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Evaluation Parameters of Hard and Soft Gelatin Capsule and Their Manufacturing Process

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ABSTRACT
In recent years, the interest in using hard gelatin capsules in developing and manufacturing medicines has increased considerably. This is most probably due to rapid advances in capsule dosage form. The choice available in terms of capsule type, the range of sizes, the capsule's attractive appearance and printing directly onto the capsule, ensure better patient compliance, product recognition and product differentiation. The demand for plant-based capsules will grow as customers look for performance, quality and lifestyle fit. The unique features of non-animal capsules offer distinct advantages in manufacturing ease, marketing, global certification, dissolution profiles, delivery of specific ingredients and more. For multiple-units, hard and soft gelatin capsules are the ideal solution. There are establishments and an 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. These considerations form a basis for new applications in oral drug delivery. Capsule manufacturers will continue to improve the materials, processes, and related technologies to this versatile dosage form.
Ker Words: Hard gelatin, Soft gelatin, Plasticizer, Opacifying agents,Stripping&Macofar.

I. INTRODUCTION

Capsule is derived from lain word capsula means small box. It is a unit solid dosage form meant for oral use in which medicament and inert substances are enclosed in a shell or envelope made or other suitable material.Capsules are formulated for carrying fixed dose of any active pharmaceutical ingredient show in figure 1.1. Capsule occupies a significant position in the drug development. They are often believed as the primary oral dosage form because of their manufacturing process compared to other dosage forms.

Gelatin has the property of disintegrating when it comes in contact with water, thereby releasing the medicament completely. Instead, of gelatin, denatured gelatin, methyl cellulose and polyvinyl alcohol can also be used to make the capsule shells. There are mainly two types of capsules which are: Hard-shelled capsules, which contain dry, powdered ingredients or miniature pellets made by e.g. processes of extrusion or spheronization. These are made in two halves: a smaller-diameter “body” that is filled and then sealed using a larger-diameter “cap”. Both of these classes of capsules are made from aqueous solutions of gelling agents, such as animal protein (mainly gelatine) or plant polysaccharides or their derivatives (such as carrageenan and modified forms of starch and cellulose).

Other ingredients can be added to the gelling agent solution including plasticizers such as glycerine or sorbitol to decrease the capsule's hardness.

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Figure:-1.1 Capsule

ADVANTAGES

- They are easy to manufacture because they avoid many unit operations such, compression, granulation and drying
- The liquid can be easily administered to the patient as a unit dose in capsule form
- The bioavailability of poorly soluble drugs increases when formulated as soft gelatin capsule.
- Capsule are elegant in appearance because available in wide range of colors.
- Capsule taste of the bitter substance can be masked by encapsulating them in capsule form
- Capsule are slippery and smooth surface facilitates swallowing
- During Capsule formulation, minimum excipients are needed.
- The rapid solubility of gelatin at gastric Ph allows fast release of the drug into the stomach
- There are less chance of counterfeiting

DISADVANTAGES

- Capsule are not suitable for highly soluble substance like Potassium Chloride, Potassium Bromide, Ammonium Chloride, etc.
- Capsule are not suitable for highly efflorescent, hygroscopic and deliquescent materials.
- Many material such as a aldehyde are incompatible with gelatin. Hence can not dispensed in capsule form.
- Filling equipment is slower than tableting, although that gap has narrowed in recent years with the advent of high-speed automatic-filling machines.
- Generally, hard gelatin capsule products tend to be more costly to produce than tablets; however, the relative cost-effectiveness of capsules and tablets must be judged on a case-by-case basis.
- Capsules are easily tampered.

TYPES OF CAPSULE

1. Hard Gelatin Capsule
2. Soft Gelatin Capsule

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Figure:-1.2 Types of Capsule

HARD GELATIN CAPSULE

Hard Gelatin Capsule are used for enclosing solid medicament or dry powders of drug substances. It is also known as dry filled capsule. They are less flexible and consist of cap and body. It is available in different size, shape and colours.Hard gelatin capsules are made of two shells: the capsule body and a shorter cap in figure 1.3. The cap fits tightly over the open end of the capsule body. The basic hard gelatin capsule shells are made from mixtures of gelatin, sugar, and water.Capsule are clear, colorless, and essentially tasteless. Hard gelatin capsule shells are fabricated and supplied empty to the pharmaceutical industry by shell suppliers and are then filled in a separate operation.

During the capsule filling unit operation, the body is filled with the drug substances and the shell is closed by bringing the body and the cap together.Two-piece capsules have been used for almost a century in the pharmaceutical field, and the gelatin has been adopted as the main material of these capsules due to its excellent characteristic as a gelatinizer.

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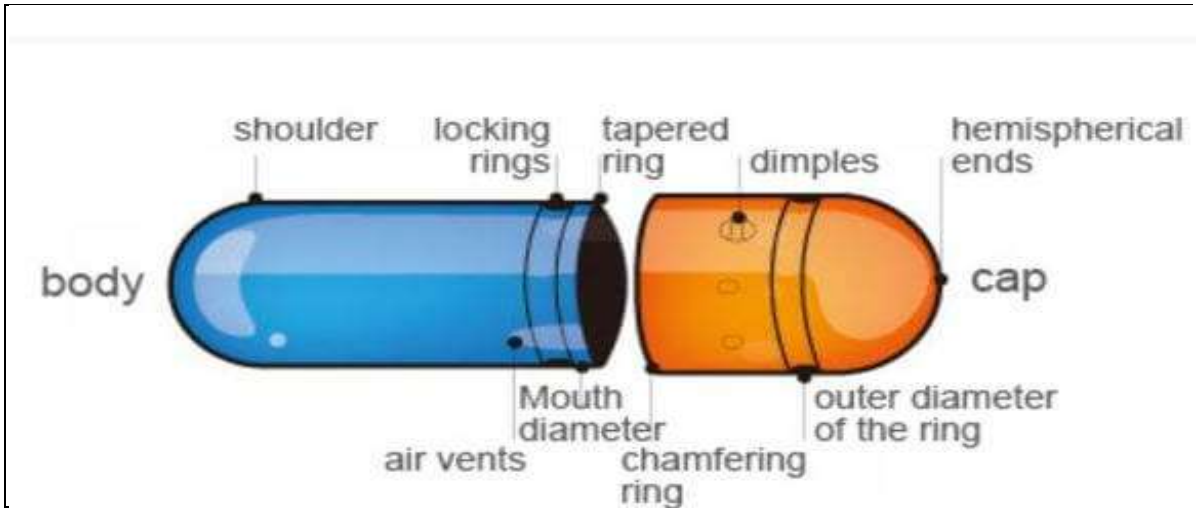

Fig: 1.3Capsule Shells.

