

# Industrial Pharmacy-I

## Unit III

# Capsules

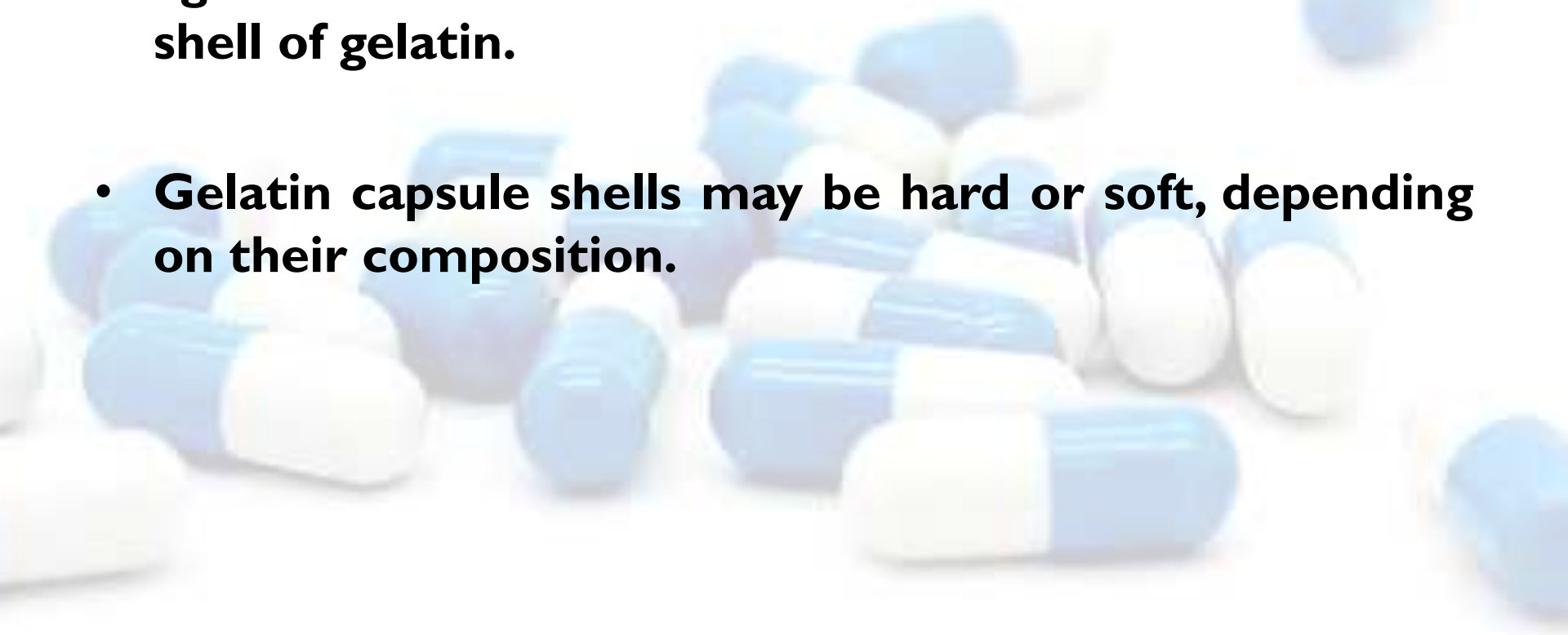
**Prof. S. S. Raut**

**K. K. Wagh college of Pharmacy, Nashik**



# Introduction

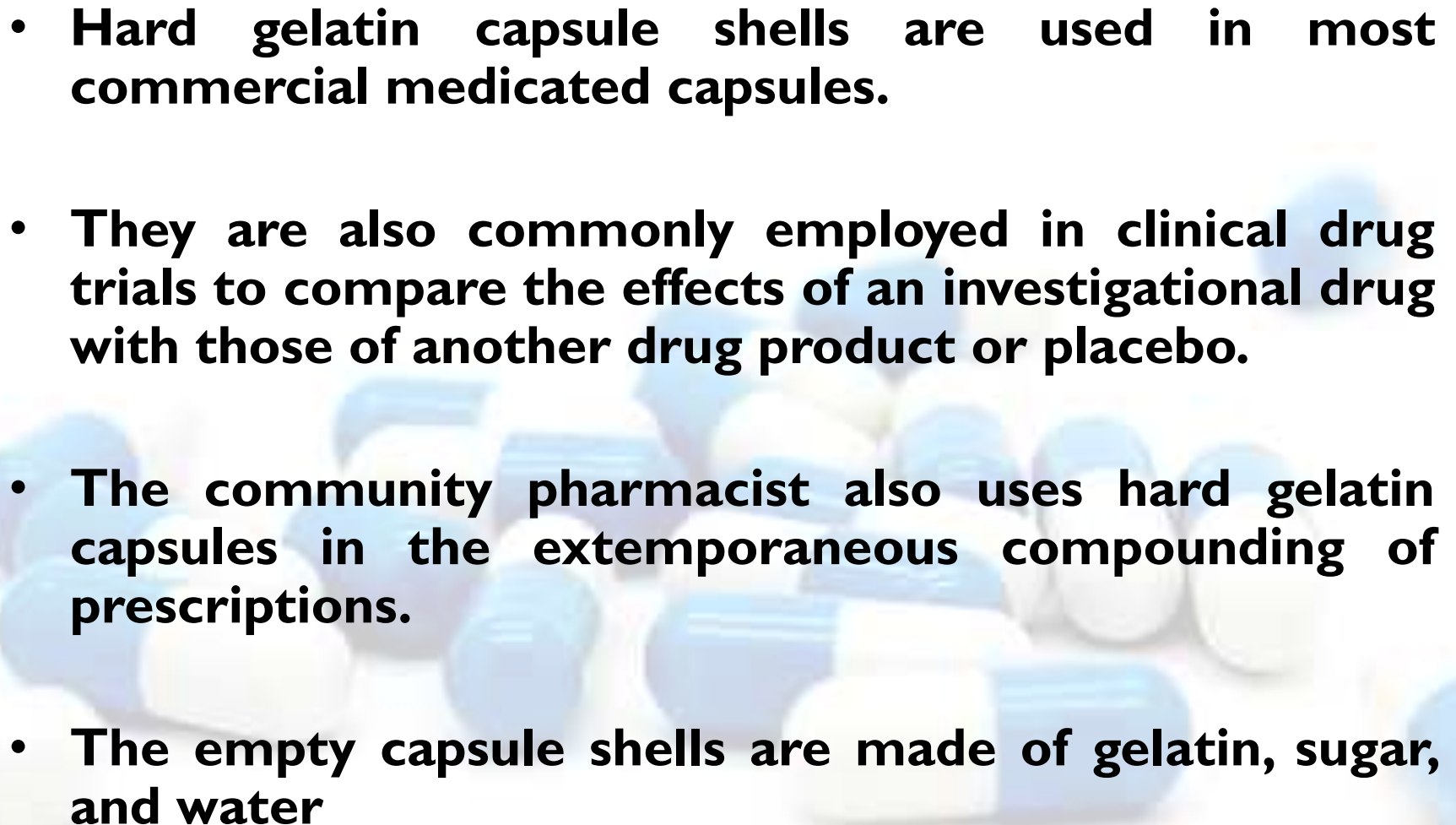
- **Capsules are solid dosage forms in which medicinal agents and/or inert substances are enclosed in a small shell of gelatin.**
- **Gelatin capsule shells may be hard or soft, depending on their composition.**



