Compositions of α-tocopheryl acetate with micellar nanocarriers and their possible using as biologically active additives

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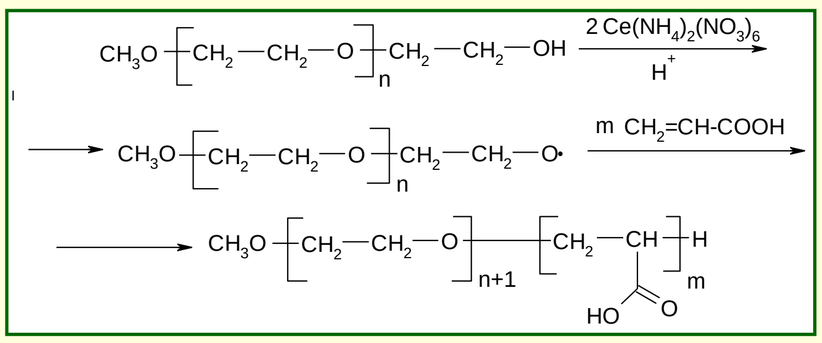
Introduction

Double hydrophilic diblock copolymers (DBCs) based on asymmetric chemically complementary methoxypolyethylene oxide and polyacrylic acid (MOPEO-*b*-PAAc) form special micellar structures with a complex "core" in aqueous solutions in the pH range <5. These micelles proved to be very effective, non-toxic, biocompatible and biodegradable nanocarriers for the delivery of a poorly soluble analogue of vitamin E, α-tocopheryl acetate (α-TOCA). In this work, the mechanisms of formation/release and stability in aqueous, aqueous/ethanol and aqueous/ethanol/salt solutions of in situ formed α-TOCA compositions with DBC micelles having different lengths of PAAc "corona" were studied using UV-Vis spectroscopy, static light scattering, dialysis and TEM.

Characterization of DBCs and their micellar nanocarriers

Synthesis of MOPEO-b-PAAc by a template radical block copolymerization of PAAc with methoxypoly(ethylene glycol)

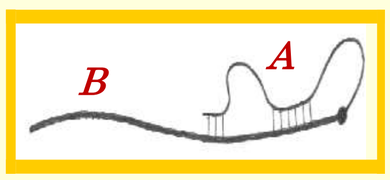


Molecular parameters of DBCs

Sample	M_{nMOPEO}, kDa	M_{nPANa}, kDa	M_{nPAAc}, kDa	M_{nDBC} a), kDa	n b)
DBC1	5.3	12.1	9.3	14.6	1.1
DBC2	5.3	23.1	17.6	22.9	2.0

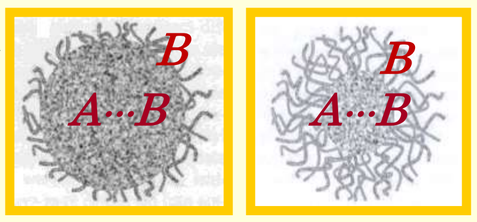
a) $M_{nDBC}=M_{nMOPEO}+M_{nPAAc}$
b) *The ratio between units of PAAc (or PANa) and MOPEO blocks*

DBCs self-assembly in aqueous medium as a function of the solution pH



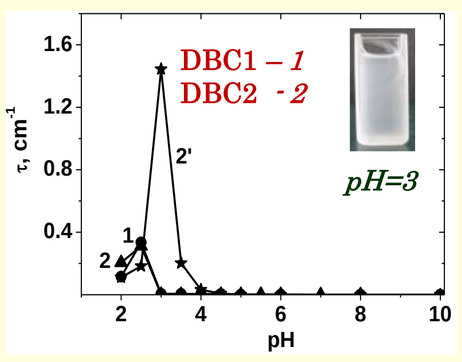
A – MOPEO block
B – PAAc block

Self-assembly
Intra PC
pH<5



"Crew-cut" *"Hairy-type"*

Type of DBC nanocarriers is "hydrophobic "core" –"hydrophilic corona"

