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PHYSICAL STABILITY OF PHARMACEUTICAL PRODUCTS

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ABSTRACT

A general survey of the physical stability of pharmaceutical products is presented. Some of the problems involved in this area are discussed and it is proposed that further attention should be given to the design of standardized tests for the evaluation of physical stability.

NOTE

This paper is based on an invited presentation given to the Industrial Pharmaceutical Technology and Pharmaceutical Analysis and Control sections of the Academy of Pharmaceutical Sciences at Anaheim, California in April, 1979.

The Academy of Pharmaceutical Sciences is to be commended on organizing this Symposium at such an appropriate time. It is the author's opinion that physical aspects of the stability of pharmaceuticals merit special attention at this juncture. We have developed a quite impressive body of knowledge of the chemical

stability of pharmaceuticals but our knowledge of physical stability is at a much less advanced stage.

It is often convenient to classify the stability problems which may be associated with pharmaceutical products under three headings: chemical, physical and biological. This system is very simple and quite useful. However, a detailed evaluation of specific stability problems reveals that in practise this classification can have severe limitations. For example, the aging of rubber condoms once classified as a purely physical process is now believed due to a complex oxidation process. Further, in some stability problems, chemical and physical or biological factors may all be involved. Thus the aging of compressed tablets, which can result in significant changes in dissolution time, probably involves both chemical and physical changes in many instances. For the purposes of this paper, we shall consider our purview to be any stability problem not conclusively identified as exclusively chemical or biological in nature. Thus, the area under consideration is both broad and multi-faceted and comprehensive coverage is not possible. Also, in contrast to chemical stability, our knowledge of the processes causing physical stability problems is in many cases quite rudimentary. Until the mechanisms responsible for physical instability are fully elucidated, it is highly improbable that we will be able to gain full mastery in this area.

Reasons for evaluating physical stability of pharmaceuticals

There are four main reasons for evaluating the physical stability of pharmaceutical products - firstly, to fulfill any relevant compendial specifications; secondly, to comply with the requirements of regulatory agencies; thirdly, to insure that the product meets with in-house release specifications; and fourthly, to provide assurance that the product will remain in a state of acceptable quality throughout the Shelf Life. This fourth objective is in many ways the most difficult to attain. The use of accelerated stability testing for the prediction of the chemical stability of many simple pharmaceutical systems is well substantiated and has a strong theoretical basis

in the Arrhenius Equation. It is very tempting to try to apply this type of approach to physical testing but those who do so are taking considerable risks. There is very little, if any, justification for this approach in physical stability testing and until theoretical justification and experimental confirmation of the validity of this practise is made available, very great caution should be exercised.

Types of test available

There are three types of test available for evaluating the stability of pharmaceutical products: official; non-official, but widely used; and specific in-house tests. The U.S.P. Disintegration Test is an official test, whereas the Roche Friabulator exemplifies a widely used non-official test. The Tablet Impact test, which is described later in this paper, is an example of an unofficial and not widely used test. It is surprising how few official tests are specifically concerned with physical stability. More attention is urgently needed in this area. There is a strong case to be made for bodies such as the Academy of Pharmaceutical Sciences or the Pharmaceutical Manufacturers Association directing attnetion to the standardization of such tests. The first stage in this process would be to collect data on the various types of unofficial tests used in industry, academia or the regulatory agencies. Later, it would be planned to publish data on standardized equipment and procedures. Complexity of equipment is not regarded, prima facie, as an advantage. The author is firmly committed to simple tests which have obvious relevance to the stress conditions to which our products are subjected. Some types of physical tests proposed for our products are too complicated. Sophisticated technology has sometimes suffocated common sense.

Types of sample tested

There are at least six different types of sample which may be tested. Firstly, attention should be directed to the physical specifications of raw materials. Tests for polymorphism and particle size are two obvious examples of properties to be considered.