- **Most filled capsules are intended to be swallowed whole.**
- **However, it is fairly common in hospitals and extended care facilities for a caregiver to open capsules or crush tablets to mix with food or drink, especially for children or other patients unable to swallow solid dosage forms.**
- **This should be done only with the concurrence of the pharmacist, since the drug release characteristics of certain dosage forms can be altered and can adversely affect the patient's welfare.**

# Advantages of capsules for oral administration

- ✓ **Easy to swallow due to their smooth and slippery nature.**
- ✓ **Easy to handle and carry.**
- ✓ **Can mask the unpleasant taste, colour and odour of drug using tasteless shell.**
- ✓ **Better bioavailability than tablets and faster onset of action than tablets.**
- ✓ **The shells are physiologically inert and easily and quickly digested in the gastrointestinal tract.**
- ✓ **The shells can be opacified (with  $\text{TiO}_2$ ) or coloured, to give protection from light.**

- **Hard gelatin capsule shells are used in most commercial medicated capsules.**
  - **They are also commonly employed in clinical drug trials to compare the effects of an investigational drug with those of another drug product or placebo.**
  - **The community pharmacist also uses hard gelatin capsules in the extemporaneous compounding of prescriptions.**
  - **The empty capsule shells are made of gelatin, sugar, and water**
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- **Empty capsule shells can be clear, colorless, and essentially tasteless.**
- **They may be colored with various FD&C and D&C dyes and made opaque by adding agents such as titanium dioxide.**
- **Most commercially available medicated capsules contain combinations of colorants and opaquants to make them distinctive, many with caps and bodies of different colors.**

- **Gelatin is obtained by the partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals.**
- **In commerce, it is available in the form of a fine powder, a coarse powder, shreds, flakes, or sheets.**

### **Types of gelatin -Type A & Type B**

- **Gelatin is soluble in hot water and in warm gastric fluid; a gelatin capsule rapidly dissolves and exposes its contents.**
- **Gelatin, being a protein, is digested by proteolytic enzymes and absorbed.**

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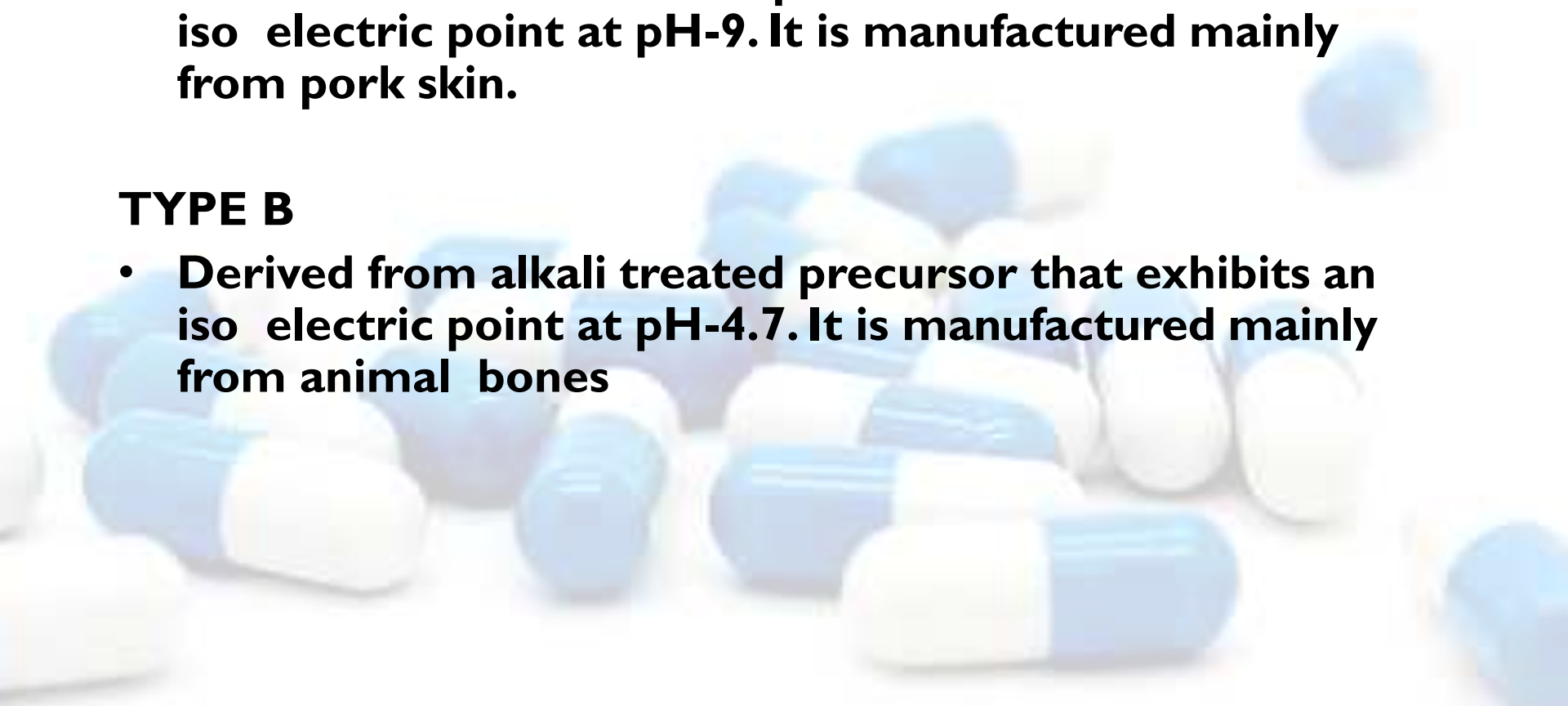
# There are two basic types of gelatin

