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The Usage of Chitosan-Functionalized Mesoporous Silica Nanoparticles as a pH Sensitive Mechanism for Drug Delivery in Cancer Treatment

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In the process of eliminating a tumor, traditional cancer therapy is typically ineffective at minimizing the number of healthy cells that are damaged or killed, and can often lead to serious side-effects on the patient's health (Abe *et al.* 2005; Liu *et al.* 2015; Khemtong *et al.* 2009). In recent years however, studies have demonstrated that the controlled release of drugs such as doxorubicin (DOX) through the usage of nanoparticles has the potential to significantly decrease the severity of these side-effects (Liu *et al.* 2015; Tang *et al*. 2011). Certain nanoparticles can be loaded with medication and modified to release this medication in response to a stimulus (such as a certain pH) in order to ensure only cancerous cells are primarily exposed to the medication, thus minimizing the quantity of healthy cells that are affected (Yan *et al.* 2010; Zheng *et al.* 2012; Fang *et al.* 2014). This has the potential to revolutionize the field of medicine and treatment of not only cancer, but multitudes of other diseases.

Recently, mesoporous silica nanoparticles (MSNs) have been investigated intensively as a candidate for controlled drug delivery to treat a variety of diseases, including cancer (Deng *et al.* 2011). MSNs are a spherical variation of silica particles that are roughly 300 nanometres across and contain pores with variable diameters of anywhere between 2 and 50 nanometres (Gan *et al*. 2014). One of the main advantages that MSNs bring to cancer therapy is their large surface area and high porosity, the aspect of the nanoparticles that primarily facilitates drug loading (Liu *et al*. 2015). Furthermore, the variability in pore diameter of MSNs allows for loading of drugs of many different sizes as well.

Additional properties of MSNs that make them a highly practical candidate for delivery of cancer-treating drugs include: low toxicity, tunable pore size, modifiable surface, biodegradability, and high chemical and thermal stability (Liu *et al.* 2015; Pourjavadi and Tehrany 2013). The biocompatibility of MSNs both *in vitro* and *in vivo* has also been illustrated by several recent studies. In addition, reports on the biodistribution and circulation properties of MSNs administered in animals by intravenous injection have highlighted the promise of these porous, multifunctional nanoparticles for *in vivo* medical applications (Zhao *et al.* 2009).

Several methods exist for synthesizing and subsequently loading drugs

onto MSNs and they usually involve exposure to a range of different chemicals and treatments at particular temperatures and pH values. The most common method for MSN synthesis is the sol-gel method, described as the formation of an oxide network through polycondensation reactions of a molecular precursor in a liquid (Liu *et al.* 2015).

However, due to the relatively low circulation life of the MSN-drug complex, simply loading the drugs onto MSNs is ineffective for their targeted release in vivo. This is because there is nothing preventing the loaded drugs from dissociating from the nanoparticles, especially after being exposed to bodily fluids (Pourjavadi and Tehrany 2013). It is for this reason that MSNs are functionalized, or coated, with other molecules that respond to stimuli, controlling the release of the medication. Chitosan proves to be a very suitable candidate to fill this role (Liu *et al*. 2015).

Chitosan, a linear polysaccharide, plays the role of a protective coating in chitosan-functionalized MSNs, preventing the loaded drugs from being prematurely released in vivo (Yan *et al.* 2010). Additionally, it acts as a control that triggers the release of the drugs in response to a pH stimulus. This stimulus occurs because of a change in pH between bodily fluids and cancer cells; the normal body fluid pH is about 7.4, while the pH value at cancer cells is generally 6.8 or lower (Liu *et al*. 2015). Once the MSN/drug/chitosan complex reaches the tumor in the patient's body, the slightly more acidic pH of the cancerous cells will initiate the dissociation of chitosan, thereby enabling the drugs to be released (Yan *et al.* 2010).

Liu *et al.* (2015) loaded ibuprofen onto MSNs, functionalized the MSNs with chitosan and tested the drug release mechanism in vitro on various pH levels. It was found that the drug delivery system was very effective; the outer layer of chitosan dissolved, thereby enabling the ibuprofen to be released under specific pH conditions. Furthermore, Fang *et al.* (2014) found that when using doxorubicin with chitosan-functionalized MSNs, the release amount of DOX was ~60% at a pH of 5.5 while it was ~15% at pH 7.4. This evidence reinforces the suitability of MSNs as candidates for drug carriers used for targeted drug release in cancer cells with an acidic pH environment.

Chitosan-functionalized MSNs have the potential to revolutionize the treatment of cancer by localizing drug administration and thereby minimizing damage caused to non-cancerous cells (Yan *et al*. 2010; Zheng *et al.* 2012; Fang *et al*. 2014). The porous nanoparticles, coated with chitosan, can be loaded with drugs such as doxorubicin, as well as many other drugs of various sizes, and released in vitro via intravenous injection (Liu *et al*. 2015; Zhao *et al*. 2009). Once the MSN/drug/chitosan complex reaches cancerous cells, the chitosan dissolves in response to the slightly acidic pH, delivering the drug directly to the tumor (Liu *et al.* 2015; Fang *et al*. 2014). This direct delivery of medication along with the low toxicity and high biocompatibility of mesoporous silica nanoparticles combine to provide a highly effective drug delivery

mechanism with fewer side-effects on the health of patients compared to conventional methods (Abe *et al*. 2005; Zheng *et al.* 2012). Chitosan-functionalized MSNs are the future of drug delivery for the treatment of cancer, and may hold promise for other diseases as well.

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