

Multifunctional Nanosponges for the Treatment of Cancer- A Review

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Abstract

Nanosponges are multifunctional drug delivery systems, which simultaneously enhance the effectiveness and reduce undesirable side effects of a number of different drugs. These tiny particles can carry large numbers of drug molecules. When attached with a molecular transporter, these nanosponges are capable of crossing various biological barriers into specific intracellular compartments, which are very difficult places for most drugs to reach. These nanoparticles circulate in the body until they encounter the surface of a tumor cell, where they adhere to the surface and begin releasing the drug in a controllable and predictable fashion. This review will discuss the properties of nanosponges that allow for such multiple functionality, as well as recent scientific advances in the area of multi-functional nanosponges for cancer therapeutics.

INTRODUCTION

For decades researchers are working to develop nanoparticles that deliver cancer drugs directly to tumors by minimizing the toxic side effects of chemotherapy. However, even with the best of these nanoparticles, only a fraction of the drug typically reaches its intended target. Several therapeutic nanocarriers have been approved for clinical use. However, to date, there are only a few clinically approved nanocarriers that incorporate molecules to selectively bind and target cancer cells (1). There are two aspects in creating an effective drug delivery system that is finding a chemical compound that has the desired biological effect and minimal side-effects and then delivering it to the right place in the body for it to do its job (2). But developing an effective targeted drug delivery system has been largely frustrated by the complex chemistry involved in the development of new systems. The development of new and complex molecules called nanosponges has the potential to solve these problems (3).

CANCER

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. The burden of cancer is increasing in economically developing countries as a result of population aging and growth as well as, increasingly with the adoption of cancer-associated lifestyle choices including smoking, physical inactivity and unhealthy diets (4,5). About 12.66 million cancer cases and 7.56 million cancer deaths are estimated to have occurred in 2008 worldwide with 56% of the cases and 64% of the deaths in the economically developing world. Breast cancer in females and lung cancer in males are the most frequently diagnosed cancers and the leading cause of cancer death for each sex in both economically developed and developing countries (6). The latest world cancer statistics report that the number of new cancer cases will increase to more than 15 million in 2020 (7).

The prevalence of cancer in India is estimated to be around 2.5 million, with over 8,00,000 new cases and 5,50,000 deaths occurring each year due to this disease (8,9). In the United States, about 16,38,910 new cancer cases are expected to be diagnosed in 2012 and about 5,77,190 are expected to die of cancer, more than 1,500 people per a day. Cancer is the second most common cause of death in the US (10). The American Cancer Society's annual cancer statistics report shows that between 2004 and 2008, overall cancer incidence rates declined by 0.6% per year in men and were stable in women, while cancer death rates decreased by 1.8% per year in men and by 1.6% per year in women. Death rates continue to decline for all four major cancer sites (lung, colorectum, breast, and prostate), with lung cancer accounting for almost 40% of the total decline in men and breast cancer accounting for 34% of the total decline in women (10,11). This decrease in mortality is due

to better understanding of tumor biology and improved diagnostic devices and treatments. Cancer therapies are currently limited to surgery, radiation, and chemotherapy. All three methods are having the risk of damaging normal tissues and incomplete eradication of the cancer (1).

Although conventional treatment options such as chemotherapy and radiation have experienced many advances over the past decades, cancer therapy is still far from optimal (12). The traditional chemotherapy suffers from delivering the drug efficiently to the tumor mass because of the inherent complexity of tumor microenvironment and the existence of P-Glycoprotein (P-gp), meanwhile, other physiological barriers such as hepatic and renal clearance, enzymolysis and hydrolysis, as well as endosomal/lysosomal degradation are also preventing drug from reaching tumor mass (13,14). In addition, the efficiency of anticancer drugs is limited by their unsatisfactory properties, such as poor solubility, narrow therapeutic window, and intensive cytotoxicity to normal tissues, which may be the causes of treatment failure in cancer (15,16). To alleviate this difficulty, decades of research have focused on developing cancer-specific drugs or delivery systems that can preferentially localize existing agents to the tumor site. Recent advances in nanotechnology promises further developments in target-specific drug delivery systems (12).

