Design of octopus-shaped macromolecules based on tert-butylcalix[4]arenes as drug delivery platforms for curcumin.

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INTRODUCTION

Water-soluble calixarenes are promising macrocyclic compounds which have found numerous applications in chemistry and biology. Due to their ability to form inclusion complexes and to accommodate various substances, the calix[n]arenes are considered promising versatile drug delivery platforms. However their drug solubilizing properties and applicability as drug delivery systems so far have not been explored in detail.

The present work is aimed at exploration of *octopus*-shaped polyoxyethylated tert-butylcalix[4]arenes (PEG-CX-4) as a drug delivery platform for the lipophilic agent curcumin.

EXPERIMENTAL

Quantitative analysis of curcumin encapsulation

For qantitative determination of loaded curcumin a validated UV-VIS spectroscopic method was used (λ=417 and λ=417 and 424 nm)

Dynamic light scattering

The size and size distribution patterns of curcumin loaded aggregates of polyoxyethylated tert-buthylcalix[4]arene were investigated by ZetaSizer NanoZS (Malvern Instruments)The parameters were evaluated from measurements in the scattering angle of 173°, at 25°C.

Cytotoxicity assay

The cytotoxicity of free and loaded curcumin was evaluated by using the MTT-dye reduction assay in panel of human cancer cell lines. The tested compounds were applied in concentration range 6.5 to 25μM for 72 h. The MTT-formazan absorbance was read on a microprocesor controlled multiplate reader (Labexim LMR-1).

RESULTS

A polyoxyethylated tert-butylcalix[4]arene has been synthesized by anionic polymerization of ethylene oxide. It is amphiphilic star-shaped macromolecule, consisting of a hydrophobic calix[4]arene core and four arms of hydrophilic poly(ethylene oxide) chains. The abbreviation of the synthesized calyx[4]arene, its theoretical and experimental degrees of polymerization (dp) of the PEO moieties are given in Table 1

Abbreviation	Theoretic dp of the PEO moieties	*Experimental dp of the PEO moieties	MW	CMC (mg/ml)
BEC-X	230	203	36 400	7

At concentrations below the CMC (1 mg/ml; 2 mg/ml; and 4 mg/ml) the PEG-CX-4 proved to drastically increase the water solubility of curcumin (11 ng/ml) by factors of 136, 400 and 600 respectively. At their CMC (7 mg/ml) the tested solubilizing agents attained a 40 000-fold increase in the aqueous solubility of curcumin (Figure 1).

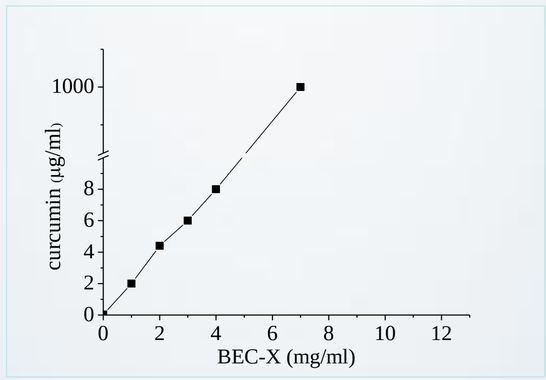

Figure 1. Increase of the water solubility of curcumin in presence of different concentrations BEC-X

The DLS data (Figure 2) revealed that the BEC-X aggregates loaded with curcumin are spherical in shape with diameter ca. 180 nm and are characterized with very high encapsulation efficiency above 98%.

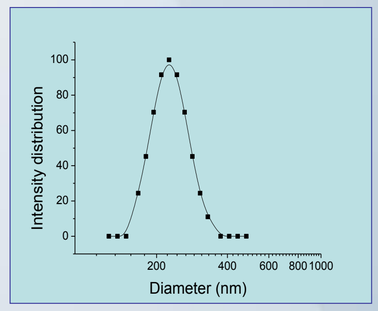

Figure 2. Particle size distribution of BEC-X aggregates loaded loaded with curcumin.

The release profile of curcumin from BEC-X carriers followed Higuchi kinetics (Figure 3).

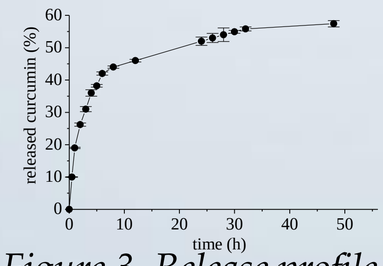

Figure 3. Release profile of curcumin from BEC-X nanoparticles at 37℃.

Formulation	IC_{50} (μmol/L) (n=8)	
	KG-1[a]	RPMI-8226[b]
Curcumin solution	13,45 ± 2,31	2,89 ± 0,77
BEC-X loaded curcumin	8,70 ± 1,44	2,22 ± 0,79

Conclusion

On the grounds of the excellent *in vitro* biocompatibility profile and the favorable physicochemical and drug loading characteristics of the tested compounds, and their ability to retain the instirsnic pharmacological properties of encapsulated drug they could be considered promising drug delivery platforms for lipophilic curcumin.