DRUG DEVELOPMENT COMMUNICATIONS, 2(4&5), 325-357 (1976)

THE DEVELOPMENT OF SEMI-SOLID DOSAGE FORMS: AN OVERVIEW

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ABSTRACT

A survey is presented of the many factors involved in developing and evaluating a semi-solid dosage form. Subject areas discussed are: pre-formulation, formulation, particle size distribution, rheology, lot to lot consistency, microbial contamination, stability, *in vivo* testing, toxicity testing, clinical evaluation and scaling-up.

PRE-FORMULATION STUDIES

In discussing the type of studies that are meaningful to undertake prior to formulating the semi-solid dosage form it is assumed that the drug to be formulated is a new chemical entity, so its physical chemical properties are unknown.

Pre-formulation work should be undertaken after the pharmacological profile of the compound has been obtained and the compound appears to be a definite candidate for an IND submission. Although pre-formulation work involves a fair amount of time and effort, the data obtained often prevent serious diffi-

culty later and can save much time, because the later in a development program a basic problem is unearthed, the more time and money is misdirected on the project.

It is convenient to record the work done in pre-formulation on a summary sheet. This sheet provides a central, handy source of information on the new drug. In addition, the blank spaces on the summary sheet serve as reminders to the investigator that some work remains to be done and additional information needs to be gathered on the compound. A third reason a pre-formulation summary sheet is desirable, particularly in a large company, is that the pre-formulation chemist is often not the individual who formulates the drug. The sheet then serves as a convenient, permanent method of transferring this information between individuals and departments as necessary.

Appendix I illustrates what a pre-formulation sheet could look like. No characteristic of the material should be taken for granted, and all properties should be recorded somewhere on the sheet.

It is appropriate to point out that at the very early stages of pre-formulation work, effort should begin in earnest on the analytica methodology required to determine the identity, purity, and stability of the new drug substance. The development of a stability assay for the semi-solid dosage form must, of course, wait until the tentative formula(s) can be established. However, at that time it becomes necessary to give a priority effort in developing a sta-

bility assay for the dosage form. Without it, much of the indicated work would be meaningless.

Let us turn our attention to the crystallography and potential polymorphism of the new drug. A compound may have the ability to crystallize into more than one crystalline specie. If the molecules of the compound are arranged in such a manner that the solid crystals differ but the liquid and vapor states are identical, the forms are called polymorphs. Notations on the sheet, such as Research Notebook Number (R.N.B.), indicate where more detailed information can be obtained. It is essential to determine if polymorphs exist for the new drug being investigated because polymorphs can differ in chemical stability, solubility, crystal shape, melting point, and several other properties. Pharmaceutical compounds that show polymorphism include steroids, antihistamines, barbiturates, and sulfonamides. In fact, a study by Kuhnert-Branstatter in 1965 (1) showed that of 48 steroids studied with melting points below 210°C., 67% exhibited polymorphism. Thirty-eight barbiturates were studied and 63% exhibited polymorphism. Of 40 sulfonamides examined, 40% existed in different polymorphic forms. In addition, she reported a number of marketed products that were unstable as a result of polymorphic changes.

The individual particles of the drug, their shape, size, and related characteristics play an important role in determining various manufacturing processes (for example, whether milling is necessary or if special techniques are required in dissolving the

drug during processing), or, most important, how does the average particle size and particle size distribution affect the efficacy of the drug? The initial information gathered, on each lot, in the pre-formulation stage often becomes invaluable later.

It is of much help to the formulator if he has solubility data in solvents that are likely candidates for use in semi-solid formulas. This information is particularly useful if several polymorphic forms of the drug can be evaluated simultaneously (assuming they exist) and the analytical methods are advanced to the point that a brief stability screening can be run in each promising solvent. This latter screening can be valuable in saving time in formulating and preventing clinical evaluation of an unstable product.

Other tests that should be done on the drug prior to formulating include stability in the presence of light, oxygen, and trace metals. Any one of these test situations could indicate a potential stability problem. Solutions to a light or oxygen instability problem might be either a special container or a processing technique, such as a nitrogen blanket. Sensitivity to trace amounts of metals could be counteracted by adding a chelating agent to the product.

FORMULATION

Let us now turn our attention to the formulation of the new drug substance. In this section will be discussed particle size and particle size distribution, rheology, microbial contamination,

equipment selection, stability testing, raw material testing, and *in vivo* pre-clinical testing.

Particle Size Distribution

One of the most important characteristics of a semi-solid pharmaceutical product, if it is a dispersed system, is the globule size or particle size of the dispersed phase. The size of the individual units of the internal or dispersed phase is a significant factor in the rate of drug release and the stability of the product. If the formulator does not critically study this aspect of his product, he is inviting trouble.

The size of a sphere (such as an emulsion globule) is uniquely determined by its diameter. Other size parameters, such as surface and volume, are fixed by the diameter.

Non-spherical particles present a problem. They have definite surface area and volume, but apparent length varies with orientation. The usual methods of measuring these types of particles involve relating some measurable property to spherically equivalent diameters. Space does not permit discussion of the many mathematical and statistical treatments available for particle analysis. However, anyone acquainted with the science of micromeritics realizes that there are a great variety of methods available for particle size analysis. A few of the commonly used ones that apply to the particle and globule size range normally found in pharmaceutical semi-solids are shown in Table I. Each method has its own particular usefulness and, also, its disad-

TABLE I

TECHNIQUES FOR PARTICLE SIZE ANALYSIS (PARTIAL LISTING)

GENERAL CLASSIFICATION	METHOD OF MEASUREMENT	SPECIFIC TECHNIQUE	SIZE RANGE (MICRONS)
Optical (Indiv. Particles)	Transmitted Light	Microscope	.25-250
Optical (Mass Effect)	Extinction of Non-Scattered Beam	Turbidimetry	0.05-50
Hydrodynamic	Gravitational Sedimentation in Liquid	Andreasen Pipette	0.5-300
Aerodynamic	Gravitational Sedimentation in Gas	Micromerograph	2.0-200
Cross-Sectional	Sieving	Conventional Screens	40 and Greater
Bulk Packing	Gas	Sub-Sieve Sizer	0.2-50
Volumetric	Displacement by Particle in Electrical Zone	Coulter Counter	0.2-300

vantages. For example, methods based on the relative motion of particles in a fluid (such as the Andreasen pipette or the micromerograph) are limited by the conditions of Stokes' Law - namely, particle radius and density, and the density and viscosity of the suspending medium. Irregularly shaped particles and aggregates of particles also are complicating factors with techniques utilizing the principle of Stokes' Law.

