MODIFICATIONS EMPLOYING HYDROPHILIC FUNCTIONAL GROUPS

A common strategy employed to increase aqueous solubility is the introduction of an ionic or ionizable group. Common esters employed to increase the aqueous solubility of drugs bearing a hydroxyl group are hemisuccinates, phosphates, dialkylaminoacetates, and amino acid esters. For drugs that have a carboxylic acid group, ester formation with the alcohol of choline or β-dimethylaminoethanol, or amide formation with the amine of an α-amino acid, has been successful in the preparation of prodrugs possessing an enhanced solubility (Amidon, 1981).

The phosphate group is acknowledged as the most commonly used promoiety to increase solubility. For example, clindamycin hydrochloride has a solubility of 3 mg/mL, while clindamycin-2-phosphate has a solubility in excess of 150 mg/mL and is hydrolyzed *in vivo* with a reaction half-life of only 10 min (Amidon et al., 1977). The disodium salts of monophosphate derivatives at the 2′- or 7-positions of Taxol yielded prodrugs with a solubility greater than 10 mg/mL, compared to 0.25 μg/mL for the parent drug (Vyas et al., 1993). Entacapone is a 3,4-dihydroxy-5-nitrobenzylidine derivative that is a potent inhibitor of catechol-*O*-methyltransferase. When entacapone was reacted with phosphorous oxychloride in dry pyridine to produce its phosphate prodrug, the aqueous solubility increased more than 1700- and 20-fold at pH 1.2 and 7.4, respectively (Leppanen et al., 2000). In addition, the prodrug demonstrated stability toward chemical hydrolysis (a $t_{1/2}$ of 2227 h at pH 7.4) and quantitative release of the parent drug due to enzyme-catalyzed hydrolysis in liver homogenate. One of the most dramatic improvements in solubility was seen with the mono- and diphosphate esters of 2-arachidonyl glyceryl ether (i.e., noladin ether), where the phosphate esters increased the solubility more than 40,000-fold, showed high chemical stability in various buffer systems, and were rapidly converted through enzymatic hydrolysis to the parent drug (Juntunen et al., 2003).

Phosphate esters have the desirable qualities of both chemical stability (Flynn and Lamb, 1970) and biological lability (Amidon et al., 1977; Amidon, 1981). There is evidence that the soluble phosphate ester is enzymatically hydrolyzed to the active agent in the body (Melby and St. Cyr, 1961; Hare et al., 1975; Amidon et al., 1977; Miyabo et al., 1981; Varia and Stella, 1984; Leppanen et al., 2000). An abundance of phosphomonoesterases in plasma, for example, was noted by Melby and St. Cyr (1961); the presence of alkaline phosphatase in the brush border membrane was also reported some time ago (Schmidt et al., 1972; Hirano et al., 1977). As a result, bioactivation of the phosphate prodrug can be rapid, as in the case of methylprednisolone (Mollmann et al., 1989).

Phosphate esters are usually freely water soluble and are sufficiently stable that solutions with practical shelf lives can be prepared (Flynn and Lamb, 1970; Hong and Szulczewski, 1984; Kwee and Stolk, 1984; Varia et al., 1984b). In contrast to phosphate monoesters of primary alcohols, the phosphomonoesters of sterically hindered aromatic (Williams and Naylor, 1971), secondary (Kearney and Stella, 1992; Sadafi et al., 1993), and tertiary alcohols (Sadafi et al., 1993; Bentley et al., 2002) experience a slow rate of bioconversion. The incorporation of a spacer group between the alcohol and the phosphate groups was able to enhance the bioconversion rate for sterically hindered alcohols (Kearney and Stella, 1992; Sadafi et al., 1993). On dephosphorylation, however, the spacer group must also degrade or be metabolized to regenerate the parent drug (Varia et al., 1984b). A prodrug of cyclosporine A has been prepared where the ionized phosphate group attached to a sarcosine-serine-(acyloxy)alkyloxycarbonyl group provides the solubilizing component of the promoiety (Lallemand et al., 2005b). One issue with orally administered prodrugs based on a phosphate ester is that, once an enzyme has regenerated the parent drug, the solubility of the parent drug might be exceeded. Precipitation of parent drug can occur, depending on the supersaturation level, drug dose, and solubility of the parent drug, as well as the level of solubilization possible by the prodrug itself or its cleaved promoiety (Heimbach et al., 2003).

Acknowledging that the triphosphate ester of nucleosides is the active form, it was discovered that their poor chemical stability and high ionic state effectively block their oral bioavailability (Pradere et al., 2014). Preparation of the monophosphate ester with a protecting group on the phosphate moiety enabled permeability across the intestinal wall (Sofia 2013), with enzymatic or chemical