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MONITORING THE STABILITY OF TOPICAL PRODUCTS

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ABSTRACT

Topical pharmaceutics must be monitored for stability to physical, chemical and microbiological criteria. These criteria are reviewed in relation to the type of dosage formulation involved. Possible bioavailability criteria are also considered.

INTRODUCTION

Topical pharmaceuticals, products intended for external use, include aerosols, liquids, suspensions, semi-solids, ointments, and even ophthalmic inserts. Implicitly we are here concerned with the final dosage form received and used by the patient. In some cases the stability of the container and of the product become one. Rather than attempt to enumerate the testing required for each type of dosage, the following discussion will review monitoring under the headings of chemical, physical, and microbiological criteria. In addition, possible changes in therapeutic utilization must be considered as a consequence of other observed changes, particularly physical.

CHEMICAL STABILITY

The criteria for chemical monitoring of topical products are no different to those required for dosage forms intended for oral or parenteral use. An active ingredient must meet the normal limits defined by the appropriate compendial monograph utilizing the defined analytical methodology. For the prediction of stability over a time period, some form of classic kinetics is usually applied, first as

$$\frac{dC}{dt} = kC^n \qquad (1)$$

followed by

$$\ln \frac{k_2}{k_1} = -\frac{Ea}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \qquad (2)$$

Equation 2 is general and applies within normally used temperature intervals regardless of the kinetic order of equation 1. In simple dosage systems, especially pure liquids, n is 0, 1, or 2. The normal rules of assessing the value of the rate constant, k_1 and then used. In more complicated systems, such as semi-solids, diffusion often becomes the rate limiting step. In these situations, n becomes a fractional term. Empirically the time dependent form of the concentration dependency can be expressed as

$$C = kt^N$$

or

$$\log C = \log k + N \log t \qquad (3)$$

This is a form alien to those utilizing only clean kinetic models. It does, however, have an amazing capability of linearizing data. Values of k developed in this manner may be utilized in equation

2 for studies at high temperatures for accelerated aging just as in normal pharmaceutical stability studies. In this regard Kennon (1) has provided an excellent review of the utilization of accelerated aging for prediction of chemical stability. Included in this review is the demonstration that, within the constraints of only the 10% decomposition range permitted for an active ingredient, often zero order kinetics may be assumed in equation 1 without introducing any significant error in the stability conclusions.

Testing schedules based upon such kinetic parameters are reviewed by Kennon (1).

In general, topical products do not present any unique problems in chemical stability that notably distinguish them from other pharmaceuticals.

PHYSICAL STABILITY

Those few products that are single phase liquids are generally completely definable for stability by chemical tests. Color, being a spectrophotometric evaluation, is classified as a chemical parameter, for purposes of stability evaluation. On the other hand, the definition of colors in lotions and semisolids is really a physical measurement (3) which can be defined by Tristimulus Values.

Problems in physical stability encompass the range from phase separation to viscosity changes, and can even include such exact terms as graininess. In principal the philosophy of equation 3 can be utilized by replacing concentration with the physical parameter evaluated, as stated in equation 4.

$$\log P = \log k + N \log t \qquad (4)$$

Wood (4) has demonstrated that such rheologic parameters as yield value, thixotropic area, viscosity, and shear stress at any given shear rate can be utilized with this relationship. Indeed linearity was demonstrated for aging studies beginning within a few hours of manufacture and continuing for over one year. In another study (5) it was demonstrated that the kinetic constants developed using this relationship in following the hydration of Veegum® could be utilized in the normal Arrhenius relation (equation 2) to evaluate activation energy.

It is of interest to note that such time relationships have been used to evaluate the long term effects of filling temperature, delayed filling of lotion products (4), as well as operatint parameters of piston fillers (6). Whether the changes that do occur during the test period projection are likely to involve changes perceptable to those using the product will depend on the criteria accepted for stability. Some guidance as to discernable differences may be obtained from the work of Barry and his associates (7, 8).

Although the viscoelastic parameters of semisolids are obviously more fundamental for the behavioral properties, to date no one would appear to have developed equivalent simple parameters to evaluate aging over the time periods required for stability evaluation of commercial products.

