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The role of nanoparticles in the albumin-cytarabine and albumin-methotrexate interactions☆

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ABSTRACT

Understanding the interactions which occur between nanomaterials and biomolecules is one of the most important issues in nanotechnology. Determining the properties of nanoparticles obtained through the use of novel methods and defining the scope of their application as drug carriers has important practical significance. Nanoparticles containing methotrexate and cytarabine obtained by a modified reverse-phase evaporation method (mREV) were characterized through the use of the UV/Vis and NMR methods. Obtained results confirmed high degree of analysed drugs encapsulation. The encapsulation efficiencies of cytarabine (AraC) and methotrexate (MTX) in $L_{DPPC/AraC/MTX}$ were found to be 86.30% (AraC) and 86.00% (MTX). The increased permeability of the phospholipid membranes, resulting from physico-chemical properties and the location of the drug, as well as from the physico-chemical properties of the phospholipids themselves, has been confirmed by increase in the length of the T1 relaxation time of protons in the $—N^{+}(CH_3)_3$ group. The study of analysed drugs release process from the liposomes has been made for bovine serum albumin, both in the absence (dBSA) and in the presence of fatty acid (BSA). Moreover two types of kinetic models (Bhaskar equation and Rigter-Peppas equation) have been used. Based on the study it has been concluded that mathematical modelling of drug release can be very helpful in speeding up product development and in better understanding the mechanisms controlling drug release from advanced delivery systems.

1. Introduction

For more than thirty years, extensive research has been performed on new techniques for obtaining liposomes and on their application in targeted delivery of drugs and other substances to specific tissues in the body.

Liposomal vesicles, although they themselves do not possess medicinal properties, can be used to transfer substances, which can significantly improve the condition of the body or preserve life. Liposomes incorporating drugs are mainly used in the treatment of cancerous tumors, diabetes, rheumatic diseases, enzymopathy, disorders associated with metal accumulation, and the like [1–3]. Liposomes can be carriers of substances of varying chemical natures, which has an impact on the method of transferring these substances [2]. The use of drugs incorporated into liposomes allows for a reduction of the dose of the active agent and of the frequency of administration, thereby reducing the overall toxicity of the drug, while at the same time providing the desired therapeutic effect.

Determining the properties of the liposomes obtained using novel methods and defining the scope of their application as drug carriers is of important practical significance.

In the case of cancer, obtaining liposomes of a size below the size of the lesions present in the vasculature of most solid tumors (380–780 nm) allows for the use of these structures in the targeted transport of therapeutic agents [2].

The use of liposomes is associated with a number of advantages: 1) drugs delivered in this manner exhibit improved pharmacokinetics; 2) their use increases the biodistribution of the therapeutic agent;

Abbreviations: mREV, modified reverse-phase evaporation method; UV/Vis, Ultraviolet–visible spectroscopy; NMR, nuclear magnetic resonance; PBS, phosphate buffered saline; DPPC, 1,2-dihexadecanoyl-*sn*-glycerol-3-phosphocholine; AraC, 1-β-D-arabinofuranosylcytosine; MTX, DL-4-Amino-N10-methylpteroylglutamic acid; BSA, bovine serum albumin; dBSA, bovine serum albumin, fatty acid free; DSS, 4,4-dimethyl-4-silapentane sulfonate; T1, relaxation time; FID, free induction decay; ε, extinction coefficient; c, concentration; l, thickness (cm); EE (%), encapsulation efficiency; R (%), release percentage; $[D]_f$, free drug after release; $[D]_{f0}$, initial free drug before release; $[D]_t$, total drug amount; $[D]_{t0}$, concentration of total drug in the original liposomes; β, dilution folds; Tc, temperature of the main transition phase; K_b, binding constant; A0, initial absorbance; S.D, standard deviation; NSB, non-specific binding; R, gas constant; T, experimental temperature; $\Delta G_{binding}$, binding free energy.

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3) their use improves the efficacy of the treatment; 4) application via liposomes limits the toxicity of drugs [4,5].

Due to the use of natural phospholipids, liposomes are biocompatible, biodegradable, and non-toxic. They constitute an excellent form of the transport of substances by both *in vitro* and *in vivo* methods. The most frequently chosen form of administration of liposomes is oral or intravenous [6].

