Chapter 03: Capsules, soft capsules and biopharmaceutical control of solid oral forms

01. hard-shell capsule or gelatin capsule:

A hard capsule, or hard-shell capsule, refers to a solid dosage form of medication that is swallowed orally. It consists of a hard, hollow shell that contains the active ingredient.

The capsule consists of two parts, the head and the body, which are cylindrical, open at one end and have a hemispherical base that fits together.

The shell is most often made from a mixture of gelatin, derived from beef bones or pig skin, or even fish, and glycerol, which serves as a plasticizer and reduces its hardness. Following the problem of mad cow disease, new materials for the shell, such as cellulose compounds, have emerged. However, the higher cost of these and, on the other hand, the use of gelatin manufacturing methods guaranteeing the absence of risk of bovine spongiform encephalitis, mean that cellulose-based capsules are rarely used; some drug manufacturers who had adopted them have also returned to conventional capsules.

The shell may also contain other elements such as colorants, antibacterial treatments, disintegrants, lubricants, surface treatments, etc. Finally, the shell may be printed, generally with the dosage of the medication.

The contents must not cause deterioration of the shell. However, digestive juices break down the shell and cause the contents to be released.

The contents of the capsule are the active component of the medication and may be the active ingredient alone, a powder containing one or more excipients and an active ingredient, or microgranules. Microgranules often have a specific function: gastro-resistance, prolonged release, etc.

The contents are introduced into one of the two parts, then the second is fitted over the first. The closure can be reinforced by appropriate means: welding, etc.

Capsules are one of the easiest pharmaceutical forms to produce, which explains their abundance. They are almost always developed as the first dosage form for solid oral dosage forms during the development of a new drug for preclinical and Phase 1 ("first in human") and Phase 2 clinical trials. However, their large-scale production is slower and more tedious than other solid oral dosage forms such as tablets, leading a number of manufacturers to change dosage forms during clinical studies.

In the United States, the combination of colors and markings on the capsule allows the identification of the drug.

a. Main Features

• Composition: A hard shell composed of two interlocking parts that contain the active ingredient.

• Content: Can be powder, granules, or liquid.

• Advantages:

o Easy to swallow thanks to the smooth shell.

o Protects the active ingredient from moisture and environmental interactions.

o Masks unpleasant tastes and odors.

• Capsule Types:

o Extended-release: Releases the active ingredient over a period of 12 to 24 hours, allowing for less frequent dosing.

o Gastro-resistant: Resists stomach acid and dissolves in the small intestine.

b. Preparing the Capsule Form:

Preparing a capsule involves mixing powders (active ingredient + excipients such as binders or diluents), packing them into a gelatin (or cellulose/pullulan) shell using a capsule filler, and then closing the capsule. The goal is to ensure a homogeneous mixture and precise dosage for each capsule.

1. Mixing the Powders:

• Mix the active ingredient with binders, diluents, and/or disintegrants to ensure proper shaping and homogeneity.

• Use a colored marker to verify the mixture.

• Crush and sift the powders to obtain a fine and uniform particle size.

2. Filling the Capsules:

• Place both parts (the short base and the long base) in a capsule filler.

• Fill the long part with the powder using a tamping accessory.

Pack the powder several times to completely fill the capsule.

• Check the consistency of the preparation.

3. Closing:

• Place the long and short ends together to close the capsule.

• Weigh the capsules to check the average weight of the plant per capsule.

2. Softgel Capsule:

Consisting of a soft gelatin shell, generally oblong in shape, designed to be dissolved by digestive juices and containing one or more active ingredients, most often in liquid or oil form.

- Softgel capsules are dosage forms widely used in the pharmaceutical, nutraceutical, and cosmetic industries due to their ability to encapsulate liquids, for better absorption of the active ingredient.

a. Main characteristic:

Softgel capsules have a single-piece shell, thicker but more elastic than that of gelatin capsules. The contents are liquid (solution, suspension, or emulsion) or pasty. The softgel capsule is manufactured during filling.

b. Preparation of the soft capsule form:

In an industrial context, the preparation of a soft capsule involves manufacturing a gelatin shell and filling it with a liquid or semi-solid mixture. The process includes preparing the gelatin, creating two thin sheets of gelatin, encapsulating them with the product, followed by drying, quality control, and packaging steps.

1. Gelatin Preparation

• Gelatin is prepared by dissolving it in water and adding plasticizers (such as glycerin or sorbitol), opacifiers, and colorants.

• This mixture is heated and homogenized to obtain a viscous and homogeneous mass.

2. Encapsulation

• The gelatin mass is stretched into two thin sheets.

• These sheets pass through a rotary die encapsulation machine.

• Simultaneously, the product to be encapsulated (liquid, suspension, or oil blend) is injected between the two gelatin sheets.

• The injection pressure and the rotation of the dies form, seal, and cut the soft capsules.

