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MODERN SUPPOSITORY MANUFACTURING*

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INTRODUCTION

Methods of manufacturing suppositories on a production scale have undergone significant development in recent years, almost entirely in Europe, in the areas of packaging machinery and suppository bases.

It is obvious that European technology far surpasses America's relatively limited experience with this dosage form. This is most likely due to the American's negative aesthetic value judgement in this area of medicament application and the resultant small market extant. It is the American pharmaceutical manufacturer's great fortune that the European demand has produced such sophisticated methods for the limited production we carry out on this side of the Atlantic.

This paper will explore the various methods that exist to produce a packaged suppository and review the technology and test methods utilized to choose suppository bases.

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MANUFACTURING SUPPOSITORIES

The Molding Of Suppositories (Out of Package)

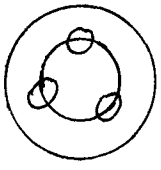
On a small scale, in a laboratory or a pharmacy, or in production, the preparation of suppositories from the prepared dilution of drug in base may be carried out in three basic ways.

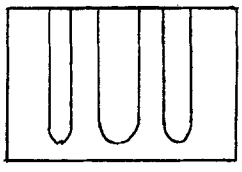
The first and oldest method is hand shaping. This is usually accomplished by weighing a proper portion (usually 2 Gm.) of mass and forming a ball with the fingers, rolling the ball into a tube with a spatula on a pill tile (starch should be used as a dusting powder) and shaping the insertion end with additional pressure while rolling.

This method and the cold compression method are useful with materials which are extremely heat labile.

Cold compression consists of forcing the mass into a mold (usually metal) by pressure. Small hand-operated presses are used in the pharmacy. Larger presses, consisting of a quadruple mold, a chamber for depositing the mass, and a screwed shaft attached to a larger wheel, may be used in larger operations. As the wheel is turned, mass is forced into the molds. Pressure is then released, the mold removed, finished pieced removed, the mold replaced, and the operation continued until the mass is exhausted. The mold should be

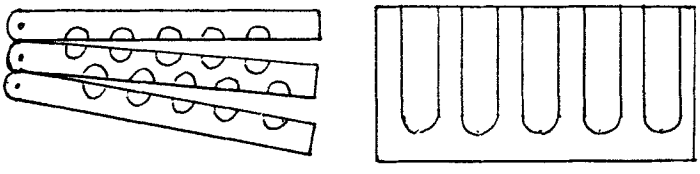
lubricated with alcohol or a soap solution so that no sticking occurs. Armstrong, Stokes, and Colton have manufactured machines of this type. On a larger scale, Colton manufactures a hydraulically operated, motor-driven, cold compressed suppository machine. The cylinder in which the mass is placed is surrounded with a water jacket for cooling purposes. Control of the movement of the piston is accomplished by electric push-buttons. All cold compression units use circular molds (see diagram below) and are limited to the conical or cylindrical shape.





The generally accepted method of suppository production is through the process of melt molding. It should be mentioned that glycerinated gelatin suppositories must be melt molded. Since the mass is designed to melt close to body temperature in the majority of cases, the mass can be made to flow with a minimum of heat input. In many preparations, care must be taken to keep the temperature as low as possible, so that the viscosity of the melt will not fall to a point which would allow heavier ingredients to seperate out.

On a small scale, hand operated molds made of various metals or plastics are used. One or fifty suppositories may be made at a time using this method. Most molds of this type are hinged on one side and have a screw clamp on the other side to hold the two sides together tightly during the molding operation. If optimum pressure is not applied, hot melted mass may seep between the mold halves and produce pieces with edges or "wings". Plastic molds have not gained as much popularity as the metal molds due to their poor heat conductivity. The rate and temperatures of cooling must be chosen based on the individual vehicle in question.



In pharmaceutical manufacturing operations, where large continuous throughputs are required, two methods have developed to meet these needs. The first is an automation of the simple melt molding operation. The second involves pre-forming a mold-package by either thermoforming plastic or embossing foil and filling mass into them. As this latter method involves a combination of two steps in the overall packaging process, this will be treated later as a seperate subject.

An excellent example of an automated suppository molding operation to produce an "unpackaged" suppository is the Crespi Molding Machine manufactured in Italy by Franco Crespi.

