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Review Article

A review on manufacturing and evaluation of capsules

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ABSTRACT

Capsules are among the most popular of all dosage forms they are chemically and physically stable, easy to administer, attractive and can be easily compounded. They can be easily tailored to make the needs of individual patients regarding dosing ingredients etc., also, more than one drug can be incorporated in each capsule to minimise the no: of dosage forms the patient must take. Special capsules can be prepared outside the norm of containing only powders. Capsule is most preferable dosage form. Till now gelatine is widely used as capsule shell material for the preparation of hard gelatine capsule and soft gelatine capsule, but due to its animal origin and cross linking property other capsule material that meets the dietary and cultural needs of vegetarian patients and also comply with the regulatory requirement of gelatin need to be invented hence various no animal origin materials such as hydroxyl propyl methyl cellulose, starch, poly vinyl alcohol copolymer etc, and evaluate as a capsule shell material.

Key words: Capsule, gelatine, hard gelatine capsule, soft gelatine capsule, capsule shell

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INTRODUCTION

Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which the drug substance is enclosed in either hard [or] soft soluble containers [or] shell of a suitable form of a gelatine. The medication may be powder or a liquid or a semi solid mass.

- Capsules are usually intended to an administration orally by swallowing them whole.
- Occasionally capsules may be administered rectally [or] vaginally.
- Gelatine capsule shells may be hard [or] soft depending on their composition[1].

History: Capsules were first patented for use in 1830 by Joseph Gerard Auguste Dublanc and Francois Achille. The first patented capsules were made from soft gelatine. In 1846 Jules Lehuby obtained a patent for two-piece hard capsules, such as those that are in us today. Since these capsules were made by hand, there was difficulty obtaining precision to get the two parts to fit the shell together well. In 1931, Aurthur calton invented a machine that make hard capsules today are based on Calton's invention[2].

Advantages:

- Neat and elegance in appearance.
- Enclosing the medication within capsule shell provides a tasteless, odourless means of administering medication.
- The solubility of gelatine at gastric Ph provides the rapid release of medication in the stomach.
- Packaged and shipped by manufacture at lower cost less breakage than liquids forms.
- The contents may be removed from the gelatine shell and employed as a premeasured medicinal powder. The capsule shell being use to contain a dose of the medicinal substance. E.g. Theo-dur sprinkle.
- Commonly embossed of imprinted on their surface the manufactures name and product code readily identified.
- The capsules are smooth and slippery in nature and easily swallowed.
- Patient compliance.
- Manufacturing of capsule is easy[3].
- Used to enclose lipids or semisolids.
- Rapid disintegration and rapid bioavailability.
- Increases rate of release of the drug.

Disadvantages:

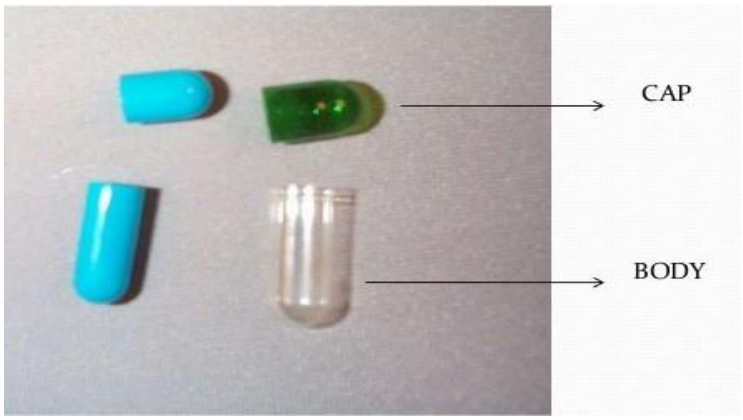
- Capsules are not suitable for liquids that dissolves gelatine, such as aqueous are hydro alcoholic solutions.
- The concentrated solutions which require previous dilution is unsuitable for capsule because if administered as such lead to irritation into stomach.
- Not useful for efflorescent or deliquescent materials. Efflorescent cause capsules to soften and deliquescent may dry the capsule shell to brittleness.
- Very soluble salts such as bromides, iodides should not be dispensed in capsules, as the rapid release of such materials may cause gastric irritation[3].

