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NANOSPONGES: POTENTIAL ANTICANCER DRUG DELIVERY SYSTEMS

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ABSTRACT

One of the most crucial problems which are faced by the researchers for the drugs especially for anti- cancer drugs is the delivery of the drugs to desired targets. Nanosponge mainly Cyclodextrin-based nanosponge (CD-NS) has played an important role in scientific research in guiding the release of anti-cancer drugs. Most of the anti-cancer drugs which have both lipophilic and hydrophilic properties can be formulated into Nanosponge (NS) for targeting and finally, the solubility, action and the bioavailability of the drug is increased effectively. NSs are prepared by reacting cyclodextrins (CD) with cross-linking polymers such as carbonyl-diimidazole, diphenyl carbonate, hexamethylene diisocyanate and pyromellitic anhydride which are nanosize, cross-linked, non-toxic, porous and stable in high temperatures. Having spherical shape, swelling properties and porous structures, as well as biologically safe and biodegradable NSs offers a higher drug loading compared to other nano carriers. This review will describes properties of cyclodextrins,types of cross linkers,different methods for loading of drugs into cyclodextrin based nanosponges and application of nanosponges as carriers for anticancer drugs.

INTRODUCTION

Cancer is a group of diseases where the abnormal cell growth that has the potential to spread to other parts of the body and the cell will lose its program and functions. Surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy by using anti-cancer drugs the as treatment. Most of the anti-cancer drugs are not site specific targeted and have poor bioavailability and poor biopharmaceutical properties [1]. This results in the rapid excretion, deterioration of the gastrointestinal fluids with nonspecific toxicity, *in vitro* stability, strong dose-dependent side effects, and lack of selectivity [2]. To overcome these disadvantages of the traditional therapeutic Approaches and to solve these problems of targeting drug especially nano-carrier based delivery systems have been extensively studied and developed. Nanocarrier (NC) is designed to deliver the therapeutic drugs directly to the site-specific targeted area. Nanomaterials and polymers used for the fabrication of nano delivery systems are soluble, safe and biocompatible and bio available [2, 3]. NC does not affect or obstruct blood vessels and the toxicity values of the nanomaterials used for drug delivery should be very low, The nanomaterials or polymers with low toxicity values only should be used to target specific diseased tissue at a safe concentration [4]. Under the nanocarriers the potential nanodelivery systems are the nanosponges

which are designed with cyclodextrins are studied extensively and used for the cancer treatment.

Cyclodextrin Based Nanosponges (CD-NSs): Nanosponges are one of the nanocarriers the researchers recently have been working on as a drug delivery agent designed to improve the efficacy of eliminating and to overcome the disadvantages of conventional drugs for the reasons described in detail above. Before elaborating on this concept, it is useful to briefly mention one of the main components, cyclodextrins.

Properties of Cyclodextrins: Cyclodextrin (CD) which consists of an enzymatic decomposition of starch, one of the most available basic polysaccharides in nature, by *Bacillus amylobacter* [5] bacteria and composed of D-glycosupranoses with α-1,4-glycosidic bonds (Figures Ia and Ib). This is water soluble, biocompatible and has lipophilic cavity and hydrophilic outer surface. Since the 1970s, it has been used in the fields of medicine, food, cosmetics, textile, catalyst, biotechnology as well as a drug delivery system in nanotechnology, pharmacology and pharmaceutical industry [6].

Chemistry of CDs: These are named α-CD, β-CD and γ-CD according to the number of glycosupranose units in their structure. For example, the structure consisting of 6 glycosupranose units by glycosidic bonds it is defined as α-CD, the structure consisting of 7 glycosupranose units βCD and the structure consisting of 8 glycosupranose units called (γ-CD) (Figure Ib). Although it is present in nature in higher bound structures, but it is not preferred because it is very difficult to obtain and can form a very few inclusion complexes with many other substances. Among all these, β-CD has been preferred as the most studied structure because of its complex cavity with many other organic and inorganic materials, high drug loading capacity, easy availability and low price. Natural CDs cannot form complexes with hydrophilic or high molecular weight drugs; however, some natural CDs exhibits toxic properties when injected intravenously [8].