A number of these methods are applicable in studying the drug component as a dry powder, but when examining the drug formulated in a semi-solid dosage form, the microscope becomes the method of choice.

When measuring fine particles, microscopy has many advantages. Microscopic examination is useful for checking completeness of dispersion and particle shape. Often the eye can discriminate between different components in a mixture or recognize single particles in an agglomerate.

With microscopy, however, it must be remembered that what is seen cannot necessarily be believed. For example, the outlines and details of a particle vary in apparent width, depending on the focus, the illumination, the refractive indices of the preparation, and most of all on the resolving power of the microscope. In addition, the apparent sharpness and fineness of the scale of the micrometer, and of the points on the object between which the measurement is made, are far from mathematically perfect, and the width of the lines which

are brought to juxtaposition is very appreciable. Other limitations could be cited, but these serve to illustrate the point.

A microscope's lower resolution limit is related to the numerical aperture of the objective and to the wavelength of light. It is usually about 0.2 micron when white light is used with an oil-immersion objective. The resolution limit should be multiplied by about 5 or 10 to obtain the smallest size measurable with any precision.

Since individual particles are measured and counted, microscopy is slow and precision suffers from a tendency to count too few particles. Also, size is essentially 3-dimensional, whereas the normal microscopical image is 2-dimensional. This factor takes on added significance if the size distribution is to be calculated on a weight basis.

The simplest microscopic method of size measurement employs a micrometer in the eyepiece. In effect, this serves the purpose of placing a ruler across the particle and measuring its "diameter" directly. Two ways of measuring statistical diameters of randomly oriented particles are Martin's diameter and Feret's diameter (Figure 1). If the measurement is made in a fixed direction from edge to edge across the particle center, irrespective of the particle orientation, the result is Martin's diameter. It is a statistical diameter because the effect of shape and orientation is averaged when many particles are measured.

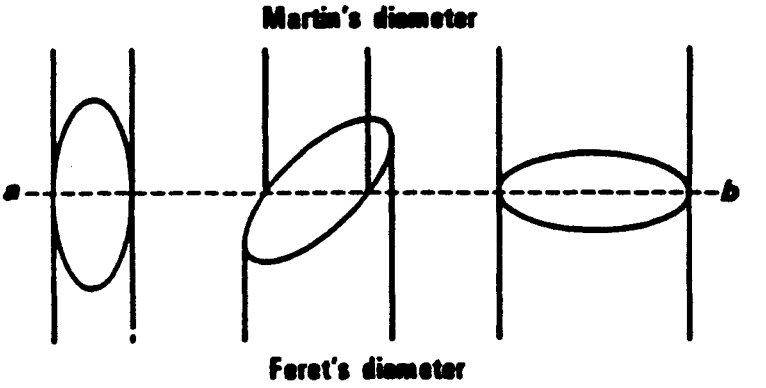

FIGURE 1

Feret's diameter is similar except that the measurement is made between two parallel tangents.

Another method uses eyepiece graticules. When such a graticule is placed over the field, its pattern of circles and rectangles of known size is seen superimposed on the microscope field. The particles are compared in area with the circles.

When particles have a definite uniform shape or crystalline form, or if they are especially needle-like, it is preferable to measure the most characteristic dimension.

Rheology

The need to clearly characterize and know the rheological properties of a semi-solid product is well known and has been repeatedly referred to in the literature (2-5). Of the basic flow curves, most pharmaceutical semi-solid products exhibit plastic or pseudoplastic flow, usually with thixotropy, which result in hysteresis loops.

The need to know the rheology of a given formulation is readily illustrated by Figures 2, 3, and 4. In each case, the active constituent remained the same, but the vehicle varied. The figures were obtained using a Ferranti-Shirley viscometer (5). In Figure 2, a combination of white petro-

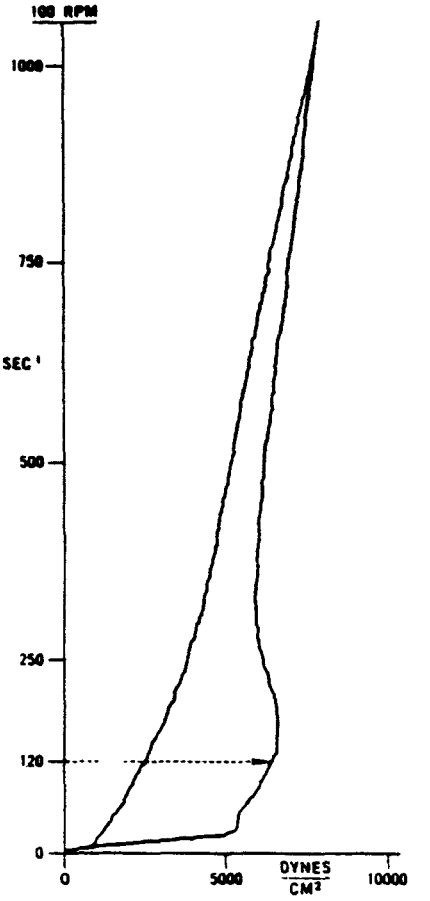

FIGURE 2
Rheogram of Ointment at 25°C

latum, anhydrous lanolin, and white wax was used to form an ointment base. In Figure 3, a jelly base of polypropylene and water was used and in Figure 4 a cream was prepared from stearic acid, glycerin, cetyl alcohol, and water.

