared spectroscopy is used to determine the interaction of solid drug moiety with the nanosponges but its application is limited to the drugs having carbonyl or sulfonyl groups. Infrared spectral studies is done to investigate the involvement of hydrogen in different functional groups. Hence, advance Fourier Transform infrared (FTIR) technique is used to identify the interaction of drug moiety with the polymer of nanosponges by scanning sample from 400-4000 cm-1 range (41,42).

Applications of nanosponges

Nanosponges have found remarkable utility in the field of pharmaceuticals due to their unique feature, biocompatibility, and versatile nature. They can be used as multifunctional carriers of pharmaceutically active agents as well as excipients in the manufacturing of capsules, tablets, suspensions, granules, and topical dosage forms. Nanosponges can encapsulate a wider range of therapeutics as shown in Table 2. They have the ability to improve the product performance and stability, reduce side effects, and provide extended release of drugs.

Nanosponges in drug delivery

The nanometric size and spherical shape of nanosponges facilitate the preparation of various dosage forms such as aerosols, topical, parenteral, and oral. Besides, it has the ability to incorporate a wide range of therapeutic agents including hydrophilic and hydrophobic drugs. To date, the majority of research done has been focused on the use of nanosponges as carriers of drugs. Oral nanosponge formulation includes the dispersed complex in suitable excipients and diluents based on the dosage form (43). Parenteral nanosponge formulations are simple solutions of complexes in sterile water or saline whereas topical nanosponge formulations are hydrogel-containing complex (43). For instance, a BCS class II drug, Telmisartan, was reported to deliver efficiently when incorporated in nanosponge preparation. The in-vitro dissolution study showed a better solubility profile of telmisartan incorporated in nanosponge preparation (44). B-cyclodextrin based nanosponges significantly enhance the in-vitro therapeutic efficacy of paclitaxel by improving intracellular penetration and cytotoxicity (45,46). Topical nanosponges of an antifungal agent, econazole nitrate, were prepared by incorporating nanosponges into the hydrogel matrix by emulsion solvent diffusion method (23,47). Recently, a novel combination of advanced cyclodextrin nanosponge with textiles has been reported for controlled delivery of melatonin topically. The formulation showed zero-order drug release kinetics in the in-vitro study (48).

Nanosponges in solubility enhancement

Nanosponges can be used to improve the aqueous solubility and dissolution profile of poorly soluble drugs by forming the inclusion complex while encapsulation. The insoluble nature of nanosponges prevents supersaturation and promotes the protection of entrapped drugs from agglomeration and precipitation. Nanosponges can incorporate both hydrophobic and hydrophilic drugs. The hydrophobic drugs are associated with the interior hydrophobic cavities whereas hydrophilic drugs occupy the external hydrophilic cavities. Lower drug crystallinity and higher thermodynamic energy result in increased drug dissolution and bioavailability. In the study, Vavia and co-workers successfully increased the solubility of Itraconazole by about 20-fold by entrapping the drug into the nanosponge formulation. Phase solubility study of copolyvidonum, nanosponge, and their combination was performed to compare the solubility efficacy of nanosponge formulation (13). Besides, Itraconazole other BCS class II drugs in which this approach has been successfully applied include Doxorubicin (49), Paclitaxel (50), Flurbiprofen (51), and Dexamethasone (52), etc. Recently, Dhakar and his team fabricated the kynurenic acid-loaded cyclodextrin nanosponge formulation to evaluate the solubility, cytotoxicity, and antioxidant activity. The solubility of the drug was observed to increase significantly when compared to the free kynurenic acid with better cytotoxicity and antioxidant activity (17).

Nanosponges as controlled and sustained delivery system

Recently the interest in developing a drug delivery system that can release the drug in a controlled and sustained manner has been mounted. It has always been a great challenge to control the release of drugs in desire predictable way to maintain therapeutic efficacy. Unique features of nanosponges have shown great potential to solve these problems. They provide the nanosize cores to load the drugs from where drugs can be released slowly and gradually. The drug release mechanism of nanosponges depends on the crystallinity and degree of cross-linking. For instance, an antiviral drug, acyclovir, having slow gastrointestinal absorption was studied by a team of researchers to identify the in-vitro release profile from the two different types of nanosponge preparations. Acyclovir was released in a sustained manner indicating the encapsulation of the drug into the nanostructures. Carb-nanosponges showed about 22% drug release whereas nanosponges showed approximately 70% drug release after 3 hours. Initial burst was not observed by either of the preparation, indicating strong adsorption of acyclovir onto the surface of nanosponges (53). Also, the nanosponges of the anti-cancer drug, doxorubicin, have been observed to deliver the doxorubicin in a time-dependent manner (49). In another study, Swaminathan and team demonstrated drug release of 20-25% after 24 hours from camptothecin-loaded nanosponges. The initial burst of release was probably due to non-included drugs present in external cavities. The initial burst was followed by a linear and sustained release profile (41). Henceforth, nanosponge can be considered a promising drug delivery system for controlled and sustained delivery.

