We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,500
Open access books available

177,000
International authors and editors

190M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Recent Pharmaceutical Developments in the Treatment of Cancer Using Nanosponges

Kapil Gore, Sankha Bhattacharya and Bhupendra Prajapati

Abstract

Nanosponges are a class of nanoparticles characterized by their sponge-like surface that ensures high loading capacity. Cancer causes high mortality and requires precise treatment without harming the body. Hence, nanoparticles are required to target medications to tumor. Nanosponges may be synthesized from various polymers and metals, giving them distinct properties. The majority of polymer synthesis entails crosslinking, while metal synthesis entails the isolation of metal nanoparticles accompanied by their assembly into sponges. Nanosponges must be functionalized to precisely attack tumors. There are several patents on nanosponges synthesis and their use. Future trends in the usage of nanosponges include simultaneous distribution of several molecules and expanding the spectrum of use from medicinal delivery to substance encapsulation for a multitude of applications. As their usage in the pharmaceutical industry grows, more emphasis should be put on toxicity-related aspects induced by the near association of cell membrane and nanosponge resulting in intracellular dissolution or reactive oxygen species (ROS) generation, which in turn damages various cellular components. Many techniques have been created to reduce toxicity, including functionalization with various materials such as antioxidants, polymers and altering nanosponges composition. As the application of nanosponges increases in many industries, the phenomenon related to toxicity must be further explored through research.

Keywords: nanosponges, nanoparticles, silver nanosponges, cyclodextrin nanosponges, cancer therapy, β-hydroxypropyl beta-cyclodextrin nanosponges, cancer therapy, β-hydroxypropyl beta-cyclodextrin

1. Introduction

Cancer is a collection of diseases triggered due to uncontrolled cell division [1]. Cancer cells are able to migrate from their original site to any other site through the vasculature is what that makes them harmful [2]. Cancer occupies the second position in list of deaths worldwide by causing 9.6 million deaths in 2018. Cancer causes a tremendous economic burden on the patient and ultimately on the nation [3]. Traditional treatments for cancer include surgery, chemotherapy and
radiation therapy [4]. The traditional therapies are now more advanced as the time has progressed. Yet, they have many drawbacks which make them ineffective for destruction of tumor [5]. Surgical treatments suffer from disadvantages such as early diagnosis, presence of micro metastases, disruptions of tumors and side effects of anesthesia [6]. Radiotherapy involves treatment with ionizing radiations with a drawback of non-discriminate action against healthy cells at the sites where cells have a rapid growth rate such as hair follicles. It causes side effects like hair loss, anemia, sores in mouth and throat, neuropathy, skin dryness, and change in skin color [7]. To prevent these side effects, nanoparticles are used that can penetrate inside the tumor due to their nanosize. It reduces not only the amount of drug used but also the associated side effects due to action at places where it is not needed [8]. Many nano-formulations such as nanosponges and nanoparticles have been invented for their delivery to cancer [9]. In this chapter, we have discussed about nanosponges, their classification, advantages, disadvantages, and how they are better than other nanocarriers. We have also enlisted the barriers affecting delivery to cancer and how nanosponges can be used to overcome them along with some applications of nanosponges along with functionalization of nanosponges to ease delivery to cancer. We have also discussed about toxicity of nanosponges and the probable mechanisms to reduce that toxicity.

2. Nanoparticles in treatment of cancer

Nanoparticles are nanosized particles containing polymers or lipids which contain drugs adsorbed or encapsulated in them [10]. One advantage of nanotechnology in cancer treatment is modifications of delivery system to achieve targeting [11]. Nanoparticle-mediated delivery of any cytotoxic agent allows control on the biodistribution of drug, hence controlling the toxicity [12]. Nanoparticles allow drugs with lower molecular weight to stay in the circulation for a prolonged period [13]. Nanoparticles being 1000 times smaller than a cancer cell can easily cross the vasculature and reach the interstitium. Due to their small size, and a relatively large surface area allows loading with large number of molecules [14]. Nanoparticles also help to remove difficulties due to innate properties of active pharmaceutical ingredient (API) such as poor solubility can be overcome by using water-soluble polymers to trap the drug within [15]. Many chemotherapeutic agents which have low molecular weight face issue of hepatic clearance, but conversion into nanoparticles prevents quick clearance [16]. Nanoparticles reduce the exposure of drugs to the environment inside the body and prevent the degradation of the drugs and the side effects due to exposure of healthy cells to cytotoxic drugs [17]. Nanoparticles are being explored to give multiple actions at the same time. The researchers Xie et al. [18] inserted curcumin into nanoparticles made from bamboo charcoal. The nanoparticles were functionalized using D-α-tocopherol polyethylene glycol 1000 succinate. Due to a nano-formulation, the system gave better internalization, and this composite dosage form showed inhibition of P-gp which increased the efficacy of treatment. At the same time, the presence of antioxidants such as tocopherol and curcumin helped to remove any reactive radicals and showed radioprotective action [18]. Ma et al. [19] synthesized nanoparticles of poly-(acrylic acid) with CoSe using the aqueous precipitation method. These particles had photothermal transfer efficiency greater than 40% and negligible cytotoxicity. These nanoparticles were loaded with doxorubicin (DOX) which was shown to release in the acidic tumor conditions in cancer.
These particles gave a synergistic cytotoxic action due to chemotoxicity as well as phototoxicity [19].

Hu et al. [20] synthesized gold nanoparticles by rapidly reducing gold chloride trihydrate. To that solution, thio-PEG and thio-glucose were added which showed covalent bonding on gold nanoparticles. Glucose was attached to take advantage of excess glucose consumption of cancer cells as compared to normal body cells. The cells were allowed to take in the Glu-GNPs which were found to be effective than only irradiation or only gold nanoparticles [20].

3. Barriers to drug delivery in solid tumors

Tumors are a major presentation in cancer which exhibit presence of abnormal cellular and extracellular elements which can create obstacles in drug delivery to cancer cells situated deep within the tumors. Below given are barriers to drug delivery in tumors and ways to overcome those barriers--.

