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ZSM-5-Doxorubicin as a Drug Delivery Platform for Doxorubicin

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Abstract

The drug delivery application of Porous Metal-Organic Frameworks (MOFs) have been investigated due to their unique structures which are built of inorganic nodes and organic ligands. In present study, zsm-5-doxorubicin was successfully prepared by applied for delivery of 5-fluorouracil (doxorubicin). Using variety of analytical methods including FTIR, FESEM, EDS, and the prepared nanostructure was characterized. Results revealed the placement of the drug in zeolite is well done and also the in vitro loading and releasing studies, for doxorubicin was evaluated. In addition, based on the in vitro cytotoxicity results, zsm-5-5Fu was able to increase cytotoxicity compared to that of doxorubicin on HT-29 cancerous cells indicating the highlighted role of this drug delivery system.

Introduction

Cancer as the most prevalent diseases worldwide is one of the main public health concerns. In spite of intensive efforts for treatment of cancer, the necessity of developing effective agents isn't ignorable [1]. Designing an ideal drug delivery system for targeting cancer cell is considered as a hot topic in life science research. MOFs with crucial features including high drug loading capacity, high surface area, as well as tunable pore size is used for drug delivery intensively [2]. MOFs plays an important role as an carriers in drug delivery because they are non-toxic as well as the uptake of drugs and getting across the cell membrane has been facilitated via controlling the size of MOFs [3].

5-florouracil (doxorubicin) is anticancer drugs which is able to induces cytotoxic and increase DNA damage [4]. Although, 5 FU frequently applied, developed drug resistance and severe side effects affected its clinical application [5]. Encapsulate of doxorubicin using various DDS could be an effective idea [6]. In present work, the drug loading capacity of zsm-5 for doxorubicin as an anticancer drug was evaluated. Upon exposure by zsm-5-5Fu the in vitro cytotoxicity against cancer cells were assessed.

Finally but contrary to the original goal of this project, which was to use a muff, because of the simpler and faster synthesis, we carried out this project with a zeolite.

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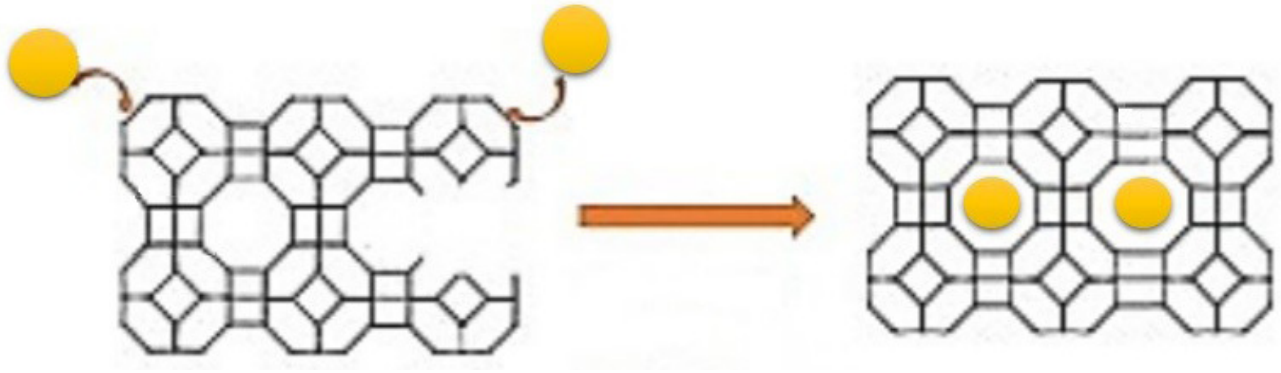

Figure 1: Placement of drug in the structure of MOF.

Doxorubicin

Doxorubicin, sold under the brand name Adriamycin among others, is a chemotherapy medication used to treat cancer. This includes breast cancer, bladder cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukemia. It is often used together with other chemotherapy agents. Doxorubicin is given by injection into a vein.

Common side effects include hair loss, bone marrow suppression, vomiting, rash, and inflammation of the mouth. Other serious side effects may include allergic reactions such as anaphylaxis, heart damage, and tissue damage at the site of injection, radiation recall, and treatment-related leukemia. People often experience red discoloration of the urine for a few days. Doxorubicin is in the anthracycline and antitumor antibiotic family of medications. It works in part by interfering with the function of DNA.

