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AN OVERVIEW OF KINETICS FOR THE EVALUATION OF THE STABILITY OF PHARMACEUTICAL SYSTEMS

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1.1 Introduction

This chapter is of an introductory nature and is not designed as a detailed review of the theory of kinetics. That topic has been dealt with, more than adequately, by a number of eminent authorities in pharmaceutics, chemistry and allied fields. Nor is this chapter planned as a comprehensive review of all instances where kinetic data pertinent to pharmaceutical systems has been recorded. Readers interested in such information are referred to the excellent contributions by Fung (1) Connors, Amidon and Kennon (2) Grimm and Schepky (3) and Carstensen (4,5). Also, other chapters in this book deal, in much greater detail, with certain aspects of kinetics and the application to pharmaceutical systems of kinetic methods. The objective of this chapter is to present an overview of the use of kinetics for the evaluation of the stability of pharmaceutical products. In this chapter the author discusses some of the main applications of kinetics in pharmaceutical stability work. Attention is also directed to aspects which have potential for future growth or are, at present, not fully exploited or subject to misunderstanding.

The underlying cause of the instability of pharmaceutical systems is thermodynamic in origin. In particular, since pharmaceutical products are

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generally characterized by a low level of entropy, $\triangle S$ values will often favor degradation. Unfortunately, although classical equilibrium thermodynamics is of proven or practical value in predicting final equilibrium positions, it is of no direct value in quantifying the rate at which such equilibrium points will be reached. Absolute stability for a pharmaceutical system is neither necessary nor practical - if a unit of a pharmaceutical product is still on the market after ten years we may not have a stability problem but we certainly have a sales or distribution problem. As far as this author is aware little, if any, use has been made of the relatively new discipline of non-equilibrium thermodynamics for the investigation of drug product stability. Perhaps this technique should be fully investigated by pharmaceutical scientists. Thus, at present classical kinetics, the starting point of which is the Law of Mass Action, has a unique role to play in pharmaceutical stability problems.

What are the effects which can be caused by instability problems in pharmaceutical products?

There are at least six possible results of drug product instability:

1. loss of active drug, (e.g., aspirin hydrolysis),
2. loss of vehicle (morphine elixir),
3. loss of content uniformity (suspension impaction),
4. reduction of bioavailability (tablet aging resulting in change of dissolution profile),
5. impairment of pharmaceutical elegance (interaction of amine drugs with spray dried lactose to give yellow spots on tablets),
6. production of potentially toxic materials (glass spicules on autoclaving solutions containing citrates).

1.2 Modes of Degradation

Degradation of pharmaceutical systems can be produced by continuous or intermittent processes. Hydrolysis of an antibiotic in aqueous solution is a continuous process whereas the degradation which can result from dropping a carton of pharmaceutical products at a loading dock is not continuous, but intermittent in nature. In general, kinetic principles can be used, with

varying degrees of success, in predicting continuous degradation, they are of much less value in dealing with intermittent problems where purely statistical approaches are of greater utility.

It is also common to classify the degradation of pharmaceutical products as being due to chemical, physical or biological mechanism. This classification, although useful, is by no means watertight. Often the degradation of a pharmaceutical product involves a combination of more than one of these mechanisms. For example, the loss of tensile strength of condoms, a physical effect, is due, in part at least, to a complex oxidation process. Kinetics has achieved wide recognition in helping to deal with chemical problems. It is less widely used for physical and biological degradation. Although, it is recognized that many of the problems we encounter in these areas are complex it is desirable that we should now be exploring in more depth the further use of kinetics.

1.3 Rate Equations

It is the present author's opinion, based on his experience as a research worker and consultant to industry, that although the mathematical relationships used in kinetics are generally well understood, the application of these equations to real pharmaceutical systems is sometimes naive and overly simplistic. Also, kinetic equations are sometimes abused by using them in situations for which there is no theoretical or practical justification. In particular, it is all too common to forget that the accuracy precision, sensitivity and specificity of our assay can sometimes place substantial limitations on kinetic interpretation of our data.

