Pharmaceutical Excipients in Drug–Drug Interaction

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1 INTRODUCTION

Drug formulations such as tablets, capsules, or injectable solutions consist of active pharmaceutical ingredients and other "inactive" ingredients that are added for many purposes. For example, surfactants are often used in formulations to solubilize water-insoluble drugs, and methylcellulose may be used to prepare drug suspensions or added to tablets as a disintegrating agent or binder. During the development of a given drug formulation, it is well understood that the interactions between the drug and excipients need to be carefully studied to ensure that the drug is stable in the formulation and that the solubility, as well as the dissolution properties in the case of orally administered drugs, is satisfactory (Kalasz and Antal, 2006).

Not all of the excipients in approved drug formulations are "inactive;" some are known to alter drug metabolism and/or transporter activities. Therefore, in the drug formulation development process, one also needs to consider whether the chosen excipients in drug formulations can alter systemic exposure of the drug itself or other potentially coadministered therapeutic agents due to interactions with drug-metabolizing enzymes and/or transporters, especially under situations where the excipients are not approved by the regulatory agencies, or if the amounts of the excipients used are higher than that used for previously approved drug formulations.

Interestingly, among the many formulation components found in marketed drug products (see FDA web site: http://www.fda.gov/cder/drug/iig/default.htm), most of the excipients that interact with drug biotransformation processes and/or transporters belong to a group known as solubilizing excipients, that is, additives used to solubilize drugs in oral and injectable dosage forms. Solubilizing excipients include *water-soluble organic solvents* such as polyethylene glycol 300 (PEG300), polyethylene glycol 400 (PEG400), ethanol, propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, dimethylacetamide, and dimethylsulfoxide (DMSO); *nonionic surfactants* such as Cremophor EL, Cremophor RH40, Cremophor EH60, D-α-tocopherol polyethylene glycol

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