## **TYPE A**

- **Derived from acid treated precursor that exhibits an iso electric point at pH-9. It is manufactured mainly from pork skin.**

## **TYPE B**

- **Derived from alkali treated precursor that exhibits an iso electric point at pH-4.7. It is manufactured mainly from animal bones**



# Properties of gelatin

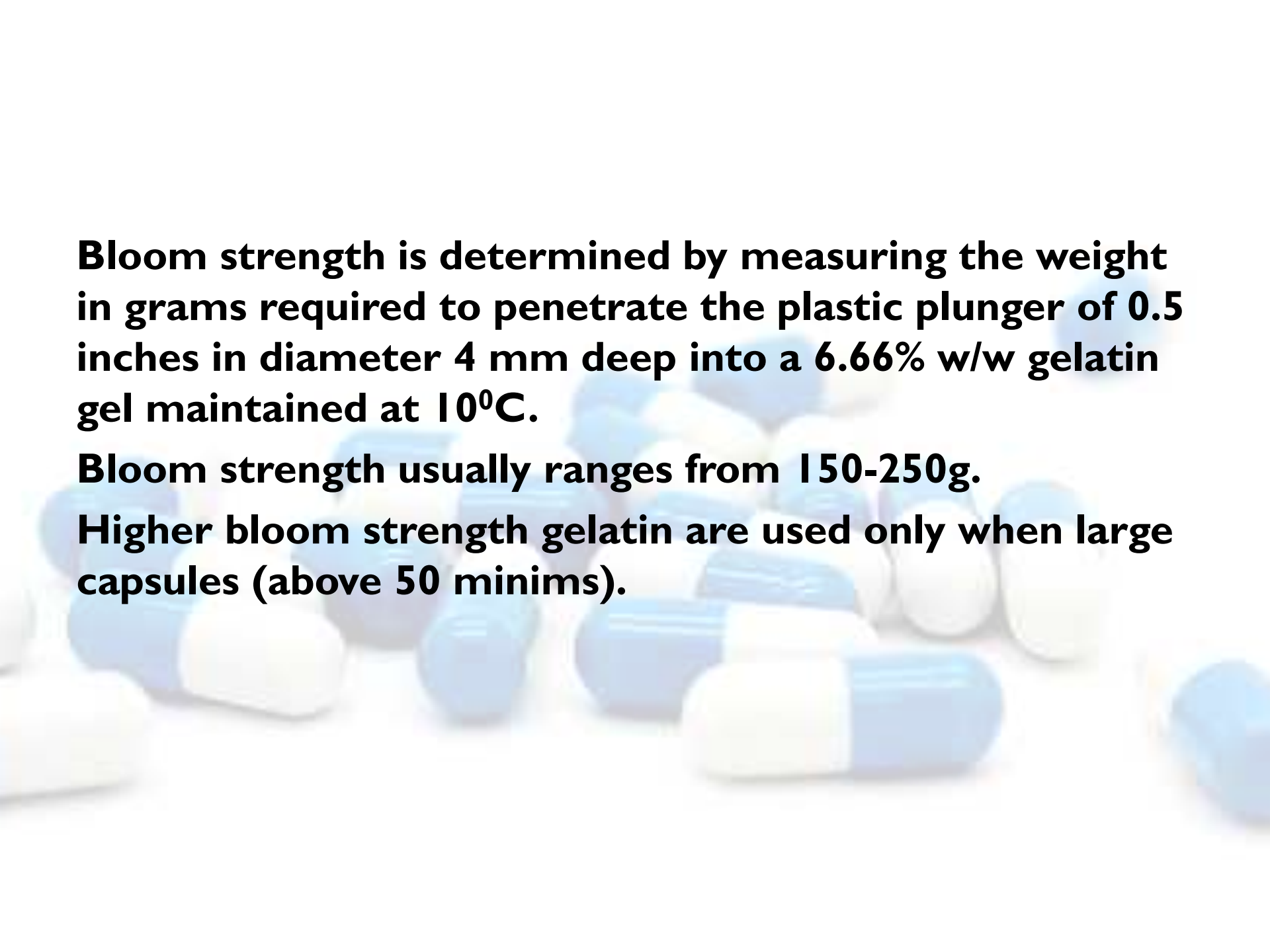
## Bloom strength

Physical stability and strength of the capsule shell is directly proportional to bloom strength.

Bloom strength is defined as the measure of the cohesive strength of cross linking between the gelatin molecules.

Bloom strength is proportional to molecular weight of the gelatin.

Whereas cost of gelatin is directly proportional to the bloom strength.



**Bloom strength is determined by measuring the weight in grams required to penetrate the plastic plunger of 0.5 inches in diameter 4 mm deep into a 6.66% w/w gelatin gel maintained at 10<sup>0</sup>C.**

**Bloom strength usually ranges from 150-250g.**

**Higher bloom strength gelatin are used only when large capsules (above 50 minims).**

- **Viscosity**

**Viscosity of gelatin is measure of a molecular chain length which is determined on a 6.66% W/V concentration of gelatin in water at 60<sup>0</sup>C.**

**Viscosity is an important parameter which determines the manufacturing of the gelatin film to produce a firm non tacky, non brittle pharmaceutically elegant product.**


**The viscosity range of gelatin can vary from 25-40 millipoise.**

**Iron content:** Is always present in the raw gelatin, and its concentration usually depends on the iron content of the large quantities of water used in its manufacture.