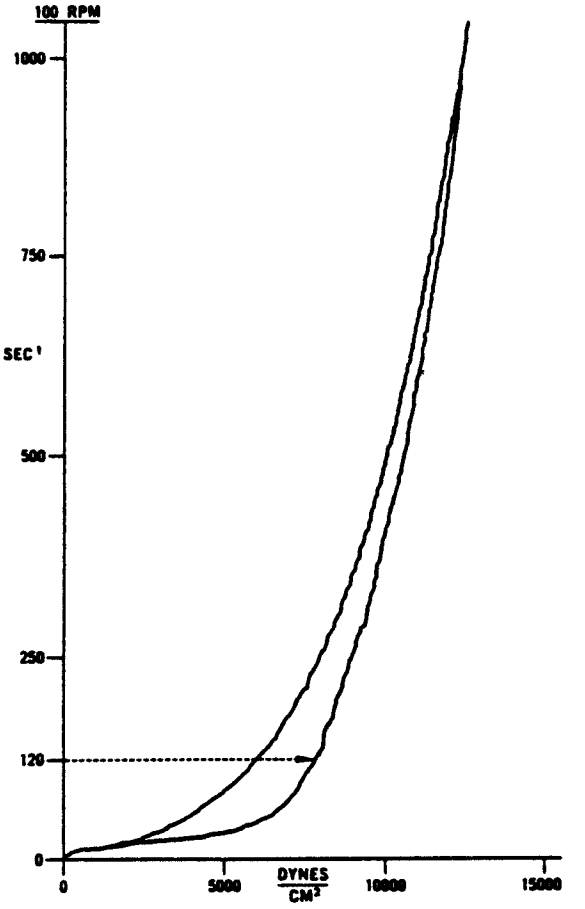

FIGURE 3
Rheogram of Jelly at 25°C

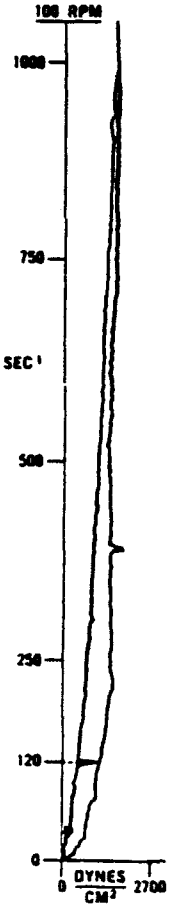

FIGURE 4
Rheogram of Cream at 25°C

An interesting application of rheology in semi-solid pharmaceutical products is the estimation of the spreading properties of various formulas. There have been several approaches to this problem.(5-7).

Lot to Lot Consistency

One concern of a formulator should be consistency of the product as many batches are made over the years. It goes without saying that if the raw materials going into the product are not consistently the same, the product will vary.

As an experimental procedure, when an incoming lot of white petrolatum was accepted by U.S.P. control methods for use in products, a sample was run on the Ferranti-Shirley viscometer. Of eight lots tested, the two that represent the extremes are shown in Figure 5. It is evident that the one batch has a greater yield value, viscosity, and thixotropy than the other. Variations of this magnitude deserve further watching. If any meaningful product or manufacturing variations result from differences of this type, a rheogram should become a routine incoming raw material test.

An interesting and potentially useful approach to the evaluation of fat and wax-like components of semi-solid pharmaceutical products is thermal analysis. The methods available include thermogravimetric analysis (TGA), differential thermal analysis (DTA), and differential scanning calorimetry (DSC).

TGA curves are obtained by slowly and uniformly increasing the temperature of a carefully weighed sample and recording the weight loss as a function of temperature.