Although the official compendia generally provide reasonable standards for many drugs, the so-called inert components have, for far too long, been neglected. Fortunately, there are now signs that efforts are being made to rectify this situation. For example, Professor Jack Cooper, who is of course an internationally respected pharmaceutical scientist, has in recent years been working vigorously as the head of a team concerned with the publication of a Codex of Pharmaceutical Excipients (1). It is also believed that the National Formulary will be giving increased attention to this important topic in the near future.

The selection of a supplier of raw materials is one of the most important decisions ever made in the development and production of a pharmaceutical product. It is the author's opinion that some companies give insufficient attention to this matter. The development of a fully validated process, as is now being required, highlights the need for rigorous controls of raw materials.

Not only should the manufacturer give considerable attention to specifications for raw materials, it is also prudent that the supplier be made fully aware of the importance of these specifications. Lanz and his coworkers have described how a difficult to identify production problem was finally traced to unknown change in the particle size spectrum of a raw material (2). There are many pharmaceutical houses which have as a standard policy the requirement that there shall be at least two acceptable suppliers for each component. This is not always possible nor is it always necessary. There are some specialty houses which supply pharmaceutical raw materials, under their own trademark, of outstanding and reproducible quality.

Samples from Pharmacy Research and Development (R & D) can be usefully tested in order to detect gross physical problems. However, it must be kept in mind that there are several limitations to the data obtained from such samples. Firstly, Pharmacy R & D samples are "short time", that is, they are normally of comparatively recent production. Secondly, scale up from the Pharmacy R & D

and laboratory to production level can introduce changes which may have an adverse or advantageous affect on physical stability. Finally, the pack used is unlikely to be the same as used in production.

Evaluation of intermediate production material can be particularly useful in alerting us to a problem at an early stage so that effective remedial action can still be taken. The sight of a modern high speed rotary tablet press spewing out tablets at a rate of thousands per minute is indeed impressive, but should some defect develop in the formulation, such as demixing, or in the process such as excessive tooling wear, a large number of defective tablets may be produced and considerable expense can result. This will be particularly serious if, as is often the case, the tablet mix can not be reworked. Thus monitoring of tablet weight or other parameters of tablets during production can be of considerable value. Similarly, evaluation of the flow properties of tablet granules or direct compression blends can alert us to problems before compaction.

Finished product samples are, of course, the samples most commonly tested. The sampling technique used must be carefully selected so that there is every reason to believe that the sample is truly representative of the whole batch. It must, however, be appreciated that we can never have complete assurance that a sample is a complete reflection of the properties of the batch. Thus, there is considerable attraction to devising non-destructive tests which can be applied to all units produced. Unfortunately, with the exception of some properties, such as tablet weight, it is not possible to use non-destructive tests. Tests of the finished product in the appropriate pack allow an informed decision to be made as to whether release specifications are met.

Tests distributed samples are routinely evaluated by some manufacturers. Obviously, since such samples have passed through the channel of distribution, they may provide important information on how the product will respond to market stress. However, although

considerable care may be taken in trying to select a fully representative channel of distribution, it is difficult, if not impossible, to be fully successful in this endeavor. Also, of course, such samples have not been exposed to "patient use stress." Temperature and mechanical stresses caused, by example, through transporting a truckload of tablets over bumpy, potholed roads in Arizona in July may be substantial, but they in no way compare with the stresses imposed when a New Jersey housewife stores her prescription tablets in an uncapped container ("because I can't undo these child proof caps") in a bathroom cabinet.

Returned samples can provide extremely valuable data on how a product can tolerate market stress; however, some people in industry feel that, very often, returned samples have been subjected to abnormal market stress, in particular, a product returned after five years on the market in no way represents the average unit which is probably normally used in a period substantially less than three years. By comparison, manufacturers' retained samples may give an over-optimistic view of product stability since such samples have been stored under carefully controlled conditions not always met within practise. Perhaps it is reasonable to regard retained and returned samples as providing information on the two likely extremes.