**Gelatins used in the manufacture of soft gelatin capsules should not contain more than 15 ppm of this element, because of its effect on Food, Drug, and Cosmetic (FD&C) certified dyes and its possible color reactions with organic compounds.**

# Composition of gelatin shell

- 1. Gelatin**
- 2. Plasticizers-**are added to gelatin mass to confer softness, hardness, elasticity and thickness to the capsule shell.  
e.g. **Glycerine, sorbitol, Propylene glycol**
- 3. Water-** water is an essential component in the preparation of gelatin mass.
- 4. Colorants-** Certain **FD&C** and **D&C** approved dyes, pigments and lakes are added to the gelatin mass.
- 5. Opacifying agents-** used to minimize transparency and to make capsule shell opaque. E.g. **Titanium oxide**

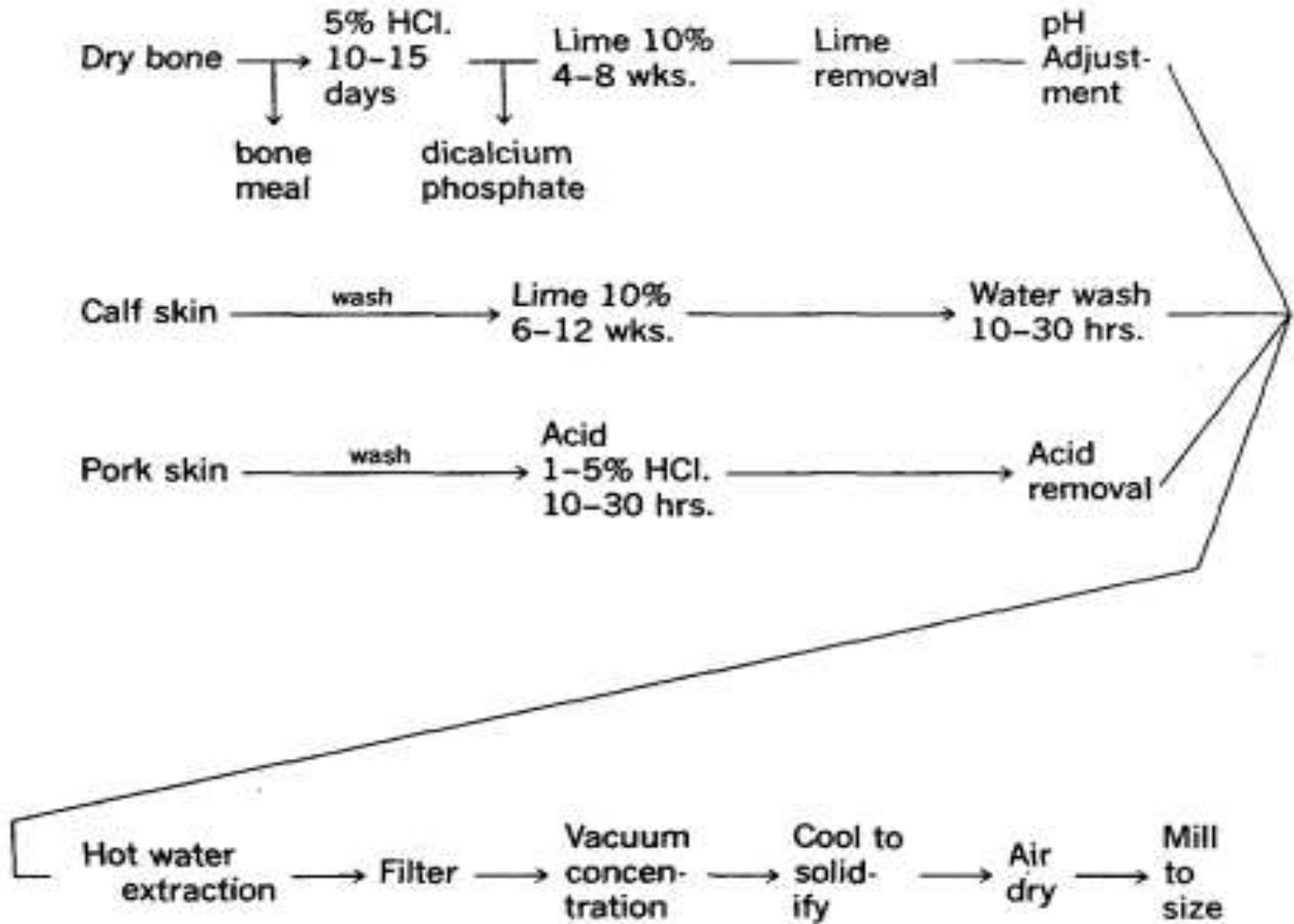
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- 6. Preservatives-** to inhibit microbial growth and to impart stability to capsule shell Methyl paraben, propyl paraben
  - 7. Flavours-**essential oil, vanillin
  - 8. Sugars-** These are used in chewable gelatin capsules to impart sweet taste and to mask objectionable taste of other ingredients. Added rarely. e.g. Sucrose
  - 9. Acids-** Fumaric acid is added to prevent aldehydic tanning of gelatin.