IMPACT OF NANOTECHNOLOGY ON CANCER

Nanotechnology is the creation and utilization of materials, devices, and systems through the control of matter on the nanometer-length scale, i.e. at the level of atoms, molecules, and supramolecular structures. These technologies have been applied to improve drug delivery and to overcome some of the problems of drug delivery for cancer treatment (17). Nanotechnology has the power to radically change the way cancer is diagnosed, imaged and treated. Currently, there is a lot of research is going on to design novel nanodevices capable of detecting cancer at its earliest stages, identifying its location within the body and delivering anticancer drugs specifically to malignant tumor cells (18).

Based on nanotechnology nanocarriers like nanoparticles, liposomes, micelles, carbon nanotubes, dendrimers, quantum dots, and nanofibers have been developed from various organic and inorganic materials. They have shown great potential in cancer therapy by enhancing the performance of medicines and reducing systemic side effects in order to gain therapeutic efficiency (16)]. Nanoparticles, by using both passive and active targeting strategies, can enhance the intracellular concentration of drugs in cancer cells while avoiding toxicity in normal cells. Furthermore, when nanoparticles bind to specific receptors and then enter the

cell, they are usually enveloped by endosomes via receptor-mediated endocytosis, thereby bypassing the recognition of P-glycoprotein, one of the main drug resistance mechanisms (19).

In 2006 a global survey showed that more than 150 companies are developing nanoscale therapeutics (20). At present 24 nanotechnology-based therapeutic products have been approved for clinical use, with total sales exceeding \$5.4 billion per annum. Among these products, liposomal drugs and polymer-drug conjugates are two dominant classes, accounting for more than 80% of the total amount (21). Even with the advances in nanotechnology and polymer chemistry at the moment only about one per cent of drugs are delivered with these nanotechnologies no matter what kind of nanotechnology it is but there is a lot of effort from different councils and also from the Government to increase this and they are hoping to increase this by 15 per cent in the next decade (22).

Despite the benefits that nanoparticles have rendered to medicine, some applications remain challenging; for instance, in vivo real-time monitoring of cellular events, specific targeting to the action site or efficient drug delivery inside the target cell (23). In addition to this, Irreproducibility in the size and shape of the particles is the major disadvantage of conventional nanoparticles. Lack of pendant functional groups is also limiting in tailoring the properties of a particle, including hydrophilicity, biodegradation rate and bioadhesion. Therefore, there remains a need for methods and compositions that overcome these deficiencies and those effectively provide functionalized, degradable nanoparticles with reproducibility in particle size and shape (24).

In this context, the design of multifunctional nanosponges could significantly improve the cancer therapy of many chemotherapeutic agents. These multifunctional nanosponges combine different functionalities in a single stable construct. These nanosponges can carry wide variety of substances and could be linked to a specific targeting function that recognises the unique surface signatures of their target cells. Simultaneously, the nanosponges can be modified with an imaging agent to monitor the drug transport process, a function to evaluate the therapeutic efficacy of a drug, a specific cellular penetration moiety and a therapeutic agent (24).

NANOSPONGES

Nanosponges are complex molecules that can be used to deliver anti-cancer drugs to targeted sites within the body. The technology is still under development, but has been shown to be up to five times more effective at delivering drugs for breast cancer, than conventional methods (25). Nanosponges have the potential to change the way drugs are delivered in the human body, making them more efficient and reducing side effects. It looks like a globe and it has a network and it is completely degradable because it is an organic structure and is a soft material. The complex molecule breaks down within the body at a predictable rate (26).

Nanosponges like the name implies are nanoparticles that are filled with medication, and that medication is slowly released overtime as the sponge starts to decompose. These are devices can be attached to a molecular transporter which carries it and its cargo across biological barriers into specific intracellular compartments, which are very difficult places for most drugs to reach. Some recent studies indicated that these nanosponges can traverse the difficult brain-blood barrier. So this way, we can use a nanosponge to hold a cancer medication, and then attach a linker that will only attach to cancer cells (22).