3.1 Biological barriers

Biological barriers include physiological components which prevent the reach of drug to tumors. To reach the desired site, the drug should circulate in the blood. Blood contains many proteins that form a structure around the drug particle called ‘protein corona’. This phenomenon is called opsonization, and such opsonized particle is destroyed by phagocytes and macrophages. The physical characters of nanoparticle are determinants of extent of opsonization [21]. To prevent opsonization, the circulatory time is controlled using polymers such as PEG [22]. Yapa et al. targeted leucocytes and neural stem cells to facilitate entry into tumors as well as targeting metastases. The nanosponges were formulated using cholesterol and a CASPASE-6 sequence ((cholesterol-(K/D)nDEVDGC)3-trimaleimide) attached to a triangular maleimide linker which were then used to join lysine or aspartic acid. These function as apoptotic bodies and destroy the tumors [23]. If the nanoparticle avoids being opsonized, it still has to face many challenges to reach to its target sites, one being endothelium of blood vessels which is selectively permeable and on the top of that, being ‘coated’ by a negatively charged glyocalyx, it further restricts the reaction of particles with endothelial membrane [24]. Haemodynamic involves movement of nanoparticles through the blood vessels. As erythrocytes flow in the centre of the vessel, the other contents of blood are forced to move along the walls of the vessel. Understanding this phenomenon in context of nanoparticles will be helpful in design of better nanoparticles [25]. Particles larger than 5–6 nm are not able to squeeze through the continuous endothelium of a ‘healthy’ capillary. But in case of tumors, endothelial lining is more permeable and does not remain continuous. So, nanoparticles larger than 6 nm can cross these gaps to enter into the tumor microenvironment [26]. Because of inadequate lymphatic drainage, those particles do not get removed from the body. There is also a disparity in the sizes of the pores, which can be found in primary tumors, metastasized tumors, and even the same primary tumor, which is another drawback of this the enhanced permeability and retention effect (EPR) effect [27].

3.2 Tumor microenvironment

After the nanoparticle crosses successfully the endothelium and enters the tumor, it still has to cross the tortuous tumor microenvironment to reach to the
tumor cells. The microenvironment consists of the tumor extracellular matrix that contains a network of collagen, elastin incorporating proteoglycans and hyaluronic acid. It maintains the tumor structure and provides nutrients and oxygen to cells. If the matrix is highly developed, it may cause the drug to get released far away from the target site [28]. Incorporating collagenase in the nanoparticles may help circumvent the collagen barrier and allow reach of nanoparticles [29]. The tumor growth cannot be infinite and is arrested because of presence of an extracellular matrix. The extracellular matrix also prevents efficient metastasis of the tumor cells. Tumor cells release various enzymes to degrade this matrix which are called matrix metalloproteinases [30]. These can be used in diagnosis of cancer as a marker. In this enzyme family, types 2 and 9 are more important in formation of tumors. Using drugs which inhibit metalloproteinases can be a best possible approach to counter this resistance [31]. Wang et al. synthesized nanosponges loaded with matrix metalloproteinase-14 inhibitor naphthofluorescein, which targets collagen in cardiovascular disease [32]. Flow of interstitial fluid in the tumor affects drug distribution as the drug exits vasculature from interstitium and finally reaches to cells. The movement occurs either by a concentration or a pressure gradient. As the blood vessel network is not uniform within a tumor, so the blood flow becomes uneven. Also, the drainage of interstitial fluid is poor due to poorly formed lymphatic network. It increases the interstitial fluid pressure. Due to high heterogeneity in tumor structure, the fluid pressure can be different for two tumors in the same organism [33]. As cancer cells prefer a type of fermentation over aerobic respiration, the amount of oxygen decreases and the number of acids increases near the centre. These conditions make the tumor resistant to certain treatments as radiation [34]. Hypoxia causes increased production of chemokines which promote angiogenesis and avoids detection from immune cells [35]. Also, the acidic pH may aid in targeting by using acid-sensitive polymers to release medication at the centre of tumor [36]. Caldera et al. synthesized nanosponges from cyclic nigerosyl-1-6 nigerose using pyromellitic dianhydride as a crosslinker. The nanosponges were prepared using high-pressure homogenization and showed swelling at lower pH which caused DOX release [37].

3.3 Cellular barriers

Cellular barriers include various cellular components which prevent the reach of the drug to intracellular environment. Many drugs show their effects inside the cell. Hence, even if the drug reaches near cancer cells inside the tumor, it has to cross the cell membrane to enter inside the cell to exert its actions. The carrier should interact with cell membrane to achieve the release [38]. Physical characteristics of carrier such as size, surface charge and hydrophobicity affect the interaction with cell membrane. Charged particles show more interaction with cell membrane. Neutral particles may crowd near cell membrane preventing any further entry into the cell [39]. Particles smaller than 200 nm get internalized by clathrin-mediated endocytosis, and those which are larger undergo clavioline-mediated endocytosis. This process is an energy-dependent process. Cancer cell membranes express many ligands which can be targeted [40]. Singh et al. [41] prepared cyclodextrin nanosponges and attached cholesterol as a functionalization moiety. Cholesterol being a major component of cell membrane facilitates easy interactions with cell membrane and hence easy penetration in cells.
3.4 Organellar and vesicular barriers

Once inside the cell, the carrier should travel to the designated target site so as to release the drug. This travel is mediated by endosomes, which is energy-dependent. Endocytosis occurs by various pathways physiologically, and the pathways may be different for different types of nanoparticles. Generally, all these pathways end up in taking contents to lysosomes where they are destroyed. Use of fusogenic lipids is advised to prevent this fate [42]. Yan et al. synthesized nanosponges and coated them with fusogenic lipids which enhanced internalization and a better delivery inside the cells [43].

3.5 Drug efflux transporters

Till the medications reach the target site, only a small fraction of original dose remains which shows its effect. Hence, many tumors contain efflux pumps which remove the drugs out of tumor cells [44]. P-glycoprotein is one such receptor to throw the drugs out of cells. Various small molecules which are P-glycoprotein inhibitors can be used to avoid the efflux [45]. Arima et al. [46] prepared nanosponges of dimethyl-β-cyclodextrin and loaded them with an immunosuppressant tacrolimus. These complexes were tested on rats where they showed increased bioavailability and dissolution rate. Pre-treatment of apical membrane with dimethyl-β-cyclodextrin showed dislodging of receptors from the membrane and successfully inhibited P-glycoprotein showing increased absorption of drugs [46].

4. Definition of nanosponges

Nanosponges are sponges of very small size with diameter less than 1 μm. These are three-dimensional networks made of polymers which act as frames to hold the drug molecules inside them. These sponges circulate the body and can release the drug at a specific site [47].