Nanosponges for protein delivery

Recently, the delivery of macro-biomolecules such as proteins and peptides has gained significant attraction from researchers. However, large molecular mass, short half-life, poor bioavailability, stability, and denaturation are the major obstacles faced by protein and peptide administration (54). Encapsulation of these macro-biomolecules into β-cyclodextrin based nanosponges can boost the solubility and improve pharmacokinetic properties. Swaminathan and his team reported new expandable cyclodextrin-based poly (amidoamine) nanosponges, fabricated by cross-linking βcyclodextrin with either poly(amidoamine) chain or with 2,2-bis-acrylamidoacetic acid for the delivery of model protein, Bovine serum albumin (BSA). BSA nanosponges showed extended release for 24 hours with improved stability up to temperature 250-300 ℃ and magnificent swelling capacity. The formulation showed a protein encapsulation efficiency of about 90% (14).

Nanosponges in enzyme immobilization

Enzyme immobilization improves the stability and modulates the selectivity and reaction rate of enzymes such as lipases. Cyclodextrin-based nanosponges can be used for stabilizing enzymes. They can preserve/enhance catalytic proficiency and support the immobilization of enzymes. In research, Boscolo and his co-worker observed that the catalytic performance of Pseudomonas fluorescens lipase was significantly enhanced when adsorbed on the cyclodextrin-based nanosponges. Lipases are important catalyzing enzymes that are necessary for the hydrolysis of triacylglycerols and trans-esterification, widely utilized in industry (55).

Nanosponges as protective agents

Nanosponges can act as a protective carrier of drugs to prevent molecular degradation from chemicals, enzymes, and light. Cavalli and his team showed the protective action of cyclodextrin nanosponges by incorporating a light-sensitive drug, 5-fluorouracil, in nanosponge formulation. Protection of the drug with significant cytotoxicity against the MCF-7 cells was observed by nanosponge encapsulated 5-fluorouracil (10). In another study, Swaminathan reported the protection of camptothecin from chemicals by loading it in cyclodextrin-based nanosponges. Chemical stability, shelf-life and prolonged drug release profile of the drug were observed by camptothecin-loaded nanosponges (41). Further, Alongi and his team studied the interaction of βcyclodextrin with 2-hydroxy-4(octyloxy)-benzophenone and triphenyl phosphite (UV stabilizers). The nanosponge formulation was observed to increase the photooxidation of polypylene by 3-fold (43).

Nanosponges as a carrier for gas delivery

Certain gases have significant roles in the diagnostic and treatment process such as oxygen and carbon dioxide. Administration of diagnostic gases in the desired dose is sometimes difficult to achieve. Nanosponges can be used as the reservoir of different kinds of gases. In the study, Cavalli and his team reported that the nanosponges can act as carriers of the gases by synthesizing three different cyclodextrin-based nanosponges and entrapping oxygen gas into it for topical application. Slower and sustained release of oxygen was observed from the formulation with an enhanced permeation profile (56).

Nanosponges as topical agents

Conventional topical products often provide drugs at relatively high concentrations for shorter periods which may lead to short-term overdosing followed by long-term underdosing. In contrast, topical nanosponges provide even and sustained release of drugs. Also, nanosponge formulation increases the penetration of the drug and reduces the side effects. For the topical preparation, drug-loaded nanosponges are encapsulated into the creams and gels. One such formulation was manufactured by Pathak and his team, wherein, econazole nitrate nanosponge was fabricated by emulsion solvent diffusion method. Econazole nitrate, a commonly used antifungal agent is applied topically for the treatment of superficial candidiasis and other skin infections. The hydrogel formulation showed improved retention time on the skin and sustained release of drug for 12 hours (47).

Nanosponges in cancer therapy

Targeting the property of nanosponges to the specific site enables to efficacy of anticancer drugs by bypassing the hurdle created by immune systems. Nanosponges efficiently bind with radiation-induced tumor cell surface receptors and trigger the drug release. Suppression of growth of various cancer cells had been reported by the single dose of anticancer drugs loaded nanosponge such as breast cancer. Camptothecin, an unstable lipophilic anticancer drug, was complexed with βcyclodextrin nanosponge to improve the solubility and stability of the drug, thereby increasing the therapeutic efficacy (41,57).

Other applications of nanosponges

Nanosponges based on cyclodextrin have strong bonding ability with organic molecules. This property of cyclodextrin-based nanosponges can be widely used in the purification of water (10). Another application of nanosponges was reported by Wong and team, wherein, they formulated three-dimensional nanosponges to fractionalize the peptides for proteomic use (58). Sapino and team prepared gamma-oryzanol-loaded nanosponges, which are used in sunscreen, to enhance skin penetration for a prolonged time period and improve the skin protection ability (59). Researchers have also entrapped essential oil in cyclodextrin nanosponge and observed prolonged release, which can be used in perfume industries (60).