Basic Component use in Hard Gelatin Capsule

1. **Gelatin**: Gelatin is by far the most common and most well-known material used to produce hard capsule shells. It is a generic term for a mixture of purified protein fractions obtained from irreversible hydrolytic extraction of collagen obtained from the skin, white connective tissue, and bones of animals.
2. **Plasticizer:**Plasticizers are added to gelatin to reduce the rigidity of the polymer and make it more pliable. Common examples of plasticizers are glycerine and polyhydric alcohol. Water is also a good plasticizer and is naturally present in the gelatin.
3. **Colourants:**Most frequently, hard gelatin capsules are coloured to enhance the aesthetic properties and also to act as a means of identifying the product. Colorants used must meet the regulatory requirements of those countries where the product will be sold. Examples of commonly used capsule colourants include synthetic dyes such as azo dyes and xanthene dyes. Iron oxide pigments are also used.
4. **Opacifying agents:**Opacifiers (e.g., titanium dioxide) may be included to make clear gelatin opaque. Opaquse capsules may be employed to provide protection against light or to conceal the contents.
5. **Preservatives:**Preservatives (often parabens esters) were formerly added to hard capsules as an in-process aid in order to prevent microbiological contamination during manufacture. Manufacturers operating their plants to Good Manufacturing Practice (GMP) guidelines no longer use them. In the finished capsules, the moisture levels, 12–16% w/ v, are such that the water activity will not support bacterial growth because the moisture is too strongly bound to the gelatin molecule.

SOFT GELATIN CAPSULE

A softgel or soft gelatin capsule is a solid capsule (outer shell) surrounding a liquid or semi-solid center (inner fill). An active ingredient can be incorporated into the outer shell, the inner fill, or both. They are oral dosage form for medicine similar to capsules. Softgel shells are a combination of gelatin, water, opacifier and a plasticizer such as glycerin and/or sorbitols.

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Fig:- 1.4Soft Gelatin Capsule

The soft gelatin capsule are produced from a single piece of gelatin. They do not have a cap and body. A soft gelatin capsule is a solid capsule (outer shell) surrounding a liquid or semi-solid center (inner-fill). An active ingredient may be incorporated into the outer shell, the inner filler or both.

Soft gelatin capsule comes in various shape and spherical, elliptical, oblong and special tube shapes with and without twist off.

Shape	**Capacity**
Spherical	0.05-5 ml
Ovoid	0.05-7ml
Cylindrical	0.15-25ml
Tubes	0.05-10ml
Pear shaped	0.3-5ml

ADVANTAGES

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- Soft gelatin capsules provide a patient-friendly dosage form for peroral administration of nonpalatable and/or soily liquids.
- Solutions or suspensions with an unpleasant odor or taste can be easily ingested in a soft gelatin capsule dosage form, which offers tidy appearance and convenient ingestion.
- The proper choice of vehicle may promote rapid dispersion of capsule contents and drug dissolution.
- Higher degree of reproducibility is achieved during the manufacture of soft gelatin capsules than is possible with powders or granules feed in the manufacture of tablets or hard gelatin capsules since the liquid fill is metered into individual capsules via positive displacement pump.
- Soft gelatin capsules can be particularly advantageous for low dose drugs that are lipid-soluble because it can allow greater uniformity of content between dosage units than the conventional tablet dosage form.
- It can also be more suitable than a tablet dosage form for the encapsulation of liquid, water-insoluble drugs.
- The capsules can be formulated to be immediate-release (IR), slow or sustained-release (SR), or enteric-coated.
- Soft gelatin capsules are hermetically sealed as a natural consequence of the manufacturing process. Thus, this dosage form is uniquely suited for liquids and volatile drugs. Many drugs subject to atmospheric oxidation may also be formulated satisfactorily in this dosage form.
- Soft gelatin capsules are hermetically sealed there are no chances of leakage.
- Colors, shapes, laser etching, and sizes are all easily customizable with soft gels.

DISADVANTAGES

- Moisture-sensitive drugs may not be stable in soft gelatin capsules due to the relatively higher water content in soft gelatin shell (20–30% w/w).
- The use of soft gelatin capsule shell imposes significant limitations on the drug formulations that can be encapsulated in this dosage form, that is, restricted to liquids and semisolids
- Soft gelatin capsules are not an inexpensive dosage form, particularly when compared with direct compression tablets.
- There is more intimate contact between the shell and its liquid contents than exists with dry-filled hard gelatin capsules, which increases the possibility of interactions. For instance, chloral hydrate formulated with an oily vehicle exerts a proteolytic effect on the gelatin shell; however, the effect is greatly reduced when the oily vehicle is replaced with polyethylene glycol.
- The major disadvantages of hard gelatin capsules are that they highly sensitive to moisture, therefore having difficulties in dealing with water-soluble materials.
- Compared to other dosage types, the manufacturing process of soft gelatin capsules is complex and it needs to be a trained person to perform the processes.
- Compared to hard gelatin, it has a limited range of drugs and excipients that are compatible to use in the formulation.
- Soft gelatin capsules are more expensive than the tablets as it requires special manufacturing equipment, storage conditions, and special packing.
- It is not suitable for highly efflorescent.