4.1 Advantages of nanosponge

Nanosponges offer advantages over other nanoparticles such as a targeted release of active constituents inside the body which is caused due to functionalization on the surface. Nanosponges allow flexibility of formulation due to various polymers used as well as stability due to the drug entering the pores of sponge. These are non-toxic, non-allergenic and non-mutagenic due to biocompatible ingredients used. As these sponges are made of biodegradable molecules, they are able to provide extended release due to slow degradation of drug. Nanosponges are stable over wide temperature range and show excellent stability over the pH range. As nanosponges have diameter less than a bacterium, the formulation is self-sterile as bacteria are unable to enter the formulation. They exhibit excellent thermal, physical and chemical stability [48].

4.2 Disadvantages of nanosponge

Nanosponges can be used for only small molecules as large molecules may not enter the nanosized pores of nanosponge. The drug loading is also affected by the degree of crystallization. Dose dumping may be observed due to sudden degradation of carrier [49].
5. Classification of nanosponges

The classification of nanosponges based on the material used is illustrated in Figure 1A [50].
Recent Pharmaceutical Developments in the Treatment of Cancer Using Nanosponges
DOI: http://dx.doi.org/10.5772/intechopen.105817

5.1 Cyclodextrin-based nanosponges

Cyclodextrins have been majorly used for the preparation of nanosponges. These are cyclic oligosaccharides. These are cone-shaped molecules made of glucopyranose units. These units are arranged around a hydrophobic hollow core which is used to trap any molecules.

Selection of crosslinkers is important to alter the properties of the final product. Crosslinkers such as epichlorohydrin give cyclodextrin nanosponges with hydrophilic pores whereas crosslinkers such as diphenyl carbonate and diisocyanates give hydrophobic nanosponges [51]. Various types of cyclodextrin-based nanosponges are enlisted in Table 1 and Figure 1B [52].

<table>
<thead>
<tr>
<th>Type</th>
<th>Crosslinker used</th>
<th>Example</th>
<th>Method used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclodextrin carbonate nanosponges</td>
<td>Carbonyl crosslinkers</td>
<td>Diphenyl carbonate</td>
<td>Thermal deposition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dimethyl carbonate</td>
<td>Solvent extraction</td>
</tr>
<tr>
<td>Cyclodextrin carbamate nanosponges</td>
<td>Diisocyanate crosslinkers</td>
<td>Hexamethylene diisocyanate</td>
<td>Solvent method</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toluene diisocyanate</td>
<td></td>
</tr>
<tr>
<td>Cyclodextrin anhydride nanosponges</td>
<td>Anhydride crosslinkers</td>
<td>Pyromellitic dianhydride</td>
<td>Solvent method</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EDTA dianhydride</td>
<td></td>
</tr>
<tr>
<td>Epichlorohydrin cyclodextrin nanosponges</td>
<td>Epichlorohydrin crosslinkers</td>
<td>Epichlorohydrin</td>
<td>Solvent method</td>
</tr>
</tbody>
</table>

Table 1. Different types of beta-cyclodextrin-based nanosponges.

5.2 Metal and metal oxide nanosponges

Metal and metal oxide nanosponges have desirable characters such as a wide surface area, small particle size and better stability. Metal oxides are being shown interest due to their ability of interaction with other species such as atoms, ions and molecules. They are able to form a porous interconnected network and show properties different than bulk. These also show magnetism and semiconductor properties. Metallic nanosponges can be made from one, two or multiple metals simultaneously. The nanosponges made from two or more metals are desirable over those made from single metal as they are more porous and based on porosity, and they can be classified as micro, meso and microporous based on the size of sponge where microporous are smaller than 2 nm, macroporous being larger than 50 nm and mesoporous lying in between them (Figure 1C) [53].

5.3 Polystyrene nanosponges

Davankov et al. [54] prepared nanosponges of linear polystyrene by causing intramolecular hyper-crosslinking. The polymer was initially chloromethylated using dichloro monoethyl ether, and this solution was added to the solution of zinc chloride in the same ether which acted as a catalyst. This mixture was heated at 40°C for 3 h. The precipitated polymer was washed and dried. This polymer is dissolved
in 2 L ethylene dichloride distilled over phosphorous pentoxide. Tin chloride solution was added which changed the colors gradually from pink to brown. Acetone was added to dissolve colored complex. The solution was allowed to cool and was washed with water. The organic layer was separated and concentrated to 20% of starting volume. The nanosponges were isolated using methanol. They were dried and stored (Figure 1D) [54].

6. Mechanism and preparation of polymeric nanosponges

For the formation of nanosponges made out of polymer, reaction conditions such as heat and solvents promote uncoiling of long polymer chains and reveal the groups for reaction with crosslinkers. Crosslinkers such as diphenyl carbonate release the phenyl group upon reaction which remains in reaction mixture, and the carbonyl group acts as crosslinkers during the formation of nanosponges. The extensive crosslinking causes winding and coiling of long polymer chains and forms pores and cavities leading to the formation of nanosponges. The prepared formulation is later purified using organic solvents such as ethanol to remove those impurities.

6.1 Melt method

Cyclodextrins are made to react with crosslinkers like diphenyl carbonate, dimethyl carbonate and disocyanates. All the dry ingredients are homogenously mixed and put into a flask and heated at 100°C. A magnetic stirrer is used to achieve uniform mixing of contents. The heating is kept up for a total of 5 h so that the reaction can take place. After allowing the mixture to cool down, the obtained solid is broken up into smaller pieces using mortar. It is then purified using the Soxhlet extraction method after being washed to remove any unreacted reactants [55]. Sadjadi et al. synthesized beta-cyclodextrin nanosponges using the melt method. A calculated amount of diphenyl carbonate was melted at 90°C in a beaker. Preheated beta-cyclodextrin was added to it. The mixture was stirred for half a day at temperature exceeding 100°C to allow reaction to get completed. The solidified product was cooled and pulverized. The product was washed using water and organic solvent and later purified using Soxhlet extraction [56].

6.2 Solvent diffusion method

6.2.1 Emulsion solvent diffusion method

Ethyl cellulose and polyvinyl alcohol are used to prepare nanosponges. Cellulose and drug are dissolved in organic solvent such as dichloromethane. Then this dispersed phase is added to continuous phase which is aqueous poly (vinyl) alcohol (PVA) solution. This mixture is stirred at high speed for a specific amount of time, and the product is filtered and dried [57]. Solunke et al. [58] prepared glilazide nanosponges using emulsion solvent diffusion method. Glilazide and Eudragit were added to organic phase, and aqueous phase was a PVA solution. Organic phase was added to aqueous phase, it was stirred, and nanosponges were collected and washed [58].
6.2.2 Quasi-emulsion solvent diffusion

This process involves polymers such as Eudragit. The polymer is dissolved into a solvent and the drug is added to the same solution. This inner phase is added to PVA solution and stirred. The product is filtered out and dried [59]. Salunke et al. [60] prepared budesonide-loaded nanosponges by quasi-emulsion solvent diffusion method. Weighed amounts of Polymethyl-methacrylate (PMMA) and Eudragit S-100 were dissolved in organic solvent containing dichloromethane and methanol in equal proportions. Dibutyl phthalate was added to enhance polymer plasticity. The organic phase was added to aqueous PVA solution and was stirred for 2 h. The prepared nanosponges were recovered by filtration and were washed and dried [60].