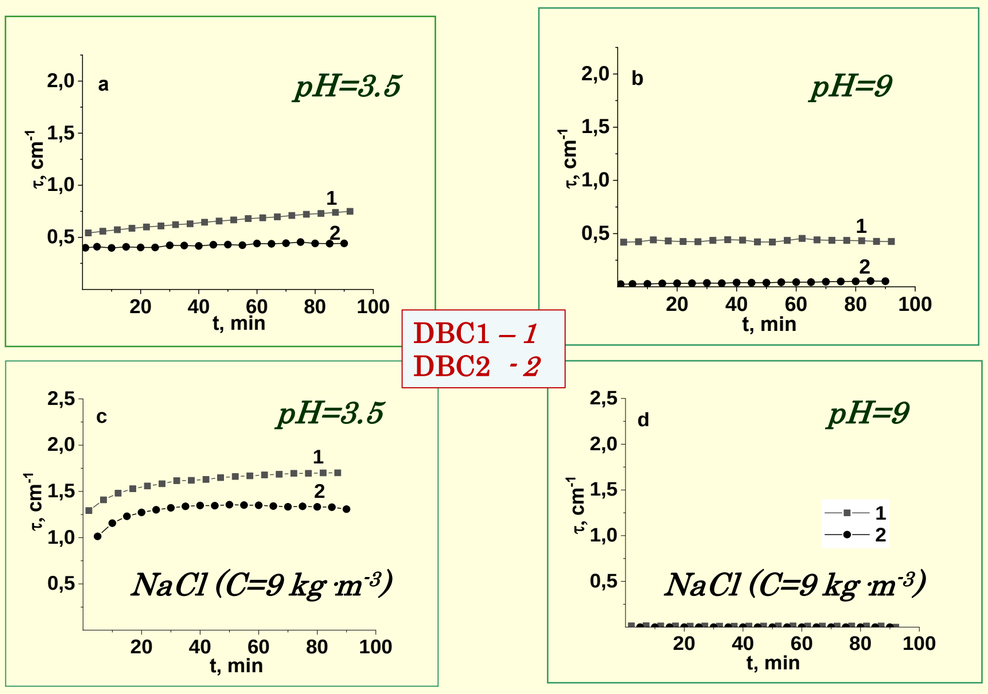


Diameters of the block copolymer micelles

Sample	C, kg·m^{-3}	pH	d_{MMM} a), nm	d_{PMM} b), nm
DBC1	0.5	2.5	4÷8	12÷68
DBC2	0.5	2.5	2÷4	8÷31

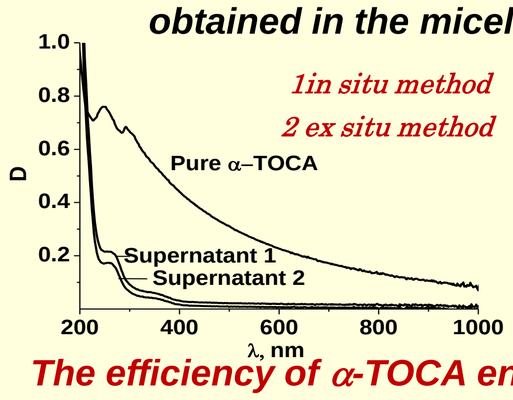
a) *monomolecular-type micelles,* b) *polymolecular micelles*

The state of DBC micelles under the influence of various environmental factors



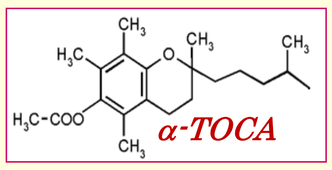
The formation/release of the in situ formed α-TOCA compositions with DBC micelles

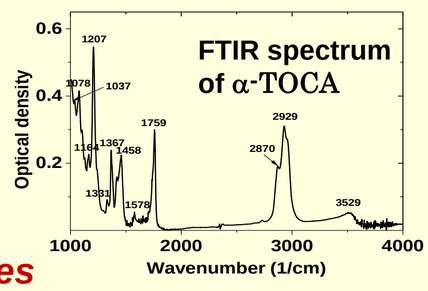
UV-Vis spectra of pure α-TOCA solutions and supernatants obtained in the micellar systems α-TOCA/DBC1



$$X_{\alpha-TOCA} = \frac{S_0 - S_S}{S_0}$$

where S_0 and S_S are the integrated intensities of the absorption bands at λ~270 nm in the UV-Vis spectra of a pure solution of α-TOCA