CAPSULE FORMULATION

Hard Gelatin Capsule Shell Formulation

It is estimated that the utilization of hard gelatin capsules to prepare solid dosage forms exceeds that of soft gelatin capsules by about 10-fold. Hard gelatin capsules are fabricated and supplied empty to the pharmaceutical industry by shell suppliers and are then filled in a separate operation. Manufacturing gelatin capsules involves a step by step process that requires strict quality control.

Manufacture of Hard Gelatin Capsule

Gelatin: -Gelatin is a tasteless protein substance which is extracted by boiling the skin, tendons, ligaments, bones of ox and pig. Gelatin are two types.

Type A which is produced by acid-catalysed hydrolysis and Type B which is produced by alkali-catalysed hydrolysis.

Due to non toxic nature of gelatin is widely used in food industry. Gelatin is readily soluble in biological fluid and it also has good film forming properties. The Molecular weight of Gelatin is 15000-250000. Show in figure 1.4

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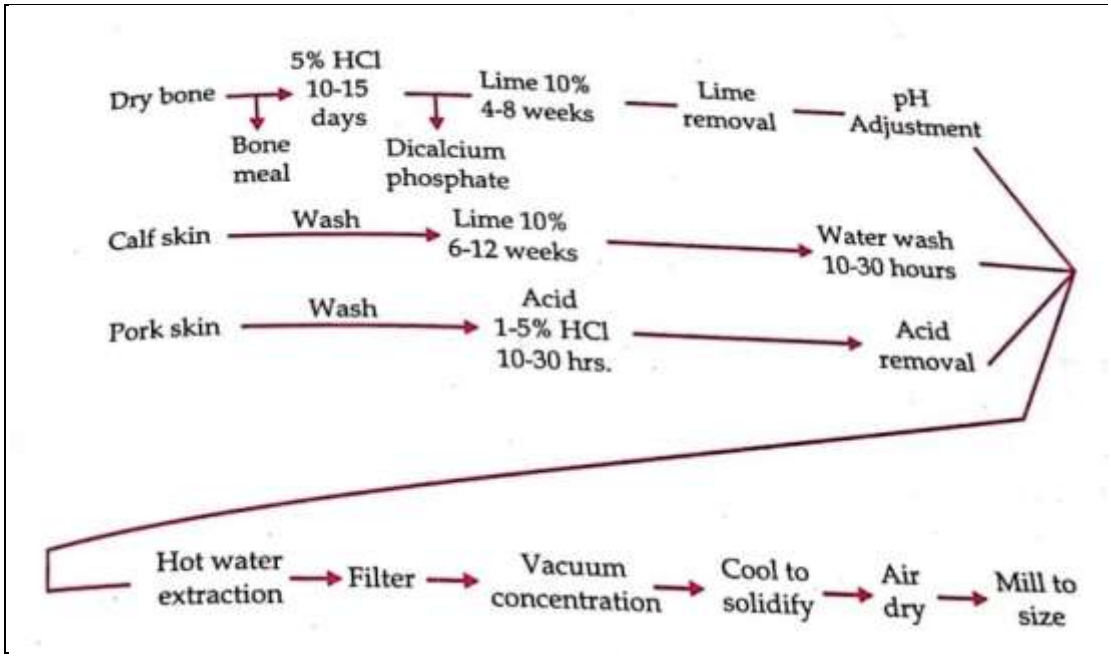

Figure:-1.4 Process of Making Gelatin

Extraction of Gelatin

a. **Inspection and Cutting:**-The rotted parts of animals are discarded. Then the bones, and skins are cut into the small pieces (12.7cm in diameter) through chopping machines.
b. **Degreasing and rotating: -**The animal parts washed under high-pressure water sprays to remove debris. Degreasing is done by soaking them in hot water. The degreased bones and skins are removed to an industrial dryer where they are roasted at about 200°F for 30 minutes.
c. **Acid and Alkaline Treatment:**-The animal parts are treated with acid or alkali for approximately five days to remove most of the minerals and bacteria and facilitates the release of collagen.
d. **Boiling:**-The piece of bones, tissue and skin are boiled in distilled water into large aluminium extractors. The liquid is collected which contains gelatin. The liquid is sterilized by flash-heating it to about 375°F for four seconds
e. **Evaporating and grinding:**-The liquid is filtered to separate out bits of bone, tissue and skin. The liquid is passed through evaporators. The gelatin is press into sheets and passed through a grinder to get fine powder.
f. **Flavoring and coloring: -**If the gelatin is to be used by the food industry, sweeteners, flavoring and coloring may be added at this point. Pre-set amounts of these additives are thoroughly mixed into the powdered gelatin.
g. **Colorants :-** Water soluble dyes (Erythrosine, Indigocarmine etc.) and Insoluble pigments (Iron oxide, titanium dioxide etc)
h. **Preservatives:** -They are used to prevent microbial growth. Eg. Methyl paraben, propyl paraben.
i. **Wetting agents :-** They are used in concentration of not more than 0.15% w/w

PRODUCTION OF HARD GELATIN CAPSULE SHELLS

All raw materials used in manufacturing should be released by Quality Control and all equipment should be validated.A concentrated solution gelatin. 35-40% is prepared using demineralized hot water, 60-70℃, in jacketed pressure vessels. This is stirred until the gelatin has dissolved and then a vacuum is applied to remove any entrapped air bubbles.The gelatin solution is transferred to stainless steel feed tanks. Dye, opacifants, preservative and any needed water are added to the gelatin in the feed tanks. The feed tanks are then used to gravity- feed gelatin into the machine for making capsule/The viscosity is measured and adjusted by the addition of hot water. Higher the viscosity the shell wall produced. The prepared mixes are then transferred to a heated holding hopper on the manufacturing machine.