6.3 Solvent method

The polymer is mixed with an aprotic solvent such as dimethyl sulfoxide. Carbonyl crosslinkers are added to this solution. The reaction is allowed to take place at a range of temperature which may not increase the boiling point of solvent. The solution is cooled at room temperature, and a large amount of water is added to it. The product is recovered by filtration [61]. Rao et al. [62] synthesized nanosponges by the solvent method by dissolving anhydrous β-cyclodextrin and diphenyl carbonate and heating that solution at 90–100°C under stirring. The prepared product was washed with water and later with organic solvents to remove any unreacted constituents. The product was dried to use later [62].

6.4 Ultrasound assisted synthesis

This method involves energy from ultrasound to carry on the reaction. The reactants are placed in the flask and heated with help of ultrasound. The mixture is allowed to react. Later the product is cooled down and broken with mortar. The product is washed with water and purified by Soxhlet apparatus [63]. Jasim et al. [63] prepared cyclodextrin nanosponges using ultrasound-assisted method. Weighed quantities of β-CD and diphenyl carbonate. The mixture was heated on an oil bath and was sonicated using a probe sonicator at 50% amplitude for 4 h. The product was broken down and washed to give final product [63].

7. Mechanism and methods of metal and metal oxide nanosponge formation

Metal nanosponges are prepared by reducing a metal salt using a suitable reagent. Surfactants or capping agents are used to control the growth rate and structure of nanosponges. Ghosh and Jagirdar [64] prepared silver nanosponges in their research activity. Silver nitrate was used as a substrate for synthesis on nanosponge. The salt was reduced to silver cations using boranes. This reaction was carried out at a temperature above 300 K. The reduced metal salt releases free metal atoms. These join together to form nanoparticles. These nanoparticles join together to form nanosponges due to their irregular joining which produce pores or gaps in the structure. This process works like bottom-up approach of synthesis of nanoparticles as they are built from the atoms themselves [64]. Different mechanisms are used to prepare metal
oxide nanosponges such as precipitation and removal from alloy. Dealloying involves removal of a more reactive metal from an alloy. Chemical dealloying is the most common method involving use of acids to react with more reactive metal to remove it from the alloy. Alloy nature and leaching conditions affect this process. Another method utilizes the mechanism of precipitation of metal separated from its salt. This separation is brought about by using reducing agents such as NaBH₄. Later, it is heated at very high temperature to deposit the metal oxide which gives out hydrogen bubbles which are responsible for generation of channels and pores which are required for drug loading. A disadvantage is the variable pore size due to uncontrolled particle size which gets sedimented. Electrochemical deposition utilizes the mechanism of movement of ions towards the oppositely charged electrodes. The ions that migrate form a thin film on the surface of metallic/metal electrode. The changes in pH, temperature and current density can be carried out to vary the properties of the sponge prepared. Another method based on hydrolysis of metal precursors and their conversion to metal species is the sol-gel method. It involves electrolysis of metal compounds in ‘sol’ phase in a solvent. After passing the electric current, the metal particles deposit on the electrode with internal pores and cavities in form of gel. The coagulation of prepared particles can be avoided by altering pH of medium. Drying is performed by evaporation or supercritical methods which evaporate the solvent and forms pores [53].

8. Advantages of nanosponges over other nanocarriers

Nanoparticles after reaching the site of action release their loaded drug all at once creating a 'burst'. Hence, effective dosage cannot be determined properly, whereas nanoparticles being made of biodegradable polymers release their drugs in a slow, controlled manner after the sponges encounter a tumor [48]. Nanosponges are soluble in aqueous as well as organic solvents. These are non-toxic carriers which are heat-stable [65]. Nanosponges are water-soluble which allow the researchers to use them for dissolution of insoluble drugs after loading them into the sponge [66]. Loading and functionalization of nanosponges is pretty easy as compared to other nanoparticles. The functional groups protruding out of nanosponge surface can be used for post-modification strategies such as functionalization [67]. Many nanoparticles have complex chemistry; hence, they cannot be scaled up easily for large-scale production. On the other hand, nanosponges made of only polymers and crosslinkers are easy to scale up for commercial production [68]. As compared to other nanoparticles, where reconstruction of nanoparticles is difficult if they lose their structure, nanosponges can be easily remade by methods such as washing with eco-compatible solvents, mild heating or changing pH or ionic strength [69]. Where many types of nanoparticles are used to contain solid medications, nanosponges can be used to encapsulate not only solids but also liquids and gaseous drugs [70]. Nanosponges can be used to load both hydrophilic and hydrophobic drugs owing to the hydrophobic core and external hydrophilic branching. Hence, these nanostructures can be flexibly loaded with hydrophilic or hydrophobic molecules [71]. Figure 2 highlights major researches on nanosponges from 2005 to 2022.

9. Methods of preparation of nanosponges

Nanosponges can be prepared with a variety of methods and then can be loaded to give a varying amount of drug loading. Kumar et al. [72] prepared cyclodextrin...
nanosponges loaded with babchi oil using tiring at high speed. Similar approaches are described in Table 2.

10. Optimization of nanosponges

Optimization involves obtaining a best combination of starting materials to get a formula which gives the desired results. Due to a simple composition, nanosponges can be optimized without much hassle, which is evident from the examples given in Table 3.