A Nanosponge is a multifunctional nanoparticle obtained by extensive internal cross-linking to scrunch a long, linear molecule into a sphere approximately the size of a protein. The backbone of scaffold structure is a biodegradable polymer which facilitates the breakdown of these sponge like structure and predictable release

of drug molecule (27,28). Nanosponges can be used as a vessel for pharmaceutical principles to improve the aqueous solubility of lipophilic drugs, to protect degradable molecules and to formulate drug delivery systems for various administration routes beside the oral one (29). By delivering the anti-cancer agent directly to the cancerous tissues, a nanosponge decreases the adverse effects on other tissues and increases its potency by delivering a higher concentration of the drug directly on the tumor cells (27). These nanosponges are very novel and versatile and can be adapted to delivery of proteins, peptides, DNA and smaller chemical compounds like most drugs (23).

The nanosponges can be synthesized to be of specific size and to release drugs over the time by varying the proportion of cross linker to polymer. The engineering capacity of nanosponge is due to the relatively simple chemistry of its polymers and cross linkers compared to many other nanoscale drug delivery systems (3,27). These nanosponges can be magnetized when they are prepared in the presence of compounds having magnetic properties and can be attached with a florescent tag to monitor where it goes (30). The tiny shape of nanosponges enables the pulmonary and venous delivery of nanosponges (31).

As compared to the other nanoparticles, Nanosponges are soluble both in water and organic solvents, porous, non toxic and stable at high temperatures. Furthermore, nanosponges show a remarkable advantage in comparison with the common nanoparticles: indeed, they can be easily regenerated by different treatments, such as washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating, or changing pH or ionic strength. For all these characteristics, nanosponges have been already employed in different applied fields, such as cosmetic and pharmaceutical sectors (32).

Nanosponges release the drug at the tumor site instead of circulating widely through the body. So, it is more effective for a given dosage and also will have fewer harmful side effects because smaller amounts of the drug come into contact with healthy tissue. They release the drug in a Predictable manner unlike many other nanoparticle delivery systems unloads most of their drug in a rapid and uncontrollable fashion when they reach their target. This is called the burst effect and makes it difficult to determine effective dosage levels.

Nanosponges are soluble in water; this allows the use of hydrophobic anticancer drugs that do not dissolve readily in water. Currently, these drugs must be mixed with another chemical, called an adjuvant reagent that reduces the efficacy of the drug and can have adverse side-effects. The nanosponges have an array of accessible side groups, which makes it easy to attach drugs to the particles.

We can functionalize the nanosponges very easily and we can load in the drug molecules very easily, which is not possible with traditional polymer nanoparticles and post modification strategies can be utilized to alter several properties of nanosponges, such as hydrophobicity, morphology, particle size, and functionality. The pendant functional groups provide the Linking to a specific targeting function and can be tailored to create the best possible characteristics for the nanosponges.

Many other drug delivery systems require complicated chemistry that will be difficult to scale up for commercial production, but the nanosponges are produced through fairly simple chemistry this enables the technology to scale up easily to commercial production levels without requiring unusual equipment or procedures. The size of the nanosponges can be controlled by varying the proportion of cross-linker to polymer, the nanosponge particles can be made larger or smaller.

This technology is Very novel and versatile and can be adapted to delivery of proteins, peptides, DNA and smaller chemical compounds like most drugs. Nanosponges can be attached with

new forms of vaccinations which allow the delivery of new weapons in a more direct way. These nanosponges can be attached with fluorescent tags to monitor where it goes. They can be formulated for targeted delivery to the lymphatic system, brain,

arterial walls, lungs, liver, spleen, or made for long-term systemic circulation. Some nanosponges developed with anticancer drugs along with the vehicle used are presented in table 1.