What should be tested

It is the author's opinion that: product, product plus package, and package alone should all be tested. Far too often in the past insufficient attention was given to the package. It is hoped that developments such as unit dose packaging will help to focus attention on the importance of the package. Many exciting changes have occurred recently in pharmaceutical packaging (3) and we now have a wide range of materials. Laminates can often combine the best characteristics of different materials. New improvements in glass technology are also of great interest to the pharmaceuti-

cal industry. Tests for packages need not of necessity always involve complicated equipment. For example, Cilento has described a simple but valuable test for determining what torque must be applied to the closure of a tablet container in order to insure that it is airtight. The test consists of placing solid CO_2 in the container and following vapor loss by weight change.

Types of stress resulting in physical stability problems

There are five basic types of stress which have major importance for the physical stability of pharmaceuticals. They are:

1. Temperature
2. Humidity
3. Gravitational force and impact
4. Abrasian, and 5 intrinsic formulation factors

Temperature is often the arch villain. By judicious choice of package, we can reduce or eliminate problems due to humidity, impact and abrasion and by knowledgable use of formulation skills, we can control over temperature. It is true that we can place explicit instructions regarding storage temperature on the label, but we would be exceedingly naive if we deluded ourselves that these instructions are always followed.

Temperature can have adverse affects on the physical stability directly or it can have a synergistic effect on degradation due to other factors such as humidity. Further, it is prudent to not only consider effects of temperature *per se* but also temperature cycling which may exacerbate the stability problems. What temperatures should be used for physical stability testing? There is no concensus about this problem. A number of formulators use surprisingly high temperatures - up to 80°C. Unless it has been clearly demonstrated that one can extrapolate from such high temperatures to normal storage temperatures, there is little point in such a cruel and unusual punishment. Data on temperatures found in North America (4) indicate that confined storage temperatures will normally only exceed 40°C. for relatively short periods of time. Unfortunately,

the success of accelerated stability tests for chemical stability, based on use of the Arrhenius Equation, has caused some workers to assume implicitly that this approach can also legitimately be used for physical stability tests. Unless there is a convincing case for the use of very high temperatures, it is suggested that physical stability tests should use temperatures not exceeding the likely maximum which market stress will present to the product. A value of 40°C. would seem to be appropriate for this purpose. (Those concerned with export of drugs to economically less developed countries might wish to consider use of 45°C. since in some of these countries, pharmaceutical products are, on occasion, stored for long periods of time at conditions of very high humidity and temperature (5).)

The selection of a minimum temperature for a temperature cycle is also a matter for debate. For many products, 5°C. is used as the lowest temperature on the cycle. There are workers who prefer to go down to -5°C. This lower temperature will certainly provide additional stress on plastic packages and closures, but cannot be justified for all products. Thus some emulsions will irreversably "crack" if frozen.

Fortunately, with a few exceptions, most people using temperature cycling use a 24 hour cycle. This approach seems reasonable as it reflects the natural diurnal rhythm.

The humidity stress applied in testing a product may be reasonably adjusted in the light of knowledge of the humidity to which the product will be exposed on the market. For example, if a tablet is packed in an aluminum foil unit dose pack, it is reasonable to assume that the relative humidity will remain low until the product is used. (however, in some cases, rise in temperature can dause water to be released from the tablet matrix which, in effect, increases the effective humidity in the vicinity of the tablet.) If a tablet is supplied in a plastic or glass container with a conventional screw cap, then the humidity to which the product may be exposed is likely to be significantly higher.

Gravitational forces, and the impact which such forces can cause, can have very significant effects on the physical stability of pharmaceutical products. As is predicted by Stokes Law, the rate of globule settling in an emulsion or particle sedimentation in a suspension is substantially affected by increase in 'g' forces. There are formulators in the industry who routinely test their emulsions by high speed centrifugation. This practise appears of dubious value unless one has good reason to believe that one can extrapolate from such high 'g' forces to those which may realistically be expected in practice. The author is not aware of any such data. Rotation at low speeeds of test emulsions is much closer to market stress and thus can be more readily justified.