Doxorubicin was approved for medical use in the United States in 1974. It is on the World Health Organization's List of Essential Medicines. Versions that are pegylated and in liposomes are also available; however, they are more expensive. Doxorubicin was originally made from the bacterium Streptomyces peucetius.

Medical uses

Doxorubicin is commonly used to treat some leukemias and Hodgkin's lymphoma, as well as cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, multiple myeloma, and others. Commonly used doxorubicin-containing regimens are AC (Adriamycin, Cyclophosphamide), TAC (Taxotere, AC), ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), BEACOPP, CHOP (Cyclophosphamide, Hydroxydaunorubicin, Vincristine, Prednisone) and FAC (5-Fluorouracil, Adriamycin, Cyclophosphamide).

Doxil (see below) is used primarily for the treatment of ovarian cancer where the disease has progressed or recurred after platinum-based chemotherapy, or for the treatment of AIDS-related Kaposi's sarcoma.

Biosynthesis

Doxorubicin (DXR) is a 14-hydroxylated version of daunorubicin, the immediate precursor of DXR in its biosynthetic pathway. Daunorubicin is more abundantly found as a natural product because it is produced by a number of different wild type strains of Streptomyces. In contrast, only one known non-wild type species, Streptomyces peucetius subspecies cesius ATCC 27952, was initially found to be capable of producing the more widely used doxorubicin. This strain was created by Arcamone et al. in 1969 by mutating a strain producing daunorubicin, but not DXR, at least in detectable quantities. Subsequently, Hutchinson's group showed that under special environmental conditions, or by the introduction of genetic modifications, other strains of Streptomyces can produce doxorubicin. His group also cloned many of the genes required for DXR production, although not all of them have been fully characterized. In 1996, Strohl's group discovered, isolated and characterized dox A, the gene encoding the enzyme that converts daunorubicin into DXR.

By 1999, they produced recombinant dox A, a cytochrome P450 oxidase, and found that it catalyzes multiple steps in DXR biosynthesis, including steps leading to daunorubicin. This was significant because it became clear that all daunorubicin-producing strains have the necessary genes to produce DXR, the much more therapeutically important of the two. Hutchinson's group went on to develop methods to improve the yield of DXR, from the fermentation process used in its commercial production, not only by introducing dox A encoding plasmids, but also by introducing mutations to deactivate enzymes that shunt DXR precursors to less useful products, for example baumycin-like glycosides. Some triple mutants, that also over-expressed dox A, were able to double the yield of DXR. This is of more than academic interest, because at that time DXR cost about $1.37 million per kg and current production in 1999 was 225 kg per annum.

More efficient production techniques have brought the price down to $1.1 million per kg for the nonliposomal formulation. Although DXR can be produced semi-synthetically from daunorubicin, the process involves electrophilic bromination and multiple steps, and the yield is poor. Since daunorubicin is produced by fermentation, it would be ideal if the bacteria could complete DXR synthesis more effectively.

Mechanism of action

Doxorubicin interacts with DNA by intercalation and inhibition of macromolecular biosynthesis. This inhibits the progression of topoisomerase II, an enzyme which relaxes supercoils in DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being released and thereby stopping the process of replication. It may also increase quinone type free radical production, hence contributing to its cytotoxicity.

The planar aromatic chromophore portion of the molecule intercalates between two base pairs of the DNA, while the six-membered daunosamine sugar sits in the minor groove and interacts with flanking base pairs immediately adjacent to the intercalation site, as evidenced by several crystal structures.

By intercalation, doxorubicin can also induce histone eviction from transcriptionally active chromatin. As a result, DNA damage response, epigenome and transcriptome are deregulated in doxorubicin-exposed cells.

NanoComposite

Nanocomposite is a multiphase solid material where one of the phases has one, two or three dimensions of less than 100 Nanometers (nm) or structures having nano-scale repeat distances between the different phases that make up the material [7].

The idea behind Nanocomposite is to use building blocks with dimensions in nanometre range to design and create new materials with unprecedented flexibility and improvement in their physical properties. In the broadest sense this definition can include porous media, colloids, gels and copolymers, but is more usually taken to mean the solid combination of a bulk matrix and nano-dimensional phase(s) differing in properties due to dissimilarities in structure and chemistry [8].

The mechanical, electrical, thermal, optical, electrochemical, catalytic properties of the nanocomposite will differ markedly from that of the component materials. Size limits for these effects have been proposed.

1. <5 nm for catalytic activity
2. <20 nm for making a hard magnetic material soft
3. <50 nm for refractive index changes
4. <100 nm for achieving superparamagnetism, mechanical strengthening or restricting matrix dislocation movement [9].

