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Magnetic Liposomes for Remote Controlled High-Molecular Drugs Release under a Low-Frequency Non-Heating Magnetic Field

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Abstract—Magnetic anionic liposomes (MALip) conjugated with magnetite magnetic nanoparticles (MNPs) are developed for the controlled release of a protease inhibitor (BBI) under exposure to a low-frequency non-heating magnetic field (LF AMF). It is shown that an increase of up to 35% of the protein release rate occurred when the MALip are exposed to the LF AMF (frequency 110 Hz, intensity 75–150 kA/m) for 5–15 min. The research provides prospects for the development of remotely controlled protein release from liposomes.

Keywords: magnetic liposomes, non-heating alternating magnetic field, controlled release of macromolecular compounds (proteins)

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INTRODUCTION

Liposomes have many advantages over other drug delivery systems; however, at the same time they have a number of drawbacks, the most significant of which is the low rate of release of encapsulated molecules.

The influence of a non-heating low-frequency magnetic field (LF AMF) with frequency *f* below 1000 Hz is the most promising among multiple approaches to the stimulus-driven drug release from liposomes [1–7]. These fields are safe for humans even at large intensity levels, penetrate deep into biological tissues, and can act selectively on magnetically sensitive materials introduced into the organism without affecting the surrounding organs and tissues [8]. Earlier we demonstrated that the LF AMF influencing magnetic liposomes with MNPs in their membranes can be used to remotely control the release of low-molecular-weight compounds from the vesicles [9].

The LF AMF decreases the stability of the lipid bilayer of magnetic liposomes (via the mechanical effect on the MNPs), which experience Brown relaxation [10]. The rotational-vibrational movement of the particles in the LF AMF can cause a mechanical strain in the membrane, leading to its disordering and, hence, to a decrease in permeability for small molecules. This approach is an alternative to magnetic hyperthermia, the method of increasing the magnetic liposomes' membrane permeability by heating the MNPs by a high-frequency (f = 200–600 kHz) magnetic field [10], and it is preferred in several aspects.

The aim of this work is to study the influence of LF AMF on the dynamics of the release of a macromolecular Bowman–Birk type protease inhibitor from magnetic anionic liposomes containing MNPs of magnetite covalently immobilized on the vesicle's surface.

EXPERIMENTAL

Materials

The following chemicals were used: iron(III) acetylacetonate, benzyl alcohol, dopamine, alpha-chymotrypsin (α-CT), Bowman–Birk protease inhibitor (BBI), tablets of a sodium phosphate buffer (PBS), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), *N*-hydroxysuccinimide (NHS) purchased from Sigma (United States), and also dipalmitoyl phosphatidyl-

Abbreviations: LF AMF, low-frequency alternating magnetic field; ALip, anionic liposomes; MALip, magnetic anionic liposomes; MNP, magnetic nanoparticle; f-MNP, functionalized magnetic nanoparticle; BBI, Bowman–Birk protease inhibitor.