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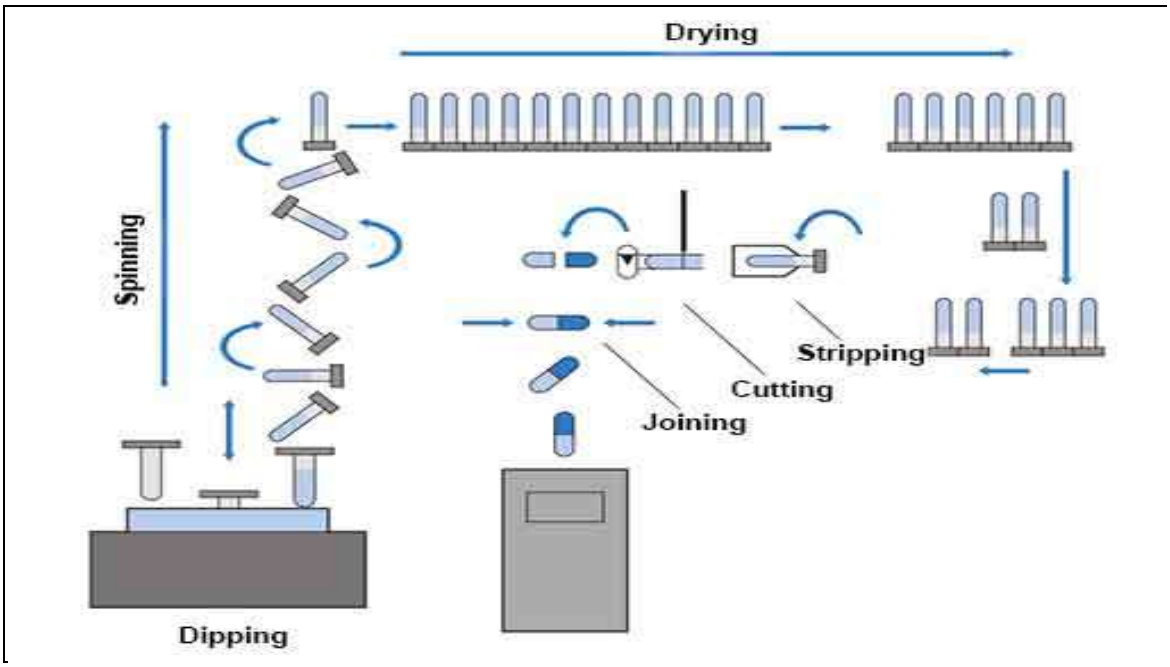

1. **Dipping:**-The plan are lubricated before using. At front end of machine is a hopper known as dip pan or pot which contain heated gelatin solution maintained at the temperature of 35-45℃.

The stainless steel mold pin is dipped into the gelatin solution which has required viscosity. This results the formation of film on the surface of each mould.

2. **Spinning:** -The bar containing pins are removed and rotated so that uniform thickness films are obtained.
3. **Drying:** -The groups of "Pin bars" are passed through drying kilns. Large volume of controlled humidity air is blowen over them. The excess water is removed during this process.
4. **Stripping:**- Now the capsules are removed from the pins with the help of the bronze jaws.
5. **Trimming:**-The excess length of capsules are removed with the help of stationary knives.
6. **Joining:-**Now both the halves of the capsules are obtained and they are joined and are ejected form the machine.
7. **Polishing:**-Acela- Octa pan are used to polish capsules and rubbed with clothes.
8. Finished capsules are pushed onto a conveyer belt. Capsule quality is monitored throughout the production process (Including size, moisture content, single wall thickness, and color).

Capsule are sorted and visually inspected. Capsule are now ready to be sterilized and packaged.

9. **Printing:-** formation, the capsule shells can be printed to improve identification. Printing can be achieved using one or two colours, containing information such as product name or code number, manufacturer name or logo and dosage details.

Printing reduces the risk of product confusion by the numerous handlers and users of the product including manufacturers, pharmacists, nurses, doctors, caregivers, and patients.

FILLING OF HARD GELATIN CAPSULES

The filling of hard gelatin capsules is an established technology, with equipment available ranging from that for very small-scale manual filling (e.g., Feton capsule filling machine), through intermediate-scale semiautomatic filling to large-scale fully automatic filling. Hard gelatin capsules can also be hand-filled one at a time, as done in a compounding pharmacy. The difference between the many methods available is the way in which the dose of material is measured into the capsule body.

The basic steps in filling hard gelatin capsules include

- Rectification of capsules (placing empty gelatin capsules on the removable plate with bodies facing downward).
- Separation of caps from bodies.

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- Dosing of fill material (The body is filled with the formulation manually using a plastic spatula, and the excess powder is removed).
- Replacement of caps/ closing capsule shells and
- Ejection of filled capsules.

Filling of liquids/semisolid formulations into hard gelatin capsules

As drug discovery continues to yield poorlywater soluble molecules, there is an increasing need for formulation techniques that can improve drug solubility. One such approach is the use of liquid-based formulations containing lipids, solvents, or surfactants, usually in combination, to improve drug solubility and bioavailability.

The final formulation may be filled through piston pump systems into hard gelatin capsules as a room temperature liquid, or as a molten semisolid.

The filling of a liquid or semi-solid formulation is dependent on the viscoelastic properties of the formulation and the need to fulfil certain characteristics at the filling temperature.

