16 Prodrugs for Improved Solubility in Water

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CONTENTS

INTRODUCTION

Prodrug is a term used by Adrien Albert to describe a chemical that must undergo bioconversion before exerting its pharmacological effect (Albert, 1958, 1964). The term, as it is applied here, will refer to a drug with a covalently bound, inactive moiety (the promoiety) that provides or enhances the desired physicochemical properties, where the promoiety must be removed upon administration to regenerate the parent drug (Stella et al., 1985; Kumar and Singh, 2013). Prodrugs are typically pharmacologically inert; enzymatic or chemical processes are necessary for removal of the inactive moiety to return the active parent drug (Ettmayer et al., 2004; Stella et al., 2007; Rautio et al., 2008; Huttunen et al., 2011). Their successful use is evident when one realizes that 33% of small molecule drugs approved in 2008 were actually prodrugs (Rautio, 2010, Stella, 2010; Huttunen et al., 2011).

The chemical or enzymatic processes that restore the parent drug might guide or limit the selection of the promoiety. As an example, esterases are present throughout the body and can be utilized in the hydrolysis of an ester functional group in a prodrug (Andurkar, 2007; Bai et al., 2014) for a drug bearing a carboxylic acid or an alcohol group (Colaizzi and Pitlick, 1982). The reconversion of the prodrug to the parent drug by enzymatic means requires that the enzyme be capable of catalyzing the reaction that cleaves the promoiety-drug linkage. Prodrugs, especially those intended for parenteral use, should exhibit a long shelf life in aqueous media and yet be rapidly reconverted to the parent drug under physiological conditions (Lallemand et al., 2005b). Chemical reversal *in vivo* should demonstrate less intersubject variability than would biochemical pathways to accomplish such reversal (Notari, 1985).

Following chemical modification of the parent drug, physicochemical properties are expected to change, including solubility, stability, and sometimes the organoleptic properties (Stella, 1975; Stinchcomb et al., 1995; Peng et al., 2010; Domião et al., 2014). The advent of property-based drug design provided numerous approaches to design and develop prodrugs to achieve improved characteristics over those of the parent drug (van de Waterbeemd et al., 2001). However, modifications to generate prodrugs can positively or negatively alter the pharmacokinetics of the parent drug by affecting absorption, distribution, metabolism, and excretion (Notari, 1973; Stella, 1975; Huttunen et al., 2011). The improvement in aqueous solubility, for example, can yield improved bioavailability;