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SOFT GELATIN CAPSULE UPDATE

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The soft gelatin capsule is a relative unknown when compared to more traditional dosage forms. The technology and equipment needed to prepare the gelatin mass and that needed to encapsulate the fill material are highly specialized and not readily available. The acquisition of this equipment and technology is not usually economically feasible. The manufacture of soft gelatin capsules has, therefore, developed into primarily a contract manufacturing activity.

Because of this, very little is known outside the encapsulation industry of the methods of production, advantages, limitations, and other attributes of the soft elastic capsule. This presentation explains the manufacturing process in order to give an understanding of current topics. Versatility of application, accuracy of dosage, content uniformity, product identification, patient compliance and other attributes are discussed. Consideration is also given to enhanced bioavailability, sustained release, and other innovations utilizing this unique dosage form.

INTRODUCTION

Within the scope of the pharmaceutical and health and nutritional industries, the manufacture and control of soft gelatin capsules is a unique operation. (By definition, a soft shell capsule is a one-piece hermetically sealed gelatin package containing a liquid, semi-solid, and unlike two piece hardshells soft gelatin capsules are formed, filled and sealed in one continuous operation.) Many companies within these industries have the capability, including equipment and facilities, to develop and manufacture dosage forms such as tablets and two piece hardshell capsules, but relatively few have the capability of producing soft gelatin capsules. In addition, the market volume usually does not support

financial investment in such a operation. As a result of this, encapsulation of soft gelatin capsules has developed into basically a contract manufacturing activity.

Because of their special properties and advantages, soft gelatin capsules are employed for a wide variety of uses, but in general are most widely used in the pharmaceutical and related industries.

USES

Soft gelatin capsules are produced in a variety of shapes, sizes, and colors and may contain one or more active ingredients. Their current applications primarily include, oral dosage forms, suppositories and topical products.

A. Oral Dosage Forms

Human and Veterinary Use
Enteric Coated
Chewables (antacids, cough/cold, vitamins)
Breath Fresheners
Chewing Gum Capsules
Sustained Release

B. Suppositories

Rectal
Vaginal

C. Special Tube Form

Topicals
Ophthalmics
Lubricants
Ear and Nose Unit of Use

D. Cosmetics

Bath Oils
Perfumes
Shampoos
Skin Creams

E. Industrial Uses

(Marking) Capsules
Ether Capsules
Grease Capsules

F. Food Uses

Soup Flavoring

HISTORY

The concept of the soft gelatin capsule has been around since the early (1833) part of the nineteenth century, and was orginally developed by two Frenchmen, Mothes and Dublanc. Their aim was to develop a dosage form to accurately dispense liquids and suspensions especially those which, because of odor or taste, were difficult to swallow. These early capsules were produced by a clipped tube or rod method, where a glass rod was dipped into a solution of melted gelatin, removed and the gelatin film allowed to congeal. The capsule film was trimmed, removed by rolling, hand filled with the appropriate liquid, and sealed with a drop of molten gelatin. Later leather and then iron molds were used for shaping the capsules and they were filled in the same manner as previously described. This process was obviously slow and laborious with a fill accuracy of only ±20% and poor yields. Because of these factors, the soft gelatin capsule was of no particular value as a dosage form. However, as technology progressed the plate process evolved. This was a batch method of preparation in which a single sheet of gelatin is placed on a bottom plate and then a second sheet of gelatin is placed on top of the medication and the top plate of the mold is pressed in place. Pressure forms, fills and seals the capsules, however, there is a greater exposure to air with this process. The Plate Process is still in use to some extent today.

It was in 1933 Robert P. Scherer, a young Detroit engineer, invented what is known as the rotary die process as a continuous means of encapsulation and this process with various modifications over the years has become the industry standard for today. That first machine is now on exhibit at the Smithsonian Institute in Washington DC. The rotary die process achieves a fill accuracy of ±1-3% and yields range in the 98-99% of theory making it comparable with other solid oral dosage forms It should be pointed out that liquid fills have a greater accuracy than suspensions and larger fill weights (150 mg or more) have better percentage accuracy than smaller capsules (fill weight less than 150 mg.).

The Accogel Process was developed in 1948 by Lederle Laboratories. It utilizes a rotary-die concept similar to the Scherer process. This process is used to fill only powders, slugs, and pelleted formulations.

The Reciprocating Die Process was developed in 1949 by the Norton Company. This process is similar to the Scherer process except capsules are formed, sealed, and cut out by vertically positioned reciprocating dies. The dies first form the capsules as open shells in the gelatin ribbons which are filled with capsule fill material. As these capsules pass through the dies again, the dies seal and cut out the capsules. The

process may be used for filling semi-solid and pelleted material.

COMPONENTS: The soft gelatin capsule is comprised of two factions; the shell and the capsule fill.