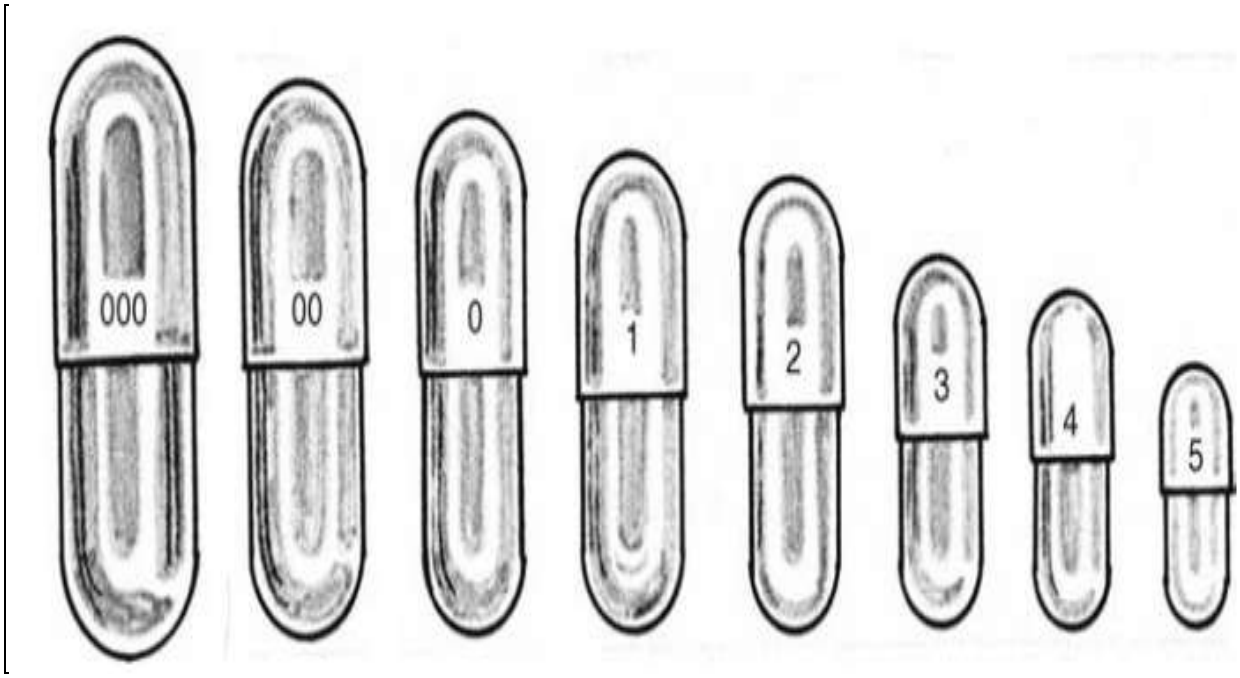
As a general rule, the formulation should have a viscosity of between 50 and 1000 Centipoise (cP) (although formulations of much higher viscosity can be suitable for manufacturing) and should not exceed 70 °C

Locking and sealing of hard gelatin capsules

For the capsules filled by manual or hand filling machines, locking and sealing is done to prevent the detachment of caps from the bodies during packaging, carrying or storing. Locking and sealing also prevents the exudation of the capsule contents. Different manufacturers adopt different methods for locking and sealing the capsules.

- Banding method
- Moistening method
- Spot welding method
- Thermal welding method
- By using coni-snap capsules

SIZE OF CAPSULES



The empty capsules are available in different size. On the capacity of capsules, they are numbered accordingly.

Capsules sizes are ranges from 000 largest to 05 smallest.

Generally, Hard Gelatin capsules are used to encapsulate between 65mg to 1gm.

According to capsule size their volume, height and diameter mention below on Figure 1.5

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Capsule size	Volume (ml)	Height (cm)	Diameter (cm)
000	1.37	2.61	0.99
00	0.95	2.33	0.85
0	0.68	2.17	0.76
1	0.50	1.94	0.69
2	0.37	1.80	0.63
3	0.30	1.59	0.58
4	0.21	1.43	0.53
5	0.13	1.11	0.49

Figure:-1.5 Capsule size Chart

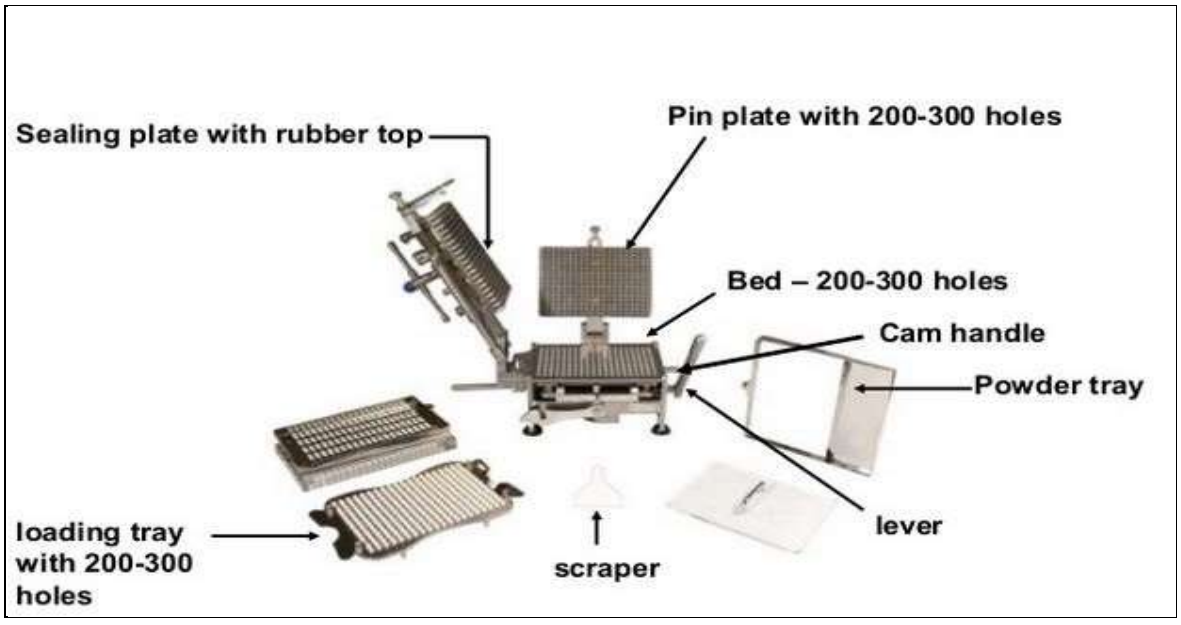
Machine For Hard Gelatin Capsules

1. Hand Operating capsule filling machine
2. Semi-Automatic capsule filling machine
3. Automatic capsule filling machine

Hand Operating Capsule FillingMachine: -

The machine is used for laboratory purpose. With 200 holes machine, approximately 5000 capsule can be prepared in one hour.

