



Int J Pharm Gen Res

**International Journal of
ADVANCED
PHARMACEUTICAL
GENUINE RESEARCH**

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Review article

Soft Gelatin Capsules-Present and Future Prospective as a Pharmaceutical Dosage Forms -A Review

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(Received: 14 August 2013;

Accepted: 23September 2013)

Abstract



The purpose of this review is to special focus on the advances of soft gelatin capsule. The term soft gelatin capsules is commonly abbreviated to 'softgels'. Soft gelatin capsules has an advantages over hard gelatin capsules is to make a liquid formulation containing the drug in a one-piece outer gelatin shell. The soft gelatin capsule is also called as "one piece". Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odors can be masked by the tasteless gelatin shell. They are suitable for encapsulation of lipid solutions, fish oil, suspensions, or paste-like formulations, making them a useful option when formulating poorly water-soluble drugs. This will inherently lead to better absorption of the active ingredient as compared with delivery in a tablet or as a powder. Development of soft gelatin capsule (soft gel) dosage form is of growing interest for the oral delivery of poorly water soluble compounds (BCS class II or class IV). This review discusses establishment and the on-going development of the manufacturing technology for liquid fill capsules with focus on progress and challenges of soft gelatin capsules formulation in oral administration for improved solubility and as an absorption-enhancing technique. This considerations form a basis for new applications in oral drug delivery.

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Key Words

Soft gelatin, capsules, softgels,
one piece capsules, fish oil

INTRODUCTION

Many pharmaceutical companies have the equipment and facilities for the development and production of tablets, liquids, and hard shell capsule products, but they usually depend upon custom manufacturers for the development and production of soft gelatin capsules¹. The custom manufacturers are specialists in the world, owing primarily to economic, patent, and technologic factors. Although few become directly involved in the manufacture of soft gelatin capsules, pharmaceutical chemist must be prepared to investigate this dosage form and to participate in its development, either in their own laboratories or in co operation with the technological personnel of a custom manufacturer. Soft gelatin capsules are one piece, hermetically sealed, containing a liquid, suspension, or a semisolid. The nomenclature for this dosage form has now been changed to soft gel. They have long been preferred dosage form for those, taking health & nutritional supplements. Soft gelatin capsules unique advantages over traditional dosage forms such as tablets, hard gelatin capsules and liquids.

ADVANTAGES

- ❖ Manufacture Liquids can be encapsulated (non water soluble).
- ❖ Small to large sizes possible.
- ❖ Elegance & Portable odor and taste masking.
- ❖ Improved drug absorption.
- ❖ Easy to swallow.
- ❖ Avoids dust handling problems during manufacture and better operator safety.

- ❖ Overcome problems with manufacture (e.g. oils, low melting point drugs) as compressed tablet.
- ❖ Dose uniformity for low-dose drugs.
- ❖ Good product stability.

DISADVANTAGES

- ❖ Soft gelatin capsules are not easily prepared except on a large scale and with specialized equipment.
- ❖ They are an expensive dosage form, when compared with direct compression tablets.
- ❖ There is a more intimate contact between the shell and its liquid contents than exists with dry-filled hard gelatin capsules, which increases the possibility of interactions.

BASIC COMPONENTS OF SOFT GELATIN SHELL

CAPSULE SHELL COMPOSITION^{2, 3}

The shell of a soft gelatin capsule is composed of gelatin, a plasticizer or a combination of plasticizers and water. In addition, it may contain preservatives, colouring and opacifying agents, flavourings and sweeteners, possibly sugars to impart chewable characteristics to the shell, gastro-resistant substances and in special cases even active compounds.

- **Water:** The ratio 45% w/w by weight of water to dry gelatin can vary depending from 0.7-1.3 (water) to 1.0 (dry gelatin) depending on the viscosity of the gelatin being used.
- **Plasticizer:** Used to make the soft gel shell elastic & pliable.