Types of capsules:

There are mainly two types of capsules. They are

1. Hard gelatine capsules
2. Soft gelatine capsules

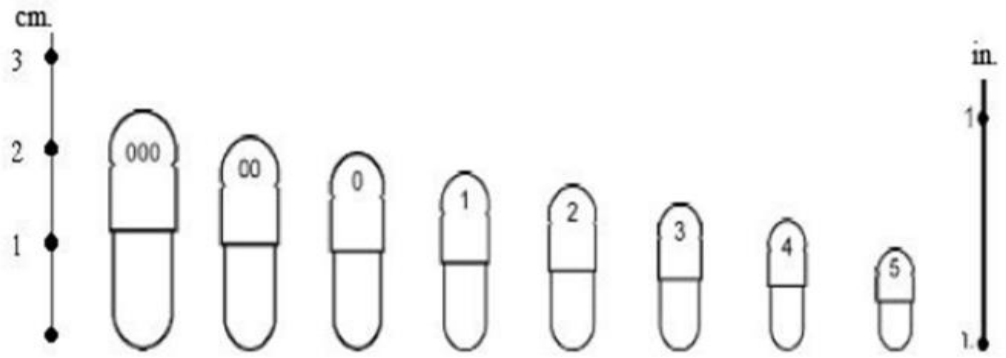
Hard gelatine capsules: The hard gelatine capsules has been conventionally used as a dosage form for prescription and over the counter (OTC). Drugs and herbal products which are formulated either as powder or pellets. This has considerably expanded Hard the range of possible formulations utilising hard gelatine capsules as a simple dosage form for oral drug delivery. It consists of two pieces in the form of cylinders the shorter piece "cap" and the longer piece "body"[4,5].



The shell consists largely of gelatine, sugar and water. Hard gelatine capsules contain 12-16% moisture. These are typically filled with dry solids that are[6]

- Powders
- Granules
- Pellets
- Tablets

Sizes of capsule:



- ❖ The largest size of the capsule is No: 000
- ❖ The smallest size of the capsule is No: 5
- ❖ The standard shape of capsules is traditional, symmetrical, bullet shape.

Size	Volume in ml	Size in mm
000	1.37	26.3
00	0.95	23.7
0	0.68	21.8
1	0.50	19.2
2	0.37	18.3
3	0.30	15.3
4	0.21	14.7
5	0.15	11.9

Formulation of capsule shell[7]:

Gelatine: It is a heterogeneous protein. There are two types of gelatine. They are Type A and Type B.

Type A: Obtained by acid hydrolysis of pork skin.

Type B: Obtained based hydrolysis of animal bone and hide portions bones and animal skin.

Plasticizers: These are added to the gelatine mass to confer softness, hardness, electricity and thickness to the capsule shell. E.g. Glycerine, sorbitol, Propylene glycol.

Water: Essential components in the preparation of gelatine mass.

Colorants: It improves their elegance.

Opacifying agents: To minimize the transparency and to make the capsule shells opaque. E.g. Titanium dioxide.

Preservatives: To prevent microbial growth. E.g. Methyl paraben, propyl paraben.

Flavour: To impart good flavour. E.g. Essential oils, Vanillin.

Sugars: It imparts taste and to mask the objectionable taste. E.g. sucrose

Solvents: It imparts elegance and palatability. E.g. oils.

Acids: Added to prevent the aldehydic tanning of gelatine. E.g. fumaric acid

Thickening agents: To adjusting the desired viscosity. E.g. methyl cellulose.

Formulation of capsule fill materials[8]:

Selection of ingredients: It is active medicament

Diluents: It is also known as fillers. E.g. lactose, mannitol

Disintegrants: To promote break up and distribution of the capsule content. E.g. CroscarmelloseSodium type A.

Glidants: They enhance the flow properties of the capsule. E.g. Starch, colloidal silica, magnesium stearate.

Surfactants: Used to maintain surface area. E.g. Sodium docusate, acetyl pyrrolidinium chloride

Antidusting agents: To prevent contamination. E.g. Inert and edible oils.

Manufacture of Hard gelatine capsules[9, 10]:

Steps involved in making empty gelatine capsules….

- Dipping
- Spinning
- Drying
- Stripping
- Trimming and joining
- Polishing

Dipping: Pairs of the stainless-steel pins are dipped in to the dipping solution to simultaneously form the caps and bodies. The dipping solution is maintained at a temperature of about 50^0c in a heated, jacketed dipping pan.

Spinning: The pins are rotated to distribute the gelatine over the pins uniformly and to avoid the formation of a bead at the capsule ends.

Drying: The gelatine is dried by a blast of cool air to form a hard shell. The pins are moved through a series of air drying kilns to remove water.

Stripping: A series of bronze jaws strip the cap and body portions of the capsules from the pins.

Trimming and joining: The stripped cap and body portions are trimmed to the required length by stationary knives. After trimming to the right length, the cap and body portions are joined and ejected from the machine.