- First tighten the handle and placed lever on the position. Now machine is ready for capsule filling. Place empty capsule on loading tray either manually or simple loading device.
- Put capsule in such a way that body is lower side and cap is upper side
- Place the filled loading tray over the bed.
- The cam handle is used to lock body of capsule at their place while the cap of capsule are separated.
- The powder tray is placed in proper positon
- Place powder onto the surface of body plate and spread with spatula to uniformity filling of each bodies. Remove excess powder.



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1. The pin plate is lowered to press the filled powder.
2. Again raise the pin plate.
3. Remove the powder tray after filling.
4. The cap holding Tray is then repositioned over the body.
5. The capsules are rejoined by manual pressure.
6. Remove the loading tray and collect the filled capsules.

Semi Automatic Capsule Filling Machine:-

Semi-Automatic capsule filling machine combine both manual and automatic method of capsule filling. It's simple in operation

- The cap and body rings are positioned under rectifier to receive the empty capsule, the caps are separated from the body by vacuum
- The body rings is then positioned under the foot of the powder hopper for filling process
- The cap and body rings are joined and positioned in front of pins.
- The pins are used to eject the closed capsule

Automatic Capsule Filling Machine:-

On large scale manufacturing various types of automatic machine are used.

Dosator Capsule Filling Machine

A Dosator machine have two segments i.e. the powder bed is on one side while the empty capsule body is on the opposite side. When the dosing block goes down, the dosator penetrates through the bed of powder. It fills the cavity at the tip of the dosator, after which the pistons compress the powder forming a slug. The dosator system moves up, then it rotates in the opposite direction. The powder moves over the section with capsule body while the empty dosator moves above the powder bed.As the dosator block moves down, the second segment penetrates the powder filled while the second segment ejects the capsule to the empty capsule.

All these process take place concurrently. This is a continuous process. The machine may have an output rate of 180000 capsule per hour.

The Nine famous companies which provides capsule filling machine of different models & types

Lilly and Parke- Davis:-Lilly Capsule filling machine, Lilly ROTOFIL.C. Filling Machine.

Farmatic:-Farmatic Model 2000/15,2000/30 and 2000/60 capsule filling machine

Hofliger and karg:-Hofliger and karg model GKF-303, GKF-602, GKF-1500, GKF-2500 capsule filling machine

Macofar:-MT-12, MT-13/1 and MT-13/2 capsule filling machine

mG2:-Model G36/4,G36/2, G37N and G38 capsule filling machine

Osaka:- Osaka Model 180 capsule filling machine

Perrry :- Perry Model CF ACCOFIL capsule filling Machine

Zanasi :-Zanasi Model LZ-64 and AZ-20 capsule filling machine

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Vehicles Used In Soft Gelatin Capsules

Soft gelatin capsules are prepared to contain a variety of liquid, paste, and dry fills. Liquids that may be encapsulated into soft gelatin capsules include the following:

- Water-immiscible volatile and non-volatile liquids such as vegetable and aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, alcohols, and organic acids.
- Water-miscible non-volatile liquids, such as polyethylene glycols, and nonionic surface-active agents, such as polysorbate 80.
- Water-miscible and relatively non-volatile compounds such as propylene glycol and isopropylalcohol, depending on factors such as concentration used and packaging conditions.

Manufacture Of Soft Gelatin Capsules

Plate process

This is the oldest commercial process used in the manufacture of soft gelatin capsules. In this process, a warmed sheet of plain or coloured plasticized gelatin is placed over a die plate having a number of depression or moulds or numerous die pockets. By applying vacuum, the sheet is drawn into these depressions or pockets to form capsule wells. The capsule wells are then filled with medication-containing liquid. A second sheet of gelatin is carefully placed on top of the filled wells followed by the top plate of the mould. Pressure is then applied to the combined plate to form, seal and cut the capsules into individual units.

This method is used for small scale preparation of soft gelatin capsules and capsules formed generally, had one flat side. The major problems with this method of manufacturing softgels were the lack of dosage uniformity, high manufacturing losses, and its labour-/cost-intensiveness. This equipment is no longer available.

Rotary Die Process

Most soft gelatin capsules are prepared by the rotary die process, a method developed and perfected in 1933 by Robert P. Scherer. This process almost eliminated all the problems associated with the plate process and produced soft gelatin capsules with improved uniformity and high standards of accuracy.In this process, two plasticized gelatin ribbons (prepared in the rotary-die machine) are continuously and simultaneously fed with the liquid, semiliquid or paste fill between the rollers of the rotary die mechanism. The forced injection of the feed material between the two ribbons causes the gelatin to swell into the left- and right-hand die pockets which govern the size and shape of the softgels as they converge.

As the die rolls rotate, the convergence of the matching dies pockets hermetically seals and cuts out the filled capsule. Schematic drawing of a rotary-die soft gelatin capsule filler.

Reciprocating Die Process (Norton Capsule Machine)

This continuous soft gelatin capsule processing technology was developed by Norton Company in 1949. This process is similar to rotary process in that ribbons of gelatin are formed and used to encapsulate the fill, but it differs in the actual encapsulating process. The gelatin ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatin ribbons. These pockets are filled with the medication and are sealed, shaped, and cut out of the film as they progress through the machinery.As the capsules are cut from the ribbons, they fall into a cooled solvent bath that prevents the capsules from adhering to one another.

Accogel Process

Although the rotary die process and reciprocating die process were capable of producing soft gelatin capsules containing oily liquids and pastes, Lederle Laboratories in 1949 developed accogel process, a continuous process that produces soft gelatin capsules containing powders and granules. The process involves a measuring roll that holds the fill formulation in its cavities under the vacuum and rotates directly above the elasticized sheet of the gelatin ribbon. The ribbon is drawn into the capsule cavities of the capsule die roll by vacuum.