Shell Composition

The major component of the shell is gelatin, and is itself a unique material. Gelatin is obtained by partial hydrolysis of collagen derived from skin, white connective tissue, and bones of animals. The blending of various fractions of this extractive process provides gelatin of consistent properties from lot to lot.

This heterogenous product derived from the irreversible partial hydrolytic extraction of treated animal collogens is commonly presented as a "natural material", but as such never occurs naturally. Collagen sources are commonly from skins and bones of sheep, cattle, or swine. The industrial production of gelatin consists of a series of steps involving multiple chemical, physical, and bacteriological processes requiring critical controls.

The physical and chemical properties of a specific gelatin are determined largely as a function of the source of the collagen used, method of extraction, pH, thermal history or degradation, and electrolyte content.

Control testing for gelatin, among other things, include viscosity, Bloom strength and iron content. Viscosity determination of gelatin is determined on a 6.67% concentration of gelatin in water. The viscosity range for gelatin is usually between 25 to 45 millipoise. Bloom is a measure of the cohesive strength of the gelatin cross-linking. In 1925, O.T. Bloom developed a instrument that has remained basically unchanged and has become the standard apparatus for testing throughout the world. Bloom or gel strength usually varies between 150 to 250 Bloom grams depending on encapsulation requirements. The Bloom is determined by measuring the weight in grams required to move a plunger 0.5 in. in diameter, 4mm. into a 6.67% gelatin gel that has been held for 17 hours at 10°C.

Iron content should not exceed 15 ppm. Concentrations above this level often cause discoloration. Iron content is usually due to mechanical contamination from equipment or absorption of iron from the water used in processing. With modern methods of water treatment, there is no need to tolerate high iron content, and gelatins containing lower iron concentrations are readily available commercially. Discoloration may often result from the combination of high iron and reducing agents in the capsule fill material (e.g. ascorbic acid).

An obvious area of concern with a substance such as gelatin is microbial contamination. Gelatin, at higher moisture levels, can be an excellent growth medium and for that reason extensive testing must be undertaken to assure that certain organisms are not present. NF XVI allows for a total bacteria count of NMT 1000 organisms per gram and the total absence of Salmonella species and E. Coli. Specifications also call for the absence of Pseudomonas, Staphlococcus and a mold and yeast total plate count of NMT 100 organisms per gram. In addition to the testing just described, other purity requirements of the NF are performed, as well as for other processing requirements such as particle size determination, gel mass clarity and color determination.

The shell composition of an SEC differs from that of hard gelatin capsules in that plasticizer is added to provide elasticity and purified water is added to decrease viscosity during the manufacturing process. The most commonly used plasticizers are sorbitol, glycerin or propylene glycol.

Additional Components which may be added include:

1. Preservatives - parabens
2. Colorants - approved dyes and natural coloring materials
3. Opacifying Agents - titanium dioxide
4. Flavoring - vanillin
5. Sweeteners - sugars, saccharin
6. Enteric Agents - To render the shell insoluble
7. Medicaments - i.e. benzocaine

Fill Composition

An important consideration in the development of a soft gelatin capsule is the character of the fill material. Materials which have been found to be compatible with the soft gelatin shell fall into three general classes:

1. Water-immiscible, non-volatile liquids (i.e., vegetable and aromatic oils)
2. Water-miscible, non-volatile liquids (i.e., polyethylene glycol and polysorbate 80)
3. Water-miscible, relatively non volatile compounds (i.e., propylene glycol and isopropanol)

Of equal importance are those materials which have been found difficult to encapsulate, and include liquids which can easily migrate through the capsule shell, such as:

1. Water, above 5% (causes swelling, evaporation from surface). Water content may be slightly higher in special cases.
2. Low molecular weight alcohols, ketones, acids, amines, and some esters (also because of acid production from hydrolysis of esters).

Fill materials can be heated up to 35°C for encapsulation. This limitation is necessary since capsule sealing temperature of the gelatin ribbons is usually between 37°C and 40°C. Solid materials or granules may be filled into soft gelatin capsules by means of the Accogel process. However, utilizing the rotary die process, solids may also be encapsulated as suspensions. Solids in this case must be 80 mesh or finer in particle size due to equipment limitations and flow characteristics. Examples of suspension media include vegetable oils, surfactants, or polyethylene glycol 400.

Determination of Capsule Size

Before describing the encapsulation process it is perhaps worth discussing the means by which capsule sizes in soft gelatin capsules are determined. The determination of capsule size is critical and in general the smaller the better. Base absorption is used as a means of determining capsule size and is expressed as the number of grams of liquid base required to produce an encapsulatable material when mixed with one gram of solid. The base absorption of a solid is governed by particle size and shape, physical/chemical characteristics, density, moisture, and hydrophilic/hydrophobic nature.