**TABLE 13-2.** Typical Shell "Hardness" Ratios and Their Uses

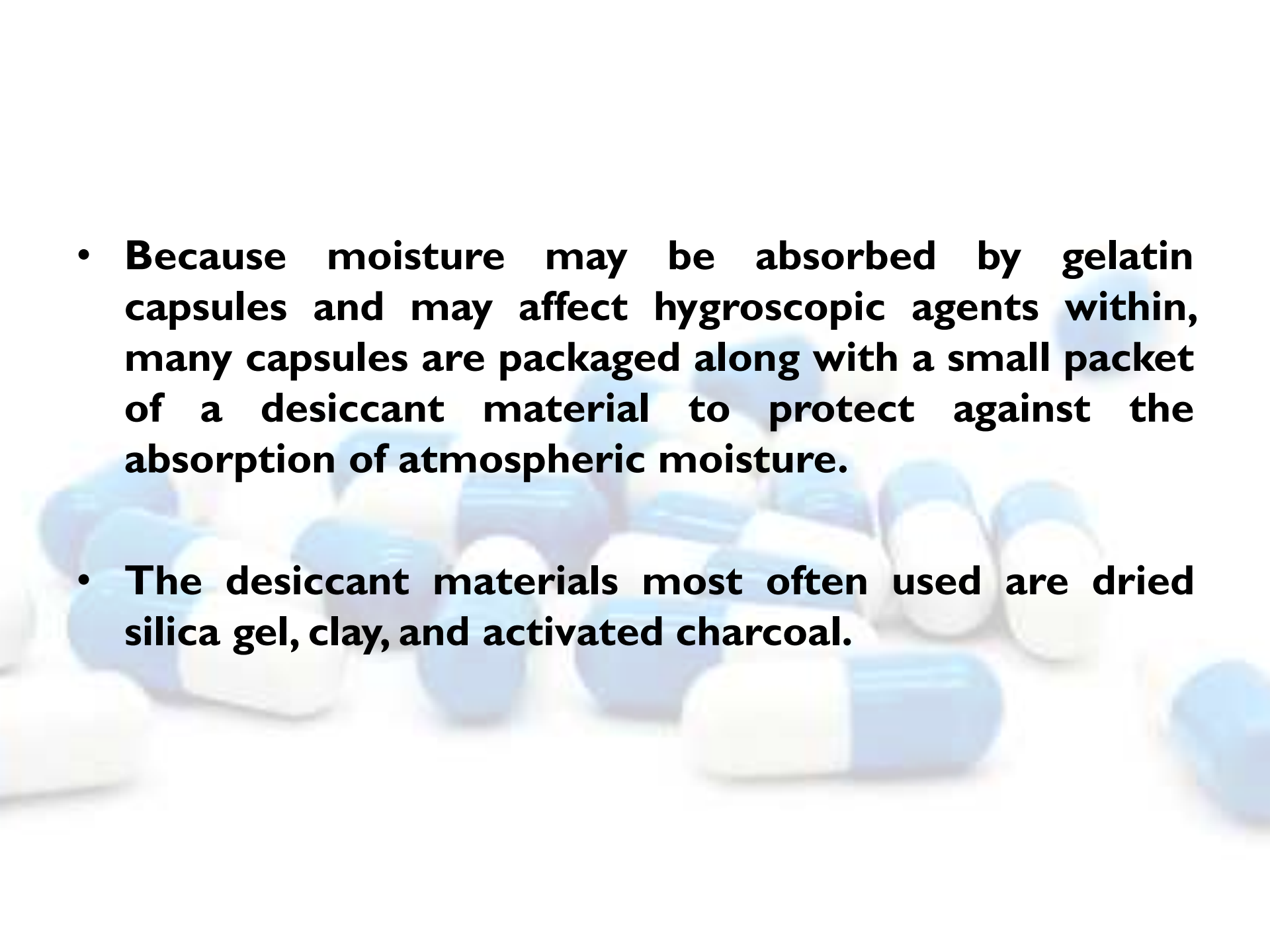
<i>Hardness</i>	<i>Ratio Dry Glycerin/ Dry Gelatin</i>	<i>Usage</i>
Hard	0.4/1	Oral, oil-based, or shell-softening products and those destined primarily for <u>hot, humid</u> areas.
Medium	0.6/1	Oral, tube, vaginal oil-based, water-miscible-based, or shell-hardening products and those destined primarily for <u>temperate</u> areas.
Soft	0.8/1	Tube, vaginal, water-miscible-based or shell-hardening products and those destined primarily for <u>cold, dry</u> areas.



# Preparation of Gelatin



- **Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist. Normally, hard gelatin capsules contain 13% to 16% of moisture.**
- **However, if stored in an environment of high humidity, additional moisture is absorbed by the capsules, and they may become distorted and lose their rigid shape.**
- **In an environment of extreme dryness, some of the moisture normally present in the gelatin capsules is lost, and the capsules may become brittle and crumble when handled.**
- **Therefore, it is desirable to maintain hard gelatin capsules in an environment free from excessive humidity or dryness.**

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- **Because moisture may be absorbed by gelatin capsules and may affect hygroscopic agents within, many capsules are packaged along with a small packet of a desiccant material to protect against the absorption of atmospheric moisture.**
  - **The desiccant materials most often used are dried silica gel, clay, and activated charcoal.**