Table 1 List of nanosponges developed for cancer therapy

S. No.	Name of the drug and Vehicle	Vehicle	Studies performed	Study Model	Reference
Polyester nanoparticles					
1	Drug: Pacli-taxel	Poly(valerolactoneepoxyvalerolactone-allylvalerolactone-oxepanedione) containing 11% epoxide and cross linked with 2,2-(ethylenedioxy) bis(ethylamine)	In vivo cytotoxicity studies	Athymic nude and C57/B16 mice GL261 murine glioma and MDA-MB-231 human breast cancer cell lines	33
2	Temo-zolomide	Copolymers poly(valerolactone-allylvalerolactone) and poly (valerolactone-allylvalero lactone-oxepanedione) cross linked with 2,2-(ethylenedioxy) bis (ethylamine)	Invitro release studies and biodistribution studies	Dialysis bag technique (dialysis membrane cut-off 3500 Da)	34
Cyclodextrin nanosponges					
3	Dexa-methazone	β - Cyclodextrin cross linked with Carbonyldiimidazole	In vitro release experiments	Dialysis bag technique (dialysis membrane cut-off 3500 Da)	35
4	Resveratrol	β - Cyclodextrin cross linked with Carbonyldiimidazole	In Vitro Release Studies	Multi compartment rotating cell with dialysis membrane (cut-off 12,000 Da)	36
			Cytotoxicity Studies	HCPC-I cell line	
			Accumulation of Resveratrol - Ex Vivo Study	Buccal Mucosa of Rabbit	
			Permeation of Resveratrol Ex Vivo Study	Pigskin	
5	Tamoxifen	β - Cyclodextrin cross linked with Carbonyldiimidazole	In vitro release studies	Multi-compartment rotating cell with dialysis membrane (cut-off 12,000 Da)	37
			Cytotoxicity study	MCF-7 cell line	
			Pharmacokinetic studies	12 male/female Sprague-Dawley rats	
6	Campto-thecin	β - Cyclodextrin cross linked with Diphenyl carbonate	In vitro release studies	Multi-compartment rotating cells with a dialysis membrane (Sartorius, cut off 12,000 Da).	38, 39
			Haemolytic activity	Diluted blood	
			Cytotoxicity study	HT-29 cell line	
			MTT and colony forming assay	Hormonal independent PC3 and DU145 cells	
			In vivo efficacy	PC3 and DU145 xenograft experiments	
			In vitro experiments of tumor cell adhesion	HUVECs as a model of endothelium	
7	Doxorubicin hydro-chloride	β - Cyclodextrin cross linked with Diphenyl carbonate	Haemolysis experiments	Human erythrocytes	40
			Invitro drug release study	Multi-compartment rotating cell with a dialysis membrane (cut-off 12000 Da)	
			Cytotoxicity experiments	HT29 cell lines	
8	Paclitaxel	β - Cyclodextrin cross linked with Carbonyldiimidazole	Invivo pharmacokinetic	Group of eight male Sprague Dawley (SD) rats	41
Alginate nanosponges					
9	Antisense Oligo-nucleotides	Alginates crosslinked with poly-L-lysine	In vitro stability study	Bovine serum	42
			Pharmacokinetics and tissue distribution studies	OF1 mice	



Figure 1 (Wherein X is chlorine, imidazolyl, or a -OR group in which R is C1-C4 alkyl and n is an integer)

TYPES OF NANOSPONGES

The nanosponges can be classified as metal nanosponges and polymeric nanosponges. The metal nanosponges includes Silicon nanosponge particles (43), Carbon-coated metallic nanosponges (44), Ag/Pt Nanosponges (45), Titanium or other metal oxide-based nanosponges (46-48) are having little importance in drug delivery. Well known examples of Polymeric nanosponges are Hyper-cross-linked polystyrene nanosponges (49,50), Alginate nanosponges (42), Cyclodextrin-based nanosponges (51), Polyester based nanosponges[52], Ethyl cellulose and polyvinyl alcohol based nanosponges (53). The common characteristic of these materials is the presence of nanoscale pores, which give them particular properties.

Hyper-cross-linked polystyrene nanosponges present spherical shape and excellent size distribution, but their surfaces are hydrophobic and therefore they do not bind to large quantities of drugs (54). Polystyrene nanosponges can be used for column packing in chromatography. Nanosponges based on Ethyl cellulose and polyvinyl alcohol was reported for topical delivery of drugs. Cyclodextrin based nanosponges, alginate nanosponges and polyester nanosponges are reported to carry anticancer drugs. This review mainly focuses on Cyclodextrin-based nanosponges, polyester nanosponges and alginate nanosponges.