Ration used is between 0.3-1.8 for soft to hard shell on dry basis. e.g. Glycerine and sorbitol.

- **Coloring Agent:** Colour used in shell has to be darker than color of encapsulating material. Color may be natural or synthetic.
- **Opacifiers:** Usually used is titanium dioxide, may be added to produce an opaque shell, when the fill formulation is a suspension or to prevent photo degradation of light sensitive fill ingredients. Concentration of opacifiers may be up to 0.5%.
- **Chelating agents:** Iron is always present in raw gelatin & should not contain iron more than 15 ppm. Additionally chelating agent may be used for preventing the reaction of iron with materials or colours.
- **Gelatin:** There are two main types of gelatin: **Type A:** produced by acid hydrolysis of animal skins. **Type B:** produced by basic hydrolysis of bovine bones. A soluble biological fluid at body temperature. It is a good film-forming material. Solutions of high concentration, 40% w/v, are mobile at 50°C.

FORMULATION FOR SOFT GELATIN CAPSULES^{4,5}

It involves liquid, rather than powder technology. Materials are generally formulated to produce the smallest possible capsule consistent with maximum stability, therapeutic

effectiveness and manufacture efficiency. The liquids are limited to those that do not have an adverse effect on gelatin walls. The pH of the liquid can be between 2.5 and 7.5. Emulsion cannot be filled because water will be released that will affect the shell.

Vehicles used in soft gelatin capsules Water immiscible, volatile or more likely volatile liquids such as vegetable oils, mineral oils, medium-chain triglycerides and acetylated glycosides.

Water miscible, non-volatile liquids such as low molecular weight PEG have come into use more recently because of their ability to mix with water readily and accelerate dissolution of dissolved or suspended drugs. All liquids used for filling must flow by gravity at a temperature of 35 °C or less.

The sealing temperature of gelatin films is 37- 40 °C.

TYPES OF FILL MATRIXES⁶

- Lipophilic liquids / oils: e.g. Soya bean oil.
- Hydrophilic liquids: PEG400.
- Self-emulsifying oils (oil + non ionic surfactant).
- Micro emulsion and nano-emulsion systems and suspension.

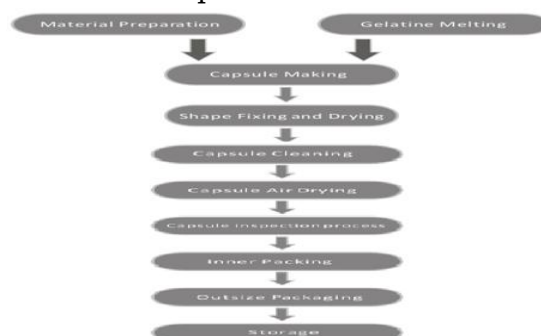


Fig 1. Shows flow chart of manufacturing of soft gelation capsules

MANUFACTURING PROCESS OF SOFT GELATIN CAPSULE

Manufacturing process of soft gelatin process divided into some steps, there are:

1. Gelatin Preparation
2. Material (Fill) Preparation
3. Encapsulation
4. Drying
5. Inspection
6. Polishing
7. Packaging

1. Gelatin Preparation ⁷

Raw granular gelatin is mixed with glycerine and water. Glycerine acts as a plasticizer in the gelatin compound. Other plasticizers can also be used either alone or in combination with glycerine, such as sorbitol. Colouring agent can also be added at this stage. The proportions of each ingredient involved in the mixture should be considered carefully because the shell material needs to be adapted to formulation and/or environmental requirements. For instance the gelatin recipe may need to be adjusted to account for acidity, water content of the fill material or high humidity environmental conditions.



Fig 2. Gelatin melting tank

After the ingredients are combined, the mixture is placed into a reactor called as gelatin melter. The reactor surrounded by a thermal jacket heats

the mixture while a very high torque tribune mixer stirs it under vacuum. At this stage, approximately 20% of gelatin mixture consists of water.