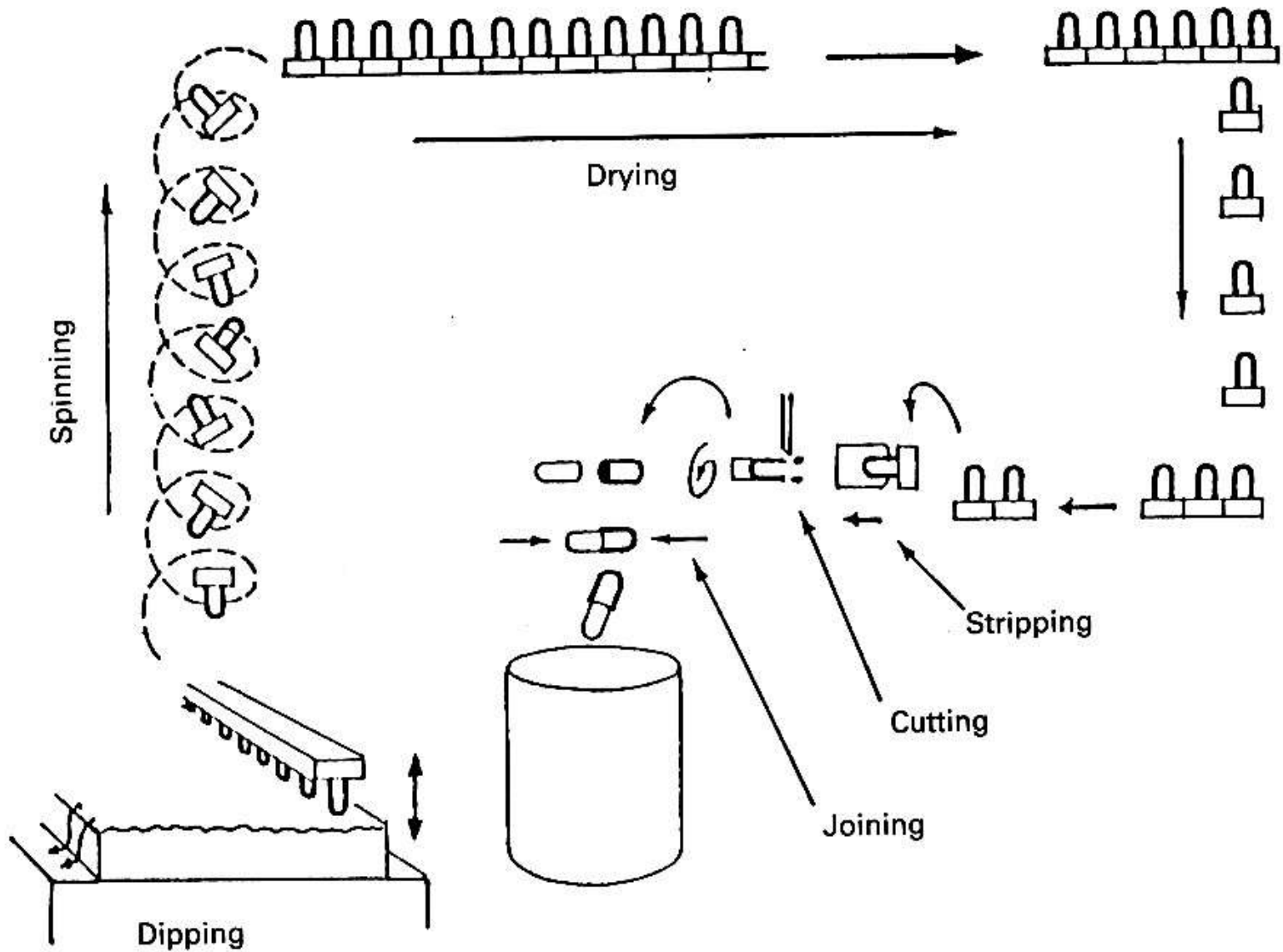
# Manufacture of empty gelatin capsules

Steps involved in making empty gelatin capsules...

1. **Dipping**
2. **Spinning**
3. **Drying**
4. **Stripping**
5. **Trimming and Joining**
6. **Polishing**

<https://www.youtube.com/watch?v=tAGvds2kH7s>

# Manufacture of empty gelatin capsules



## **Dipping:**

**Pairs of the stainless steel pins are dipped into the dipping solution to simultaneously form the caps and bodies.**

**The dipping solution is maintained at a temperature of about 50<sup>0</sup>C in a heated, jacketed dipping pan.**

## **Spinning:**

**The pins are rotated to distribute the gelatin over the pins uniformly and to avoid the formation of a bead at the capsule ends.**

## **Drying :**

**The gelatin is dried by a blast of cool air to form a hard shells.**

**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.**

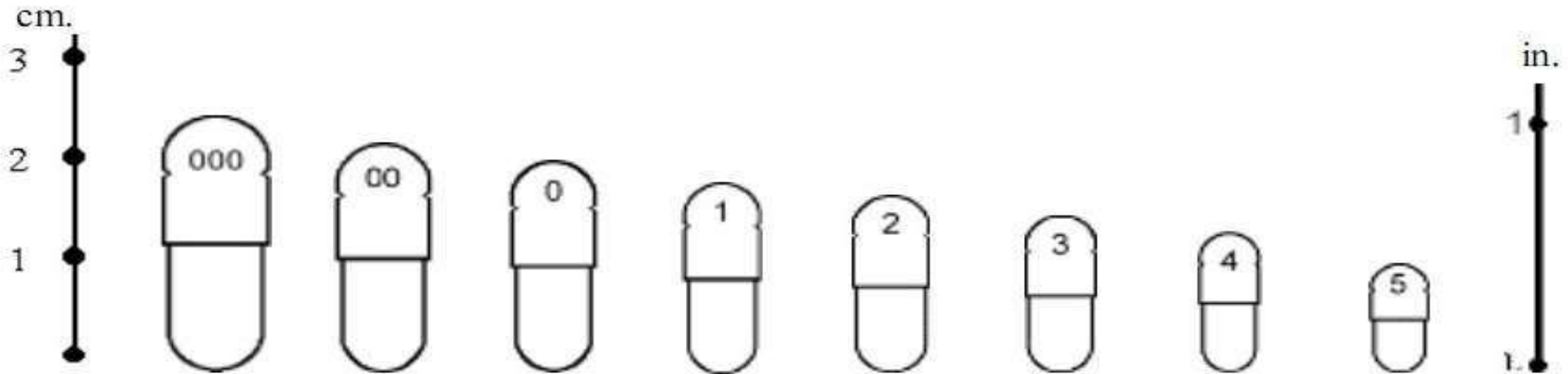
**After trimming to the right length, the cap and body portion are joined and ejected from the machine.**



## Size of capsules

<b>Size</b>	<b>Volume in ml</b>	<b>Size in mm (length)</b>	<b>Diameter</b>
<b>000</b>	<b>1.37</b>	<b>26.3</b>	<b>9.9</b>
<b>00</b>	<b>0.95</b>	<b>23.7</b>	<b>8.5</b>
<b>0</b>	<b>0.68</b>	<b>21.8</b>	<b>7.6</b>
<b>1</b>	<b>0.50</b>	<b>19.2</b>	<b>6.9</b>
<b>2</b>	<b>0.37</b>	<b>18.3</b>	<b>6.3</b>
<b>3</b>	<b>0.30</b>	<b>15.3</b>	<b>5.8</b>
<b>4</b>	<b>0.21</b>	<b>14.7</b>	<b>5.3</b>
<b>5</b>	<b>0.15</b>	<b>11.9</b>	<b>4.9</b>

