Liposomal formulations for delivery of curcumin-pegylated calix[n]arenes inclusion complexes

Elena Drakalska [1], Denitsa Momekova [1*], Georgi Momekov [1], Liudmil Antonov [2], Desislava Budurova [3], Nikolay Lambov [1], Stanislav Rangelov [3].

[1] – *Medical University of Sofia, Faculty of Pharmacy*
[2] – *Bulgarian Academy of Sciences, Institute of Organic Chemistry*
[3] – *Bulgarian Academy of Sciences, Institute of Polymers*

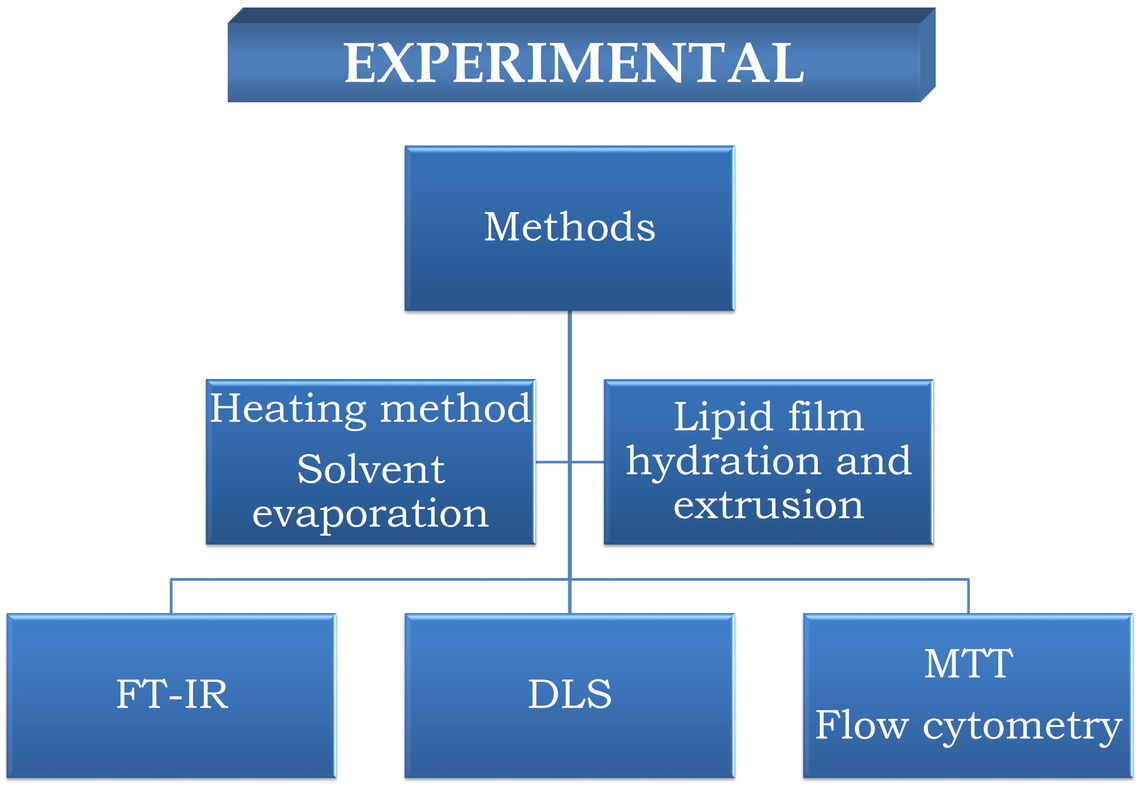
* - dmomekova@yahoo.com

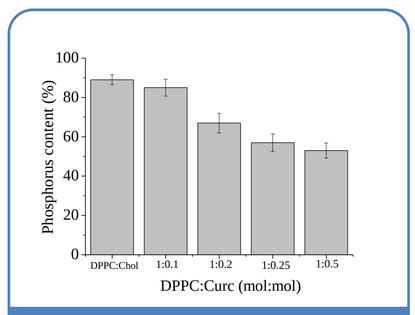
INTRODUCTION

Curcumin, the constituent of Curcuma longa, is considered a very promising anticancer agent due to its potent and pleiotropic antineoplastic activity and low nonspecific toxicity to normal cells. However the clinical realization of its potential has been limited due to its poor aqueous solubility and very low systemic bioavailability. A possible aproach to overcome these limitations is the design of nanosized vechicles of curcumin.

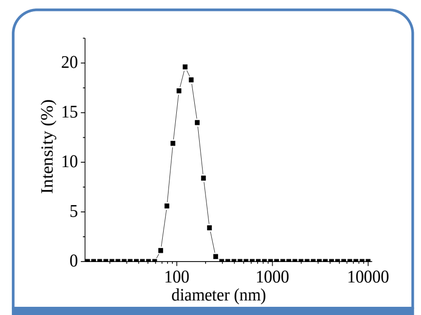
The present work reports the preparation, characterization and in vitro evaluation of antineoplastic activity of novel curcumin-in pegylated calix[4]arenes – in liposomes nanoparticles.