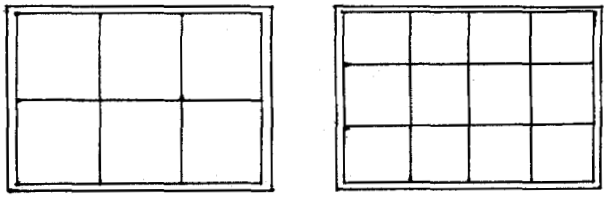
The heart of the Crespi operation is a set of 80 molds, each with twelve cavities in a straight line. These molds are hinged at the top for release of the finished pieces through the opened bottom. The 80 molds are arranged in four rows of 20 each which stretch from the mouth of a refrigeration unit to about two molds past a dual filling station. The two inner rows proceed (driven by an eccentric cam arrangement) stepwise (each step the length of one mold) past the filling stations where individual tubes enter each cavity and inject molten mass to about one-eighth inch above the cavity to allow for shrinking on cooling. At this point, the mass is at about 40-45°C. As the molds proceed toward the cooling unit, under a plexiglass hood, they are exposed to a temperature close to 4°C. In front of the cooling unit, a transfer device switches the molds from the inner rows to the outer rows one at a time, and they proceed in the opposite direction. At this stage, or soon thereafter, the mass has usually solidified completely. About halfway back along the outside track, the molds pass by scraping stations which remove the excess solidified base above the mold cavities. This material, which can be quite copious (15-20% of the mass), is collected from beneath the tracks regularly and

is recycled back into some point in the manufacturing process. After scraping, the molds proceed to the vicinity of the filling stations where they are mechanically opened, releasing the finished suppositories onto a conveyor belt which will load them into containers for storage. The empty molds then move further past the emptying station to a transfer device which switches them back onto the inner tracks. At this point, they move one step toward the filling station and are sprayed with lubricant. With filling, the process repeats. The monitoring of temperatures is quite important in this process and recording thermometers constantly read the machine hopper to control the temperature of the incoming mass, as well as the filling head and cooling track temperatures. Again, these temperatures may be varied depending on the nature of the suppository base employed and its cooling characteristics. If this is not considered, overly brittle or unsolidified pieces may result.

A rotary version of this machine is also available.

The Packaging of Molded Suppositories

In the pharmaceutical dispensing of suppositories, the most common package is a simple cardboard box, divided into six or twelve compartments inside by a thin paperboard divider as shown below.



Glycerin suppositories (for bowel evacuation) are usually packaged unseperated in glass jars. Very few other suppository products are packaged this way.

The majority of commercial suppositories are seperated from one another by either individual wrapping or wrapping in strips of paper, foil, or plastic construction.

The first method of accomplishing the individual wrapping function, and one still employed by some firms, was the use of a candy wrapping machine, such as the type manufactured by the Forgrove Machinery Company, Ltd., of Leeds, England.

In this sort of operation, usually carried out in an air conditioned room or on "chilled" suppositories, the piece is fed from a hopper (or by hand, depending on the machine) to the center of a strip of wrapping material. This may be anything from waxed paper to a medium gauge aluminum foil, depending on the stability or vulnerability of the product. After the piece is positioned, the material is cut to length and folded back over the piece, producing a tube. The semi-wrapped piece is then picked up by a rubber padded clamp, the ends of the tube of material are twisted by clamps

and the wrapped piece is moved forward to an ejecting position where it is allowed to fall down a chute. This machine can wrap about 7000 pieces an hour in this fashion.

The two methods of strip packaging suppositories which were previously manufactured on other equipment both consist of heat sealing material around the units.

In the first method, aluminum foil is sealed around the units. An example of this operation is the Uhlmann V110/S. Two rolls of hot-sealing aluminum foil, such as aluminum blank 25-30 mm or cellulose backed aluminum 12-15 mm, are fed through a system of rollers. These rollers are designed to hold the tension on the sheets at a low level but without producing slack.

These two sheets feed between the jaws of a heat sealing device, with variable temperature, whereupon a suppository is fed onto the lower sheet. At this point, the sheets are held fairly taught. The heat seal jaws close, sealing the foil sheets together on all four sides of the suppositories, and simultaneously cut a perforation in the foil between pieces. The raw suppositories are fed by means of a rotating disc which can either be manually or automatically fed.