Future perspectives

In the near future, healthcare and pharmaceutical industries might use nanosponges as a remedy to the various existing chemical, physical, and biological problems concerned with disease therapy. The extensive targeting feature of the nanosponges might attract its exploration as diagnostic agents, especially in cancer imaging. It has the ability to stabilize the unidentified cancer biomarkers which readily undergoes enzymatic degradation even before detection. Targeting the bioactive compound faces great challenges such as optimization of safe and efficient delivery of bioactive into the cytosol. Loading these compounds into the nanosponges conjugated with special linkers will ensure the release of the compound in a controlled manner instead of burst release which is exhibited by other nanoparticles. However, loading of such drugs into

Table 2. Various drugs encapsulated in nanosponge drug delivery system.

Nanosponge vehicle	Drug	Indication	Model	Remark	Ref
Cyclodextrin	Temoporfin	Tumor	Pharynx squamous Cell carcinoma	Inhibited the cellular uptake	(61)
Cyclodextrin	Doxorubicin	Breast cancer	Mice	Enhance the antitumor activity	(49)
Dimethyl carbonate	Curcumin and Caffeine	Psoriasis	In-vitro	Enhance the antipsoriatic activity	(62)
Cyclodextrin	Oxyresveratrol	Prostate and colon cancer	HT-29, HCT-116 and PC-3 cancer cell	Better inhibition of cell viability	(63)
Cyclodextrin	Febuxostate	Bioavailability	SD rats	Improved the oral bioavailability	(64)
Phi29 DNA polymerase	DNA	Breast cancer	MCF-7 cell	Induced apoptosis and enhancer anticancer activity	(65)
Cyclodextrin	Imiquimod	Topical disease	In-vitro	Enhanced penetration	(66)
Cyclodextrin	Paclitaxel	Cancer	HUVE cell, C57/BL6 and B16-BL6 cell	Inhibited growth and angiogenesis	(50)
Cyclodextrin	Kynurenic acid	Neuroprotectiv, antioxidant and free radical scavenging	In-vitro	Increased solubility and antioxidant activity	(17)
Cyclodextrin	Resveratrol and Oxyresveratrol	Solubility, Cytotoxicity and photo-stability	In-vitro	Increased solubility, better stability and antioxidant activity	(67)
Cyclodextrin	Norfloxacin	Bacterial infection	Sepsis model	Enhanced permeation and improved antibacterial activity	(68)
Cyclodextrin	Ellagic acid	Solubility and bioavailability	Male white rabbit	Improved the oral bioavailability	(69)
Cyclodextrin	Atorvastatin	Bioavailability	SD rats	Improved the oral bioavailability	(70)
Cyclodextrin	Flurbiprofen	Solubility	In-vitro	Improved diffusion.	(51)
Cyclodextrin	Rilpivirine	Solubility and bioavailability	Rats	Improved solubility and oral bioavailability	(71,72)
Diacrylated Pluronic F 127	Heparin	Anti-coagulant bioacivity	In-vitro	Decreased anti-coagulant activity and sustained release of growth factors	(73)
GoldDicopper oxide	Doxorubicin	Breast cancer	MCF-7 cell	Minimize the toxic effect and enhance the therapeutic efficacy	(74)
Cyclodextrin	Erlotinib	Cytotoxicity and bioavailability	MIA PaCa2, PANC-1 and SD rats	Improved the oral bioavailability and increased toxicity	(75)
Cyclodextrin	Gabapentin	Bioavailability	Male wistar rats	Improved the oral bioavailability	(76)

nanosponges might need "molecular transporters" to pull the drug-carrying nanosponges into the targeted cancer cells. The future is also likely to witness the nanosponge compositions with the ability to deliver the vaccines.

Conclusion

Nanotechnology has minimized all the processes at the nanometric scale. The multifaceted approach of nanotechnology has led to the development of many formulations that are advantageous over the other conventional formulations. The application of technology has led to the utilization of many software used for the optimization of formulations. The obstacles in formulation development such as the burst effect, stability problems, and drug loading issues can be overcome by employing these miniature systems as drug delivery carriers. The degree of crosslinking is varied to optimize the viscoelasticity of the desired formulation. The stimuli-activated nanosponges and molecularly imprinted nanosponges can be employed for effective drug targeting. Nanosponges find their applications as the carriers of both lipophilic and hydrophilic drugs, carriers of protein, peptides and enzymes, biomarkers, and, purifiers also in the field of cosmetics. The future research goals must be to reduce the cost of synthesis of nanosponges on a large scale and also to avoid the adverse effects of the polymers employed.

Contribution of authors

Not applicable

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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