For the zero and first order rate equations, it is of course obvious to any sixth grade math student that plots of C (reactant drug concentration) as a function of time will produce radically different curves. Thus if a sufficiency of experimental values of C, of acceptable precision and wide enough range, is available we can readily distinguish if a given reaction is zero or first order. However, unless we know the precision of our data we can not be sure whether we will be justified, at say the 95% confidence level,

in identifying a process as zero or first order. Although, the literature does contain a number of sound papers describing the application of statistical methods to pharmaceutical stability data, there are still too many workers who are apparently unaware of the value of statistical techniques. The paper by Boudreau and Harrison (6) is a good expamle of a sound statistical approach to pharmaceutical stability.

One other aspect which complicates this problem is the fact that in pharmaceutical stability we are, for practical purposes, often only interested in the first 10% of the degradation reaction. Thus it is often the case that our range of experimental concentration values can be distressingly small and this further inhibits our ability to differentiate a zero from a first order reaction.

Tests for goodness of fit of our experimental data to zero or first order rate equations can be of material assistance in deciding which order the reaction which we are investigating is following. Since, in may instances, we have data from a number of experiments in which the sample times are very similar, it is useful to apply Brothers' Near Neighbour Test which gives us a more realistic value of the number of degrees of freedom in our data than would otherwise be the case.

Of course, there are empirical approaches to drug product stability which do not require a complete understanding of kinetic pathways. However, when one is using accelerated stability methods, such as those which exploit the Arrhenius equation, knowledge of the order is, of course, essential. Kinetic data is only as good as the experimental method used to generate the raw data. Fortunately, chromatographic methods, especially HPLC, often lend themselves readily to the development of stability indicating assays of acceptable precision (7,8).

1.4 Effects of Temperature on Reaction Rates

Temperature is important in pharmaceutical stability for both practical and theoretical reasons. Of all the factors which can adversely affect drug product stability, temperature is probably the only one which appropriate

pack selection can not control, at least in part. As many of us have learned from bitter experience, instructions such as "Store in a Cool Place" can too often be classified as a pious hope rather than a realistic expectation. Thus, we have an obvious practical reason for exploring temperature effects on drug product stability.

The theoretical interest in temperature effects derives, to a considerable extent, from the Arrhenius equation (Eq. 1) which relates temperature (T) and rate constant (k),

$$\log k = \log A - (E_a / 2.303RT) \qquad \text{(Eq. 1)}$$

where A is the frequency factor, E_a is the energy of activation, and R the Gas Constant.

This equation has been validly exploited for the prediction of shelf life of pharmaceutical products. It has also, on occasions, been terribly abused.

A plot of log k as a function of reciprocal temperature will, if the Arrhenius relationship is observed, give a straight line plot of an intercept on the ordinate of log A and slope $-(E_a/2.303R)$. Therefore, if values of k are available at elevated temperatures (say 40,45,50, and 60°C), it may be possible to estimate the shelf life at room temperature. The use of accelerated stability tests can indeed be useful in predicting the likely shelf life of products providing the Arrhenius relationship does indeed govern the temperature dependence of the reaction (9). However, far too often the authors still see this equation abused.

The phenomenon of tablet aging is an area which has attracted considerable interest recently. The mechanism, or mechanisms, responsible for the aging effects are incompletely understood at present. Results of tablet aging - significant changes in disintegration and dissolution times - are often of considerable practical importance and have, unfortunately, sometimes resulted in recalls. There does not appear to be any experimental or theoretical data which would reliably allow the use of an Arrhenius approach to predicting the extent of tablet aging. Similarly, there is no justification for assuming

that changes in tablet hardness can always be used as quantitative indicators of aging (10). Bolton has recently published (11) an interesting paper which considers the stability of release rates for sustained release pharmaceuticals. Chowhan and his co-workers have reported a comparative evaluation of aqueous film coated tablet formulations subjected to high humidity aging (12). These and other papers in this area clearly indicate that tablet aging is indeed complex. Until such time as reliable data is available to justify the use of an Arrhenius approach this temptation should be resisted.

Even when a system may reasonably be used for an Arrhenius type approach it is of course essential to have reliable information on the precision of the data. Also, two point Arrhenius plots, although they always have a correlation coefficient of 1.00, must be used with great caution!