## Shapes of capsule



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

**For human use, empty capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available.**

**Larger capsules are available for veterinary use.**

# Preparation of filled hard gelatin capsules

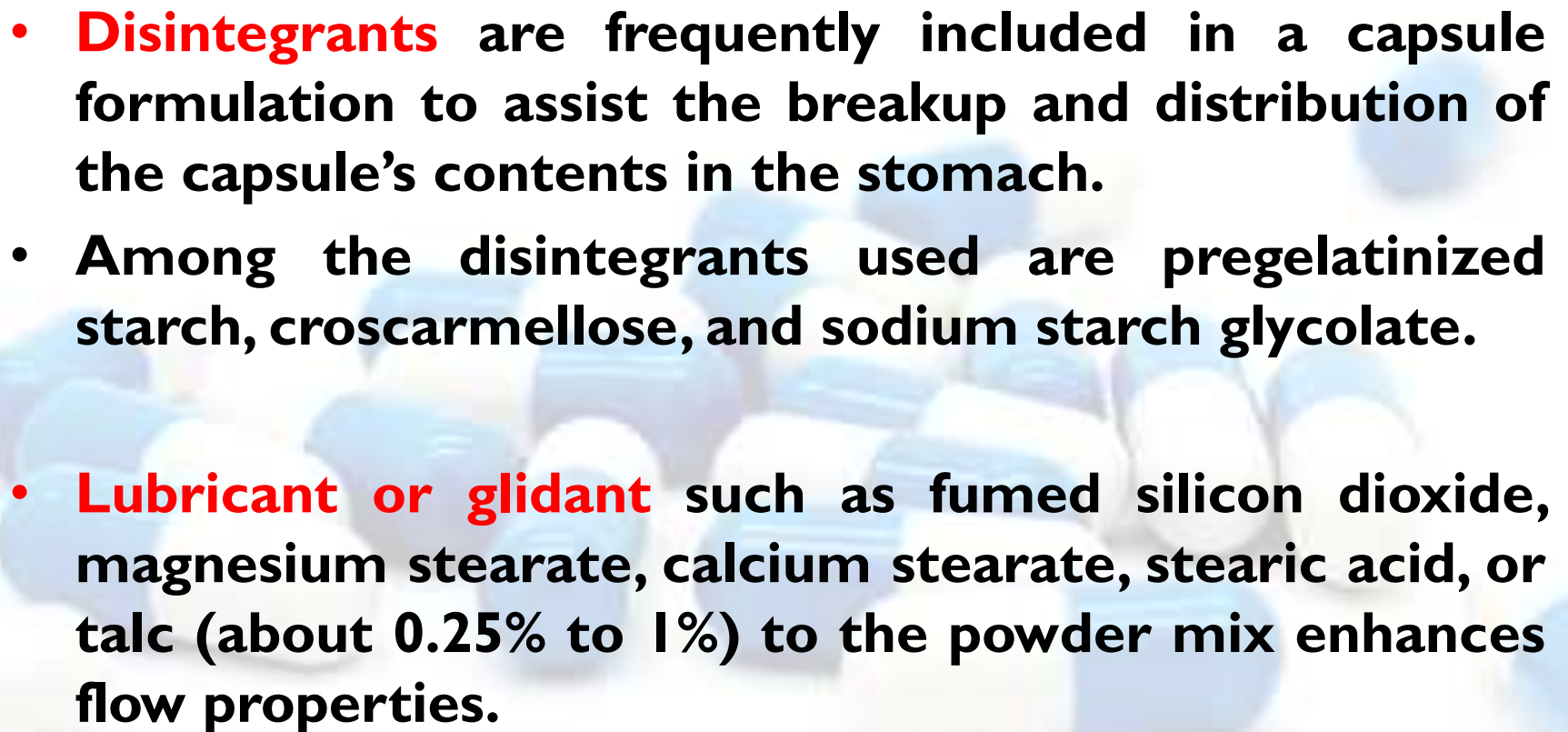
The large-scale or small-scale preparation of filled hard gelatin capsules is divided into the following general steps.

1. Developing and preparing the formulation and selecting the capsule size
2. Filling the capsule shells
3. Capsule sealing (optional)
4. Cleaning and polishing the filled capsules