Cyclodextrin based nanosponges

Cyclodextrin are cyclic, nonreducing oligosaccharides characterized by a typical toroidal cone shape. The atom arrangement in the space is such that the inside cavity is lipophilic, while the outside of the torus is highly hydrophilic (55). The lipophilic cavity enables the cyclodextrins to form inclusion complexes which are stable in solution with organic molecules of suitable polarity and dimensions (56).

However, native CDs are incapable of forming inclusion compounds with certain molecules, such as hydrophilic or high-molecular-weight molecules and their inclusion constants rarely exceed the value of 10^3 . Recently it has been reported that cyclodextrins cross linked with carbonate bonds are capable of encapsulating a wide variety of substances with inclusion constants of about 10^8 - 10^9 (57).

The hyper cross linked polymers of cyclodextrins called 'nanosponges' because of their particular 'nanoporous structure' and they can advantageously carry water insoluble drugs. These Nanosponges have proved very useful in various applications ranging from environmental decontamination to controlled drug delivery and release (58).

Cyclodextrin-based nanosponges can form inclusion and non-inclusion complexes with different types of lipophilic or hydrophilic molecules (59). The interaction with nanosponges can increase the solubility of poorly water-soluble drugs and their dissolution rate. Consequently, nanosponges can markedly increase the solubility of molecules with very low aqueous solubility, like anticancer drugs, steroids and anti-inflammatory drugs (60). These nanosponges increase the aqueous solubility of lipophilic drugs to large extent compared to hydrophilic substances. This difference may be due to the higher number of lipophilic sites available for the complexation of lipophilic drugs in comparison with hydrophilic drugs (61).

Cyclodextrin based nanosponges can be obtained by reacting the selected cyclodextrin with a suitable cross-linking agents like diisocyanates, diarylcarbonates and carbonyl diimidazoles, carboxylic acid dianhydrides, and 2,2-bis(acrylamido)acetic acid (62). The cyclodextrins can be natural (α , β , γ), preferably β -cyclodextrin or partially chemically modified, such as methyl β -cyclodextrin, alkyloxy carbonyl cyclodextrins (58).

Among the many compounds suitable for use as cross-linking agents, particularly interesting results have been obtained using

active carbonyl compounds such as carbonyldiimidazole, dimethyl carbonate and diphenylcarbonate (62). The nanosponges obtainable by reacting cyclodextrins with carbonyl compound of formula X-CO-X is represented in the figure 1 and figure 2.

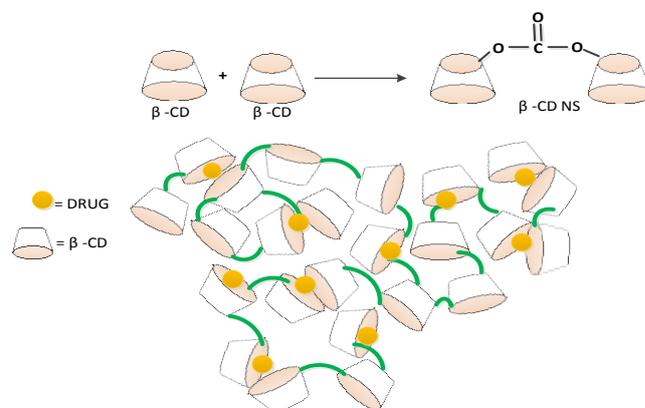


Figure 2 Cyclodextrin based carbonate nanosponge

CD-based carbonate nanosponges are insoluble in water and all organic solvents and do not swell appreciably; they are nontoxic, porous, and stable above 300°C (62).