Impact stress can seriously affect the physical integrity of compressed tablets, particularly if a large number is packaged in a container. Surprisingly there seems to be no generally accepted test for such stress. Some workers use an impact test in which 50 tablets are dropped, one at a time, down a meter glass tube, one at a time, onto a stainless steel plate. No more than one tablet shall show any cracking or chipping.

Abrasion of tablets is widely tested by use of a friabulator, such as the Roche Friabulator. There does not seem to be any general agreement as to what is an acceptable result of such a test. Some formulators will accept up to 2%, others feel that 1% is the maximum. It would be useful to see data on this topic published.

The intrinsic formulation factors which can affect the physical stability of pharmaceutical products vary greatly with different dosage forms. For example, for suspensions zeta potential (6) is an important fact.

What dosage forms should be tested for physical stability?

Unfortunately, there are still many formulators who seem to equate stability almost entirely with the chemical integrity of the drug substance. At present, many of us concerned with isues

related to generic substitution are trying to explain to the public and politicians the importance of the dosage form in terms of therapeutic response. It is therefore somewhat ironic to find some formulators still implicitly equating the chemical stability of drugs with the total stability of the drug product. There are others who seem to believe that, whereas physical stability problems may be an important consideration for dosage forms such as emulsions or suspensions, they need not be considered for products such as compressed tablets. I reject this view.

There is a considerable variation in the attention given to physical stability testing. If grades were awarded to those of us concerned with stability testing and the assignment of expiration dates, I suggest that, at present, while many of us would get an A or B for chemical testing, we would receive only a C or D for physical testing.

Obviously for a simple aqueous solution, it is difficult to imagine physical stability problems per se but even for such products one must always remember that the product consists of dosage form plus container and all containers are subject, to some extent, to physical stability problems.

The physical stability of compressed tablets certainly merits additional attention. The literature contains reports of tablet aging which, in some cases, can seriously modify dissolution. It is also known that FDA recalls have been caused by this problem and thus, particularly for new formulations, aging and other physical aspects of tablet stability should be carefully investigated (7, 8, 9, 10).

Physical Stability tests for tablets

The four main types of physical test applied to compressed tablets are designed to evaluate:

(a) Sensory properties (color, odor, taste),

(b) The capacity of the tablet to remain as intact unity of mass (hardness, friability impact),

(c) Uniformity of dose (tablet weight, flow properties of granules or direct compression tablet mix, content uniformity tests),

(d) Disintegration and dissolution.

Sensory properties of tablets are of considerable importance in terms of patient acceptability and sometimes can indicate that the product is unlikely to perform its normal therapeutic function. The smell of vinegar associated with samples of aceytsalicylic acid tablets stored without sufficient protection from humidity is a clear indication of hydrolysis of the drug. Quite commonly, however, sensory changes in tablets, although readily detected by most people, are not necessarily associated with any significant change in the ability of the tablet to perform satisfactorily. For example, it is well known that when drugs containing an amino functional are formulated into tablets using spray dried lactose, a very obvious mottling of the tablet surface may rapidly become apparent. Content uniformity assays of such tablets may well indicate no detectable loss of drug, but, of course, no manufacturer would market such products. The sensory properties of the tablet are, however, of great importance for patient acceptability and we must not forget the role which psychological factors, as well as biochemical factors, play in eliciting pharmacologic response. A clean white lustrous tablet is impressive and placebo effects cannot be discounted. It is surprising how carefully some patients examine their tablets. I have been told cautionary stories by friends in industry of how when certain tablets have had to be reformulated and the new version had a minor, barely noticeable difference in color, a number of patients have immediately complained.

Color can be evaluated in a semi subjective manner using standard color charts or tiles. Matthews, Matsumoto and Shibata (11) have described the use of a microreflectance photometer to measure color uniformity and gloss of tablets.