Filling of hard gelatine capsules[10,11]:
Various filling machines are available

- Eli-lily and Co
- Farmatic
- Hofliger and Karg
- Zanasi Nigris
- Parke-Davis
- Osaka
- Macofar SAS

These machines differ in their designs and output.

Advantages of hard gelatine capsule:

- Easy to swallow
- Masking capacity
- Protection of medicament.
- Therapeutically inert and easy to digest.
- Easy to handle and carry.
- Different sizes are available.
- Product identification
- Provide enteric and sustained release effects.
- Moisture content.
- No need of complicated machinery.
- Filling of incompatible in the same.

Disadvantages of hard gelatine capsule:
Highly soluble salts [e.g., iodides, bromides, and chlorides] generally should not be dispensed in hard gelatine capsule. Their rapid release may cause gastric irritation. Filling equipment is slower than tableting.

Soft gelatine capsules: Solid dosage forms are becoming a popular dosage form for the administration of liquids, suspensions, pastes and dry powders in the dietary supplement industry and they differ from hard gelatine capsules in various terms[12].

A soft gel capsule is one piece, hermetically sealed soft gelatine shell containing a liquid, a suspension or semisolid referred to as fill. They are formed and filled and sealed in one continuous operations, preferably by the rotary die process. Depending on the polymer forming the shell, they can be sub divided into two categories, namely soft gelatine capsule and non-gelatine soft capsules. The majority of soft capsules are made from gelatine owing to its unique physical properties that make it an ideal excipient for the rotary die process. Other various components of soft gelatine capsules are given[13]

- Gelatine
- Glycerine or polyhydric alcohol
- Water or moisture
- Preservative
- Colorant
- Markings
- Opaquest
- Flavours may be added and up to 5% sucrose may be included for its sweetness and to produce a chewable shell.

Manufacturing of soft gelatine capsules:
It is manufactured by four methods. They are

- Plate process
- Rotary die process
- Accogel machine
- Bubble method

Rotary die process: The materials to be encapsulated flows by gravity. The gelatine sheets are feed on rolls contain small orifice hinded up with the die pocket of the die roll Two plasticized gelatine ribbons are continuously and simultaneously fed with the liquid or paste fill between the rollers of the rotary ide mechanism where the capsules are simultaneously filled, shaped, hermetically sealed and cut from the gelatine ribbon. The sealing of the capsule is achieved by mechanical pressure on the die rolls and the heating [37-47 C] of the ribbons by the wedge[14].

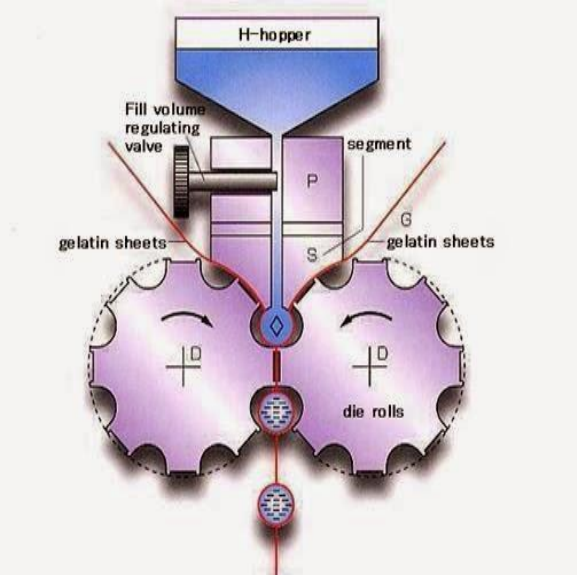


Plate process: Place the gelatine sheet over a die plate containing numerous die pockets. Application of vacuum to draw the sheet into the die pockets. Fills the pockets with the liquid or paste. Place another gelatine sheet over the filled pockets and sandwich under a die press where the capsules are formed and cut out[15].

Accogel capsule machine: It consists of mainly 3 parts:

- Measuring roll
- Die roll
- Sealing roll

As the measuring roll and die rolls rotate, the measured doses are transferred in to the gelatine linked pockets of the die roll. The continued rotation of the filled die converges with the rotating sealing roll where a second gelatine sheet is applied to form the other half of the capsule. Pressure developed between the die roll and sealing roll seals and cuts out the capsules[16].

Bubble method:
The globlex mark II capsulator produces truly seal less, one piece- soft gelatine capsules by a "bubble method". A concentric tube dispenser simultaneously discharges the molten gelatine from the outer annulus and the liquid content from the tube. By means of a pulsating pump mechanism, the liquids are discharged from the concentric tube orifice into a chilled-oil column as droplets that consists of a liquid medicament core within a molten gelatine envelope[17].