Fig 3. Heated tank

This process takes around 3 hours until the gelatin turns into a molten liquid mass. As soon as the liquid gelatin mass is ready for encapsulation process, it is transferred to ground heated tanks which are wheeled into the clean room where the main encapsulation machine is. Because the only way to keep the gelatin mixture as liquid is to keep it warm otherwise it will solidify like jelly. It is really important to plan and schedule the gelatin production in terms of time and quantity. At least, it requires 2 shift operation.

2. Material (Fill) Preparation ⁵

A homogeneous fill material plays a vital role to ensure the uniformity of each soft gel dose. Various equipments should be available such as processing tanks, high-shear mixer, homogenizer and variety of mills is used.

There are two types of fill materials: oil mixtures or pastes.

Oil mixtures are very easy to formulate. The oils are mixed, deposited into a ground material tank and moved into the hopper of the

encapsulation machine (i.e., vitamin E, fish oils).

Pastes are oils or polyethylene glycols added with powders. Two important factors that affect the homogeneity and flow of the paste should be considered:

1. Particular size of powder in order to allow homogeneous mixture, powder particles must not be thicker than 80 mesh.

2. Viscosity of the mixture. If the mixture is not thin enough, it will not flow correctly through the machine injections.

Natural or artificial flavours, sweeteners and fragrances are commonly used to make chewable soft gels or to mask the unpleasant taste and odour of the fill material such as fish oils. These can go into fill or gelatin material.

3. Encapsulation ⁸

Encapsulation is the manufacturing process that brings the gelatin shell and the fill material together to form Soft gel capsules. It takes place in a closed environment called clean room where the relative humidity is around 20%. The gelatin shell and fill material are brought together simultaneously in the encapsulation machine.

The process is basically performed as described; a pump delivers the warm gelatin over two chilled drums which are located at both opposite sides of the machine, through a spreader box that sits over each drum. The revolving stainless steel drum is about 24" in diameter and exposed to 400 CFM of 57-59°F air at 20% RH. The warm liquid gelatin flows over the drums and this transforms the liquid gelatin into two solid ribbons of gel. The left and right ribbons pass over rollers which feed them through two die rolls. These die rolls determine the

shape and size of soft gels and cut the Soft gel shell from the ribbons as they turn around.

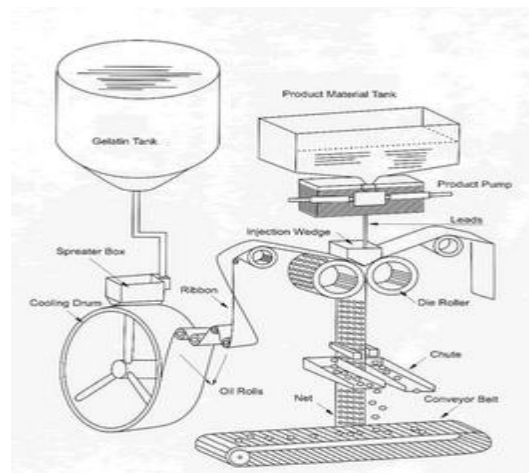


Fig 4. Rotary die filling machine



Fig 5. Automatic filling machine.

Simultaneously, a sensitive and high accuracy, positive displacement pump delivers the fill materials into a heated wedge which sits between rotary dies. This wedge injects the fill material into the die cavities between ribbons just right before the die rolls cut the ribbons and seal the two halves together. The cool, dry air congeals the gelatin as the drum rotates so that a tacky, elastic band rolls off of the other end. This thin band is then automatically formed into capsules; filled with medicine, vitamins or other products sealed and dropped into a tray. If the air blowing against the drum has too low a temperature, the gelatin will set too rapidly and humidity are too high, or the air

become brittle which can cause the manufacturing process to grind to a halt. Too high of an air velocity will disturb the consistent thickness of the gelatin ribbon being formed. If the air temperature velocity is too low, the gelatin will not solidify into a ribbon. Thus, the need for constant control of the air being introduced to the drum is critical in the process. From the capsulating machines, the soft & moist capsules are transferred to drying drums or chambers for rapid drying. The extent of moisture to be removed during drying depends upon the size of the capsule, the number of capsules, and the period of time over which this moisture can be removed.