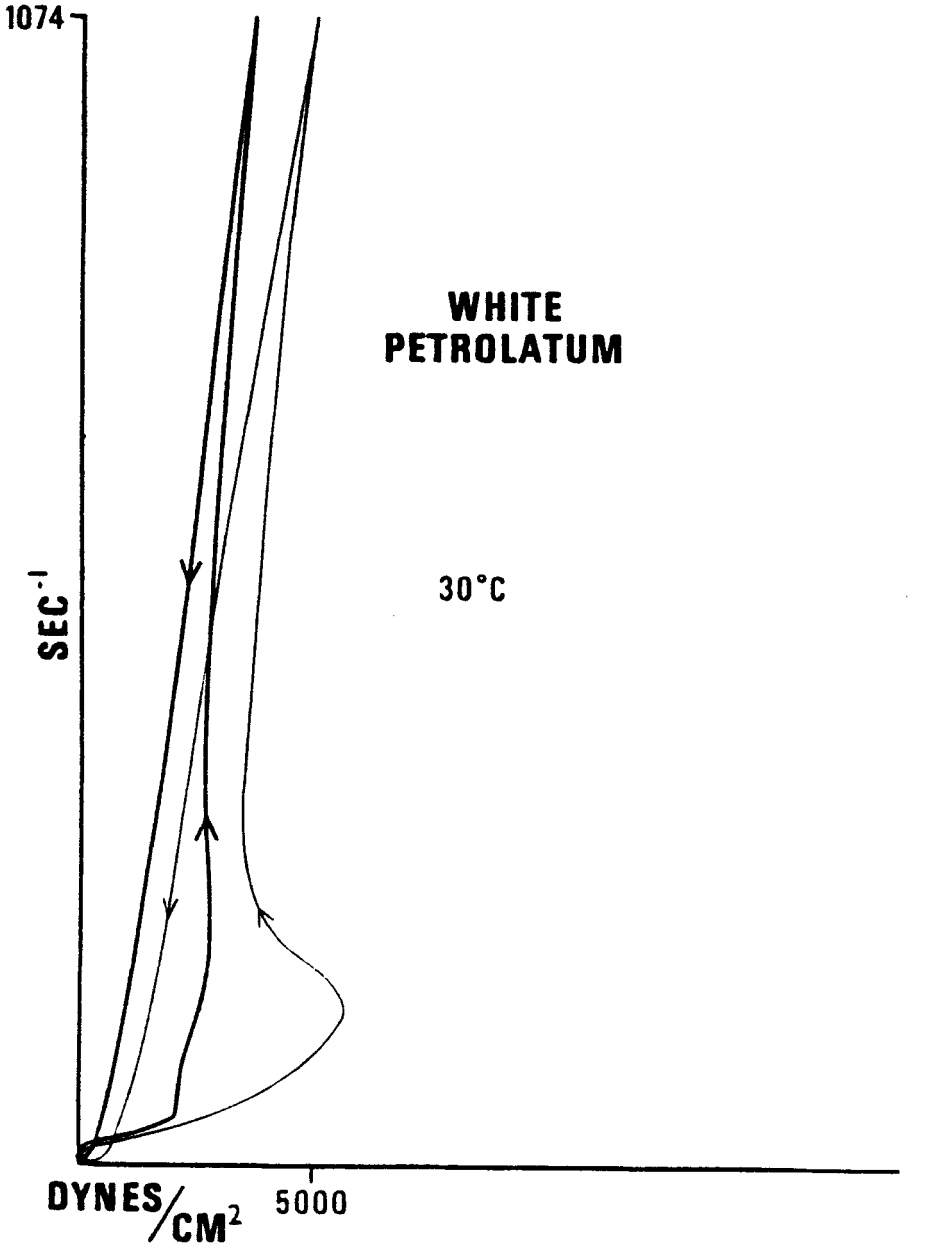

FIGURE 5
Rheogram of White Petrolatum at 30°C

In contrast, DTA enables the comparison of the temperatures of a thermally inert reference material and the sample, both being in the same temperature environment. As the temperature of the environment chamber is increased, the evolution or absorption of thermal energy by the sample causes its temperature to momentarily lead, or lag, when compared to the reference material. This results in downward (endothermic) or upward (exothermic) peaks at known temperatures.

The third thermal method available is DSC. This method holds the most promise with fats and waxes. This method measures the energy (in calories) required to keep the temperature of the sample and the reference material the same as the environmental temperature increases or decreases. When the sample absorbs or evolves energy, more or less power is required by the sample holder to maintain it at the same temperature as the reference holder. Consequently, DSC permits qualitative and often quantitative analysis of the crystalline structure of the material under study. For example, the crystallinity of fats determine their texture and appearance. The total area of the melting peak is proportional to the amount of crystallinity, and the peak shape is, in the absence of polymorphic forms or solid state transitions, a measure of crystallite size distribution, because the more perfect the crystallite the higher the temperature it tends to melt at (8).

The curve is quite dependent on the thermal history of the sample and can vary considerably depending on that history. Because waxes are less sensitive to variations in crystallizing conditions than are fats, crystalline peaks for most waxes are mirror images of their melting peaks.

Thermal "finger printing" of formulation materials for semi-solid products has several potential uses, one of which may be the assurance of consistency in raw materials. A DSC curve for a raw material sample of anhydrous lanolin is shown in Figure 6.

Microbial Contamination

The formulator must bear in mind that, microbially, each product is unique. Each potentially new product should be challenged with a spectrum of microorganisms and then observed for a period of several months (this allows the microorganisms to adjust to their new environment). Two aspects that should be kept in mind are (a) the final product, in its exact form, must be tested and (b) production batches must also be challenged with microorganisms, too, even if all laboratory lots looked free of contamination, because there is a potential for contamination to be introduced in the production environment that is not inherent in the raw materials and laboratory area. In production, if the preservative system breaks down, for whatever reason, multiplication of microorganisms is generally rapid and overwhelms the preservative system. Consequently,

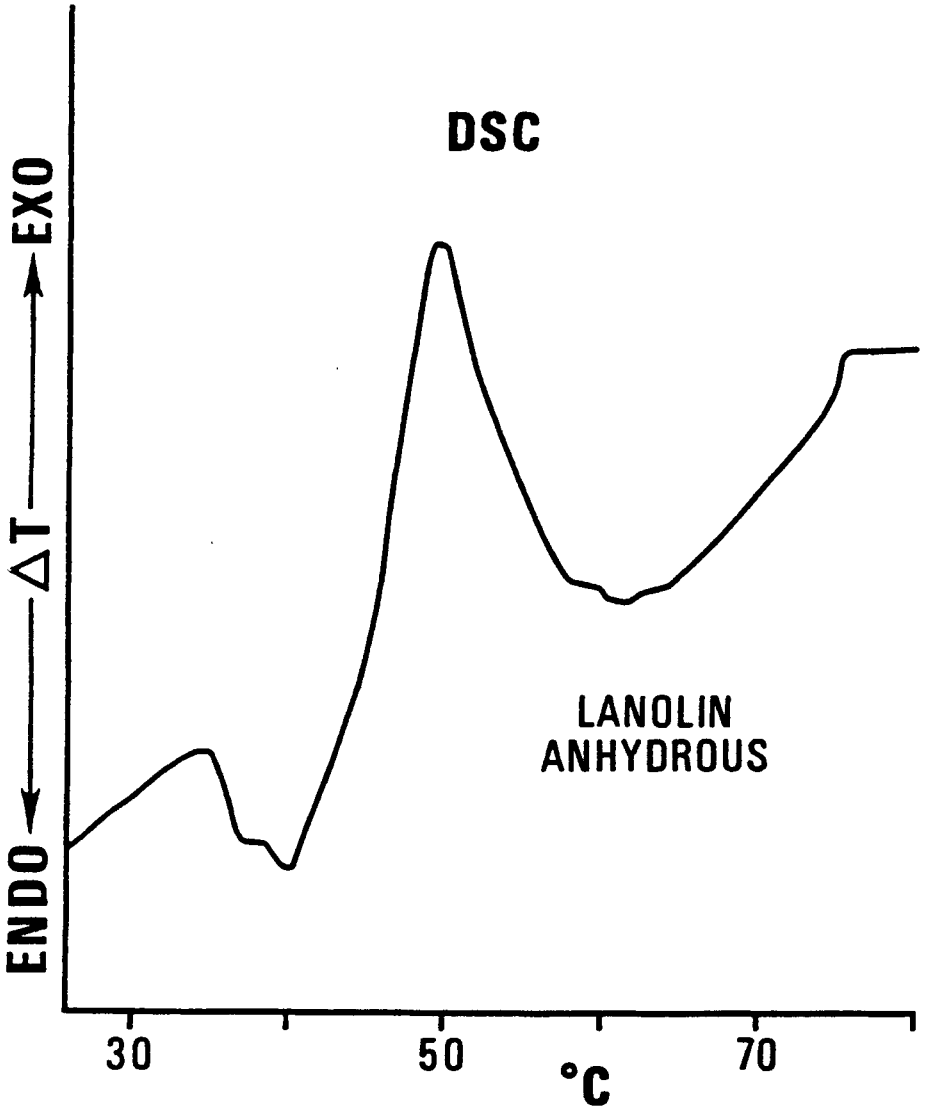

FIGURE 6
Differential Scanning Calorimetry Curve
Lanolin (Anhydrous)

detection is easy. When this occurs, studies should be initiated to change the processing or upgrade the preservation system. In any event, under no circumstances should a product be "over preserved" to compensate for a poor manufacturing process.