Nanocomposites are found in nature, for example in the structure of the abalone shell and bone [10]. The use of nanoparticle-rich materials long predates the understanding of the physical and chemical nature of these materials. Some researchers investigated the origin of the depth of color and the resistance to acids and bio-corrosion of Maya blue paint, attributing it to a nanoparticle mechanism. From the mid-1950s nanoscale organo-clays have been used to control flow of polymer solutions (e.g. as paint viscosifiers) or the constitution of gels (e.g. as a thickening substance in cosmetics, keeping the preparations in homogeneous form). By the 1970s polymer/clay composites were the topic of textbooks, although the term "nanocomposites" was not in common use [11].

In mechanical terms, nanocomposites differ from conventional composite materials due to the exceptionally high surface to volume ratio of the reinforcing phase and/or its exceptionally high aspect ratio. The reinforcing material can be made up of particles (e.g. minerals), sheets (e.g. exfoliated clay stacks) or fibers (e.g. carbon nanotubes or electrospun fibers) [12]. The area of the interface between the matrix and reinforcement phase(s) is typically an order of magnitude greater than for conventional composite materials [13]. The matrix material properties are significantly affected in the vicinity of the reinforcement. Some scientists be aware that with polymer nanocomposites, properties related to local chemistry, degree of thermoset cure, polymer chain mobility, polymer chain conformation, degree of polymer chain ordering or crystallinity can all vary significantly and continuously from the interface with the reinforcement into the bulk of the matrix. This massive quantity of reinforcement surface area means that a relatively small amount of nanoscale reinforcement can have an observable effect on the macroscale properties of the composite [14].

Zeolite

Zeolites are a group of crystalline materials made up of evenly sized pores and tunnel systems. When purifying VOCs and hydrocarbons, we use a synthetic hydrophobic zeolite. When the contaminated air passes through the material, the hydrocarbons are adsorbed. The material can adsorb a certain amount of hydrocarbons before needing to be regenerated [15,16].

A smaller flow of hot air is then directed through the material so that the hydrocarbons release from the zeolite in a higher concentration. This enables more cost-effective incineration. One of its strengths is that it is non-combustible–meaning it can withstand very high temperatures [17]. This means that we are also able to purify volatile hydrocarbons such as fumes emitted from vulcanization, plastic smoke and styrene, all of which require very high temperatures during regeneration. The resistance to high temperatures and the structure of the material also allows the zeolite to be completely regenerated – meaning that the VOCs completely release from the zeolite when heated. This means that the system maintains its high purification rate year after year and that the material does not have to be replaced, which gives it a long lifespan and a minimal need for maintenance [18]. Our systems have an availability of over 99% and a lifespan exceeding 25 years. Combining the benefits of zeolite with our 30 years of experience in working with air purification gives our customers a supremely sustainable and customized system with low operating costs and high availability.