After the wrapping has taken place, excess foil is trimmed off by means of roller knives and the strips are cut into cartonable lengths. The foil may be purchased with

advertising if desired. The output of this machine is 5500-6500 suppositories per hour.

The second method consists of thermoforming a package in two halves, placing the piece in one half and sealing the halves. An example of this process is the Uhlmann KPIL machine.

Two rolls of thermoformable plastic film (eg. PVC-Aclar or PVC-Polyethylene) are fed througn a heating plate. When plastification temperature has been reached, the films are passed to the vacuum forming station where each is thermoformed on a female mold by means of compressed air. The suppositories are fed into the formed open halves by vibrators and tubes. The two halves and suppositories then go through a heat sealing station to form the package which is then cooled and perforated. This film may also be printed beforehand. This type of machine can package as many as 25,000 suppositories per hour.

In Package Molding

The most significant advance in suppository manufacturing in recent times was the development of methods for molding the suppository directly in its own wrapping. Both foil and plastic versions of this technique have been developed.

The problems with this sort of an operation are related to the shape of the piece desired and the completeness of the

seal between pieces. The form of the finished product must be defined by the wrapping material absolutely now, rather than simply providing an adequate cover. An insufficient seal at any point along the perimeter of the suppositories would have the same effect as a mold with insufficient pressure: edge production.

Dott. Bonapace & Company of Milan, Italy manufacture a line of filling machines which inject melted suppository mass into pre-molded PVC "Rotoplast" containers. Model BP-4/6 has a throughput of 5,400 suppositories per hour whereas model BP-12/13 can form 12,000 per hour, both utilizing only one operator.

As received, the "Rotoplast" containers are open at the top and in rolls. The line of opened pre-formed containers is fed under a three nozzle dosing unit which injects a pre-measured amount of mass into each container. The temperature of the stainless steel vessel which holds the melted mass and that of the dosing unit are thermostatically controlled within 0.5°C. The filled containers are then conveyed onto a supporting disc on a rotating table. On this table, they are cooled by means of a closed circuit air conditioning unit, set to any desired temperature, for a minimum of fifteen minutes. This slow cooling is designed to avoid the deformations and cracking which can occur with certain bases if cooling is carried out at a too rapid rate. The table then rotates to present the solidified container reel to

the entrance of the sealing unit and an empty disc at the exit of the dosing unit. There are five discs on the table at any one time. On the sealing unit, the upper part of the containers are preheated by infrared rays and passed through sealing jaws. The sealed containers are trimmed on their top edge and are cut into prespecified lengths of from 2-3 suppositories. A coding device then imprints the package which finally passes a counting unit.

A machine built on the same principle, but using a film of PVC (90 micron) and Polyethylene (30 micron) as a protective package, is manufactured by Lamp S. Prospero of Modena, Italy.

The final category of in-package suppository molding machinery are those machines which accomplish both the package forming function and the filling and sealing functions, all in the same unit. These types of machines are build by the Hofliger and Karg (H&K) firm of West Germany.

One of these, their model Servac 162S, has a thermoforming operation similar to the Uhlmann KPIL previously described. PVC thermoformed containers are led through dosing, sealing and refrigeration segments in a similar manner to their Servac 200S machine, which is described in detail below. The Servac 200S uses a foil laminate as a packaging material.

Two rolls of 40 micron aluminum foil, laminated with 12.5 micron oriented polypropylene, inside coated with heat-

sealable lacquer, with web widths of from 50 mm to 65 mm, are loaded onto spring-held sprockets. The rate and tension of the film pull-off is controlled by an electromagnetic brake clutch. Both film strips are fed into a cutting station which divides each segment into six sections, each to contain one suppository. The cutting step is to allow for spreading of the film rather than tearing during the embossing step. The embossing tool, constructed to individual shape preference, may be adjusted slightly up to the limits of sheet stretchability. At this station, the film is shaped to the final dimensions of the desired finished suppository.

The embossed strips are then guided by rollers into a sealing tool. A horizontally arranged V-shaped positioner separates the strips at the filling end so that material may enter at that point. The sealing temperature is about 150°C.

The hot melt is pumped into filling chambers from the feed hopper by an adjustable position displacement pump. During filling, the intake holes are closed and the pump plungers serve to empty the chambers. The entire unit is kept warm by circulating hot water.