The test most widely used which may indicate the ability of a tablet to remain as a unit of mass is the hardness test. As has been previously indicated, the friability and impact tests are probably superior in their abilities to predict the performance of a tablet under market stress, however, there can be no denying that the crushing strength hardness test is probably the most widely used test of this type. The Schleuniger (or Heberlein) Tester appears to be becoming the most popular in U.S. Industry. Marshall has published useful comparative data on the various hardness testers (12). Although the hardness test is a useful quality control test, its importance is sometimes over-emphasized. There are some formulators who appear to believe that measurement of tablet hardness is a universal test for evaluating the physical stability of tablets and if tablet hardness is invarient, so are all other significant tablet properties. This assumption is not always valid. One new area where tablet hardness is becoming increasingly important is the evaluation of tablet cores prior to using aqueous coating solutions. A large number of pharmaceutical companies are in the process of converting from organic coating solvents to aqueous and it has been observed that the new process often requires unusually hard tablets.

Uniformity of dose is one of the most important properties of a compressed tablet. For tablets with a high percentage active weight uniformity is a good indicator of content uniformity but for tablets with a low percentage active, this test is of less value. The increasing use of high speed tablet presses mandates that in-process controls be used in tablet production and there is good reason for the success of equipment such as the Manesty "Sentinel". Indeed we may reasonably expect to see further developments in tablet press controls with dedicated slave computers closing the loop and controlling many press settings.

Content uniformity tests per se are, of course, the most important test for drug content. There can be no doubt that the official tests have improved very significantly during the last

decade or so, but there is still room for further improvement. In particular, there is a strong case to be made for increasing the sample size (13).

Jordan and Rhodes (14) have recently reviewed the use of recording powder flow meters for pharmaceutical purposes and they have suggested that such equipment can be most usefully applied for the evaluation of flow problems which can result in poor content uniformity.

The disintegration test has to some extent fallen into disrepute and been suplanted by the dissolution test. It is still, however, a useful quality control test. Dissolution tests are also of value for biological availability is less certain. Unless, as with digoxin, it has been clearly proved that dissolution test data is a simple function of in vivo performance, it is improper to assume such a relationship.

Reference has already been made to the problem of tablet aging. Reports from the University of Rhode Island and elsewhere indicate that there is probably more than one mechanism responsible for this phenomena. At present we do not have sufficient information to delineate the full extent of this problem. It is known that a wide variety of excipients and matrices can be involved. Changes in tablet hardness do not necessarily reflect changes or dissolution and there appears to be no justification, at present, for using an Arrhenius Equation type approach to predict the extent of this problem. Although it is still too early to make any definite recommendations on how to approach this problem, it seems possible that storage of test products at 25°, 30°, 35° and 40°C., at several different humidity levels, for a period of 40 days may be sufficient to detect systems likely to suffer from this problem. It must be emphasized, however, that this conclusion is tentative.

Physical stability of disperse systems

The pharmaceutical literatures contain numerous papers concerning formulation approaches designed to contain physical stability problems of emulsions and suspensions (15). In particular, the

controlled aggregation concept introduced by Haines and Martin (16) has proved of great value in the formulation of suspension (17, 18). The recommendations made by Cooper (17) regarding techniques for evaluating pharmaceutical emulsions and suspensions are most useful.

In recent years, pharmaceutical researchers have given increasing attention to intravenous fat emulsions and these microemulsions have certain physical stability characteristics quite distinct from coarser emulsions (19). It seems that it may be possible to sterilize these products by autoclaving (20).

Conclusions and Recommendations

1. Physical stability of pharmaceutical products is not presently always receiving the attention which it deserves.
2. There would be merit in developing a set of standardized tests for evaluating the physical stability of pharmaceutical products.
3. Further basic research on the mechanism responsible for physical stability problems would be most useful.
4. Quantitative data on the range and extent of physical stress to which pharmaceutical products are subjected, both in North America and elsewhere, is needed.

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