The cyclodextrin nanosponges are solid particles with spherical morphology and can be used directly to prepare oral or injectable formulations using conventional techniques and excipients. For injectable formulations, the complex may be simply mixed with suitable vehicle and for oral administration nanosponges can be dispersed in a mixture of excipients like diluents, lubricants and anticaking agents suitable for the preparation of tablets and capsules. These nanosponges can be magnetised when they are prepared in the presence of compounds having magnetic properties (58).

Preparation of cyclodextrin based nanosponges

For the preparation of cyclodextrin nanosponges two methods are reported by Trotta et al. In the First method involves carrying out the reaction in a suitable solvent (55), where as the second method involves the reacting natural cyclodextrins with an organic dicarbonate in the absence of a solvent and under sonication (31).

Method I: Synthesis in solution at high temperatures

Take the excess quantity of carbonyl compound, preferably in a molar ratio (Crosslinker/Cyclodextrin) of 4 to 16, in a suitable solvent, in particular in a polar aprotic solvent such as dimethyl formamide, dimethylsulfoxide. Depending on the carbonylating agent used and on the required reaction time, the reaction can be carried out at temperatures ranging from 10°C to the reflux temperature of the solvent (55).

After completion of the reaction, allow the solution to cool at room temperature. Then grind the obtained solid in a mortar or mechanical mill and add excess quantity of bidistilled water to remove either impurities or nonreacted carbonyl derivative. Recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and grind to obtain homogeneous powder (3,62).

Method II: Ultrasound assisted synthesis

Take the required quantity of anhydrous cyclodextrin and the carbonyl compound, preferably a molar ratio (Crosslinker/Cyclodextrin) of 4 to 16 into a flask. Place the flask

in an ultrasound bath filled with water and heated to temperature between the ambient temperature and 90°C. Sonication can be continued upto 5 hours. Then allow the mixture to cool and break the product roughly. Wash the product with excess quantity of bidistilled water to remove the non reacted cyclodextrin and then wash in soxhlet with ethanol to remove the residual carbonate (31). The nanosponges obtained by this method will be spherical and uniform in size (3).

Polyester nanosponges

Degradable aliphatic polyesters like poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(ϵ -caprolactone) (PCL), and their polymers have received considerable importance in the medical and pharmaceutical field. They used as drug delivery systems, implant materials and diagnostic systems. For drug delivery purposes the polyester materials are administered in the form of nanoparticles, as they are able to cross physiological barriers and release the drug in a controlled manner (63).

Traditional biodegradable polyester nanoparticles are typically self-assembled from linear polyesters chains. The disadvantage of conventional polyester nanoparticles is the irreproducibility in size and shape of particles. Another drawback of conventional biodegradable polymers, based on other aliphatic polyesters, is the lack of pendant functional groups, which can make physicochemical, mechanical and biological properties difficult to modify. In conventional polyester nanoparticles, the drug pay load generally will not be more than 5% (24).

It has been recognized that the degradation behavior of nanoparticles and release profile of the encapsulated drug molecules are important factors in the development of

nanoparticles for cancer treatment. The release kinetics of Traditional polyester nanoparticles are challenged by a rapid release of drug molecules in the first 24-48 h followed by a slower release. These release profiles typically prevent the establishment of reliable dosages and results in multidrug resistance (64).

To alleviate the deficiencies of conventional nanoparticles compositions, a discrete functionalized polyester nanoparticles in selected nanoscale dimensions via controlled intermolecular chain cross-linking process has been reported by Eva Harth et al. These novel nanoparticles has been prepared by controlled coupling of epoxide functionalized polyesters with 2,3'-(ethylenedioxy)bis(ethylamine) to give well defined nanoparticles with narrow size distribution and selected nanoscopic size dimensions (63,64).

Preparation of Polyester nanosponges

Diverse functionalized polyesters, synthesized with pendant functionalities via ring-opening copolymerisation of δ -valerolactone with α -allyl- δ -valerolactone, α -propargyl- δ -valerolactone and 2-oxepane-1,5-dione, were prepared as linear precursors which facilitated 3-D nanoparticles with functionalities such as amines, keto groups, and alkynes for post modification reactions as shown in figure 3 (65).