11. Morphological characterization

Morphological characterization involves various instrumental methods to analyze the morphology of prepared nanostructure. Transmission electron microscopy (TEM) involves scanning a sample with a beam of focused electrons which is transmitted through the sample to understand composition of particle. Argenziano et al. [86] prepared β-cyclodextrin nanosponges loaded with paclitaxel. Pyromellitic anhydride was used as a crosslinking agent. Methods such as high-pressure homogenization were used to reduce the particle size. The analysis was performed on Philips CM 10 device. The sample was prepared on formvar-coated copper. The coated samples were air-dried. The results showed that spherical particles were formed. The size was in nano-range due to application of high-pressure homogenization in the synthesis of nanosponges [86]. Scanning electron microscopy involves scanning a sample using an electron beam focused on sample which is then converted into signals. Mady and Mohamed Ibrahim (2018) prepared nanosponges using β-cyclodextrin and diphenyl carbonate crosslinker in DMF as solvent. The mixture was sonicated and refluxed using water and ethanol to remove impurities. Scanning electron microscopy was carried out using model LEO-435 VP, Cambridge (UK). It was used at 15 KV accelerating
<table>
<thead>
<tr>
<th>Polymer</th>
<th>Drug</th>
<th>Loading method</th>
<th>Loading efficiency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-Cyclodextrin</td>
<td>Babchi oil</td>
<td>Blank NS were dispersed in water. Excess amount of babchi oil was added and stirred for 24 h. The suspension was centrifuged. The supernatant was freeze-dried</td>
<td>21.47% w/w maximum and 14.23% minimum</td>
<td>[72]</td>
</tr>
<tr>
<td>β-Cyclodextrin</td>
<td>Griseofulvin</td>
<td>Drug dispersed in aqueous colloidal dispersion of NS having PVP. Suspension was stirred and centrifuged. Supernatant was freeze-dried</td>
<td>Maximum 47.2% and minimum 20.20%, based on formation of ternary complex</td>
<td>[73]</td>
</tr>
<tr>
<td>β-Cyclodextrin</td>
<td>Celecoxib</td>
<td>Method 1: Drug and polymer were dissolved in dimethyl formamide. This solution was stirred. Crosslinker was added to same solution. (internal phase) This was added to water (external phase) and stirred. The suspension was lyophilized</td>
<td>After using N,N-methylene bisacrylamide, 22.11 ± 0.41 to 26.26 ± 0.24% Loading was seen.</td>
<td>[74]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Method 2: Drug and polymer were dissolved in dimethyl formamide. (internal phase) This was added to crosslinker in water (external phase) and stirred. The dispersion was lyophilized</td>
<td>After using glyoxal, 22.48 ± 0.23 to 24.85 ± 0.47% loading was achieved</td>
<td></td>
</tr>
<tr>
<td>B-Cyclodextrin</td>
<td>Piperine</td>
<td>NS were suspended in water and stirred. Then the drug is gradually added. The dispersion was sonicated and then stirred. The suspension was centrifuged to remove excess of drug. The supernatant was lyophilized and stored in a desiccator.</td>
<td>Loading efficiency was 42.6 ± 1.1%</td>
<td>[75]</td>
</tr>
<tr>
<td>B-Cyclodextrin in Fe₃O₄ nanoparticles coated by β-CD</td>
<td>Curcumin</td>
<td>Nanoparticles were dispersed in PBS. Curcumin solution in acetone was added to the suspension. Mixture was shaken overnight in dark. The product was separated using a magnet and washed by de-ionized water</td>
<td>Loading efficiency was 96% at 1:2 ratio of drug: carrier</td>
<td>[76]</td>
</tr>
</tbody>
</table>
Recent Pharmaceutical Developments in the Treatment of Cancer Using Nanosponges
DOI: http://dx.doi.org/10.5772/intechopen.105817

Voltage, and different resolutions were used to obtain images. The images showed a perfect spherical shape of loaded nanosponges. Some drug particles were present on the surface as well as numerous porous channels were present on the surface. As compared to blank nanosponges, drug-loaded nanosponges were more porous [87]. Atomic force microscopy involves interactions of probe with sample through up-down and side-to-side movement along area of sample which is checked using a laser beam. Choudhary et al. [88] synthesized two peptides. And these linked peptides were attached to a trimaleimide frame. It gave two structures with positive and negative charge. Then using those differently charged structures, two variants were formed having 15 and 20 subunits, respectively. These two types of structures were mixed under conditions mimicking human body which resulted in the formation of nanosponges. 0.05 M stock solution of NS was prepared in PBS, and a drop was added on a freshly prepared mica sheet. The buffer was removed using nitrogen stream for 2 min. Bruker Innova AFM system was used to take the pictures using a TESPA-HAR probe in tapping mode. Spring constant was kept 50 N/m and operated at a frequency of 350 KHz. Images were taken at a scan rate of 1 Hz. The structures with 15 subunits showed formation of bundles made from three to five subunits. The structure with 20 subunits formed excellent nanosponges in the range of 80–115 nm [88].

<table>
<thead>
<tr>
<th>Method</th>
<th>Drug</th>
<th>Loading Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-Cyclodextrin Camptothecin</td>
<td>Drug was added to aqueous nanosponge suspension and stirred for 24 h in dark. The suspension was centrifuged to separate free drug. Colloidal supernatant was freeze-dried</td>
<td>Loading efficiency was 38% w/w [77]</td>
</tr>
<tr>
<td>B-Cyclodextrin Curcumin</td>
<td>Curcumin dissolved in dichloromethane. Nanosphges were added to this solution and triturated till solvent evaporates. The product was dried</td>
<td>46.45 ± 0.54 mg and 48.37 ± 0.47 mg of curcumin/100 mg of F1 and F2 respectively [78]</td>
</tr>
<tr>
<td>B-Cyclodextrin Nifedipine</td>
<td>Prepared nanosphges and nifedipine in excess were mixed and were suspended in distilled water. The mixture was sonicated and then stirred. Aq. Suspension centrifuged to separate free drug. Supernatant was lyophilized</td>
<td>Encapsulation efficiency was 78.4 ± 0.24% [79]</td>
</tr>
<tr>
<td>Ethyl cellulose Lansoprazole</td>
<td>Drug and polymer were added to dichloromethane. This disperse phase was added to aq. PVA solution. Mixture stirred for 2 h. Prepared NS were filtered and dried</td>
<td>Entrapment efficiency was 86.93 ± 0.65% in F2 [80]</td>
</tr>
</tbody>
</table>

Table 2. Methods of preparation of nanosponges.
Photon correlation spectroscopy involves measuring Brownian motion of particles as a function of time which is recorded by scattering of laser where scattering is directly proportional to particle size. Yakavets et al. [89] synthesized nanosponges from ethyl cellulose, PVA and pleuronic F68 by emulsion solvent diffusion technique. The particle size was measured using a Nano ZS-90 (Malvern instruments Ltd., UK) at an angle of 25°. The sample was diluted 10 times and analyzed. The composition F2 showed minimum particle size at 83 nm [89]. Wang and Schaaf [90] synthesized size-controlled Au-Ag nanosponges. Their structural characterization was carried out using SEM and TEM. Advanced techniques, such as focused ion beam, were used to reveal the hybrid composition of nanosponges. 3D structural properties were analyzed using techniques such as synchrotron X-ray nanometrography. Atom probe tomography can be used where the obtained images are aligned again and again to allow reconstruction of particle image and thus to obtain the parameters. Nanosponges have peculiar optical properties due to their complex structure. Properties such as optical scattering and photoluminescence can be measured using