After filling, the depth of which may be adjusted during operation for weight control, the filled containers pass through a final sealing unit which closes the filling

holes. The sheet is then fed by a system of synchronously controlled clamping jaws, since rollers would no longer be applicable, to a cutting station which divides the strip into segments of 24 to 30 suppositories each. Package size cutting is then accomplished by rotary knives. Using thin vertical rollers, positioned between the suppositories, the cut strips are fed onto a conveyor belt which carries the strips through the cooling station which is usually between 10 C. - 20C. depending on material. After solidification, the pieces are discharged for further cartoning. About 12,000 suppositories an hour can be made this way.

The advantages of this type of operation are many. Bulk handling costs are decreased substantially because of the obviation of an intermediate form (unwrapped pieces). No salvage is generated to be recycled into later batches. Strict temperature control is always maintained. A minimum of operation time is needed for a high production rate.

SUPPOSITORY BASE TECHNOLOGY

With the exception of the polyethylene glycols, (utilized for rapid partitioning of hydrophilic active ingredients in suppositories intended for systemic effects), all suppository bases are natural or semi-synthetic mixtures of fatty acid triglycerides.

The properties sought in an ideal base are as follows:

1. Solid at room temperature - no refrigeration required.
2. Rapid melting at any body temperature (35.5°C - 38.5°C).

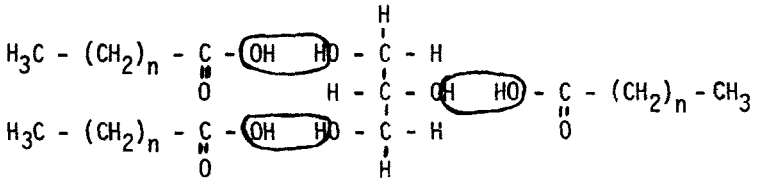
3. Non-reactive with active ingredients and adjustments.
4. Non-irritating to rectal mucosa.
5. Good chemical and physical stability.

If the proper mixture of triglycerides is chosen, and if your drug doesn't hydrolyze fatty acid esters, there is an excellent chance of meeting all the above requirements.

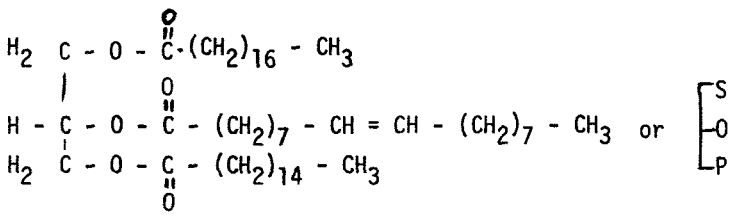
Chemically, triglycerides are fatty acid tri-esters of glycerin (see below). Their structures are abbreviated by using an E and the first letters of the fatty acids esterified. The most common fatty acids found in these compounds are listed below.

C12 = lauric	C18 = stearic
C14 = myristic	C18(1) = oleic
C16 = palmitic	C18(2) = linoleic

Triglyceride Structure



eg. 2 - OLEO PALMITO STEARIN (found in Cocoa Butter)



As can be seen above, a triglyceride may be identified by defining only its middle component.

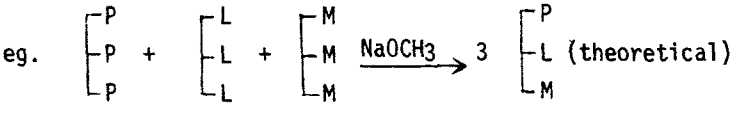
The only naturally occuring mixture of triglycerides which approximates meeting the above requirements is Cocoa Butter or Theobroma Oil. Unlike the semi-synthetic bases discussed below, Cocoa Butter contains a large percentage (about 40%) of unsaturated fatty acids moieties, mainly 2-oleopalmitostearin. Because of this, it has a lower melting range than ideally desired. (32-25°C as opposed to 34-36°C) It's polymorphic behavior is widely documented and, being a natural product, it is subject to fairly wide batch to batch variation.

Semi-synthetic bases are made by three basic processes, each aimed at producting a mix of triglycerides which melt in the range of interest.