3. Finishing and Packaging

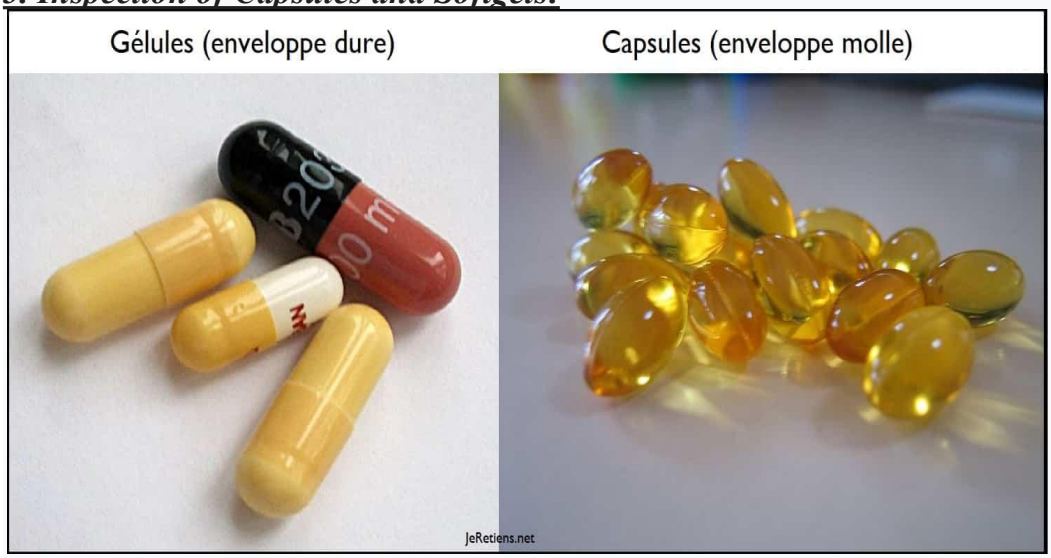
• Drying: The capsules are dried in a controlled environment to adjust their hardness and stability, usually in several stages over an extended period.

Quality Control: Capsules are inspected for defects (cracks, improper filling, etc.), either manually or mechanically.

• Printing: Capsules can be printed to include the product name or dosage information (optional).

• Packaging: Finally, the capsules are packaged in blister packs or bottles, with labels and tamper-evident seals, in accordance with regulations.

3. Inspection of Capsules and Softgels:



The inspection of softgel capsules and gelcaps includes physicochemical quality tests (hardness, dissolution, mass, content), visual inspections (appearance defects, contamination), microbiological, and stability tests. Verifying filling uniformity and compliance with regulatory standards are also essential to ensure the safety and efficacy of the final product.

Inspection Scope

• Uniformity of mass and content: The weight of each capsule is checked. This is done by weighing the entire capsule, emptying it, and weighing the empty shell, and calculating the weight of the contents.

• Physicochemical tests:

o Hardness: Devices such as the Gelomat measure the compression force required to deform the capsule to ensure its integrity is sufficient to withstand handling.

Dissolution and Disintegration: These tests determine whether the capsules disintegrate properly and whether the active ingredient is released according to the expected conditions.

• Visual and Appearance Checks:

Visual Inspection: Inspectors or automated machines look for defects such as cracks, chips, deformations, or misprints. Camera-equipped machines can also be used to automatically sort non-compliant capsules.

Cleaning and Polishing: Capsules are cleaned to remove surface residue and excipients. This may involve tumbling or washing with a solvent.

• Safety Checks:

Microbiological: Tests are performed to detect any potential microbial contamination.

Stability: The stability of the active ingredients is assessed over time.

Importance of Control

Guarantee safety: Testing ensures that the capsules do not contain any defects that could harm the consumer's health.

• Ensure efficacy: Dissolution and disintegration tests ensure that the medication is released correctly.

• Comply with standards: Testing processes ensure that products comply with current official and regulatory standards.

• Preserve the manufacturer's reputation: Only a high-quality product can be marketed, thus ensuring customer satisfaction and the manufacturer's positive image.

3. Biopharmaceutical testing of solid dosage forms:

Biopharmaceutical testing of solid dosage forms aims to ensure that the medication is optimally released and properly absorbed by the body. It includes tests such as disintegration (to verify dissolution) and dissolution (to measure the release rate of the active ingredient). Other important controls are breaking strength, friability (for tablets), mass uniformity and content uniformity.

Disintegration and Disintegration Tests

• Disintegration: A test to verify that the tablet or capsule breaks down in a liquid medium within a specified time.

• Dissolution: A test that measures the amount of active ingredient released over time. For rapid-release forms, dissolution must be complete in less than 15 minutes, according to standards.

• Modified-release testing: For extended- or delayed-release forms, the tests are more complex to ensure that the active ingredient is released over the expected time.

Physical Tests

• Mass Uniformity: Verifies that the tablets or capsules have a constant mass, which is crucial for dosing accuracy.

• Friability: Measures the fragility of uncoated tablets, which must withstand handling and shipping.

• Breaking Strength: Evaluates the strength of tablets. Breaking strength is a measure of the force required to break the tablet.

Content Controls

• Content Uniformity: Ensures that each dosage unit contains the correct amount of active ingredient.

Other Important Tests

• Microbiological tests: Verify the absence of contamination by bacteria, fungi, or other microorganisms.

• Stability tests: Evaluate the drug's ability to maintain its physical and chemical characteristics over its shelf life.

• Form-specific conformity tests: Additional tests may be required for special forms such as enteric-coated tablets or effervescent tablets.