These functionalized polyester nanoparticles can be efficiently attached with targeting units and dendritic molecular transporter entities to form potent carrier systems for targeted drug delivery and transport across biological barriers (66,67).

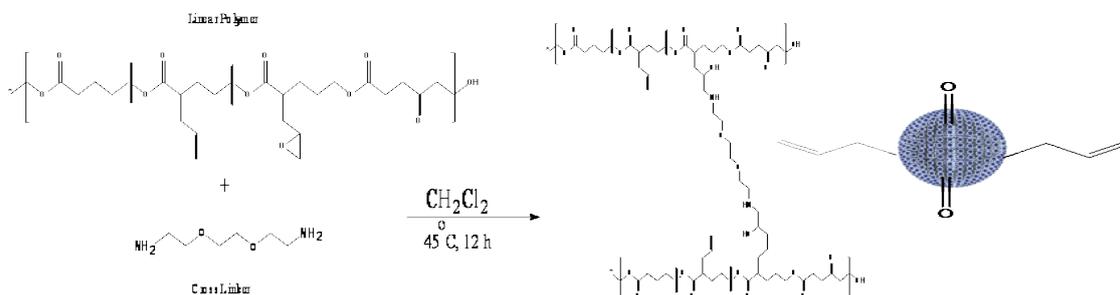


Figure 3 Synthesis of functionalized polyester nanosponges

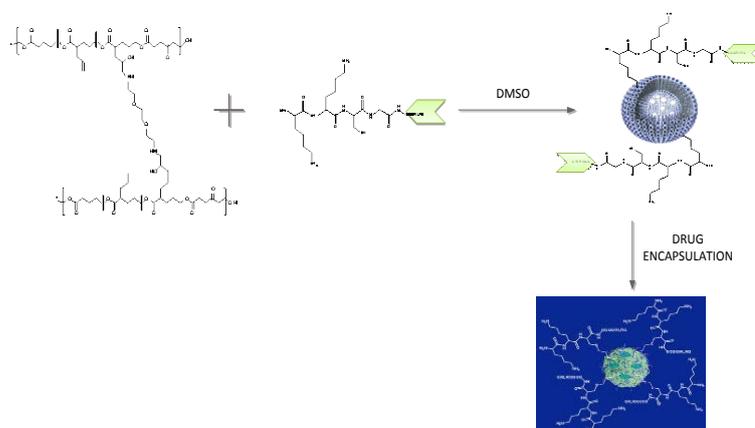


Figure 4 Attachment of ligands with polyester nanosponges

These novel nanocarriers are capable to entrap high concentrations of hydrophobic therapeutics and maintain a linear release profile which can be tuned to the demands of the tumor release as a result of the adjustable supramolecular architecture

accomplished through an intermolecular cross-linking technique. The nanoparticle formation and control over the nanoscopic dimension is primarily influenced by the degree of epoxide entity

and the amount of 2,1'-(ethylenedioxy)bis(ethylamine) as cross linking reagent.

Alginate nanosponges

Alginate is a naturally occurring, water-soluble, linear unbranched anionic polysaccharide consisting of linear copolymers of α -L-guluronate and β -D-mannuronate residues (68). The monomeric units are grouped in three ways: blocks of alternating guluronic and mannuronic residues, blocks of guluronic acids and of mannuronic acids (69). Alginate has been reported as mucoadhesive, biocompatible, non-immunogenic substance which undergoes dissolution and biodegradation under normal physiological conditions (70). Alginates have not been found to accumulate in any major organs and have shown evidence of in vivo degradation (71).

The solubility of alginate in water depends on the associated cations. Sodium alginate is soluble in water, whereas calcium induces the formation of a gel (72,73). Apart from the interaction with calcium, alginate may also form complexes with polycations such as polybenzimidazole (PEI), chitosan, or basic peptides like polylysine and polyarginine (74). The development of alginate based drug delivery systems makes use of the ability of this polymer to undergo gelation in presence of divalent cations (75,76). This property can be used to produce a pre-gel consisting of very small aggregates of gel particles, followed by the addition of an aqueous polycationic solution to make a polyelectrolyte complex coating. Poly-L-lysine (PLL), a cationic natural polymer, has been used to combine with alginates to prepare nanoparticles (77).