The least costly method starts with Corn Oil which is hydrogenated to reduce unsaturation (eg. oleic → stearic) thereby increasing the percentage of solid triglycerides at room temperature. The lower melting triglycerides are then removed either by pressing or by solvent extraction. This sort of process produces what is known to fats and oils manufacturers as a "hard butter". (See inexpensive process, figure A.)

A moderate method of narrowing the natural spread of variation in triglyceride melting points to achieve a mix

with a tighter melting range involves interesterification. In this process, Palm Oil, Palm Kernel Oil, and Coconut Oil (chosen for high lauric acid moiety content) are refined to remove any free fatty acids, deoderized to remove volatiles, hydrogenated as above and then interesterified. This final step effectively distributes all the fatty acid moieties more equally among the glycerin molecules, creating a statistical curve of triglyceride melting points. Sodium Methoxide is the catalyst for this reaction. (See moderate process, fig. A)

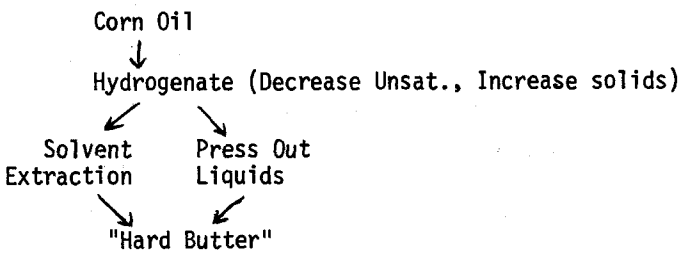


The premium method, and the most versatile, involves re-esterification. Coconut Oil is hydrolyzed into glycerin and its component fatty acids. The fatty acids are separated by fractional distillation, the desired ratio is chosen, and these acids are re-esterified with the glycerin, producing a "customized product". This process is only carried out in Europe at present. (See premium process, fig. A)

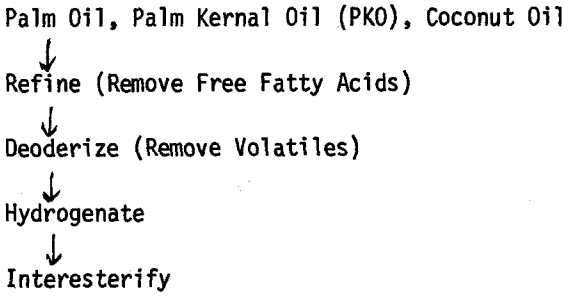
TESTING OF SYNTHETIC BASES

In order to evaluate a suppository base for individual product requirements, the following parameters are usually investigated.

INEXPENSIVE PROCESS



MODERATE PROCESS



EXPENSIVE PROCESS

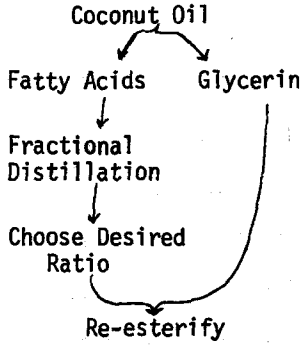
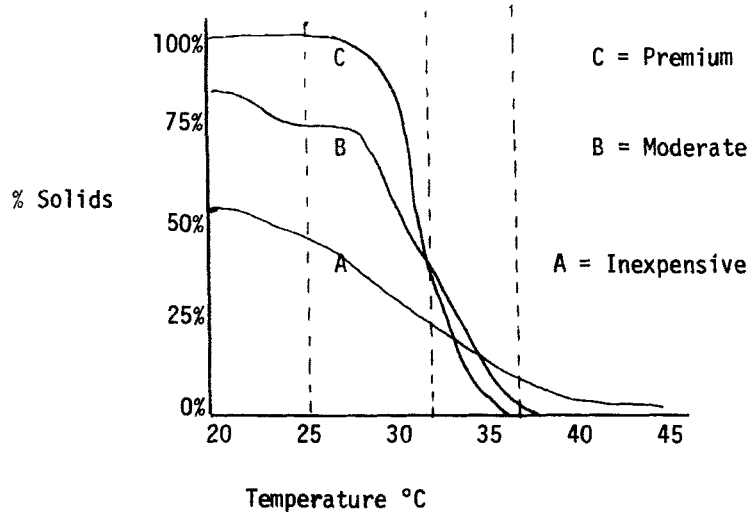


Figure A.