To determine a base absorption value for a given solid compound, a definite amount of the solid material is weighed and placed in a tared beaker. In another tared beaker, a specific amount of liquid material is weighed. Next, small increments of the liquid base are added to the solid and stirred. This is continued until the mixture attains suitable flow characteristics for an encapsulatable product.

Since the minim per gram factors are additive, it is convenient to have charts of common materials available for which these values have been determined, for calculation of capsule size and fill volume.

Production Process

The production process for soft gelatin capsules consists of two separate phases. The first step we will discuss is how the gelatin mass used to encapsulate the fill is prepared.

The gel mass is prepared by adding water and plasticizers, such as sorbitol, glycerin or propylene glycol to dry gelatin. The amount of plasticizer is the determining factor as to how hard or soft the resulting capsule shell will be. This mixture is mixed in a suitable mixer until a full hydrated fluff has been achieved. The fluff is then added to a melter and under vacuum and high temperature control the mass is melted until a clear gel is obtained. The gel is transferred into electrically heated holding receivers. The gel mass

may now be used directly as is in encapsulation or it may require the addition of one or more ingredients such as coloring agents, flavoring agents, opacifying agents or preservatives. These agents are added by means of a high speed mixer. The gel mass is checked for clarity, color and consistency as well as moisture content to insure that the gel will run properly on the capsulation machine.

The compounding of the capsule fill material is the second phase of the pre-encapsulation process and involves the various aspects of pharmaceutical manufacturing including steps such as weighing, milling, mixing, homogenization and deaeration. The removal of air from suspensions is essential prior to encapsulation, in order to assure that proper fill weights are maintained.

Capsules are produced on a rotary die machine which is fed by two tanks of material; one tank contains molten gelatin at a temperature of 60°C to 65°C and the other the fill material, at approximately 20°C. The molten gelatin flows down two heated pipes through two heated spreader boxes onto two separate large cool-casting drums, where flat, solid ribbons of gel are formed. The ribbons are fed into the encapsulation mechanism. Two-tone capsules may be produced by utilizing two separate tanks of different color gelatin, each supplying one of the ribbon casting drums. Liquid fill material in the other tank flows under gravity through a tube leading to a positive displacement pump. Accurately metered volumes of the liquid fill material are injected from the wedge (heated to 37-40°C) into the space between gelatin ribbons as they pass between the die rolls. The combination of die size and injection volume determines the capsule size. The injection of liquid forces the gelatin to expand into the pockets of the dies which form the shape of the capsules. The ribbon continues to flow past the heated wedge and is pressed between the die rolls, where the capsules halves are sealed together by application of heat and pressure. The capsules are cut out automatically from the gelatin ribbon by the dies and are transported through a solvent wash.

During the encapsulation phase, a number of in process checks are made including such items as seal thickness checks, which are measured by means of microscopic examination of a cross section of a capsule shell. In addition, fill weights, shell weights, and ribbon thickness are controlled. The capsules are automatically transferred from the solvent wash and into a rotating infrared dryer. The dryer consists of a series of baskets which are timed to open at prescribed intervals. The capsules are subjected to a tumbling action, dry air, and when desired, infrared light.

After the capsules are removed from the dryer, they are inspected, placed on shallow trays and placed in drying tunnels until the shell and fill moisture reaches the desired level. Then they undergo inspection, and are transferred to closed containers to await further processing and at this point the drying cycle is essentially over.

If desired, a brand, logo or other identification may be printed onto capsules. Current technology utilizes both linear and spin printing methods. Two sided printing is also possible.

A final belt inspection occurs as the finished capsules are packaged by weight into bulk containers.

Quality Control is, of course, a critical element in the manufacturing of soft gelatin capsules. Testing begins with the receipt of raw materials and continues through the mixing, encapsulation, drying and packaging operations. It includes physical, chemical and microbiological evaluations to assure conformance with regulatory, client and inhouse specifications.

Dynamic Fluid Transfer

A few comments are in order regarding the fact that the soft gelatin capsule represents a dynamic dosage form in which changes occur during the manufacture and drying phases of production. These must be understood to provide a satisfactory and stable final product. Studies have shown that the ability of the shell to serve as an oxygen barrier is influenced by several factors, including the type and amount of plasticizer used and the relative humidity. These factors control the equilibrium water concentration in the capsule shell, which is responsible in large part for the characteristics of the soft gelatin capsule dosage form. The movement of water between the shell, fill material, and/or atmosphere is an important consideration in the formulation and manufacture of this type of capsule. At the time of manufacture, the water content of the capsule shell is relatively high. During the drying process, water leaves the shell to the atmosphere by evaporation. Simultaneously, water may transfer from shell into the fill material temporarily, depending on the relative hydrophilic/hydrophobic nature of the fill. As the drying proceeds, this interior water may partition back into the shell and pass ultimately into the atmosphere before an equilibrium water concentration is established finally in the capsule shell. Such dynamic fluid transfer influences the formulation of sparingly soluble materials, materials which are easily hydrolyzed, and readily oxidized components, and should be a consideration in the selection of components of the proposed soft gelatin capsule.