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Model used</th>
<th>Dependent var.</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Box-Behnken</td>
<td>Polymer conc (mol)</td>
<td>Particle size depends directly on polymer concentration</td>
<td>[81]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crosslinker conc (mol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reaction time</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Particle size</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entrapment efficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3(^2) full factorial design</td>
<td>Amt of β-CD (gm)</td>
<td>As B-CD conc increase and porosity increases.</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amt of DPC (gm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porosity</td>
<td>Zeta potential depends on particle size only.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zeta potential</td>
<td>Drug loading depends upon DPC conc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug loading</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3(^2) full factorial design</td>
<td>THCL:EC ratio (w/w)</td>
<td>Particle size reduced as stirring rate increased.</td>
<td>[83]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stirring rate (rpm)</td>
<td>Entrainment efficiency decreased by increasing stirring rate.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Particle size</td>
<td>Production yield increases as polymer conc increases.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Production yield (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entrapment efficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Robust model</td>
<td>Amount of EC</td>
<td>Particle size increases with increase in drug-polymer ratio.</td>
<td>[84]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amount of PVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Particle size</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entrapment efficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2(^3) full factorial design</td>
<td>Amount of HP-β</td>
<td>Particle size decreases with increase in concentration of CDI and β-CD.</td>
<td>[85]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amount of β-CD</td>
<td>% Entrapment efficiency increases with increase in concentration of HPβ-CD and β-CD.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amount of CDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Entrapment efficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Particle size</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Optimization of nanosponges.
dark field florescence confocal microscopy [90]. The analytical techniques may vary with use of the final product. Maity et al. [91] synthesized nanosponges of acidic aminosilicates for the purpose of catalysis. Those were analyzed using morphological characterization techniques such as SEM and TEM which confirmed the formation of nanosponges as well as their porous structure. X-ray diffraction studies were carried out to understand the percentage of aluminium precursors. 1-D and 2-D NMR studies were carried out to understand the locations of catalytically active sites of nanosponges. A temperature-programmed desorption study using ammonia was carried out to understand the distribution of acidic sites in nanosponges and to identify their correlation with NMR data [91].

12. Encapsulation efficiency

Encapsulation efficiency indicates the amount of drug which gets successfully entrapped in a nanoparticle. Rezaei et al. (2019) prepared cyclodextrin nanosponges loaded with ferulic acid where three ratios of β-CD: crosslinker taken namely 1:2, 1:4 and 1:8 were synthesized. To determine the encapsulation efficiency, drug-loaded and blank nanosponges were suspended in ethanol and sonicated at room temperature separately. The sonicated dispersions were filtered using a filter paper with pore size of 0.45 μm. Ferulic acid content was determined using UV-visible spectrophotometry at 319 nm. The analysis showed that nanosponge prepared with 1:4 ratio of β-CD to crosslinker showed maximum encapsulation as lower ratio resulted in an insufficient amount of crosslinking and a ratio of 1:8 showed hyper-crosslinking, hence reducing the amount of encapsulated ferulic acid [92]. Dhakar et al. [93] prepared cyclodextrin nanosponges loaded with resveratrol and oxyresveratrol. The prepared nanosponges were added to water to give a solution of 10 mg/ml, and drugs were added in different ratios of drug: nanosponge, i.e. 1:2, 1:4 and 1:6. The mixtures were stirred for a day in dark after sonicating them for some time. The supernatant was collected after centrifugation of formulation, and it was lyophilized to give a dry powder. The powder was subjected to High-performance liquid chromatography (HPLC) analysis to understand loading of the drugs. The powder was taken in vials containing ethanol and sonicated for an hour. It was analyzed using High-performance liquid chromatography (HPLC). The drug loading was maximum in the ratio of drug to nanosponge which is 1:4, since saturation solubility was achieved. The encapsulation efficiency of the nanosponges was found to be 77% for resveratrol and 80% for oxyresveratrol. In addition, the encapsulation demonstrated an increase in the solubility of previously insoluble compounds. Diphenyl carbonate and beta-cyclodextrin were used to make nanosponges in various molar ratios, including 1:2, 1:4, 1:6, 1:8, and 1:10. Through the process of freeze-drying, which involved adding specific amounts of blank nanoparticles and babchi oil to water, stirring, and sonicating for a day, they were loaded with the babchi oil. The mixture was centrifuged to remove the oil which did not enter the inclusion complex. The supernatant was removed and freeze-dried. A specific amount of NS were added to dimethyl sulfoxide and sonicated to separate drugs from complex. The samples were analyzed using UV spectrophotometer at 265 nm. The encapsulation efficiency was observed in the range 62–93%. The maximum efficiency was present in formulation with the molar ratio of cyclodextrin to carrier 1:4. In formulations with higher number of crosslinking agents, hyper-crosslinking resulted in less loading [72]. Appleton et al. [94] prepared β-cyclodextrin nanosponges by reacting polymer, triethanolamine
and pyromellitic dianhydride in DMSO at 90° in an RBF. The prepared product was solidified, washed and ground. The coarse product was ground and purified with acetone using Soxhlet extraction. Insulin was loaded in blank carriers by mixing an acidic solution of drug in a solution of nano-formulation where the ratio between insulin and nanosponges was 1:5. The mixture was stirred, and the sediment was lyophilized. Such prepared nanosponges were added to a mobile phase in a proper concentration and sonicated. The solvent was analyzed using UV spectrophotometry. The encapsulation efficiency was 91% [94]. The product was washed using water and ethanol and later purified using Soxhlet extraction. For loading, solvents such as ethanol, methanol, acetone and only essential oil were tested for four different time intervals from 1 to 4 days. A weighed quantity of nanosponges were placed in a microtube, and coriander essential oil dissolved in a solvent was added. The mixture was stirred at room temperature to facilitate loading. Then the sample was centrifuged to separate the loaded nanosponges and was freeze-dried. After freeze-drying, the samples were dispersed in acetone and stirred for a day which were later centrifuged to separate the acetone supernatant. The obtained supernatants were analyzed using Gas chromatography–mass spectrometry (GC-MS). Five major constituents such as pinene, cynene, camphor, linalool and geranyl acetate were used to detect quantitatively [95].

