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Development of curcumin–cyclodextrin/cellulose nanocrystals complexes: New anticancer drug delivery systems

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ABSTRACT

The synthesis of curcumin–cyclodextrin/cellulose nanocrystals (CNCx) nano complexes was performed. CNCx were functionalized by ionic association with cationic β-cyclodextrin (CD) and CD/CNCx complexes were used to encapsulate curcumin. Preliminary in vitro results showed that the resulting curcumin–CD/CNCx complexes exerted antiproliferative effect on colorectal and prostatic cancer cell lines, with IC_{50}s lower than that of curcumin alone.

Cancer is a degenerative disease which leads to uncontrolled tumor cell proliferation. Anticancer treatments suffer from limitations and often result in significant side effects. Poor water solubility, low availability and low efficiency of chemotherapeutic agents are among the major hurdles for effective chemotherapy treatment. Curcumin, a polyphenol derivative, is the main bioactive constituent extracted from the rhizomes of *Curcuma longa*.[1] It possesses various biological and pharmacological properties, including antioxidant,[2] anti-inflammatory,[3] antibacterial,[4] anti-Alzheimer,[5] antispasmodic, anticoagulant and anticancer activities,[6] and is devoid of major side effects.[7] Its anticancer activities (on lung, colon, liver and breast cancer cells, etc.)[8] have attracted our attention for this work. Nevertheless, potential properties of free curcumin are hampered by poor solubility due to its hydrophobicity and low bioavailability combined with low stability in solution that results in rapid clearance from blood.[9] To overcome these problems, many groups have used nanotechnology approaches for better medical application. So, a number of drug delivery strategies have been adopted to incorporate or encapsulate curcumin into nanogels, mesoporous silica nanoparticles (MSN), or attach to metallic nanoparticles (Fe_3O_4, gold, etc.).[10–12] In connexion with our research program on vectorization of biomolecules for anticancer applications (RGD peptides, polyamines, iron oxide nanoparticles, mesoporous silica nanoparticles (MSN), etc.),[13,14] we have recently developed nanobiomaterials which are able to specifically target tumors, thanks to the Enhanced Permeation and Retention (EPR) effect, and to destroy them by action of the transported drug (photosensitizers).[15] This new delivery system for anticancer drugs consists of cellulose nanocrystals (CNCx) which benefit from uniform nanorod shape, good mechanical strength, liquid crystalline character, high specific surface area, biocompatibility, biodegradability and sustainability.[16] Obtained by acid-hydrolysis of cotton fibers, these nanowhiskers are defined as elongated rod-like nanoparticles, 100–200 nm long, 10–20 nm wide and 5–10 nm thick.[17] Their surface can be easily modified, increased or designed relation with the drug to be delivered.[18,19] In this work, we took advantage of the negative charges present on CNCx surfaces in order to form ionic complexes with cationic cyclodextrins. Cyclodextrins (CDs) are cyclic oligosaccharides consisting of six (α-), seven (β-) or eight (γ-) D-glucopyranose units linked by α-(1,4) glycosidic bonds. They are well known to form inclusion complexes with guest molecules.[20] β-CD is the most commonly used, due to its relatively easy synthesis, its low price and also to the large number of a polar molecules which can fit into its internal cavity. CNCx were loaded with β-CD after functionalization by reaction with glycidyltrimethyl ammonium chloride (GTMAC). In the present paper, we describe the influence of

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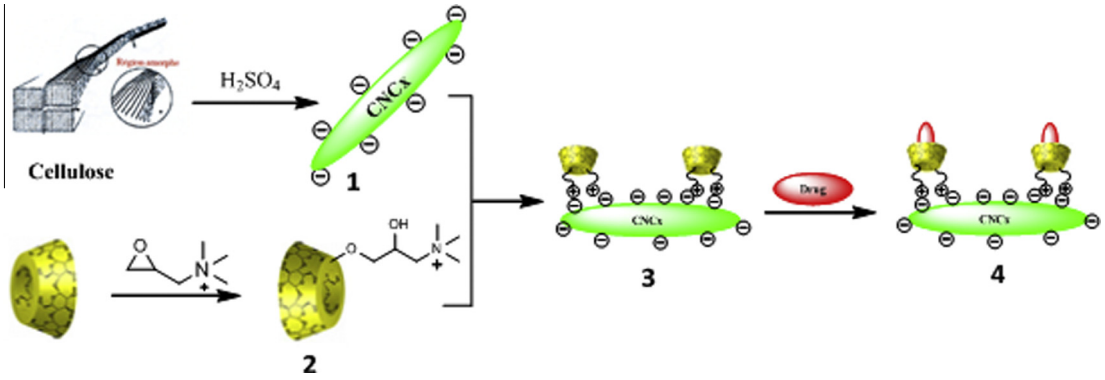

Scheme 1. Synthesis of curcumin I–CD/CNCx complex.