The measuring rolls empty the fill material into the capsule-shaped gelatin cavities on the die roll. The die roll then converges with the rotating sealing roll covered with another sheet of elasticized gelatin. The convergence of two rotary rolls creates pressure to seal and cut the formed capsules..

Seamless process (Bubble Method)

The seamless technique produces one-piece soft gelatin capsules without the use of dies. The process is often referred to as a bubble method that creates seamless, spherical soft gelatin capsules called pearl. In this process, a molten gelatin stream flows though the outer nozzle of a concentric tube at a constant rate, and the medicated liquid formulation is dispensed through the inner orifice by means of a precision metering pump.

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The emerging stream is broken up into an intermittent but steady flow of uniform-sized by a pulsating mechanism, leading to the formation of droplets enveloped in molten gelatin. The formed capsules are quickly removed from the nozzle, slowly congealed, and automatically ejected from the system.

Quality Control Tests For Capsules

In capsule formulation development and during filling of capsules, a number of quality control tests are performed to ensure that capsules produced meet the requirements as specified in official compendium and conventional requirements established by the industries over the years. These tests will be discussed in three stages: in-process testing, finished product testing and shelf-life testing

In-process quality control tests for capsule drug products

In-process quality control tests for capsule drug products are carried out at predefined intervals during the product manufacturing, by the manufacturing personnel, and their results recorded on the batch record. Adverse findings in these tests can be used as a guide to altering the manufacturing-process parameters.During the encapsulation of soft gelatin capsules, the following parameters are usually closely monitored and controlled:

- Gel ribbon thickness and uniformity across the ribbon.
- Soft gels seal thickness at the time of encapsulation.
- Weight of the capsule fill and its variation from capsule-to-capsule.
- Weight of the capsule shell and its variation from capsule-to-capsule.
- Moisture level of the capsule shell before and after drying.
- Visual inspection, fill weight, and fill-weight uniformity are the key in-process tests used for hard gelatin capsules.

Finished product quality control tests for capsule drug products

Finished capsules are subjected to a number of tests in accordance with compendial standards and regulatory requirements for unit dose capsule products. These batteries of tests help identify whether the batch is acceptable for marketing or its intended usage, the finished capsules are evaluated by the following tests:

- **Permeability and sealing:-** Soft gelatin capsules are tested for physical integrity (absence of leakage) by visual inspection. Similarly, hard gelatin capsules are tested for any breach of physical integrity (breakage or opened cap and body).
- **Potency and impurity content:-** All capsules are tested for drug content (potency, as a per cent of label claim). In addition, most drug products are tested for related substances or impurities. These must meet predefined specifications for a batch to be acceptable.
- **Weight variation:- test** The uniformity of dosage units may be demonstrated by determining weight variation or content uniformity. The weight variation method is as follows.
- **Weight variation test for hard gelatin capsules:-** Ten hard gelatin capsules are usually weighed individually and the contents are removed. The emptied shells are individually weighed and the net weight of the contents is calculated by subtracting the weight of the shell from the respective gross weight. The content of active ingredient in each capsule may be determined by calculation based on the per cent drug content in the formulation.
- **Weight variation test for soft gelatin capsules:-** For soft gelatin capsules, the gross weight of 10 gelatin capsules is determined individually. Then each capsule is cut open with a suitable clean, dry cutting instrument (e.g., scissors or a sharp open blade), and the contents are removed by washing with a suitable solvent (that dissolves the fill but not the shell). The solvent is allowed to evaporate at room temperature over a period of about 30 minutes, followed by weighing of the individual washed shells. The net contents are calculated by subtraction and the content of active ingredient in each of the capsules can be determined by calculation based on the per cent drug content in the formulation.

Fill-weight variation of capsules is often a function of equipment setup and filling operation. An automated capsule sizing machine and/or weight checker is frequently used to discard over- or under filled capsules.

- **Uniformity of content:-** This test is performed only when the content is specified in the individual monographs and when capsules fail weight variation test. If the weight of capsules is completely filled no need of this test. Unless

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otherwise stated in the monograph for an individual capsule, the amount of drug substance, determined by assay, is within the range of 85.0% to 115.0% of the label claim for nine (9) of ten (10) dosage units assayed, with no unit outside the range of 75.0% to 125.0% of the labelled drug content. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes.

- **Disintegration time test for capsules:-** Disintegration of hard and soft gelatin capsules is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. The compendial disintegration test for hard and soft gelatin capsules follows the same procedure and uses the same apparatus described in the article "Quality Control Tests for Tablets". The capsules are placed in the basket-rack assembly, which is repeatedly lowered 30 times per minute into a thermostatically controlled bath of fluid at 37 ± 2 ˚C and observed over the time described in the individual monograph.
- **Dissolution test for capsules**:- Drug absorption and physiological availability depend on the drug substance being in the dissolved state at the site of drug absorption. The rate and extent of dissolution of the drug from the capsule dosage form is tested by a dissolution test. This test provides means of quality control in ensuring that, different batches of the drug product have similar drug release characteristics and also, a given batch has similar dissolution as the batch of capsules that was shown initially to be clinically effective.
- **Moisture content**:- Water content of the entire capsule or the capsule contents are determined by Karl Fisher titrimetry to enable the correlation of water content with the degradation profile or drug-release characteristics of capsules.
- **Moisture permeation test**:- The USP requires determination of the moisturepermeation characteristics of single-unit and unit dose containers to assure their suitability for packaging capsules. The degree and rate of moisture penetration is determined by packaging the dosage unit together with a colour-revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for colour change (indicating absorption of moisture) and comparing the pre-test and post-test weight of the packaged unit.
- **Microbial content**:- The capsules are tested to ensure lack of growth of bacteria and mould by microbiological tests. These tests are usually carried out by incubation of the capsule contents in a growth medium and counting the colonies formed after a predefined period of time. Selection of the growth medium and duration of the test, as well as maintenance of aseptic conditions during the testing, are critical to successful assessment of microbial contamination by this method.
- **Shelf-life test**:-These tests are frequently carried out after defined periods of storage at predetermined conditions. They help to assign and verify the shelf life and usability of the drug product. Stability testing of capsules
- **Stability testing of capsules**:- is performed to determine the physicochemical stability of the drug substance in the finished drug product under specified package and recommended storage conditions intrinsic stability of the active drug molecule and the influence of environmental factors (e.g., temperature, humidity, light), on formulation components, and the container and closure system.