13. Nanosponges for delivery of anticancer drug

Anticancer drugs are notoriously famous for their side effects which can be decreased by the use of nano-formulations which reduce the dose required and hence the side effects. Wang et al. synthesized nanosponges from DNAzyme-containing ZnO to release therapeutically active ROS [96]. Table 4 indicates such similar results and show enhanced action of dosage forms over administration of single API.

14. Functionalization of nanosponges

Functionalization involves attachment of various functional group or functional molecules on nanoparticle surface. Such a process imparts targeting properties to the nanoparticle. Femminò et al. functionalized cyclodextrin nanosponges using oxygen to relieve hypoxic conditions in ailments such as tumors [103]. Some examples of functionalization of nanosponges using chemical as well as biological functional ingredients are shown in Table 5.

15. Future trends

Nanosponges have been limited for catalytic action or use as a carrier. Mostly simple nanosponges or those with basic functionalization are synthesized and used for delivery of single therapeutic agents, but the future trends are nanosponges that have been designed for storage of phase change materials. 3-D carbon-based materials such as nanosponges are preferred for loading of phase change materials which can be applied in locations such as operation tables, storage of medical and pharmaceutical products. Nanosponges can show advantages for application of both solid- and liquid-phase change
<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
<th>Cancer type</th>
<th>Studies performed</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>B-cyclodextrin</td>
<td>Breast cancer</td>
<td>Human MDA-MB231 and MCF-7 cell lines, mouse 4T1 (DOX-sensitive) and EMT6/AR10r (DOX-resistant) cell lines, efficacy using MTT assay</td>
<td>Concentration-dependent inhibition of cell viability which was more than doxorubicin</td>
<td>[97]</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>B-cyclodextrin conjugated with glutathione</td>
<td>Lung cancer</td>
<td>Human lung carcinoma cells (A549 cells), MTT assay to determine efficacy</td>
<td>Dose- and time-dependent inhibition of proliferation of A549 cells. Nanosponges showed better effect at lower dose than only erlotinib.</td>
<td>[98]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>B-cyclodextrin</td>
<td>Melanoma</td>
<td>Types of human cell lines used—A375, M14, JR8, RPMI7932, PCF-2 and LM. Types of mice cell lines used—B16-BL6</td>
<td>The formulation showed increased oral bioavailability and efficacy as compared to free drug. The formulation showed considerably lesser toxicity as compared to free drug. The formulation also showed inhibition of metastasis and growth.</td>
<td>[99]</td>
</tr>
<tr>
<td>Ferulic acid</td>
<td>B-cyclodextrin</td>
<td>Breast cancer</td>
<td>MCF7 cell lines for human breast cancer and 4T1 cell line for mouse breast cancer, using MTT assay</td>
<td>The cytotoxicity was observed at concentration above 500 μM. The cytotoxic effect was time-dependent. As the formulation enhanced the solubility, the inhibitory concentration was reduced.</td>
<td>[92]</td>
</tr>
<tr>
<td>Strigolactone</td>
<td>B-cyclodextrin conjugated with glutathione</td>
<td>Prostate cancer</td>
<td>DU145 and PC-3 prostate cancer cells, efficiency studied using MTT assay</td>
<td>The free drug as well as nanosponges inhibited the cell proliferation. This activity on the formulation was dependent on intracellular GSH amount.</td>
<td>[100]</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>B-cyclodextrin</td>
<td>Breast cancer</td>
<td>MCF-7 cell lines for human breast cancer were used, and MTT assay for checking the proliferation</td>
<td>The complex showed high loading, sustained release, and aqueous dispersion. The cytotoxicity was found to be reduced due to sustained release effect</td>
<td>[101]</td>
</tr>
</tbody>
</table>
Naphthofluorescin was conjugated with Poly(VL-AVL-EVL) T-Peptide_ACPP and cyanine-3 hydrazide. RAW cells and HT1080 cells were used; MTT assay was used for efficacy testing. The formulation was able to locate collagen in the presence of MMP2 enzyme. Both cell types showed a good extent of internalization.

Doxorubicin Oligonucleotide DNA MCF-7 cells and Hs 578 Bst cells were used for analysis, and MTT assay was used for efficiency. The DNA nanosponges were broken down at acidic pH. These carriers were able to overcome barriers and target cells. The cytotoxicity was similar to free drug due to less release.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
<th>Cancer type</th>
<th>Studies performed</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naphthofluorescin</td>
<td>Poly(VL-AVL-EVL) conjugated with T-Peptide_ACPP and cyanine-3 hydrazide</td>
<td>RAW cells and HT1080 cells were used; MTT assay was used for efficacy</td>
<td>The formulation was able to locate collagen in the presence of MMP2 enzyme. Both cell types showed a good extent of internalization.</td>
<td>[32]</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Oligonucleotide DNA</td>
<td>MCF-7 cells and Hs 578 Bst cells were used for analysis, and MTT assay was used for efficiency</td>
<td>The DNA nanosponges were broken down at acidic pH. These carriers were able to overcome barriers and target cells. The cytotoxicity was similar to free drug due to less release.</td>
<td>[102]</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Nanosponges for delivery of anticancer drugs.
Recent Pharmaceutical Developments in the Treatment of Cancer Using Nanosponges
DOI: http://dx.doi.org/10.5772/intechopen.105817

Materials. Carbon nanosponges have high loading and can be filled with a high number of materials. And nanosponges do not behave to changes in temperature [108–110]. Korea Ceramic Technology Institute developed a thermosponge for the treatment of cancer. It is a thermoresponsive nanosponge used for delivery of both hydrophilic and hydrophobic drugs. This nanosponge is made up of a core of poly-D, L-lactide which is loaded with a hydrophobic drug and the outer covering is made up of Pluronic-F127 which is loaded with a hydrophilic drug. The drugs can be released at the same time or the drug entrapped in the core may be released at a later time showing a prolonged release. The system is biodegradable and biocompatible, hence showing very less to no toxicity at all.