4. Drying

Drying process purpose is to decrease the moisture content to create a hard and durable finished soft gel capsules ready for packaging. After the soft gels are formed through the die rolls, they contain around 20 percent water. This amount of water content is needed to keep the gel flexible enough to form the capsules.

Drying process requires an environment with low relative humidity in the air but not hot air. This process divided into two stages:



Fig 6. Fluid bed tumble drier for soft gel

- **First stage**

Performed by a tumble dryer consists of sections. This equipment tumbles the soft gels around 30 to 40 minutes and removes approximately 25 percent of the water content in the soft gel capsules.

- **Second stage**

Soft gel capsules are spread on stackable trays and transferred to the drying room or tunnel where high air flow exists and they stay around 24 to 48 hours or until the soft gels become hard enough. This process is called natural manual drying. By using a fully automatic Soft gel drying machine, this long drying process time can be reduced to a few hours which enables you to save time and money.



Fig 7. Soft gelatin capsule drying machine

Typically the environment to be maintained for effective and rapid drying corresponds to a dew point of 25° F or an absolute humidity level of 20 grains per pound of air. The following are typical design conditions: Temperature Humidity 78°F 15% RH 68°F 20% RH In order to achieve the controlled air requirement listed above, refrigeration equipment alone becomes uneconomical, impractical and cumbersome to design, operate and maintain. On the other hand

desiccant type dehumidifiers combined with refrigeration can offer a simple and economical solution to controlling both temperature and humidity levels as low as necessary. Dry-Air desiccant dehumidifiers have been utilized in many capsulating and soft gel manufacturing applications all over the world resulting in millions of dollars saved annually.

5. Inspection & In Process Control for Finished Product ⁹

Due to air pockets in the gelatin and fill material and district production tolerances, the Soft gel capsules may vary in size and need to be inspected visually. Any misshaped, damaged and/or not fully filled capsules are removed manually by using an inspection table. Manual inspection process can be preferred if you have small batch size production but if you intend to manufacture soft gel capsules in mass quantities. Manual inspection will be time consuming process which leads to accuracy problems. In order to reduce process time and increase the accuracy, fully automatic soft gel sorting machine equipped with electronic sensors can be used to sort and remove the damaged, misshaped, broken etc. gelatin capsules. Two to three percent is an acceptable reject rate.

In-process testing

During the encapsulation process the four most important tests are:

- ❖ The gel ribbon thickness.
- ❖ Soft gel seal thickness at the time of encapsulation.
- ❖ Fill matrix weight & capsule shell weight.

- ❖ Soft gel shell moisture level and soft gel hardness at the end of the drying stage.

Finished product testing

- ❖ Capsule appearance.
- ❖ Active ingredient assay & related substances assay.
- ❖ Fill weight.
- ❖ Content uniformity.
- ❖ Microbiological testing.

6. Polishing

The final step before packaging is to clean and polish the Soft gel capsules to remove any mineral oil or glycerine that the capsules may have on their exterior skin. Tumbling is the most used production method to clean the Soft gel capsules among others such as washing with solvent.

7. Packaging

There is no difference between packaging soft gels and traditional tablets or hard capsules. Any finished Soft gel product should be stored in an environment with temperature around 20-24 °C and relative humidity 35%.