EXPERIMENTAL

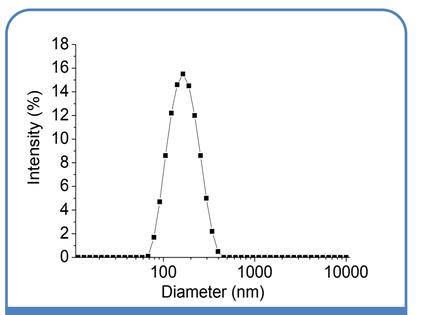




Phosphorus content recovery



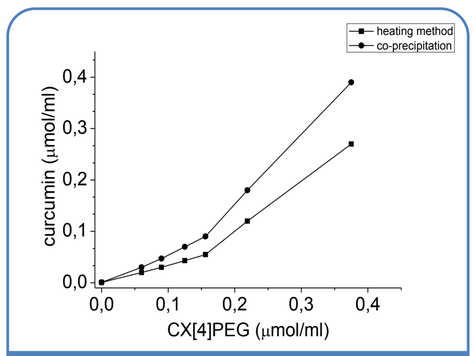
Size distribution of curcumin loaded DPPC liposomes



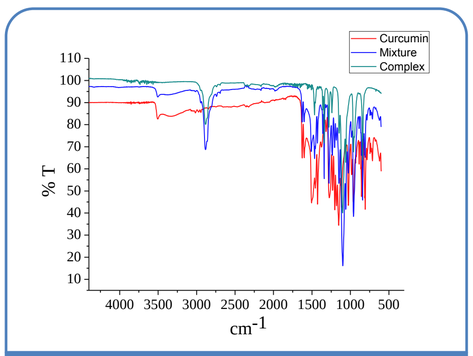
Size distribution of CX[4]arene:curcumin loaded DPPC liposomes.

Formulation	Diameter (nm)	IP	ζ-potential (mV)	Entrapment efficacy (%)	Amount of encapsulated curcumin (μg/ml)
DPPC: CHOL	124 ± 4.2	0.096 ± 0.002	-22	-	-
DPPC: CHOL:CURC	145 ± 3.6	0.14 ± 0.04	-26.3	98	240
DPPC: CHOL:CURC: CX[4]arene:curcumin	147 ± 4.2	0.135 ± 0.08	-20,8	82	345

RESULTS



Phase solubility diagrams of curcumin in aqueous complexation media containing various concentration of CX[4]arene.



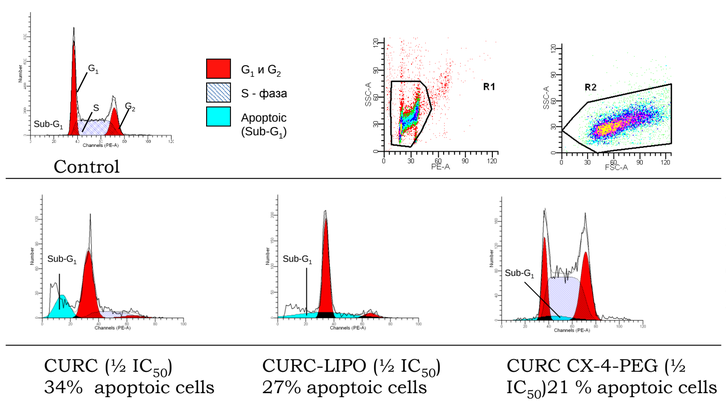
IR spectra of curcumin, curcumin – CX[4]arenes physical mixture and inclusion complex.

Parameter	Heating method	Solvent evaporation method
Stability constant (K_c)	325 μM^{-1}.ml	1072 μM^{-1}.ml
Solubility enhancement factor (δ)*	40 960 %	59 445 %

Cytotoxicity study

Formulations	IC_{50} (μmol/L) (n=8)	
	KG-1[a]	RPMI-8226[b]
Curcumin (DMSO solution)	13,45 ± 2,31	2,89 ± 0,77
Liposomal-PEG-CX-4 curcumin	2,19 ± 0,71	0,59 ± 0,21
PEG-CX-4 curcumin complexes	8,70 ± 1,44	2,22 ± 0,79

[a]acute promyelocyte leukemia; [b]multiple myeloma; [c]MI-modulation index = $IC_{50\ (free\ curcumin)}$/ $IC_{50\ (curcumin\ formulation)}$.



Pro-apoptotic activity of free curcumin, liposomal-PEG-CX-4 (CURC-LIPO)curcumin and PEG-CX-4 curcumin complexes (CURC-CX-4-PEG) after 24 hours treatment.

CURC (½ IC_{50}) 34% apoptoic cells

CURC-LIPO (½ IC_{50}) 27% apoptoic cells

CURC CX-4-PEG (½ IC_{50})21 % apoptoic cells

CONCLUSION: Thus on the grounds of the excellent in vitro biocompatibility profile and the favorable physicochemical and drug loading characteristics of the tested liposomal nanoparticles, and their ability to retain the instirsnic pharmacological properties of encapsulated drug they could be considered promising drug delivery platforms for lipophilic curcumin.

ACKNOWLEDGEMENTS

Financial support from National Science Fund of Bulgaria, Grant № ДФНИ Б01-25/2012 and ДЦВП 02-2/2009 is gratefully acknowledged.