However, let me not give the impression that the Arrhenius equation is not a tool of great value when used appropriately - it certainly is. A number of distinguished pharmaceutical scientists have shown considerable ingenuity in manipulating the Arrhenius equation. For example, Rogers (13) introduced the programmed temperature rise technique and a number of other workers have also introduced interesting modifications to the use of the Arrhenius equation. Thus, Fung has recently presented information on a computer method which, by transformation of the basic rate equations and truncation of the Arrhenius plot, allows direct conversation of the raw experimental data to give an estimate of shelf life (14).

Yang has published a useful study of the use of the non-isothermal accelerated kinetic study in pharmaceutical development. He very properly pointed out the limitations of this approach (15,16,17).

Yang also considered the effects of errors in the estimation of the activation energy and shelf life caused by using an incorrect order in any accelerated stability test. He pointed out that when it is virtually impossible to determine kinetic order, zero order can be assumed so that a conservative estimate of shelf life will be obtained.

Zoglio and his associates and other workers have discussed the linear temperature: time accelerated stability study method and this method merits

consideration by those wishing to use an Arrhenius approach (18). Two interesting papers which deal with statistical aspects of the Arrhenius equation have been published by Yarwood and his co-workers (19) and Porterfield and Capone (20).

One factor which should not be neglected in deciding whether or not to use an Arrhenius approach is the likely energy of activation (E_a) of the degradation reaction. For pyrolysis a value of about 60 k cal $mole^{-1}$ is likely: for solvolysis a value in the region of 20 k cal $mole^{-1}$ is probable whereas for photolysis the E_a value is likely to be only about 3 k cal $mole^{-1}$.

Of the various methods by which drugs can degrade chemically, hydrolysis and oxidation have probably the greatest importance. The two processes have some rather intersting differences. The kinetics of hydrolysis and the effects of such factors as pH in terms of general or specific acid base catalysis have been rather fully explored and are often relatively simple. A number of pharmaceutical scientists have published studies defining the pH:stability profiles of a variety of drugs (21,22). Unfortunately, interesting though these studies are there are obvious limitations in varying the pH of pharmaceutical formulations.

By contrast the kinetics of oxidative degradation of drugs are often partly obscure and in many instances quite complex involving both serious and side reactions. The kinetics of auto-oxidation commonly follow a chain reaction sequence and can offer a series of quite difficult challenges to the investigator. However, the formulator faced by the problem of preparing a dosage form with an acceptable shelf life will, in many instances, be able to select an antioxidant which will give adequate protection for drugs degrading by oxidation whereas for drugs which hydrolyse the range of control mechanisms may be very much less effective. For example, we still have not been able to prepare a stable liquid aspirin preparation using G.R.A.S. materials which have been approved for marketing in the United States.

1.6 Physical Degradation

The kinetics of physical degradation of pharmaceutical products has been less completely explored than chemical kinetics. In recent years, how-

ever, many pharmaceutical scientists have become increasingly aware of, and fascinated by, the importance of physical stability and more researchers are now investigating the kinetics of physical degradation. However, it would be improper not to state frankly that our knowledge of the factors controling many of the mechanisms of physical degradation is still depressingly pauce. Earlier in this chapter brief reference was made to the phenomena of tablet aging. Although several research groups are presently investigating this problem, the author is unaware of any reliable kinetic model which has been demonstrated to be validly applicable in this area.

The kinetics of aggregation of particles in a pharmaceutical suspension has been investigated, with some success, by a number of research groups and the controlled aggregation method of formulation of these products has become quite widely used. This work has exploited the D.L.V.O. theory (18) developed originally for so-called model colloidal suspension and based on the Smoluchoski equation which predicts aggregation rates.

The original equations allowed all interparticulate collisions to result in aggregation. Later a collision efficiency factor was introduced in order to define slow aggregation (23,24,25).

However, even in this area of physical stability our knowledge of the kinetics is often only semiquantitive at best. There are several significant differences between the model systems on which the original D.L.V.O. theory was based and the system which we employ in pharmacy. Pharmaceutical suspensions are relatively coarse and heterodisperse, often with a quite high solids content, and an external phase which is multi-component in nature (25).