The battery of stress-testing, long-term stability and accelerated stability tests help determine the appropriate storage conditions and the product‟s anticipated shelf life.

Packaging And Storage Of Capsules

Packaging and storage of Hard Gelatin Capsules:- Finished hard gelatin capsules normally contain an equilibrium moisture content of 13 to 16%. This moisture is critical to the physical properties of the shells since at lower moisture contents (18%) they become too soft and may lose shape. It is therefore important to avoid extremes of temperature and to maintain a relative humidity of 40 to 60% when handling and storing capsules. The bulk of the moisture in capsule shells is physically bound, and it can readily transfer between the shell and its contents, depending on their relative hygroscopicity.

The removal of moisture from the shell could be sufficient to cause splitting or cracking, as has been reported for the deliquescent materials potassium acetate and sodium cromoglycate. Conditions that favour the transfer of moisture to powder contents may lead to caking and retarded disintegration or other stability problems.Hard

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gelatin capsules can be individually protected by enclosure in strip or blister packs. In the former, the units are hermetically sealed in strips of aluminium foil or plastic film. In the latter one of the films enclosing the units is formed into blisters. An ideal foil or film for these packs should be:

- Heat stable
- Impermeable to moisture, water vapour, air, and odours
- Strong enough for machine handling
- Reasonably easy for patients to tear and open

Packaging and storage of Soft Gelatin Capsules:-Soft gelatin capsules generally contain the medicament dissolved or dispersed in oils or hydrophilic liquids (i.e., fill liquid). The inherent flexibility of the soft gelatin capsule is due to the presence of plasticizers and residual moisture in the capsule shell. Thus, the soft gelatin capsule is a more dynamic system than conventional tablets. The atmospheric moisture may permeate into the capsule shell or into the fill liquid. The drug or fill liquid may migrate into the capsule shell, while the plasticizer or residual water in the gelatin shell can potentially migrate into the fill. Volatile components in soft gelatin capsules may escape into the atmosphere. It is these characteristics that must be considered when designing a shelf life stability program for soft gelatin capsules.

In most instances, the recommended storage conditions are stated on the label in which case it is imperative to maintain stability. Normally, the recommended storage conditions for empty capsule shells are 15 to 25°C and a relative humidity of between 35% and 65%. This condition is designed to minimize moisture absorption or loss, and the resultant changes in physical dimensions, during the encapsulation operation. While there is no strict guidance for stability testing of soft gelatin capsules, there are a couple of guidelines available that will help evaluate the storage conditions and length of study required for specific formulations of soft gelatin capsules.In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test the thermal stability, and if applicable, its sensitivity to moisture or potential for solvent loss. If it is determined that a particular product is heat sensitive, then these drug products should be stored under an alternative lower temperature condition which will eventually become the designated long-term storage temperature. For example, a 30°C storage condition versus a 40°C condition may be justified.

II. CONCLUSION

From the above premises, capsules are solid preparations in which drug substance(s) and/or excipients are enclosed in either a soft or hard gelatin shell. The shell is normally made from gelatin or other suitable polymeric material and results in a simple, tasteless, odourless, elegant, easy-to-swallow dosage form without the need for a secondary coating step.Depending on the composition of the capsule shell, capsules may be classified as either hard or soft capsule, with soft capsules possessing a flexible, plasticized gelatin film. The shells may be composed of two pieces in the form of cylinders closed at one end; the shorter piece, called the „cap‟ and the longer piece, called the „body‟, or they may be composed of a single piece. The two-piece capsules and one-piece capsules are commonly referred to as hard-shell capsules and soft-shell capsules respectively. There are also specialty applications such as capsules that can be loaded into dry-powdered inhalers, add reagents as part of a diagnostic kit, and occasionally soft-shell capsules intended for rectal or vaginal insertion as suppositories. Also, In the recent advancements, non-gelatin capsules have been discovered, which do not contain gelatin as it‟s shell-forming agent. Under this category of capsules are the HPMC, PVA and starch capsules.Also, the basic steps in filling hard gelatin capsules include; rectification of capsules, separation of caps from bodies, dosing of fill material replacement of caps/ closing capsule shells and, ejection of filled capsules, which is then followed by locking and sealing, polishing and brushing among others.

On the other hand, soft gels are manufactured using the following methods; plate process, rotary die process, reciprocating die process, accogel process and, seamless process. The soft gelatin manufacturing and filling occurs simultaneously. The quality control process s involves the in-process testing, finished product testing and shelf-life testing. The in-process quality control tests for soft gelatin capsule drug products are carried out at predefined intervals during the product manufacturing which involves; gel ribbon thickness and uniformity across the ribbon, soft-gels seal thickness at the time of encapsulation, weight of the capsule fill and its variation from capsule-to-capsule, weight of the capsule shell and its variation from capsule-to-capsule and, moisture level of the capsule shell before and after drying.Visual inspection, fill weight, and fill-

weight uniformity are the key in-process tests used for hard gelatin capsules.

The main aim of packaging of filled capsules is to prevent contamination and moisture gain or loss during long term storage. They are plastic blister packed or aluminium foil strip packed or packaged in glass or other materials which are designed in such a way that they prevent exposure of capsules to excessive humidity.On the other hand, the storage which can be for a very long time period requires proper maintenance of temperature and humidity.

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