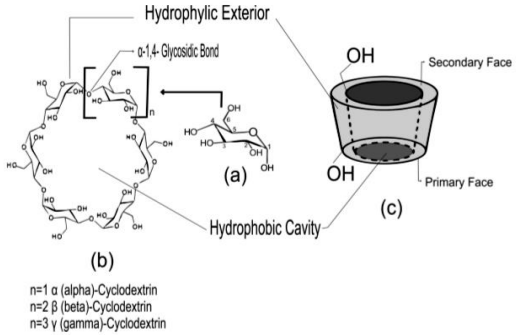

Figure I: Schematic representations of **a:** general chemical structure **b:** chemical structure and dimensions for α-, β and γ-cyclodextrin **c:** the tridimensional structure of cyclodextrins.

Therefore, in order to overcome all the limitations of natural CDs and to improve their properties, many chemical modification studies have been conducted to increase their physicochemical properties and to use them as a nanotechnological drug delivery system. One of them is the formulation and development of NSs by the reaction of natural CDs with crosslinkers, and that NSs are applied as a nanodrug release system which has been first time demonstrated [9]. Nanosponges are hyper-crosslinked cyclodextrins having nanoscale spongy pores and a three-dimensional network, which can be obtained with a certain amount of α, β and γ. Cyclodextrins crosslinked with an appropriate amount bof crosslinking agent. So that, they can keep the hydrophobic and hydrophilic drugs in their cavity. NSs are generally prepared from β-cyclodextrins, because among natural (α, β and γ) CDs, β - CD has the highest complexity and stability due to the appropriate cavity size with the crosslinkable polymers. Briefly, The NSs are non-toxic high temperature stable structures [10] prepared by reacting cyclodextrin (β-CD) with the crosslinking polymer such as carbonyl-diimidazole, diphenyl carbonate, hexamethylene diisocyanate and pyromellitic anhydride (Figure II). Compared with natural CD, these form higher sites of interaction with drugs and higher drug encapsulation complexes. NSs are being explored as a promising nanocarrier system to improve drug solubility, prevent drug degradation,

increase permeability, and control drug release [10]. For this purpose, paclitaxel, camptothecin, quercetin, telmisartan, meloxicam, tamoxifen, nifedipine, erlotinib, acetylsalicylic acid, captopril, ibuprofen, lansoprazole and enalapril are used as a nanocarrier for various drugs [11-14].

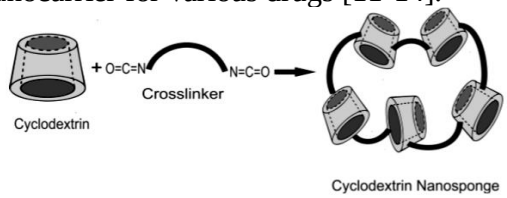

Figure II: Cyclodextrins are linked with crosslinking polymer to form cyclodextrin Nanosponge.

Categories of Nanosponges Based on the Associated Cross Linkers with Cyclodextrin Polymers

NSs are synthesized by using four main types of crosslinking polymer materials, such as carbonyl crosslinkers, diisocyanate linkers, anhydride crosslinkers, and epichlorohydrin.

a. Carbonate nanosponges:

Carbonate Nanosponges containing carbonate bonds between two cyclodextrin monomers were prepared by solvent extraction, thermal desorption or microwave and ultrasound assisted by synthesis methods using carbonyl crosslinkers such as diphenyl carbonate, carbonyl imidazole, dimethyl carbonate. These may be amorphous or crystalline according to the synthesis methods used. For example, by using the melting method, a crystalline structure is obtained, while using the solvent method an amorphous nanosponge are obtained. Various drugs such as paclitaxel, tamoxifen, reservertol, telmisartan, curcumin, itraconazole, 1-DOPA, camptothecin, erlotinib, and quercetin are available with this type of nanosponge [15].