Equipment

Another facet of formulating that can be overlooked, is the equipment that will be used in production to manufacture the product. Scale-up problems will be reviewed briefly a little later. It is suffice to point out at this time that the formulator should look ahead and anticipate the probable production conditions. For example, all laboratory batches should not be made in a Waring Blender, unless one intends to use a Waring Blender in production.

Stability

Another aspect of formulating semi-solid products that needs to be reviewed involves the general topic of "stability testing." As is commonly recognized, a new product stability program normally involves several storage combinations of heat, humidity, and light plus several containers and various packaging materials. When embarking on a stability program, two major factors should be considered. Firstly, time is important and irretrievable, so accelerated conditions and a variety of packaging materials are necessary to assure early leads in answering the questions of "Which formul ?", "Which package?", and "What expiration date?". Without accelerated conditions, the study remains cumbersome and very time consuming. The second important

factor to bear in mind is that the Food and Drug Administration normally requires data on three lots of the exact formula in the exact package for the period of the dating desired.

Stability testing may be divided into two principal categories--chemical and physical. It is important to follow a product from a number of aspects to insure that nothing distressing occurs late in development or early in production. It is of great help to a formulator if a sensitive and accurate stability assay is available in the early stages of product formulation. A thin-layer chromatograph should be run periodically as a check on the analytical method and to assure an intact active compenent.

In addition, at frequent intervals, microscopic examination of the active ingredient in the formulated product should be done to insure that polymorphs are not forming. It is not unusual for differences in stability between two apparently identical batches to be traced to the presence of different polymorphic forms of the drug in the two batches. When creams are prepared, the use of the wrong polymorph can result in phase inversion to a more stable form.

A metastable crystal form of a drug was suspended in the cream base shown in Figure 7. After six months under refrigerated conditions, nucleation of the more stable (less soluble) form resulted in the photomicrograph shown in Figure 8. After fifteen months in the refrigerator, the crystals had grown