It has been demonstrated that during transport the stability and permeability of the liposomal membrane changes through interaction with the components of blood plasma. The interactions of plasma proteins and liposomes lead to increased permeability of phospholipid membranes, and thus increased release of the drug encapsulated therein. Based on *in vitro* studies, serum obtained from different animal species displays varying degrees of efficacy [7,8].

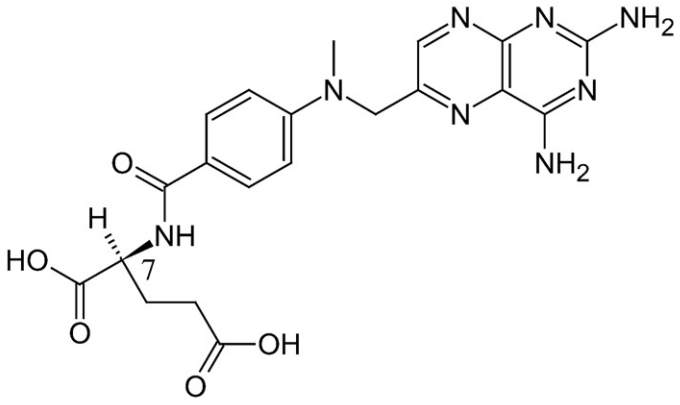
The specific nature of the structure of albumin derived from different animal species, and in particular the differentiated hydrophobicity of the molecules, described by Dimitrova et al., is likely to affect the binding parameters of albumin liposomes [7].

Aggarwal et al. [9] suggest that the degree of bonding between liposome and albumin depends on: the lipid composition, the preparation method and experimental conditions such as pH or temperature and the albumin-lipid molar ratio. The research results presented also demonstrate that, in the case of small liposomes, a larger surface to volume ratio (as compared to other carriers) causes proteins to exhibit a greater tendency to bind to nanoparticles than in the case of liposomes of a larger particle size [10].

An assessment of the binding of a drug with plasma proteins is a crucial element in preclinical studies [11–13]. This is extremely important in understanding the pharmacokinetics and pharmacodynamics of the drug. Of course, no less important are the factors determining the effectiveness of the transport of nanoparticles, such as size, shape, surface charge, surface modifications or route of administration.

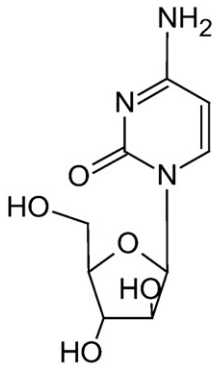
This article presents the pioneering studies of the incorporation of cytarabine and methotrexate (Fig. 1) into liposome vesicles and their interactions with serum proteins. In literature, there is no information about the simultaneous incorporation of these drugs, in spite of the fact that they have been used in many cancer therapies (COMLA, AMOPLACE, BVAM, F-MACHOP, HIC-COM, MOPLACE) [14,15].

The main goal of the study was the analysis of encapsulation degree and cytarabine and methotrexate release process from the liposomes obtained by mREV method. In order to simulate the model of interaction between nanoparticles and protein macromolecules fatted and defatted bovine serum albumin has been used.



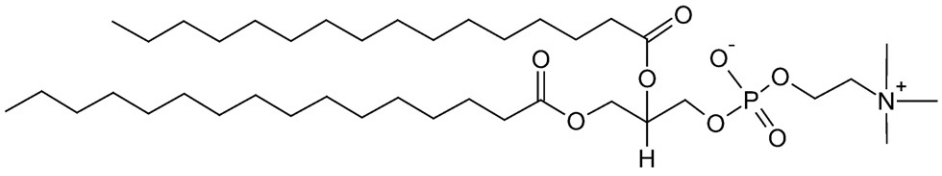
Methotrexate (MTX)

DL-4-Amino-N10-methylpteroylglutamic acid



Cytarabine (AraC)

1-β-D-arabinofuranosylcytosine



DPPC

1,2-dihexadecanoyl-***sn***-glycerol-3-phosphocholine

Fig. 1. Structures of the investigated drugs and DPPC.