b. Carbomat nanosponges:

NS prepared by solvent method under an anhydrous / nitrogen atmosphere at room temperature to 70°C are obtained by reacting cyclodextrins with cross-linkers such ashexamethylene diisocyanate and toluene diisocyanate in a molar ratio of 1: 2 to 1: 8. Initially, synthesized by DeQuan Li and Min Ma [16, 17] in 1998, such NSs were developed for the treatment of water, including the removal of dissolved organic carbon such as nitrophenol. The final step is to prepare molecularly imprinted nanosponges for the encapsulation of substances such as steroids, dyes and dextromethorphan using diisocyanate crosslinkers [18].

c. Anhydride nanosponges:

Anhydride Nanosponge are also prepared by the solvent method in the presence of a base such as pyridine or triethylamine to accelerate the polymerization by using cross linkers such as pyromellitic dianhydride ethylene diaminetetra acetic acid dianhydride of the cyclodextrins at room temperature. Cyclodextrin: cross-linking molar ratios ranging from 1: 2 to 1: 8 are used for preparation. Numerous studies have been conducted to encapsulate various drugs such as doxorubicin, meloxicam, ibuprofen and acetylsalicylic acid with this type of NS [19].

d. Epichlorohydrin cyclodextrin nanosponges:

The NSs are prepared by dissolving cyclodextrins in a basic medium such as sodium hydroxides using cross-linking agents such as epichlorohydrin are more hydrophilic in nature. Such nanospongs which exhibit high chemical resistance and adjustable swelling capability have been used to encapsulate drugs such as creatinine and captopril, enalapril, silazapril, but in some studies a cross-linking molar ratio of up to 1:10 with cyclodextrin has been studied [20].

Preparation methods of NSs:

Cyclodextrin based nanosponges are commonly prepared by dissolving any selected type of CD in a suitable solvent, then by adding a catalyst if necessary and finally adding a desired type of crosslinkers under continuous mixing or sonication [21].

Approaches used in the synthesis of cyclodextrin based nanosponges

a. Melt method:

In this method, the CD is heated and reacted at 100°C on a magnetic stirrer for about 5 hours with excipients such as selected crosslinker, solvent such as dimethylformamide (DMF) or reaction

accelerator catalyst. The product is brought to room temperature and decomposed ,washed to remove unreacted basic components and formed by-products using a suitable solvent (such as ethanol) [22]. Purification is the most critical and important step in this method since the by-products used of different structure will be formed according to the type of crosslinker used which finally results in the toxicity of the by-products and remains in the final product.

b. Solvent method:

According to this method, CD (usually β –CDs) is mixed with a polar aprotic solvent, in particularly dimethylsulfoxide or dimethylformamide (DMSO / DMF), and carbonyl compound crosslinking polymers such as diphenyl carbonate (DPC), dimethyl carbonate (DMC) or carbonyldiimidazole (CDI) are added to optimize the process based on the crosslinker / polymer molar ratio. This reaction is carried out at temperatures ranging from 10°C to reflux for 1 to 48 hours. The melting step is eliminated compared to the solvent method. After cooling to room temperature, an excess of purified water is added to remove unreacted products and the product is then filtered under vacuum. The product is purification is done by prolonged soxhlet extraction with ethanol for complete recovery and further purification. The product is then dried and milled in a mechanical mill to prepare a homogeneous powder. The product obtained is a solid nanoparticle with high dissolution power for molecules that are slightly soluble in water with a spherical morphology.

c. Ultrasound assisted synthesis:

