Some misconceptions of kinetic analyses of pharmaceutical systems

A. K. GALWEY

formerly Queen's University, Belfast

Kinetic investigations are usually undertaken to determine the reactivity of a selected reactant mixture or the stability of a particular compound. Measured rate data may be interpreted to formulate a reaction mechanism and possibly to identify the rate determining step. The theory applied to obtain insights into reactivity controls has been developed largely from studies of homogeneous reactions. However, many of those rate processes that are of greatest interest to pharmacists do not proceed exclusively in the gas or the liquid phase. The purpose of the present paper is, therefore, to discuss some modifications to the theory that are necessary when considering reactant systems that include crystalline materials. If the various significant characteristics of rate processes occurring in solids are not correctly incorporated into the theory applied, the conclusions drawn therefrom may be misconceived or even misleading.

An important feature of some types of solid state reactions is that the chemical changes occur preferentially within an active reactant-product contact interface that advances through the reactant particle. This reaction model provides some useful principles that can be applied, perhaps with modifications, to a wider range of processes in which solids participate. It is a characteristic feature of interface reactions that the shape of the product yield-time curve is determined by systematic changes in the geometry of interface disposition as reaction proceeds. From various applicable reaction models, a set of rate equations has been developed which are particularly appropriate in the kinetic analyses of solid state decompositions. These expressions contrast with those used for homogeneous reactions, which are based on concentration terms that are not generally acceptable for interface processes and in some other types of reactions of solids.

Parameters that control or, at least, influence rates of reactions in solids include the following effects that are either absent, or operate differently, in gaseous or liquid phase reactions. The role of intracrystalline diffusion across a solid product barrier layer has been identified and characterised in reactions that form a new substance interposed between and, therefore, separate reactant particles. Similarly, diffusion may determine the release rates of volatile products from some decompositions in crystals. Kinetic characteristics of reactions in solids are frequently sensitive to particle sizes, shapes, degree of compaction and sometimes to the prevailing atmosphere, particularly when there is reversibility. Solids also exhibit self-heating/cooling. Some reactions proceed at different rates in the solid and in the melt (or solution), the theory of reactions accompanied by fusion (or dissolution) has not been extensively developed. Melting may occur on production of a liquid intermediate, by eutectic formation with a product or accumulation of a solvent released such as water. Chemical changes sometimes proceed more rapidly in the liquid where the stabilizing attractive intracrystalline forces are relaxed. There is also the increased stereochemical freedom to adopt the most effective reactant configuration for chemical change.

Variations in reaction rates with temperature are normally correlated and extrapolated using the Arrhenius equation, which is generally accepted as being applicable to rate processes in crystals. However, the theoretical significances of the terms 'activation energy' and 'frequency factor' as used in reactions on, in or between solids are different from those established in the theory of homogeneous kinetics.

This contribution will be concerned with the kinetic analyses of chemical changes that occur in crystals or in mixtures containing both solid and melt with emphasis on systems that are of greatest interest to pharmacists. The application of system-specific rate equations will be discussed, to draw attention to the limitations and uncertainties that may be inherent in the existing theory.

Some consideration will be given to the dependence of reaction rates on temperature and the application of the Arrhenius equation to data extrapolation.