Even when equations have been developed to allow for some of these differences their application to "real" pharmaceutical systems has not always been successful. However, progress is being made in this area, Zapata and co-workers (26) have recently achieved considerable success in applying D.L.V.O. theory to freeze-thaw instability of gels.

One aspect of physical stability kinetics which merits special attention is the effect of variation of gravitational force on sedimentation rate. The rate of sedimentation of a dilute assembly of spherical, monodisperse units is

governed by Stokes Law. Although many pharmaceutical systems do not comply with all of the assumptions required for full compliance, agreement between the predicted and experimental data is sometimes surprisingly good. However, some workers evaluating the kinetics of physical stability of emulsions have attempted to use an increased "g" force test of short duration in an attempt to predict the long term emulsion stability at normal "g" forces. Obviously, one can see that this type of approach is analagous to accelerated stability testing based on the Arrhenius equation discussed earlier. However, the author is unaware of any theoretical relationship which justifies this method nor of any body of reliable quantitative data which would allow, on an empirical basis, the use of this method. Therefore, there appears to be little, if any, value in this method. In particular, when high speed centrifuges are used to generate high "g" forces, it is felt that we are merely imposing a cruel and unusual punishment on our emulsions. (There may be rather less objection to "g" forces closer to normal). Unless we are planning on sending our products into space by rocket, the practical value of this method of predicting sedimentation kinetics would seem to be distinctly limited.

1.7 Microbial Degradation

The effect of micro-organisms on the stability of pharmaceutical systems is receiving more attention than previously and indeed consideration of the microbial status of pharmaceutical products is no longer restricted to parenteral and ophthalmic products. It is outside the scope of this chapter to give detailed consideration of this topic. Suffice it to say that microbiological factors can cause physical and chemical stability problems. For example, the F.D.A. Case History of Recalls reports a case of an exploding emulsion. The cause of this problem was contamination with a nonpathogenic yeast.

The kinetics of microbial growth have been well defined in many instances. Also, the kinetics of microbial kill in sterilization processes has been explored in some detail particularly for sterilization by wet heat. There is also some good work being reported on the kinetic aspects of antimicrobial

preservative action although it must be admitted that there are still many questions to be answered in this area.

1.8 Summary

There can be no doubt that when used appropriately kinetic methods can be powerful tools in defining the stability of pharmaceutical systems. Also, a thorough understanding of the kinetics of a decomposition process can very often allow a useful insight into the selection of strategies which will reduce or eliminate such problems.

However, as has been pointed out in this chapter care must be taken not to apply kinetic approaches when the precision of the input data is unacceptable for the desired purposes or not well supported on theoretical or experimental grounds.

Significant progress is being made in expanding the use of kinetics in such areas as preformulation (27) and although many of the systems which pharmaceutical formulators deal with are very complex, and can be subject to both physical and chemical degradation, there is good reason to expect that in time kinetics will be of greater applicability for pharmaceutical stability studies (28,29,30).

The practising, industrial, pharmaceutical scientist has two reasons for interest in the application of kinetics to pharmaceutical systems. As a scientist, she or he, is concerned with exploring the validity of present or new applications of kinetics. As a member of a research team for which a major objective is to market pharmaceutical products, the acceptability or non-acceptability of kinetic data by regulatory agencies is also a matter of concern. It must be admitted that these two considerations do not always point to the same conclusion. The dichotomy can become particularly complex for a company developing kinetic data to be submitted to a number of regulatory agencies. Unfortunately, different national regulatory agencies have policies concerning kinetic data which show significant differences. Indeed, different groups within the same agency sometimes have policies on kinetic data which do not coincide. The product scientist must therefore make every

effort to keep up to date with the policies and procedures of agencies with which they may have an interest.

Later chapters in this book deal in more detail with certain specialized aspects of kinetics and with the views of regulators on the application of kinetics.

Kinetics clearly has a valuable role in our studies of the stability of pharmaceutical systems. However, this discipline is not a universal panacea for stability and should not be exploited in an unknowing, invalid manner.

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