The problems of phase separation, particularly creaming of lotions, have frequently utilized centrifugal force as predictor of long term gravitational effects. Thus Menczel and associates

(9) found that the log-log relationship described their observations of de-emulsification under centrifugal stress. Unfortunately this, in common with virtually all other published work in the area of phase separation, involves the use of simple systems which will spontaneously separate within, at the most, a few months. Since such studies are generally academic in nature, it is essential that separation occur spontaneously well within the time period allotted for the investigation. Virtually no studies represent commercial products exhibiting reasonably satisfactory periods of shelf-life.

Conventional centrifugation has been extended in stress capability by the use of the analytical ultra centrifuge. Typical of the work done in this area is that of Garrett (10) and of Vold (11).

It is of interest to note that in suspension systems Foernzeler, Martin, and Banker (12) showed that centrifugal sedimentation velocity was a function of the reciprocal of the degree of thixotropy for the system. Subsequently Wood (13) showed that an even better linear relationship could be obtained using the reciprocal of the yield value. This is in line with the observations (14, 15) reported on the yield value necessary to establish a given degree of suspendability.

In a series of papers Lin (16-19) has demonstrated the important in oil-water emulsions of the initial phase location of the surfactant, the conditions of phase inversion, and the migration between phases of the surfactants as factors in emulsion stability. The observation that surfactant does indeed migrate in time is

very critical to many properties of emulsions and even semisolids. As will be seen later, this migration could conceivably affect microbiological activity and even bioavailability.

CONTAINER INTERACTIONS

If metal ion contamination or product discoloration occurs as a consequence of product container interaction, these factors can be routinely evaluated as chemical stability. In addition the container must be considered for any changes that affect the practical or esthetic aspects of the product delivery. Thus pinholing in collapsible tubes or in aerosol cans is obviously unacceptable. Likewise corrosion in or plugging of an aerosol valve are equally unacceptable. These are the normal problems of the packaging industry and do not, per se, constitute unique problems because they are topical pharmaceuticals.

MICROBIOLOGICAL STABILITY

Preparation of topical products to be sterile at the time of initial use can be normally achieved without difficulty through sterilization techniques and/or the use of suitable preservatives. Polli (20) discussed the stability of rheological properties after various types of sterilization procedures for a variety of Topical products.

However a more serious situation can exist when a topical pharmaceutical becomes contaminated during use, either from an external source or from the patient. In the latter case, it can become a vehicle for the transfer of infection from one site to another. This problem is receiving growing attention in cosmetic

as well as pharmaceutical products, and indeed many pharmaceutical papers have been published in cosmetic journals (21-24).

Critical to stability evaluations, then, is the residual preservative capacity after appropriate sotrage periods (24, 26). This area will receive increasing attention in the future as regulatory standards become more rigid.

Since opthalmics are considered as topicals, the potential problems in the contamination and cleaning of soft lenses should be mentioned. As more types become available, and the use of ophthalmic inserts as drug carriers becomes more widespread, generalized procedures for sterility maintenance will become essential.

BIOAVAILABILITY

Unfortunately, the effectiveness of topicals has rarely received any form of bioavailability determination. Certainly, as a class these have not had the attention that has been given oral preparations. Rarely have oral products been evaluated for possible changes in bioavailability during their period of permissible shelf-life. With the advent of dissolution testing as a compendial specification, we may now begin to see data on age effects for tablets.

For percutaneous absorption, the vehicle can provide dramatic differences in the degree of effective absorption (27-29), so that generic inequivalency is already a proven fact. As was already mentioned Lin (18) had demonstrated that a surfactant emulsifier does migrate with age in oil-water emulsions. It obviously must follow that it would be fortuitous if the effective bioavailability did not change as a result of such a migration.

Ophthalmic liquid products are variable in effective delivery because of dilution and wash out by tears so that thickened preparations may give somewhat better average results (30, 31). Obviously any viscosity loss on storage would negate this possible advantage.

It is of interest that use of soft lens material as a drug carrier is already commercial. The delivery capacities of the different materials is quite different (32) and nothing has yet been published on the changes in delivery that might occur with aging.

SUMMARY

The stability evalution of topical pharmaceutical products is not, in principle, different from that of any other pharmaceutical. It requires the evaluation with time of those parameters important to effective use of the product, including any esthetic property that could influence the patients compliance with the desired regimen.

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