Solid Fat Index

A useful profile of the character of a synthetic suppository base is its Solid Fat Index. This is a graph which plots % solids versus temperature. From this graph, one can visually determine the solidification and melting ranges, the molding character of the base, its surface feel, and its "snap" or hardness.



Looking at bases A, B, and C above, one can see the variation in different bases available on the market in terms of solid content in various temperature zones.

The first parameter to be seen is melting point or zero solids. Even though base A has a high melting point, it may still be too soft at room temperature, because of it's low

solids content at 25°C, and require refrigeration. This is because different triglycerides in the base are melting in various regions. This is also why the melting point of a base is not necessarily a measure of its melting properties.

The solidification point is the point at which most of the room temperature solid content starts to melt. The area between the melting and solidification points is called the melting range. Note the variation in melting range between re-esterified base C and solvent extracted base A.

The hardness of a suppository will be determined by the solids content at room temperature. Base C will be quite hard and have a good "snap".

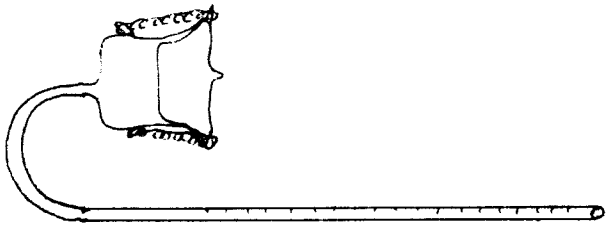
Since finger temperature is about 32°C, one can predict the feel of the suppository in the hand by the solids content at that temperature. A dry hand feel can be expected of bases exhibiting a solids content over 30% at 32°C.

Molding characteristics of bases can be predicted from the slope of the curve between molding (mass) temperature and room temperature. If base C was cooled too rapidly, it would be quite brittle, whereas base A would not. In order to properly form base C into suppositories, a slow cooling process must be employed.

The properties desired in any base must be determined by therapeutic and marketing objective for each product formulated.

Dilatometry

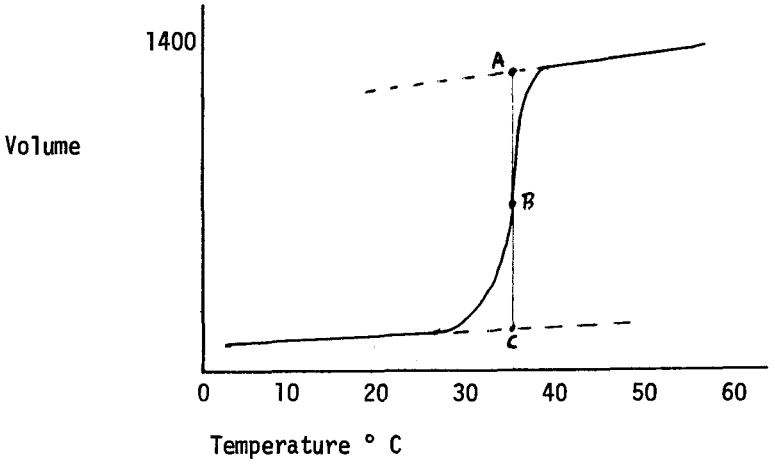
Solid Fat Index curves are generated from Dilatometry data. A dilatometer is a device for measuring the volume differences in materials over a temperature range. It consists of a chamber connected to a long, narrow vertical column.



The column is graduated in micro-liters up to 1400. About 1.5 ml of a 1% Potassium Dichromate solution is put in first, followed by molten base at about 60°C. The chamber top is carefully attached, as not to introduce any air into the material, and is secured with stainless steel springs. The entire apparatus is placed in a constant temperature bath so that only the indicator solution is above the water level.

Temperatures are changed and allowed to equilibrate and volume readings (corrected for glass expansion) are graphed.

Lines are extrapolated for the all liquid and all solid portions and proportional distances are used to calculate percent solids. For example, in the above graph, the percent solids is $\frac{AB}{AC}$ X 100% at 35°C.



Modified Krowczynski Test or "Softening Time"

A useful test of finished suppositories is a simple modification of the method developed in Poland by Lesek Krowczynski. It consists of a U-tube with a constriction which holds the suppository in the tube, which is submersed in a constant temperature water bath. The bath, which may be set at various temperatures of interest, should be controlled within 0.1°C. A unit with both cooling and heating capabilities is suggested for this accuracy in the 37°C range.