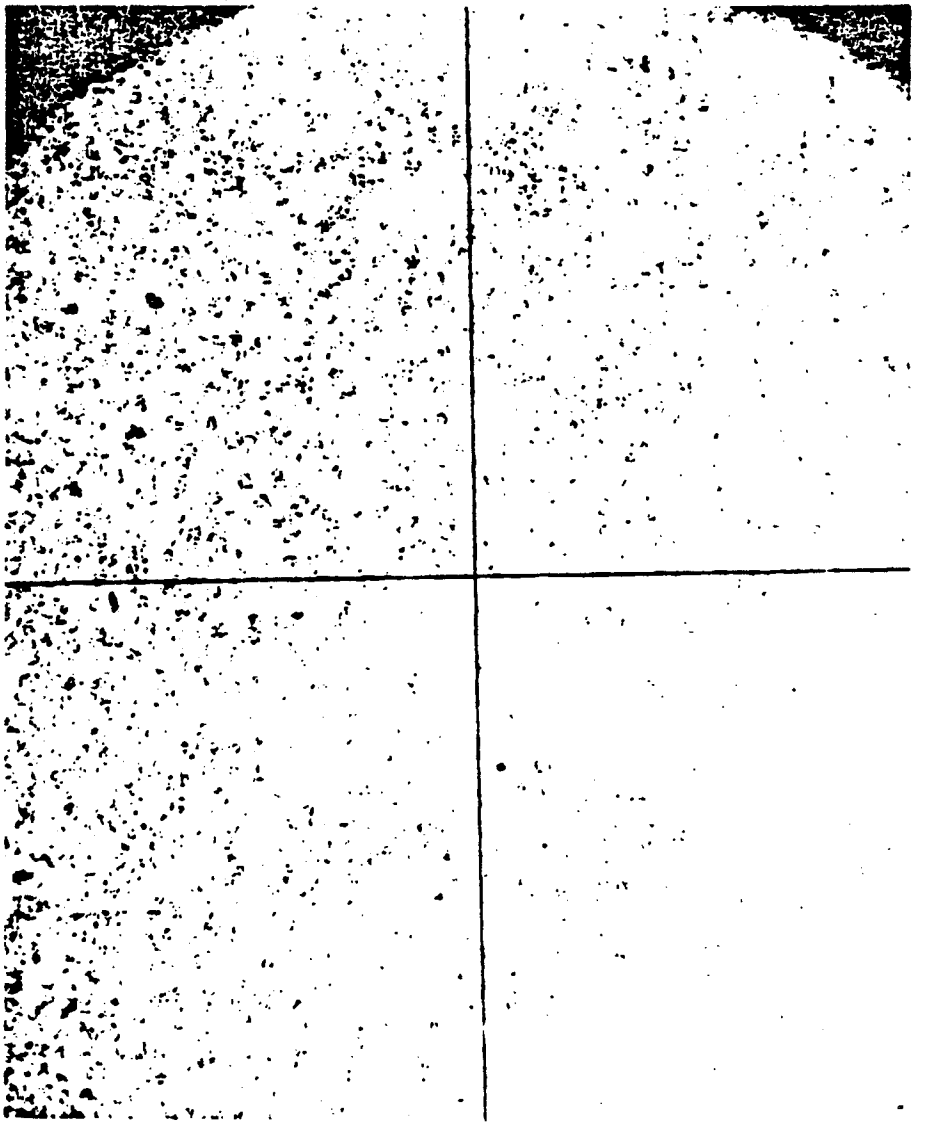

FIGURE 7
Cream Base, Freshly Prepared

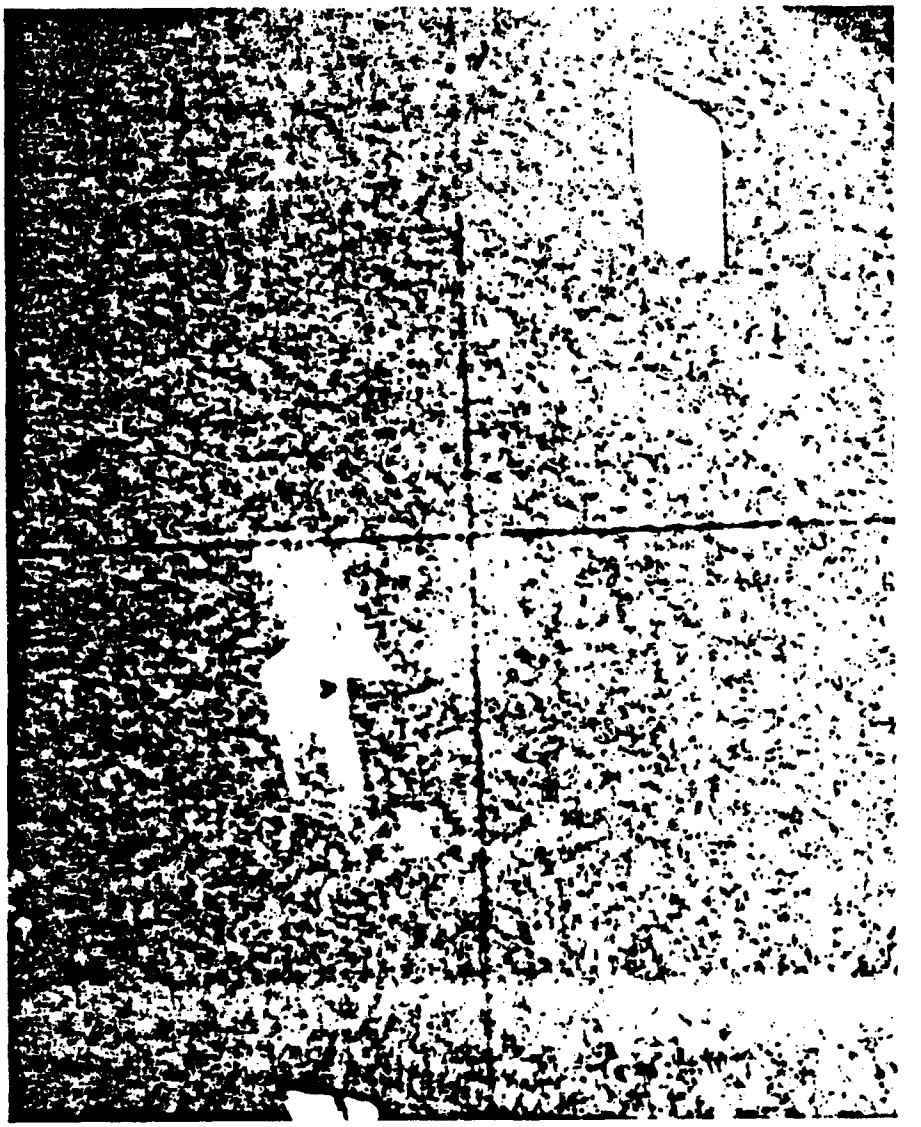

FIGURE 8
Cream Base, Stored at 5°C for 6 Months

substantially (Figure 9). Incidentally, at this point, a microscope was not needed to see the crystals! Chemically, this cream still assayed 100% of the original amount of drug after fifteen months.

Usually, the best approach is to formulate using the least soluble polymorph of the drug. This approach also would hold true for any non-active suspended solid component of the cream. Haleblian has recently written an excellent review article on the subject of crystalline modification of solids and its importance to formulation (9).

The single most important physical stability evaluation tool remains the trained, observant pharmacist. With his own careful and thorough organoleptic observations and the aid of an instrument for more subtle changes, he can detect and remedy most of the physical stability problems that occur.

In Vivo Testing

Before the product is given extensive clinical evaluation, two additional test programs should be undertaken. One is an *in vivo* test of the product's effectiveness. The other is the toxicity testing required for the IND and NDA reports.

Many *in vivo* screening methods to determine efficacy have been proposed over the years. An example of one that has proven useful in evaluating topical steroid products is the McKenzie-Stoughton vaconstriction test (10). Vaconstriction

