151g Modeling the Influence of Cyclodextrins on Oral Absorption of Saltform Drug in Immediate and Controlled Release Delivery

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Increasing interest in the delivery of drugs with poor bioavailability has caused significant achievements in drug delivery technologies such as cyclodextrins, lipid-based systems, and polymers. Low absorption of an orally dosed drug through the intestinal membrane is one of the important factors causing poor bioavailability. Percent absorption in the gastrointestinal (GI) tract depends on orally dosed drug dissolution, precipitation and permeation through the intestinal membrane. Predicting the influence of a drug delivery technology on these processes and on drug absorption can be very beneficial in formulation design. This can be accomplished via the development of models of the intestinal drug delivery system with mathematical expressions for the key processes that incorporate parameters representing physical and chemical properties of the drug to be delivered, the drug delivery device, and the intestinal environment.

Cyclodextrins (CD) are cyclic oligosaccharides which are known to help dissolution kinetics of insoluble drugs by forming inclusion complexes. There are many studies showing the enhancement of oral bioavailability by complexation between CD and drug as well as the failure of CD to enhance oral bioavailability [1]. There is often incomplete understanding what physical and chemical properties of drug and drug delivery technology have the greatest effect on drug bioavailability.

A model was developed to understand the ability of CD to enhance oral absorption of insoluble drugs. Since many drugs are formulated with saltforms of active compounds, the model was designed to predict the influence of CD dosed with saltform of the drug as a physical mixture. The model includes mathematical expressions for dissolution, absorption and precipitation of saltform drug administered as a physical mixture with CD. The dissolution expression is based on the Noyes-Whitney equation considering an unstirred boundary layer around the dissolving particle and the flux of free drug as well as complexed drug from the dissolving particle. Precipitation is explained in two stages with two different expressions: nucleus growth and precipitation. Absorption is considered as a first order process which is proportional to free drug concentration in the intestinal lumen. Complexation of drug and CD is assumed to be in equilibrium. The model was designed for immediate release (IR) as well as controlled release (CR) in which the solid drug is introduced to the intestinal environment in equal amounts over the release time.

The mathematical expressions were incorporated into MATLAB® and the data obtained from the simulations were analyzed by a statistical program, JMP®. Model inputs include the properties of drug (solubility, molecular weight, diffusivity, pKa), drug delivery technology (dose, CD to drug ratio, release time), the biological environment (pH, permeability, GI tract volume) and CD (binding constant, dose, molecular weight, diffusivity). Model output includes the concentrations of all species (drug and CD) in solution as well as dissolution, absorption and precipitation rates as a function of time. Simulation results obtained for 12 hours post-dosing for both CR and IR cases showed different trends depending on key parameter values. For CR, the percent dose absorption is over 70% and higher than for IR in general for the parameters studied. However, CD has negative effects on absorption of drug in CR formulation by decreasing free drug concentration via complexation. It was also seen that CD increases drug absorption in IR case by decreasing precipitation kinetics. Precipitation may occur during the passage of saltform drug through the GI tract. Experimental validations are in progress. Simulation results show the utility of modeling the ability of CDs to influence absorption for rational dosage form design for both IR and CR.

1. V.J. Stella, R.A. Rajewski. Cyclodextrins:Their future in drug formulation and delivery. Pharm. Res. 14:556-565 (1997).