



Transfer of lipophilic drugs between liposomal membranes and biological interfaces: Consequences for drug delivery

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Abstract

This review paper describes the present knowledge on the interaction of lipophilic, poorly water soluble, drugs with liposomal membranes and the reversibility of this interaction. This interaction is discussed in the context of equilibrium and spontaneous transfer kinetics of the drug, when the liposomes are brought in co-dispersion with other artificial or natural phospholipid membranes in an aqueous medium. The focus is on drugs, which have the potential to partition (dissolve) in a lipid membrane but do not perturb membranes. The degree of interaction is described as solubility of a drug in phospholipid membranes and the kinetics of transfer of a lipophilic drug between membranes. Finally, the consequences of these two factors on the design of lipid based carriers for oral, as well as parenteral use, for lipophilic drugs and lead selection of oral lipophilic drugs is described. Since liposomes serve as model-membranes for natural membranes, the assessment of lipid solubility and transfer kinetics of lipophilic drug using liposome formulations may additionally have predictive value for bioavailability and biodistribution and the pharmacokinetics of lipophilic drugs after parenteral as well as oral administration.

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1. Introduction

The parenteral and oral administration of lipophilic drugs is often problematic because of their low water solubility. In order to administer a therapeutic dose of these drugs, formula-

tions containing solubilisers and/or formulations with a high dissolution rate are an absolute necessity to deliver the drug. Phospholipids can be used to solubilise such drugs. When diacyl-phospholipids with a cylindrical shape are dispersed in water, lipid vesicles comprising a phospholipid bilayer, which surrounds an aqueous compartment are formed spontaneously. Therefore, they can encapsulate hydrophilic and bind amphipathic as well as lipophilic drugs.

Since the introduction of liposomes into the world of intravenous drug delivery research (Olson et al., 1982; Stamp and Juliano, 1979; Gabizon et al., 1982), liposomal formulations for lipophilic drugs have been developed and successfully, introduced on the market (Banerjee, 2001; Gregoriadis, 1995). Specific examples of such drugs are amphotericin B (Albelcet[®], AmBisome[®]) and benzoporphyrin (Visudyne[®], Verteporfin for injection).

Abbreviations: BPD-MA, benzoporphyrin-mono acid derivative; CyA, cyclosporin A; DCP, dicetylphosphate; DMPC, 1,2 dimyristoylphosphatidylcholine; DMPG, 1,2 dimyristoylphosphatidylglycerol; DOPC, 1,2 dioleoylphosphatidylcholine; DOPS, 1,2 dioleoylphosphatidylserine; DPPC, 1,2 dipalmitoylphosphatidylcholine; HDL, high density lipoproteins; LDL, low density lipoproteins; POPC, 1-palmitoyl; 2-oleoylphosphatidylcholine; MPS, mononuclear phagocytotic system; PC, phosphatidylcholine; PG, phosphatidylglycerol; ZnPc, zinc phthalocyanine

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