Advantages of soft gelatine capsules:

- Easy to administer
- Easy to manufacture
- Liquids can be encapsulated [non-water soluble] small to large sizes possible
- Elegance
- Portability
- Odour and taste masking
- Ready availability of drug hence faster action
- Specialised dosage forms can be made

E.g. chewable, extended release, cap tabs etc. Can be used for ophthalmic preparations e.g. aplicaps, vaginal or rectal suppositories.

Disadvantages of soft gelatine capsules:

- Water soluble materials are difficult to incorporate
- Highly moisture sensitive efflorescent materials cannot be incorporated, they may cause softening /leaching
- Deliquescent materials cannot be in corporate, they may cause hardening or brittle capsules.

Difference between hard gelatine and soft gelatine capsule[18]:

Characteristics	**Hard gelatine capsule**	**Soft gelatine capsule**
Small batches manufacturing ability	**Yes**	**No**
Scale up	Simple and in house	Large quantities of drug substances required and must be outscored.
Fill temperature	Max.**70^{0}c**	Max.35^{0}c
Plasticizers in shell	No	Yes

Risk of drug migration	Low	High for drug soluble in plasticizer
Permeability of shell to oxygen	Low	High due to plasticizer and varies with moisture content
Sensitivity to heat and humidity	Low	High due to plasticizers
Hygroscopic excipients	High concentration must be avoided	Can be tolerated due to presence of plasticizer in shell
Capsule dimension	Constant	May vary.

Evaluation tests for capsules:

- Content uniformity
- Disintegration test
- Weight variation test
- Dissolution test
- Moisture permeation test

Content uniformity: The amount of active ingredient should be within in the range of 85% to 115% of the label amount for 9 of 10 capsules, with no unit outside the range of 70% to 125% of label amount[20].

Weight variation test: 20 capsules are taken at random and weighed. Their average weight is calculated, then each capsule is weighed individually and their weight is noted. The capsule passes the test if the weight of individual capsule falls within 90-110% of the average weight[21].

Disintegration test: Place 1 capsule in each of the 6 tubes of the basket and suspend the assembly in water at $37^0C\pm2^0C$, which is repeatedly immersed 30 times per minute. The capsules pass the test if no residue of drug or other than fragments of shell remains No.10 mesh screen of the tubes[22].

Moisture permeation test: According to USP the unit dose container is packed along with dehydrated pellets, which have the property of changing colour in the presence of moisture. The weight of test capsule is compared with the under-test capsules. Difference in weights gives the amount of moisture absorbed[23].

Dissolution test for capsules: Place 1000ml of water having a temperature of 36.5^0 to 37.5^0in to the vessel. Place specified number of capsules in basket 7 adjust the speed to 100 rpm. Withdraw the required volume for every 10-min time interval. Filter and determine the amount of active ingredient. The sample passes the test if the amount of active ingredients in the solution is not less than 70 % of the standard amount[24].

Storage, stability and packing of capsules:

Capsules should be packed in well closed glass or plastic containers and stored at temperature not exceeding 30 ^{0}C. Capsules are individually enclosing in strip and blister packing. In strip packing the capsule is hermetically sealed within the strips of an aluminium or plastic film. In blister packs, a press forces the capsule through the backing strip.

Capsules having a larger shelf life in unopened glass bottles than in strip pack and but this is reversed[25].

Storage: Storage for hard gelatine capsules should be 24^0 to28^0C.The moisture content exceeding between 12-15%. When the capsules are stored at high humidity, it may absorb the moisture content and it may lose it shape.at low humidity they loss the water from the shell and they become brittle.

The ambient humidity and temperature levels for storage of hard gelatine capsules are as follows,

Minimum=35%RH, 15^0c
Best possible =50%RH, 200c
Maximum=65%RH, 25^0c

Soft gelatine capsules already being high in water content it requires extra caution during storage. They should be stored in air-conditioned area where humidity does not exceed 45%RH at 21-24^0c[26].

Stability: Stability is defined as ability of dosage form to maintain its physical, chemical, microbiological, therapeutic and toxicological identification right from the date of formulation and packing until its therapeutic action[27].

Accelerated stability tests for capsules are performed to determine the integrity of gelatine capsule shell and for determination of shelf life of capsules. The capsule shells must be equilibrated to known atmospheric conditions with relative humidity of about 20-30% at 21-24^0c. The capsules must be used for further tests only after re-established the equilibrium at room temperature.

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