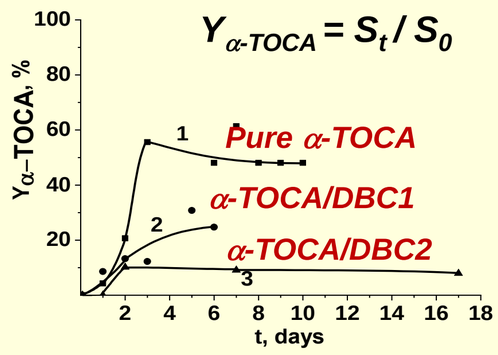




The degree of α-TOCA release ($Y_{\alpha-TOCA}$) in the dialysis against deionized water

Dialysis method

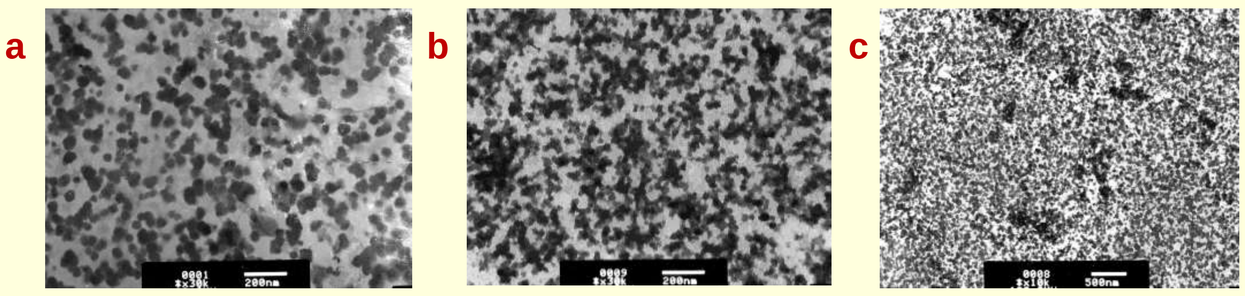
$Y_{\alpha-TOCA} = S_t / S_0$



The efficiency of α-TOCA encapsulation with copolymer micelles

System a)	$C_{\alpha-TOCA}$, kg/m^3	Encapsulation method	S_0, nm	S_S, nm	$X_{\alpha-TOCA}$ b), wt%
α-TOCA/DBC1	0.25	*in situ*	118.12	1.28	98.9
		ex situ		1.18	99.0
α-TOCA/DBC2	0.29	*in situ*	134.42	0.67	99.5
		ex situ		0.65	99.5

a) C_{DBC} = 1.0 kg·m^{-3} . b) *The degree of α-TOCA encapsulation.*



TEM images of (a) DBC1 micelles; (b, c) their compositions with α-TOCA

Conclusion

- **A wide spectrum of morphological forms of the MOPEO-*b*-PAAc micellar carriers could be produced by variation of the absolute and relative length of both the blocks.**
- **All types of DBC micelles showed high binding degrees (about 100 %) of α-TOCA, which did not depend on the encapsulation pathway ("*in situ*" or "*ex situ*").**
- **The gradual release of a vitamin E analogue from both micellar nanocarriers into an aqueous and aqueous/salt medium under the influence of a concentration gradient of α-TOCA has been proved. The rate and efficiency of α-TOCA release was determined by the structure of DBC micelles.**
- **Encapsulated α-TOCA was *in vivo* fully digested by the white mice and showed increased biological activity, which allowed reducing its therapeutic dose by 25 times. The α-TOCA composition with DBC nanocarrier was tested *in vivo* also in a group of sows as a dietary supplement. The positive effect of the micellar form of α-TOCA on the metabolic processes in the sows, as well as on increasing the productivity of sows and the safety of born piglets, was established.**