Monoacyl- and Diacyl-Phospholipids: The Natural Oral Solubilizers for Poorly Water Soluble Drugs

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Introduction: Phospholipids are usually associated with liposomes and emulsions in parenteral, dermal or cosmetic formulations. However, a much greater importance should be attached to these natural, versatile, amphiphilic emulsifiers, dispersants and solubilizing agents, that can be administered orally without restrictions (GRAS ("generally recognized as safe") status by the U.S. FDA; see 621CFR184.1400 US FDA and 721CFR184.1063 US FDA) [1,2]. Phospholipids can be obtained e.g. from soybeans and egg yolk. Phosphoglycerides with two fatty acid chains are called diacylphospholipids and phosphoglycerides with one fatty acid chain are called monoacylphospholipids (or lysophospholipids) (see Figure 1 for examples).

a) b)

Figure 1. (a) Diacyl- and (b) monoacyl-phosphatidylcholine

Nature shows how it is possible to take up poorly soluble drugs in the gastrointestinal tract with the aid of (endogenous and formulation related) phospholipids (Figure 2) [2 -4].

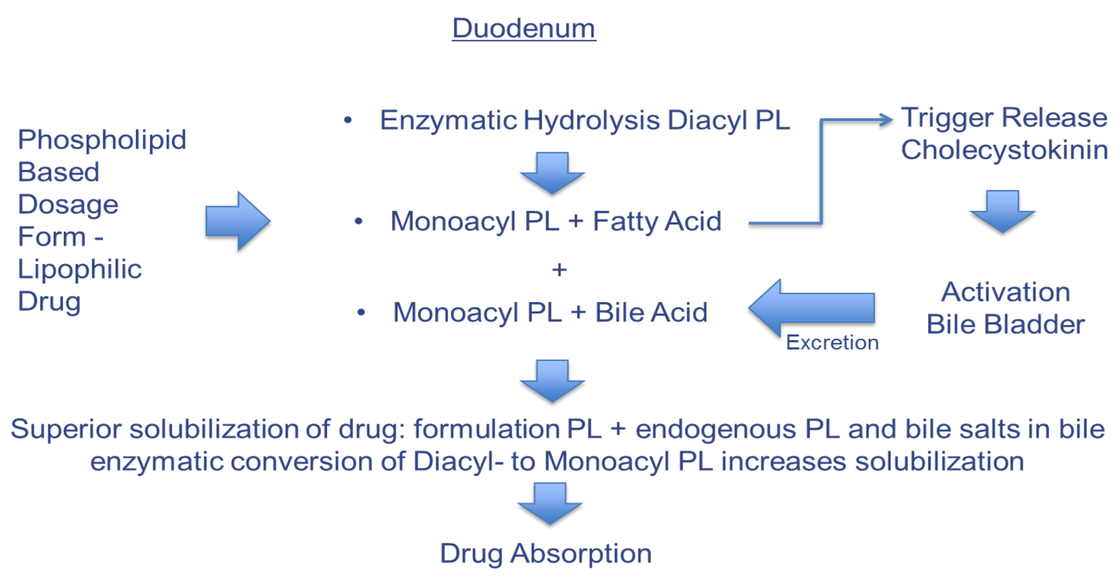

Figure 2. Fate of phospholipid-containing dosage forms in the GI tract

Purpose: The affinity of various poorly water soluble drugs for saturated and unsaturated diacylphospholipids and monoacylphospholipids was determined. The dissolution properties of a drug/lipid complexes, with indomethacin as example, were assessed.

Materials and methods: Phospholipids were from Lipoid GmbH, Ludwigshafen, Germany. Drug/lipid complexes were prepared by dissolving drug and lipids at a predetermined ratio in solvent. After removal of the solvent, the dry residue dispersed in water. The resulting dispersion was filtered through a 0.45 µm pore size PVDF filter and the degree of solubilization of the drug in the lipids was derived from the drug concentration in the dispersion before and after filtration by means of HPLC. The dissolution properties of the formulations were assessed using USP Apparatus 2 at 75 rpm and 37^{0}C. The formulations were dispersed SGF for 60 min and them double concentrated FaSSIF was added and the dissolution followed for another 120 min.

Results and Discussion: The lipid affinity of drugs appears to be individual and lipid specific. In general, a low lipid affinity for the saturated phospholipids 80H und 90H was found for all studied drugs. Low or no affinity for all investigated lipids were found for albendazole, griseofulvin, nifedipin and digitoxin. High affinity for natural, unsaturated phospholipid fractions was found for terfenadine, indomethacin, simvastatin, silymarin, naproxen, carbamezepin and hydrocortison. The affinity for monoacyllipids for these drugs was, in general, higher. A very high affinity for monoacylphospholipids was found for clofazimine, cotrimazole, fenofibrate, glibenclamide, spironolactone, progesteron and ketoconazole. In general, the lipid affinity of poorly water soluble drugs follows the sequence: Monoacyl-PC>Unsaturated Diacyl-PC> Saturated Diacyl-PC.

The dissolution characteristics of various indomethacin-lipid formulations with unsaturated diacylphospholipids (S 45, S 75; 90G) or monoacylphospholipids (LPC 20, LPC 65, LPC 80) at a 1 : 10 w/w drug/lipid and drug suspension are provided in Tables 1 and 2.

Phospholipid	Physical Mixture	Complex
None	0	
90G	2	60
S 45	0	0
S 75	0	2
LPC 20	0	1
LPC 65	10	45
LPC 80	20	45

Table 1. Lipid and formulation dependency of the degree of dissolution of indomethacin [%] in SGF after 60 min

Phospholipid	Physical Mixture	Complex
None	40	
90G	48	65
S 45	55	80
S 75	50	80
LPC 20	60	80
LPC 65	70	75
LPC 80	60	80

Table 2. Lipid and formulation dependency of the degree of dissolution of indomethacin [%] in SGF/FaSSIF after 180 min

Conclusion: The lipid affinity of poorly water soluble drugs is individual, lipid and formulation specific. In general, the lipid affinity of poorly water soluble drugs follows the sequence: Monoacyl-PC>Unsaturated Diacyl-PC> Saturated Diacyl-PC. The complexation of poorly water soluble drugs results in an increased degree of in-vitro dissolution. Diacylphospholipids may also be suitable as solubilizers because in-situ/in-vivo monoacylphospholipids may be formed and secretion of bile may be triggered.

References:

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Lipoid