A glass rod is placed at the top of the suppository. The time for the rod to pass completely through to the constriction is recorded as the "softening time". This may be plotted versus temperature, used as a quality control parameter, or used as a measure of physical stability over time (See figure B)

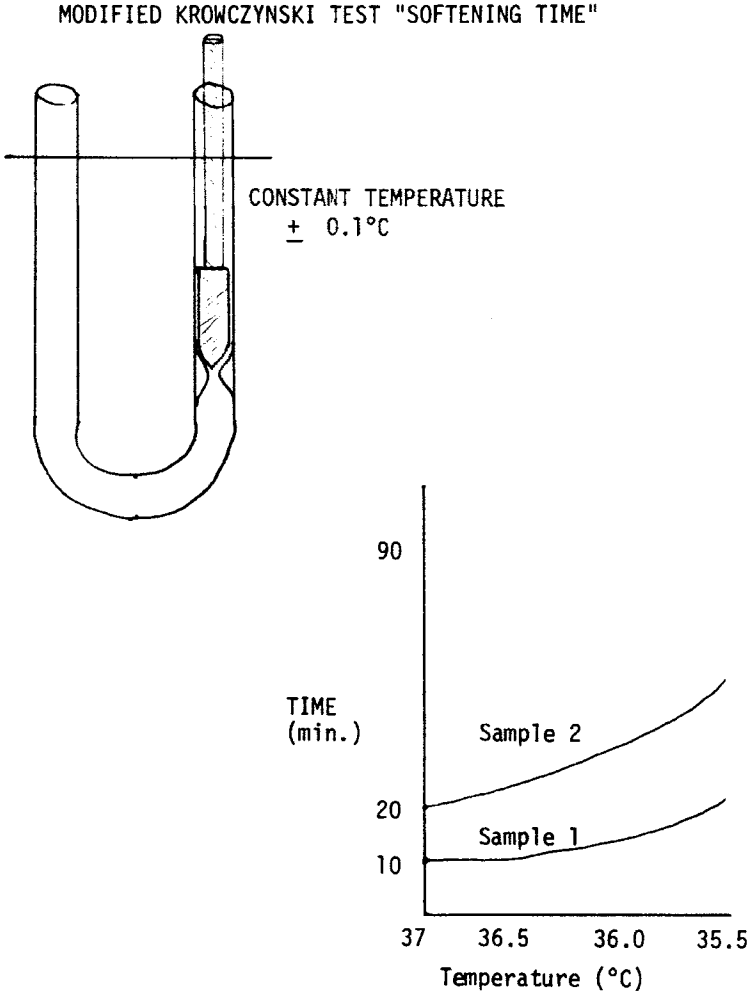


Figure B

OTHER TESTS

The Saponification Value is the mg of KOH needed to saponify 1 Gm. of fat. The usual range is around 200. This is useful in judging the amount and type of glycerides that are present.

The Hydroxyl Value (range 10-75) is the mg of KOH which would neutralize the Acetic Acid acetylated by 1 Gm. of fat. This is a measure of unesterified glyceride bonds and a measure of stability for acidic active ingredients.

The Iodine Value (Number), a measure of unsaturation, is the number of weight parts of Iodine able to bond 100 weight parts of fat (range 1-7). This and the Peroxide Number (meq. of Oxygen in 1 Kg. of fat) are measures of ease of oxidative decomposition and rancidity.

The Acid Number, usually quite low, is the mg. of KOH needed to neutralize the acids present in 1 Gm. of fat. This pH test will show residual fatty acids.

The Iodine Color Number (usually around 3) is the mg. of free I_2 in 100ml of KI solution to produce the shade of the sample in a 25 mm layer.

The Solidification Point (Shukoff Method) is a temperature versus time plot of the cooling rate of a fat in a vacuum flask. At the cessation of rapid temperature drop, the point is taken.

CONCLUSION

A wide range of equipment is available for producing this dosage form. The best method for each application must be based on throughput requirements and the special problems unique to each product.

Since the base is the single most important parameter effecting the manufacturing and molding proceses, it behooves both the formulator and the process scientist to understand as many properties of these materials as possible.

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