Biophys. Struct. Mech. 6, 233–234 (1980)

Biophysics of Structure and Mechanism

Short Communication

Induced Drug Release from Lipid Vesicles in Serum by pH-Change

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Abstract. Drugs can be released from lipid vesicles by pH-change in calf, horse or human serum when pH-sensitive trigger molecules are incorporated in the vesicle lipid bilayer. The lipid composition is so chosen that the drug release is best performed at 37° C. Specific drug targeting is envisaged to loci of the body with lower than physiological pH, such as primary or metastatic tumors.

Key words: Liposomes – pH-induced drug release – Cancer.

Release of drugs from liposomes as a function of pH could allow them to be specifically targeted to areas of low pH in the body. Such pH-sensitive lipid vesicles were constructed from diheptadecanoylphosphatidylcholine (DHPC), dipalmitoylphosphatidylcholine (DPPC) and palmitoylhomocysteine (PHC). The PHC was synthesized to serve as a pH-sensitive trigger molecule in the vesicle bilayer (Kreutz 1972). Above pH 7 the PHC-molecule is in an open conformation and forms stable vesicles with DHPC and DPPC, below pH 7 it is found in a closed conformation (thiolactone-ring) which destabilizes the vesicle bilayer resulting in drug release. The lipid composition of the vesicles was chosen in order to maximize drug release at about 37° C, e.g. a threefold release compared with the release at 23° C at pH= 6.8 (Yatvin et al. 1978). The vesicles contained a highly quenched fluorescent compound (200 mM), carboxyfluorescein (CF) (Weinstein et al. 1977). Excess CF outside the vesicles was removed by Sephadex G 50 filtration. Drug release from vesicles was monitored by an increase in serum fluorescence. When small unilamellar liposomes (see Yatvin 1978) composed of 70% DHPC, 18% DPPC, and 12% PHC were exposed to either calf, horse or human serum at pH's ranging between 6 and 7.4 a differential release of encapsulated CF was obtained. The pH-induced leakage

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0340-1057/80/0006/0233/$ 01.00

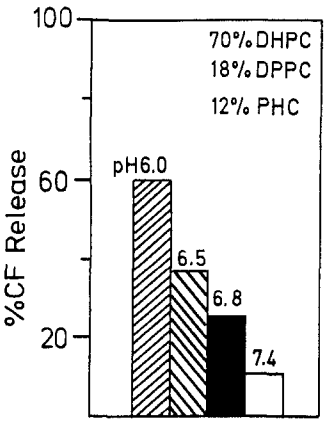

Fig. 1. Representation of the extent of drug release in serum at four different pH-values from DHPC-DPPC-PHC-vesicles

of CF in serum was greatest between 37° C to 39° C. It was approximately 3-fold higher at pH 6.5 than at 7.4 and 5-fold greater at pH 6.0 (see Fig. 1). With charged phospholipids such as PA, PE or PS comparable pH-effects could not be achieved up to now. The rational for developing such pH-sensitive vesicles is that tumors have interstitial pH-values significantly below normal serum. Thus, targeting of drug to both a primary tumor as well as metastatic lesions may be an achievable goal. Furthermore, sites of inflamation and infection also have lower than physiological pH-values which may also result in preferential drug release from pH-sensitive liposomes in these areas.

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Received May 16, 1980/Accepted July 1, 1980