Modelling Drug Dissolution in the Laboratory and in Humans plus *Trí Ghalar gan Náire*

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Between oral administration of a tablet and the patient experiencing the effect of the drug, there are a number of steps or processes. The first of these is dissolution, whereby the drug is released from the tablet and goes into solution in the gastric fluid. Once in solution, the drug is absorbed across the wall of the gut into the blood stream, which carries it to the organs and tissues of the body. Drug leaves the blood and enters these organs and tissues and in some of them it binds to particular receptors initiating a cascade of events resulting in the drug's effect on the body. Some of the organs eliminate the drug from the body by metabolism or excretion causing the concentration of drug in the blood to fall, as a result of which the drug leaves the tissues and returns to the blood. This drop in tissue drug concentration results in a reduction and eventual cessation of the drug's effect. Drug dissolution, being the first step in this sequence, potentially controls all subsequent steps. The rate at which a tablet dissolves depends on the physicochemical properties of the tablet and is therefore amenable to being manipulated by altering the formulation and manufacturing conditions of the tablet. Controlling the rate at which dissolution occurs is the objective of much of the work that is carried out by pharmaceutical scientists because of its influence on the time course of the drug effect.

It is difficult and time consuming to study drug dissolution in human subjects (*in vivo*). The alternative is to study drug dissolution in the laboratory (*in vitro*) using a glass beaker of dissolution medium under controlled conditions. Such *in vitro* studies are based on the supposition that a relationship exists between *in vitro* and *in vivo* dissolution and consequently the *in vitro* studies act as a surrogate for human studies.

The conventional approach to establishing an *in vivo–in vitro* relationship is based on a methodology which suffers from a number of statistical deficiencies. For example, the correlation structure of the data is ignored, a regression analysis with the independent variable subject to measurement errors is used and the final model may predict fractions dissolved lying outside the [0,1] interval. This paper describes a nonlinear mixed effects model for such data which does not have these shortcomings and illustrates its use by means of an example.