More recently Aynie et al. have developed a process which leads to the preparation of spongelike alginate and polylysine nanoparticles. Alginate nanosponges which are sponge-like nanoparticles containing many holes that carry the oligonucleotides. The new carrier system was prepared by crosslinking alginates with the aid of poly-L-lysine (PLL). The excess of positive lysyl residues provides interaction of oligonucleotides ionically and leads to efficient association with alginate nanoparticles. Thus, the system used for the transport of oligonucleotides is a spongelike structure with particle size of about 300nm as shown in figure 5 (78).

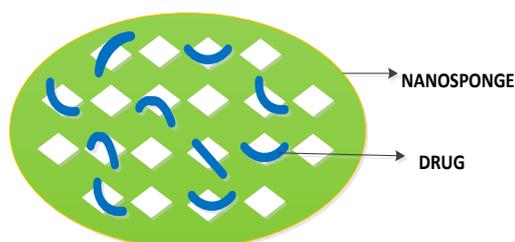


Figure 5 Alginate nanosponges

These alginate nanosponges have several advantages over other nanoparticles. They include (a) These are prepared in an aqueous medium without any organic solvent. (b) The drug loading is very easy. (c) The drug will be intact in the conditions of the preparation and it can be protected. (d) The drugs can be localized in the core of the particle instead of being in association at the surface of a particle. (e) Nanosponges protect oligonucleotides from proteins and enzymes, and do not change the DNA conformation through electrostatic force (79).

Preparation of Alginate nanosponges

The preparation alginate nanosponges involve two steps. First, gelation of a sodium alginate solution by the addition of calcium

chloride under magnetic stirring to obtain a calcium alginate pregel. Second, the Poly-L-lysine(PLL) was added to form a polyelectrolyte complex with the free remaining negative charges of the pregel, leading to a colloidal nanosponges (78). The schematic presentation of preparation of alginate nanosponges is given in figure 6.

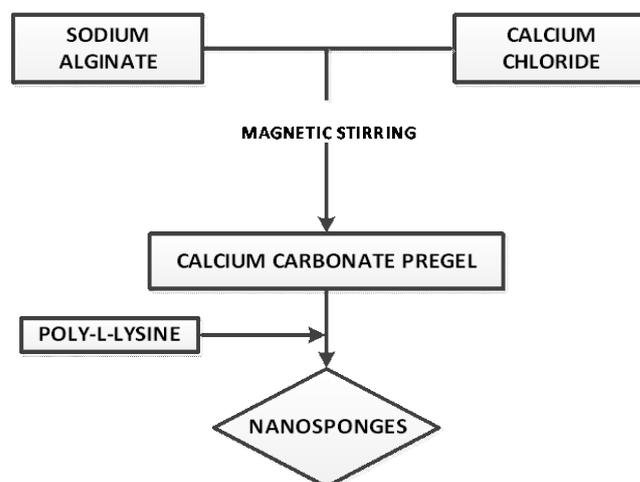


Figure 6 Preparation of alginate nanosponges

CONCLUSION

Nanosponges are unique in their capability to entrap high concentrations of wide variety of substances and maintain a predictable linear release profile, which can be adjusted to the demands of the tumor type. Polymer chemistry allows for many variations, whereby polymeric nanosponges can be easily manipulated without the loss of their desired physical, chemical, and biological properties. In one manner, this principle can be used to greatly improve the function of the nanosponges in cancer therapy through the attachment of tumor-specific targeting ligands.

Nanosponges are unique in their capability to entrap high concentrations of wide variety of substances and maintain a predictable linear release profile, which can be adjusted to the demands of the tumor type. The nanosponges can be easily functionalized without affecting the particle formation and cross-linking procedure. The availability of functional groups provides the opportunity to tailor the physical and chemical properties of the nanoparticles. These cross-linked structures are readily soluble in organic solvents without affecting their 3-D architecture. This property enables to load the drugs after formation by dissolving in a suitable solvent.

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