Recommended Storage Conditions

It has been noted that conditions of storage such as temperature and relative humidity can influence the chemical and physical stability of the soft gelatin capsules as a finished dosage form. Control of such conditions during storage, packaging, and dispensing insures the delivery of an elegant, quality product. Recommended storage conditions for the soft gelatin capsule include a temperature range of 59-86°F (15-30°C) and a relative humidity of not more than 50%. Either extremely high or low temperatures or relative humidity should be avoided. Shipping of bulk capsules should be under controlled conditions.

Dosage Form Features and Utilization

The soft gelatin capsule is a unique dosage form and as such offers advantages over other dosage forms. Included in these advantages are:

1. Bioavailability Enhancement (stability)
2. Versatile oral rectal, vaginal and topical applications
3. Superior means of delivering liquids (bad odors/taste)
4. Precise dosage control
5. Reduces potential of cross contamination in powders
6. Protects contents from contamination, oxidation and light
7. Patient Preference Studies - demonstrate appeal to consumers:
   a. Available in wide ranges of color, shapes, and sizes
   b. Outstanding visual appeal
   c. Easy to swallow
8. Also patent protection and line extension

We have previously outlined the various applications of the soft gelatin capsules as a dosage form, but I would like to comment in a little more detail on some of the additional areas of soft gelatin capsule technology which has been explored in more recent times. Among these areas are:

1. Enteric Coating of soft gelatin capsules in order to provide protection for the capsule from acid degradation in the stomach. An enteric coating allows the capsules to pass through the stomach and into the small intestine before it dissolves.

2. A Sustained Release system for soft gelatin capsules is feasible in the form of a semi-solid matrix fill material. The advantages offered by the soft gelatin capsule is its' uniqueness in the market, it is less expensive dosage form to prepare and it offers improved security over the hardshell capsule. NDA submission has been made to serve as a model for this dosage form and several projects are currently underway with major pharmaceutical companies using this technology.

3. Chewable Soft Gelatin Capsules can be developed for a wide variety of medicinal use. One method involves the incorporation of chewing gum base with gelatin, which leaves a residue of chewing gum in the mouth. Another method utilizes a chewable gelatin shell. This technology has a variety of applications including childrens analgesics and vitamins, as well as cough-cold preparations.

4. Reduction of Ulcerogenic Potential of drugs has been another area of interest for soft gelatin capsules. In one such study, which has been published, dexamethasone was utilized successfully to demonstrate the advantage that can be achieved with this dosage form for drugs which exhibit this problem. This particular study demonstrated that a solution dosage form of dexamethasone disperses quickly in the stomach minimizing the possibility of high local concentrations.

5. Enhancement of Product Stability has been demonstrated with numerous compounds.

6. Enhancement of Bioavailability is another major area of interest for the soft gelatin capsules in recent years. Bioavailability, as defined by the FDA, is "the rate and extent to which the active drug ingredient or therapeutic moeity is absorbed from a drug product and becomes available at the site of action." Studies have been done comparing the bioavailability of Theophylline in a soft gelatin capsule to that of a Theophylline elixir (a water-alcohol solution containing the drug). Studies, both in vivo blood level and in vitro dissolution profiles, have demonstrated that relatively insoluble drugs are released faster from soft gelatin capsules than tablets in many instances. The classic example is digoxin of which much has been published. Other compounds studied which exhibit enhanced bioavailability are temazepam, flufenamic acid, prednisone, theophylline, phenytoin, triamcinolone, propranolol, phenytoin, indoxole and steroids.

Conclusion

The soft gelatin capsule is truly a unique dosage form and does offer many advantages not found in conventional dosage forms. Because of this, consideration should always be given this dosage form when developing new compounds, considering bioavailability or stability problems, or endeavoring to extend a products market life. The limitations of the soft gelatin capsule are primarily those of the incompatability of certain materials with the gelatin shell and the need for controlled temperature and humidity storage conditions. These are far outweighed by the advantages of the dosage form. Any drug compound

that is soluble or dispersible in oils or hydrophilic liquids may be formulated as a soft gelatin capsule. This dosage form can be considered as an alternate for tablets or two-piece hardshells that are difficult to compress into tablets, or exhibit powder mixing and flow problems, that degrade during storage, or that exhibit poor bioavailability. In addition, a soft gelatin capsule saves in the cost of raw materials or may offer improvements in the drugs therapeutic performance which could be significant. Be assured that the uniformity achievable with soft gelatin capsules will meet all of your specifications as a dosage form.

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