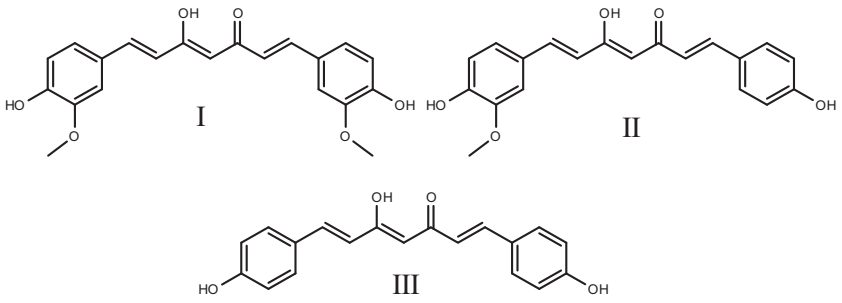

Figure 1. Chemical structures of curcumin I, II and III.

Table 1
Rate and percentage of curcumin complexed

Assay	CD/CNCx (mg)	Curcumin in CD/CNCx (M)	Rate of curcumin *per* g of CD/CNCx (mmol/g)	Loading ratio of Cur (w/w) (%)
1	2	2.3×10^{-4}	0.226	8.3
2	2	2.75×10^{-4}	0.276	10.1
3	5	6.0×10^{-4}	0.24	9.0

β-CD/CNCx on curcumin I (Cur I) delivery along with the antiproliferative effect of Cur I–CD/CNCx complexes; these tests were conducted on colon and prostate cancer cell lines.

The synthesis strategy is described in Scheme 1. Firstly, CNCx **1** was obtained by classical sulfuric acid hydrolysis procedure and characterized as previously described (Fig. S1).[15,21]

In parallel, cationic β-CDs **2** were obtained by reaction of glycidyltrimethyl ammonium chloride with β-CD in alkaline aqueous medium according to Chisholm and Wenzel.[22] These authors showed that the best inclusion capacity of cationic β-CD was

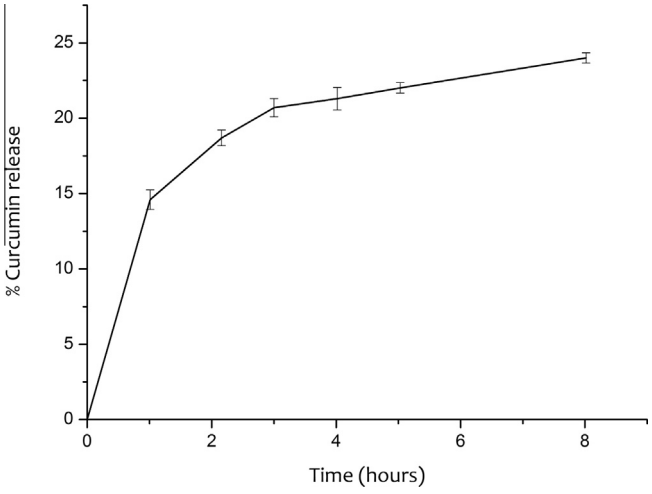

Figure 3. release of curcumin I from Cur–CD/CNCx in $H_2O/CHCl_3$.

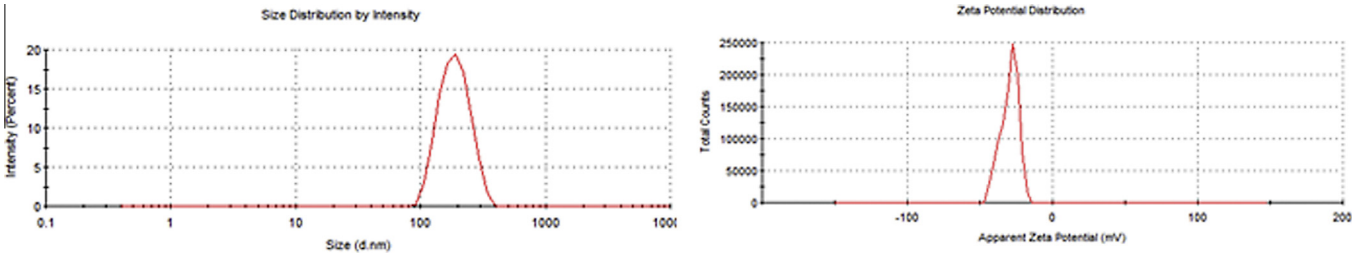

Figure 2. DLS size distribution and zeta potential of Cur–CD/CNCx **4**.