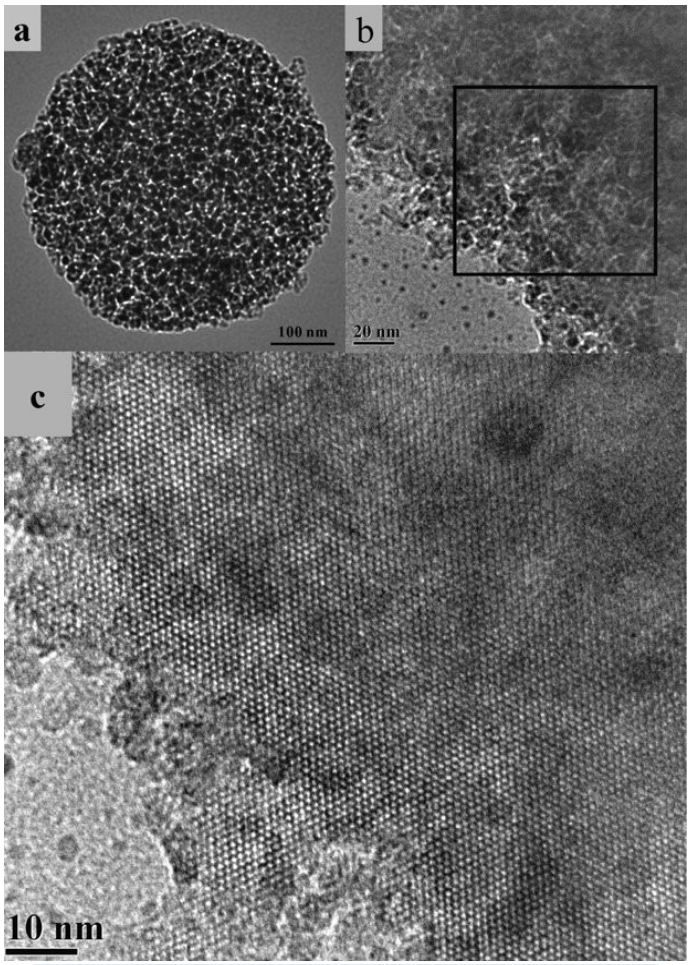

Figure 2: TEM images **(a,b)** of mesoporous ZSM-5 microsphere of different magnifications and the HR-TEM image **(c)** from the area marked by a black square in **(b)**.

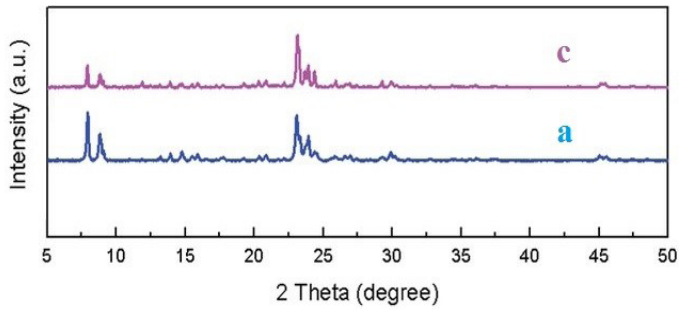

Figure 3: XRD patterns of ZSM-5 samples obtained doxorubicin: **(a)** ZSM-5 **(c)** ZSM-5-doxorubicin.

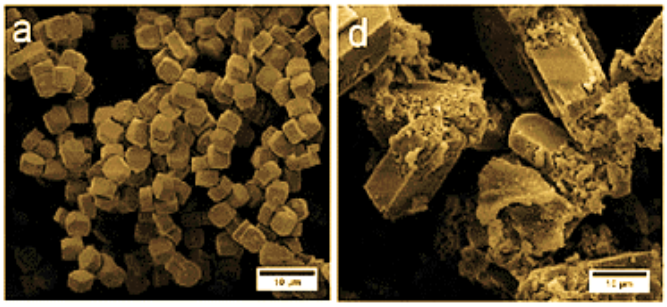

Figure 4: SEM images of ZSM-5 samples obtained doxorubicin: **(a)** ZSM-5, **(d)** ZSM-5-doxorubicin.

Reversible hydration and dehydration

During drying it comes to the removal of free and bound water from the crystal grid, which is then counterbalanced back in contact with materials such as stored grain and feed, pet litter, in flue gas to prevent condensation and the like [19]. Clinoptilolite stabilize moisture at a low dose of volume and avoid the adverse effects of water [20].

Results and discussion

Characterization

The chemical structure of the zsm-5-5Fu was characterized with different analytical methods such as XRD, SEM & TEM.

Drug loadings and release

The MOF- with the proper size and the accessible porosity could be used for loading and release of doxorubicin. The loading capacity of zsm-5 under physiological condition (pH 7.4) was investigated.the results showed high Drug Loading Capacity (DLC) (90%) and Drug Loading Efficiency (DLE) 70% by UV–Vis spectroscopy. The results of release profiles of zsm-5-5Fu revealed sustained for 72 h despite with an initial rapid release.

Cytotoxicity assay

In order to determine the in vitro cytotoxicity of the zsm-5, doxorubicin drug, and zsm-5-5Fu HT-29 cell lines, MTT assay was conducted. The obtained results of the cell viability assay showed that zsm-5-5Fu and doxorubicin drug inhibited cell growth in a time and dose-dependent manner while the zsm-5- showed less growth inhibition after 48 h compared to drug loaded zsm-5 and free drug doxorubicin. Based on this results, one may conclude that MOFs with low toxicity could be used effectively for biological applications in the future [3].

Conclusion

In this study, zsm-5 was applied for delivery of doxorubicin. The obtained nanostructure poses spherical morphology with an average diameter of 39-52 nm. Results showed the high loading capacity (90%) and sustained drug release behavior. Moreover, upon exposure by zsm-5-5Fu, higher cytotoxicity than those for zsm-5 and doxorubicin drug against PC3 cells was determined indicating zsm-5-5Fu may could be a promising anticancer drug delivery system in the future.

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