In this method, Nanosponges are synthesized spherically and uniformly under 5 microns using the ultrasonication technique [22]. NSs that are obtained by reacting CDs with crosslinkers such as diphenyl carbonate (DPC) or pyromellitic dianhydride (PMDA) under sonication in the absence of the solvent. Anhydrous βCD and DPC are mixed in a 250 mL flask in the absence of a specified molar ratio of solvent. The flask is then placed in an ultrasound bath (filled with water) and heated at 90°C and sonicated for 5 hours. The mixture is than allowed to cool and then ground in a mortar and first purified by distilled water to remove unreacted polymer, then by soxhlet extraction with ethanol for further purification. The product is than dried under vacuum and stored at 25°C for subsequent use. The main advantages of this method is that it can be replaced by processes with a high energy input, such as probe sonication, and no organic solvents should be used. Microwave-assisted synthesis, is a simple method for synthesizing cyclodextrin-based nanosponges, is one of the most important advantages compared to other methods in that it has a four-fold reduction in reaction time, high crystallinity, homogeneous particle size distribution and homogeneous crystallinity [23].

APPLICATIONS

NSs prepared from cyclodextrins are considered to be one of the best novel systems that can be used as drug carriers in pharmaceutical formulations. Molecular encapsulations of the drug and other modifications with appropriate cyclodextrin based nanosponges can overcome disadvantages such as insolubility, permeability, sensitivity, etc., and facilitate safe and efficient delivery of drugs [24]. Nanosponges can advantageously carry water insoluble drugs and BCS (Biopharmaceutical Classification System) based class-II and IV drugs and can be also used to increase the dissolution rate, solubility and stability of such drugs. NSs structures are unable to entrap flavours by adsorption and thus cannot mask unpleasant flavours and also convert liquid substances to solids. NSs can absorb odorous material and thereby facilitate to remove from organic materials, water and other products. Some reports suggest that β-CD based nanosponges can deliver the drug to the target sites three to five times more effectively compared to direct injections. Particularly good results were obtained by using carbonate based nanosponges in the delivery of some anticancer drugs such as paclitaxel and campothecin. Nanosponges are solid in nature and can be easily formulated as oral, parenteral, topical or

inhalation dosage forms. For oral administration, the complexes may be dispersed in matrices of excipients, diluents, lubricants and anti-caking agents suitable for the preparation of capsules or tablets. A few examples of CD based nanosponges used in the treatment of cancer are given in Table 1.

Table No 1: CD based nanosponges used in the treatment of cancer

Drug	Therapeutic activity	Nanosponges vehicle	Attributes	Administration route	References
Curcumin	hepatocellular carcinoma	β-CD, dimethylcarbonate	Enhanced activity, solubilization	Parenteral	24
Tamoxifen	breast cancer	β-CD	Increased solubility	Oral	25
Temozolomide	glioma	β-CD , phenyl carbonate	site targeting	Oral	26
Resveratrol	antioncogenic	β -CD	Increased solubility and permeability	Oral	27
Quercetin	Antineoplastic	β–CD, diphenyl carbonate	Increased solubility and photostability	Oral	28
ETB glutathione	lung cancer, ovarian cancer	β–CD	Enhanced site targeting and reduced cell toxicity	Oral	29
doxorubicin	Cervical malignancy	γ–CD	Protects from acidic environment	Oral	30

CONCLUSION:

In the light of such findings, it may be concluded that cyclodextrin-based nanosponges are a novel class of biocompatible, versatile crosslinked polymers that greatly can enhance the solubility performances of their parent CDs. They are able to include lipophilic as well as hydrophilic drugs and release them in a controlled and predictable manner at the site of target, thus increasing their bioavailability. By controlling the polymer to crosslinkers ratio, the particle size and release rate can be modulated to better fit the application. They could be used to improve the aqueous solubility of lipophilic drugs, and protect the active moieties from physicochemical degradation. They have been found to be promising materials for immediate technological use for drug entrapment and as novel drug carriers. Because of their small size and spherical shape, nanosponges have the potential to be Formulated into a wide range of dosage forms such as parenteral, aerosol, topical, tablets and capsule.

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