16. Conclusion

In this review, nanosponges and their synthesis, characterization, optimization and applications regarding cancer have been discussed. According to the literature,

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Functionalized by</th>
<th>Rationale</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLGA</td>
<td>Cancer cell membrane</td>
<td>By coating with cancer cell membrane, the particle shows homologous binding and biomimetic and targeting capacity. It possesses properties of a cancer cell to allow targeting.</td>
<td>[104]</td>
</tr>
<tr>
<td>Carbon quantum dot-polyethylene glycol bisacrylate</td>
<td>Hydrazine</td>
<td>The carboxyl groups of Crosslinked carbon quantum dots (CQDs) were amidated using hydrazine to imine to give an acid labile bond which will be broken down in acidic tumor environment.</td>
<td>[105]</td>
</tr>
<tr>
<td>Fe₃O₄ nanoparticles coated with B-CD nanosponge</td>
<td>Folic acid</td>
<td>Fe₃O₄ nanoparticles as a core to provide clear visualization during MRI. Folic acid for smart drug delivery and specific targeting.</td>
<td>[78]</td>
</tr>
<tr>
<td>B-cyclodextrin</td>
<td>Cholesterol</td>
<td>Cholesterol is a major component of cell membrane. Attachment of cholesterol on surface of nanosponges allows biodhesion and enhances cellular uptake.</td>
<td>[41]</td>
</tr>
<tr>
<td>Gold nanosponge</td>
<td>Poly (N-isopropylacrylamide-methacrylic acid-1,4-dioxane, octadecyl acrylate)</td>
<td>pH- and thermal-responsive polymer.</td>
<td>[106]</td>
</tr>
<tr>
<td></td>
<td>EpDT3</td>
<td>An aptamer which binds to EpCAM, a biomarker present on cancer cell, helps on targeting.</td>
<td></td>
</tr>
<tr>
<td>Reduced graphene oxide-lipid nanosponge</td>
<td>Protein Lf (Lactoferrin)</td>
<td>Lactoferrin shows selectivity towards cancer cell and inhibits cancer cell proliferation and migration.</td>
<td>[107]</td>
</tr>
</tbody>
</table>

Table 5. Functionalization of nanosponges.
nanosponges can be classified based on their starting materials which could be polymers, metals, metal oxides, etc. Polymer nanosponges can be manufactured by methods such as melt method, emulsion method, solvent method and ultrasound-assisted method. Metallic nanosponges are manufactured by methods such as dealloying and sol-gel methods. Factors related to drugs or process parameters influence formation of nanosponges. These process parameters were used by many researchers to optimize the formulation of nanosponges to give the optimum results related to loading efficiency, particle size and encapsulation efficiency. Polymer structure also affects the formation of nanosponges. Tumors are important manifestations of cancer and provide many challenges to deliver drugs inside the tumor where dividing cells are located. These challenges can be overcome by the process of functionalization with chemical moieties or biological entities such as cell membrane fragments. Such prepared nanosponges can be characterized with many methods such as SEM and TEM which are reported in literature. Toxicity of nanosponges may be a growing concern due to their ever-increasing role in multiple industries. According to the literature, nanosponges are safe for use as a carrier. But their nanosize may alter their properties, and hence reactivity causes toxicity due to processes such as physical interaction, ROS generation and intracellular dissolution. Many methods have been reported in literature such as using antioxidants and altering the material available to reduce this toxicity.

Declaration of interest statement

Authors declare there are no conflicts of interest.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>cyclodextrin</td>
</tr>
<tr>
<td>NS</td>
<td>nanosponges</td>
</tr>
<tr>
<td>PVA</td>
<td>poly (vinyl) alcohol</td>
</tr>
<tr>
<td>PBS</td>
<td>phosphate buffer saline</td>
</tr>
<tr>
<td>EC</td>
<td>ethyl cellulose</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethyl formamide</td>
</tr>
<tr>
<td>PEG</td>
<td>poly (ethylene) glycol</td>
</tr>
<tr>
<td>HP-β</td>
<td>hydroxypropyl beta cyclodextrin</td>
</tr>
<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
</tr>
<tr>
<td>P-gp</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>DOX</td>
<td>doxorubicin</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxy ribonucleic acid</td>
</tr>
</tbody>
</table>
Author details

Kapil Gore¹, Sankha Bhattacharya¹ and Bhupendra Prajapati²*

1 Department of Pharmaceutics, School of Pharmacy and Technology Management, SVKM’S NMIMS Deemed-to-be University, Shirpur, Maharashtra, India

2 Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Gujarat, India

*Address all correspondence to: bhupendra.prajapati@ganpatuniversity.ac.in, bhupen27@gmail.com

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References


Recent Pharmaceutical Developments in the Treatment of Cancer Using Nanosponges
DOI: http://dx.doi.org/10.5772/intechopen.105817


[23] Yapa AS et al. Peptide nanosponges designed for rapid uptake by leukocytes and neural stem cells. RSC Advances. 2018;8(29):16052-16060


[27] Maeda H. Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity. Advanced Drug Delivery Reviews. 2015;91:3-6


[34] Raghunand N, Gillies RJ. pH and drug resistance in tumors. Drug


[51] Swaminathan S, Cavalli R, Trotta F. Cyclodextrin-based nanosponges: A versatile platform for cancer nanotherapeutics development. Wiley Interdisciplinary Reviews:
Recent Pharmaceutical Developments in the Treatment of Cancer Using Nanosponges
DOI: http://dx.doi.org/10.5772/intechopen.105817


[56] Sadjadi S, Heravi MM, Malimir M. Bio-assisted synthesized Ag (0) nanoparticles immobilized on SBA-15/cyclodextrin nanosponge adduct: Efficient heterogeneous catalyst for the ultrasonic-assisted synthesis of benzopyranopyrimidines. Applied Organometallic Chemistry. 2018;32(4):e4286


[67] Allahyari S et al. Cyclodextrin-based nanosponges as promising carriers for


[69] Pawar S, Shende P. A comprehensive patent review on β-cyclodextrin cross-linked Nanosponges for multiple applications. Recent Patents on Nanotechnology. 2020;14(1):75-89


Recent Pharmaceutical Developments in the Treatment of Cancer Using Nanosponges
DOI: http://dx.doi.org/10.5772/intechopen.105817

Pharmaceutical Nanotechnology. 2019;7(5):343-361


[95] Simionato I et al. Encapsulation of cinnamon oil in cyclodextrin nanosponges and their potential use for antimicrobial food packaging. Food and Chemical Toxicology. 2019;132:110647


Artificial Cells, Nanomedicine, and Biotechnology. 2018;46(5):1064-1075


[102] Zhang K et al. DNA nanosponge for adsorption and clearance of intracellular miR-21 and enhanced antitumor chemotherapy. ACS Applied Materials & Interfaces. 2019;11(50):46604-46613