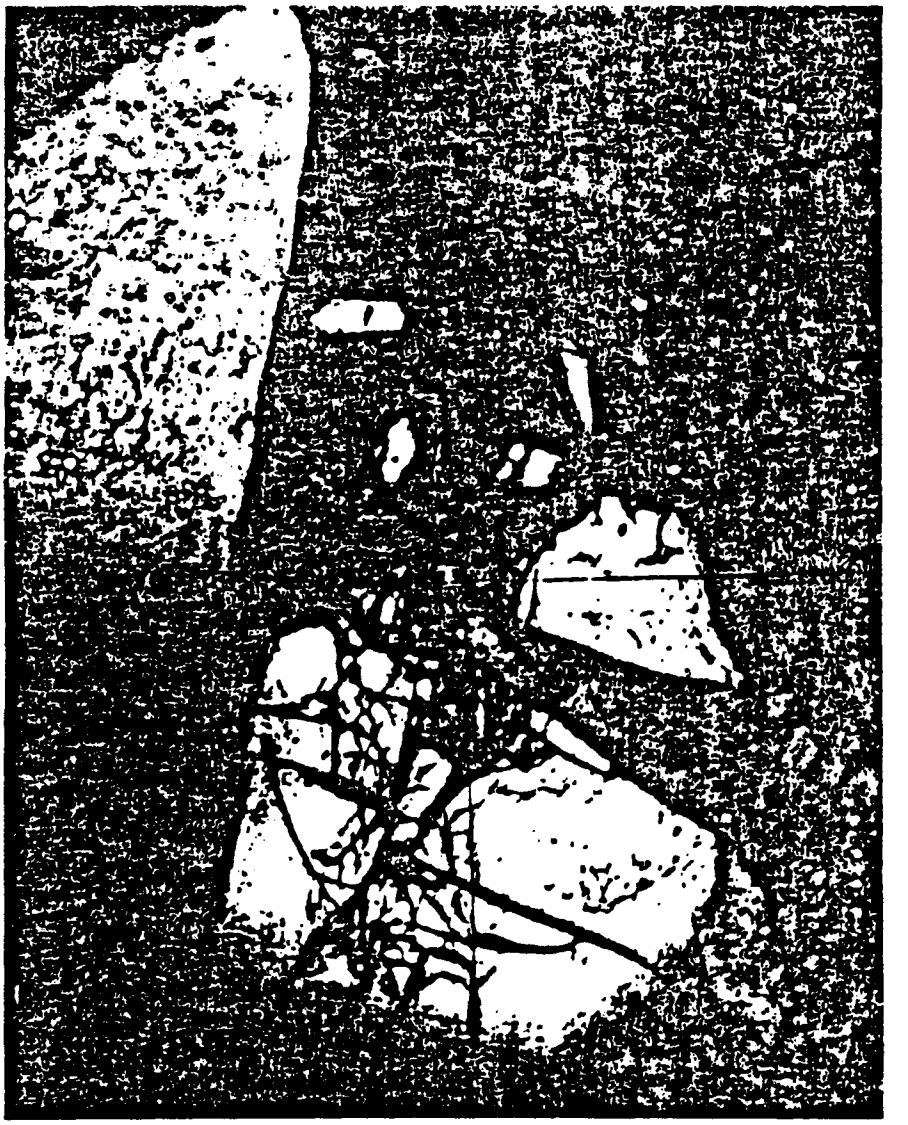

FIGURE 9
Cream Base, Stored at 5 °C for 15 Months

is an index of the percutaneous absorption of a steroid. In this test a small amount of the product (for example, 1 mg.) is applied to the forearm of human volunteers and covered with an occlusive material, such as Saran Wrap. Eight to twenty-four hours after application, the Saran Wrap is removed and the degree of vasoconstriction at each site is noted. Normally, no attempt is made to grade the degree of vasoconstriction, and it is expressed as either "present" or "absent". Through the use of a technique such as this, several potential formulas can be readily screened for their effectiveness.

When doing tests of this type, care must be exercised to make the tests double-blind and symmetrically paired. In all cases, placebos should be an integral part of the study because ointment and cream bases are rarely true placebos, but often produce an improvement through their emollient and protective properties.

Toxicity Testing

Prior to beginning the clinical trial, toxicity testing must have been completed. The amount of testing required depends upon the magnitude of the clinical trial. One very important fact should be kept in mind before beginning the toxicity work--the formula tested for toxicity and sensitization must be the exact formula to be sent for clinical trial. Any change in the formula after this point necessitates re-

running of the toxicity studies and the resultant loss in time and money.

Before beginning Phase I of the clinical trial for a topical product, the test program outlined in Appendix II must be completed. Eight rabbits, four male and four female, are normally used in the first phase of the study. All are shaved and in addition, the skin of four of the animals is abraded. The product is applied after shaving and covered with an occlusive dressing is then removed, the animals kept under observation for fourteen days. If any deaths occur, the animals are necropsied.

In the portion of the test program involving the eye, 0.1 ml. of the product is applied to an eye of each of six rabbits (the other eye serving as a control). The rabbits are observed for seven to twenty-one days. If any significant damage results, the studies are continued.

The running of an oral safety test in two species of animals completes the toxicology needed before beginning Phase I of the clinical trial.

As the clinical trial is expanded, additional toxicological studies must be undertaken. Before Phase II begins, a twenty-one day subacute dermal toxicity study must be done. The product is usually applied to the animals at one, three and ten times the intended clinical dose.

In Phase III, the clinical trials need not await the completion of the toxicity program, but the Phase III toxicity must be well ahead of the Phase III clinical trial. Toxicology consists of a ninety day subacute toxicity study in adult animal sensitivity testing.

Finally, if the drug is absorbed through the skin (or if it cannot be shown that it is not absorbed), reproductive studies must be done.

Clinical Evaluation

The clinical evaluation of the dosage form is the most expensive and critical phase of product development. All of what has been done prior to this point has been done in an effort to insure a safe and reliable product for the clinician.

The monitoring physician has the key role in the conduct of the clinical trial program. The monitoring physician first must establish what the clinical protocol is going to be. With topical products, this must consist of carefully controlled, double-blind studies involving the vehicle without the active ingredient(s) as a control. Care must be exercised to involve a sufficient number of patients to make the studies statistically meaningful. If it is intended that treatment of several clinical conditions are to be calimed for the product, each must be evaluated separately. Throughout the course of the study, there is a continuing dialogue between the FDA and the monitoring clinician (see Figure 10).