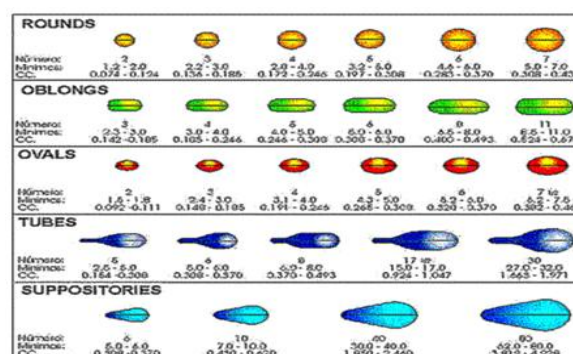


Fig 8 . Different shapes of soft gelatin capsule

Formulation factors affecting drug availability from capsules

The overall dissolution rate of a drug from capsules may be regarded as a function of several variables:

- ❖ The dissolution rate of the shell.
- ❖ The rate of penetration of the dissolution medium into the powder.
- ❖ The rate at which the powder mass de aggregates.
- ❖ The amount and nature of adjuvant such as diluents, surfactant (infused).
- ❖ Drug particle size.
- ❖ The composition and characteristics of the capsule shell.

EVALUATION OF COMMERCIAL CAPSULES ¹⁰

- Content uniformity.
- Weight Uniformity.
- Disintegration and
- Dissolution.

Content uniformity

- ❖ 30 capsules are selected and 10 of these are assayed individually.
- ❖ At least 9 of these contain 85–115% of drug and none contain below 75–125% of drug.
- ❖ If 1 to 3 of them fall outside of 85–115% limits, the remaining 20 capsules are individually assayed and the requirements are met if no fewer than 27 contain 85–115% of drug and none contain less than 75–125% of drug.

Weight Uniformity

- ❖ This test applies to all types of capsules and it is to be done on 20 capsules.

Method

- Weigh an intact capsule.
- Open the capsule without losing any part of the shell and remove the contents as completely as possible.
- Weigh the shell.
- The weight of the contents is the difference between the weighing.
- Repeat the procedure with a further 19 capsules Selected at random.
- Determine the average weight.

Limit

Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in the table below, and none deviates by more than twice that percentage.

Disintegration

The disintegration test determines whether tablets or capsules disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions.

Method

According to the B.P. and applies to hard and soft capsules.

- Introduce one capsule into each tube and suspend the apparatus in a beaker containing 600 ml water at 37 °C. If hard capsules float on the surface of the water, the discs may be added.
- Operate the apparatus for 30 minutes; remove the assembly from the liquid.
- The capsules pass the test if ,

- No residue remains on the screen of the apparatus or,
- If a residue remains, it consists of fragments of shell or,
- If a soft mass with no palpable core.
- If the disc is used, any residue remaining on its lower surface should only consist of fragments of shell.

Dissolution

- The dissolution test is carried out using the dissolution apparatus official in both the U.S.P. and N.F.
- The capsule is placed in a basket formed from 40-mesh stainless steel fabric.
- A stirrer shaft is attached to the basket, and the basket is immersed in the dissolution medium and caused to rotate at a specified speed.
- The dissolution medium is held in a covered 1000 ml glass vessel and maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ by means of a suitable constant-temperature water bath.
- The stirrer speed and type of dissolution medium are specified in the individual monograph.

APPLICATIONS

- As an oral dosage form of ethical or proprietary products for human or veterinary use.
- As a suppository dosage form for rectal use, or for vaginal use.
- As a specialty package in the tube form, for human and veterinary single dose application of topical, ophthalmic, and optic preparations, and rectal ointments.

CONCLUSION

Interesting advances have recently been made in the area of developing liquid and semi-solid formulation in a soft gelatin capsule to address particular bio performance issues, namely an increase of bioavailability and decrease of plasma variability by improving solubility and absorption-enhancing techniques. Although the soft gel capsules have many advantages, they also face stability problem, mainly for the soft capsules stored for longer than six months. After this time, their soluble products decreased and the remnants cannot be re-dissolved and/or reabsorbed into the gastrointestinal tract. These problems could be investigated as a research subject.

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