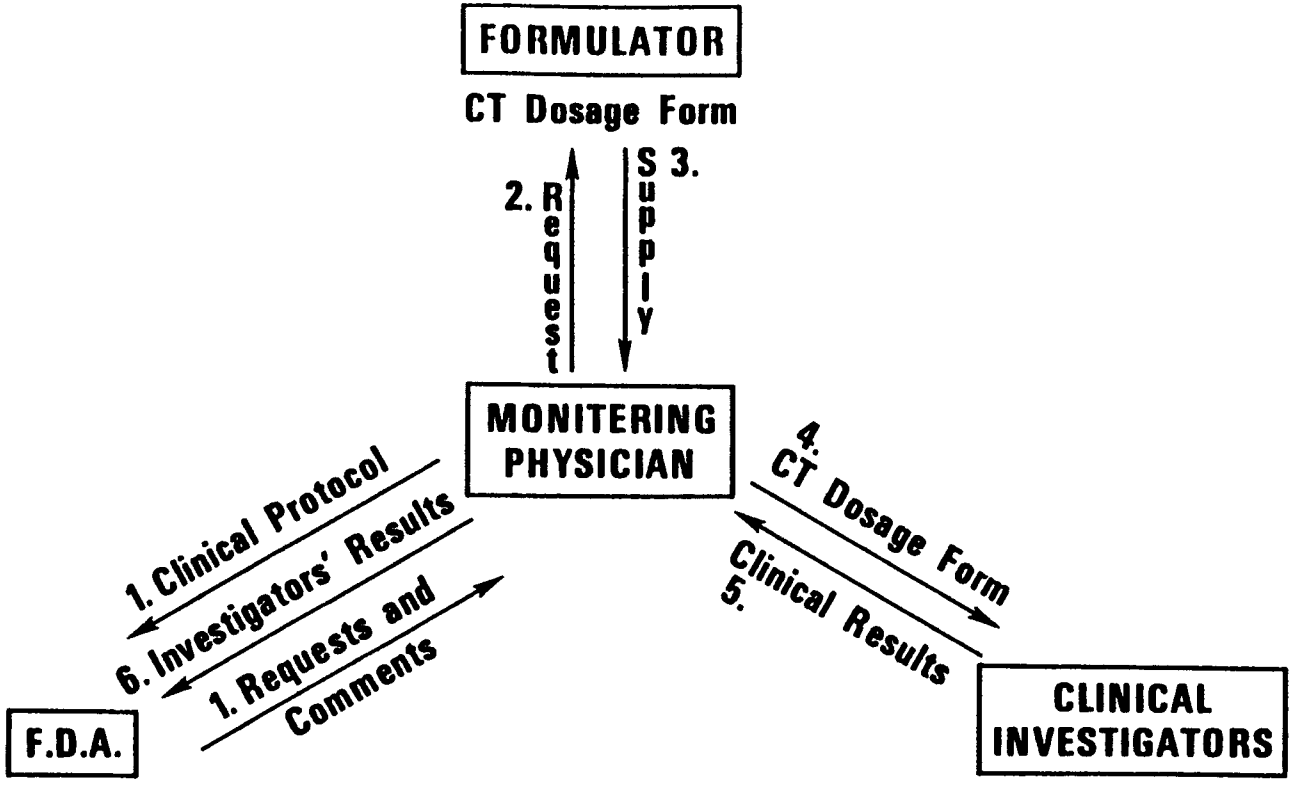

FIGURE 10
Clinical Trial Scheme

When the clinical program has been filed with the FDA, the monitoring physician requests a sufficient amount of material from the formulator to initiate the clinical program. Before the dosage form is released to the custody of the monitoring physician, the new drug substance and the formulated product must be thoroughly evaluated to insure proper potency and safety. Stability studies must also be initiated so that if the product becomes subpotent or physically unstable during the course of the clinical trial, it can be recalled before any harm can result to the patients in the study.

After release of CT material to him, the monitoring physician supplies it to the clinical investigators whom he has previously contacted and previously discussed the clinical program with. As the clinical investigators use the product, they begin sending in reports to the monitoring physician. He evaluates these and in turn sends them to the FDA.

Although the concept shown in Figure 10 is oversimplified, it does convey the principal framework under which the clinical trials are conducted.

Scaling-Up

As the development of the new product progresses, an increasing amount of thought is given to production size lots of the formula. When the product leaves the laboratory and progresses to pilot plant size quantities for the Clinical Trial Program,

the formulator obtains the first meaningful experience as to what, if any, the scale-up problems will be.

It is wise to have, in the pilot plant, smaller models of the actual production equipment to be used. In this manner, more meaningful scale-up evaluations may be made. Despite adherence to similar or identical equipment, any time a batch size is significantly changed (for example 10 times larger or smaller), there will be some differences due to the fact that the conditions cannot be identical (shearing forces, heating and cooling times, filling times, etc.). The reader is directed to a recent review (11) for more information on scaling-up semi-solid products.

ACKNOWLEDGMENTS

The assistance of Mr. W. Gibson, Mr. T. Cole and Dr. D. Sondack is gratefully acknowledged.

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APPENDIX I
PRE-FORMULATION SHEET

Compound Number_____

Chemical Name_____

_____

Chemical Formula

Color_____ Odor_____

Appearance_____ Taste_____

Other_____

Polymorphism

Crystalline R.N.B. #

Anhydrate_____ ( )

Hydrates_____ ( )

_____ ( )

_____ ( )

Solvates_____ ( )

_____

Amorphous_____ ( )

Equilibrium Moisture Content of Crystal Forms

(R.N.B. #)

TGA Curve _____ (R.N.B. #)

DTA Curve_____

DSC Curve_____

Particle Characteristics (R.N.B. #)

Polymorphic Form Studied_____

Particle Shape_____

Average Particle Size_____

Particle Size Distribution_____

Comments_____

_____

Solubility at 25°C. (R.N.B. #)

Polymorphic Form Studied_____

Distilled Water_____mg./ml.

Isopropyl Myristate_____mg./ml.

Isopropyl Alcohol_____mg./ml.

Mineral Oil_____mg./ml.

Propylene Glycol_____mg./ml.

Tween 80_____mg./ml.

etc.

Also

Solubility at 4°C. and

Solubility at 37°C.

Additional Stability (R.N.B. #)

APPENDIX I (continued)

In the presence of:

Light

Daylight_____ _____

Fluororescent_____

Trace Metals

Iron_____

Copper_____

Oxygen_____

APPENDIX II

Toxicity Studies - Topical Products

Before Phase I of Clinical Trial

Skin

Rabbits - Abraded and non-abraded
Apply - cover with dressing for 24 hours
Observe for 14 days
Autopsy - if indicated

Eyes

Rabbits - Apply - observe for 7 - 21 days

Acute Oral Toxicity

2 species

Before Phase II of Clinical Trial

Skin

Rabbits - 21 day subacute dermal toxicity
Observe for additional 14 days
Occlusion and abrasion
Run blood and urine samples
Autopsy

For Phase III of Clinical Trial

Skin

Rabbits - 90 day subacute dermal toxicity
Run blood and urine samples
Autopsy

Sensitivity Testing

Guinea Pigs - Apply, omit, reapply
Compare Formulation vs. Placebo
vs. Untreated

Reproductive Studies

Systemic Toxicity