# Developing the formulation and selecting the capsule size

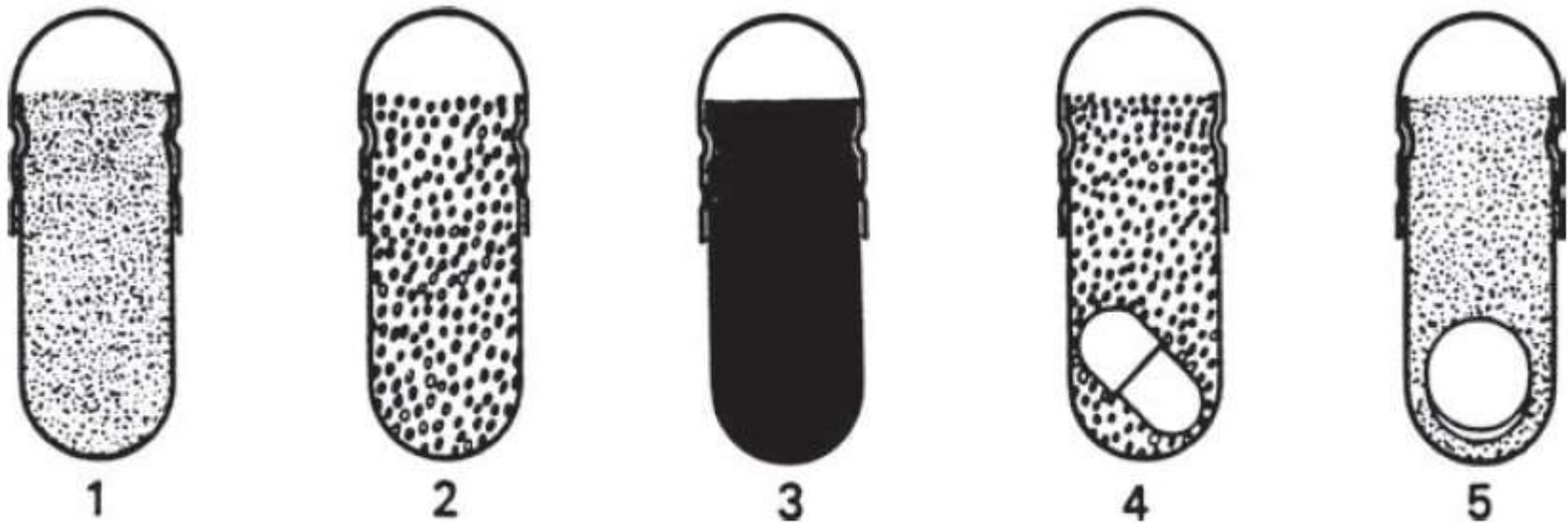
## Additives

- **A diluent or filler** may be added to the formulation to produce the proper capsule fill volume.
- **Lactose, microcrystalline cellulose, and starch** are commonly used for this purpose.
- **In addition to providing bulk, these materials often provide cohesion to the powders, which is beneficial in the transfer of the powder blend into capsule shells.**

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- **Disintegrants** are frequently included in a capsule formulation to assist the breakup and distribution of the capsule's contents in the stomach.
  - Among the disintegrants used are pregelatinized starch, croscarmellose, and sodium starch glycolate.
  - **Lubricant or glidant** such as fumed silicon dioxide, magnesium stearate, calcium stearate, stearic acid, or talc (about 0.25% to 1%) to the powder mix enhances flow properties.

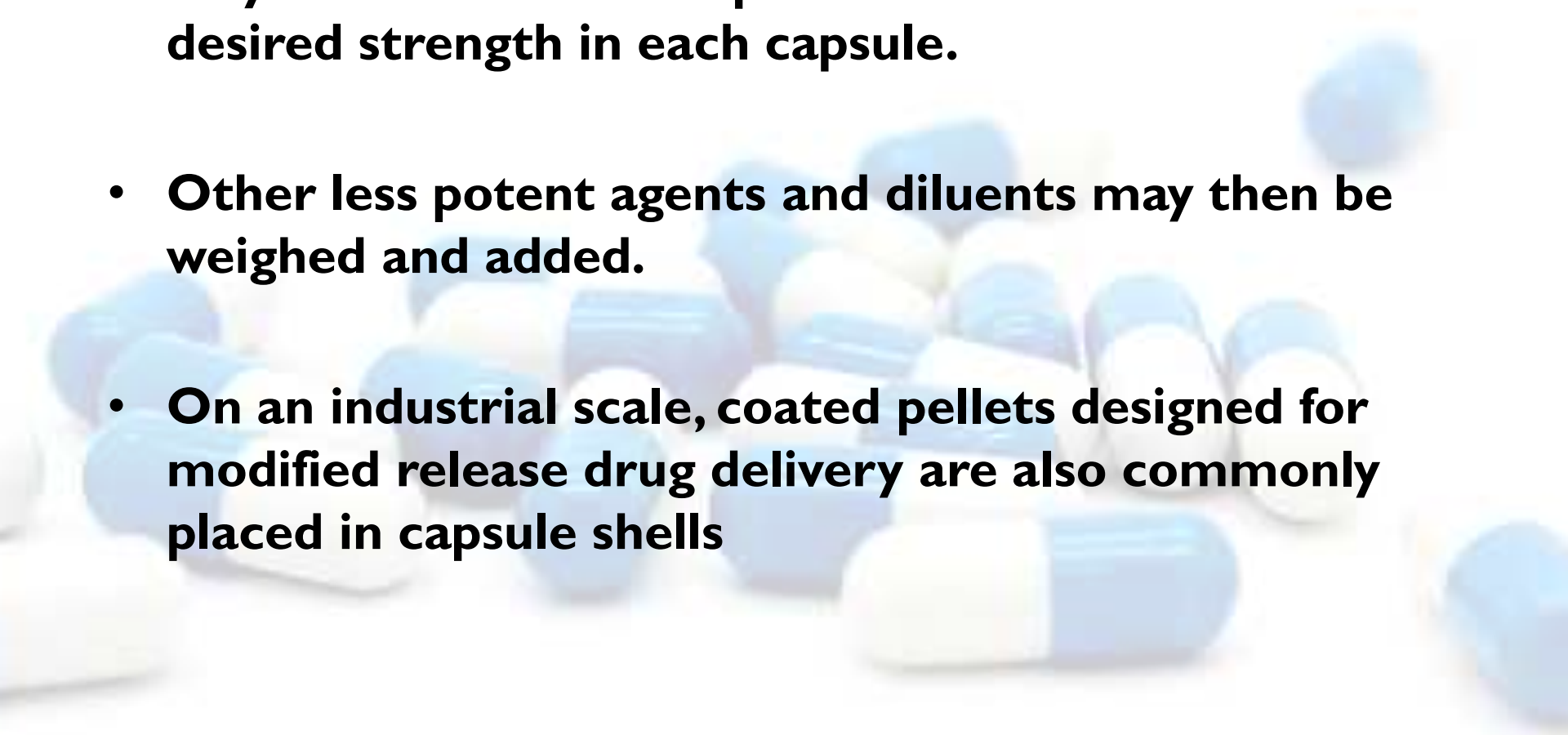
- When magnesium stearate is used as the **lubricant**, the water proofing characteristics of this water-insoluble material can retard penetration by the gastrointestinal fluids and delay drug dissolution and absorption.
- **Surface-active agent**, such as sodium lauryl sulfate, is used to facilitate wetting by the gastrointestinal fluids to overcome the problem
  - **Hydrophilic SAA-** Sodium docusate SLS, Sodium stearate
  - **Lipophilic SAA-** Glycery monostearate
- **Protective Sorbent** –to retard moisture adsorption by hygroscopic agents
- **Anti-dusting agents** –dusting of potent drug may cause health complications to operators
- Any FDA approved edible oil commonly used as anti-dusting agents

- **Inserting tablets or small capsules into capsules is sometimes useful in the commercial production of capsules and in a pharmacist's extemporaneous preparation of capsules.**
- **This may be done to separate chemically incompatible agents or to add premeasured amounts of potent drug substances.**



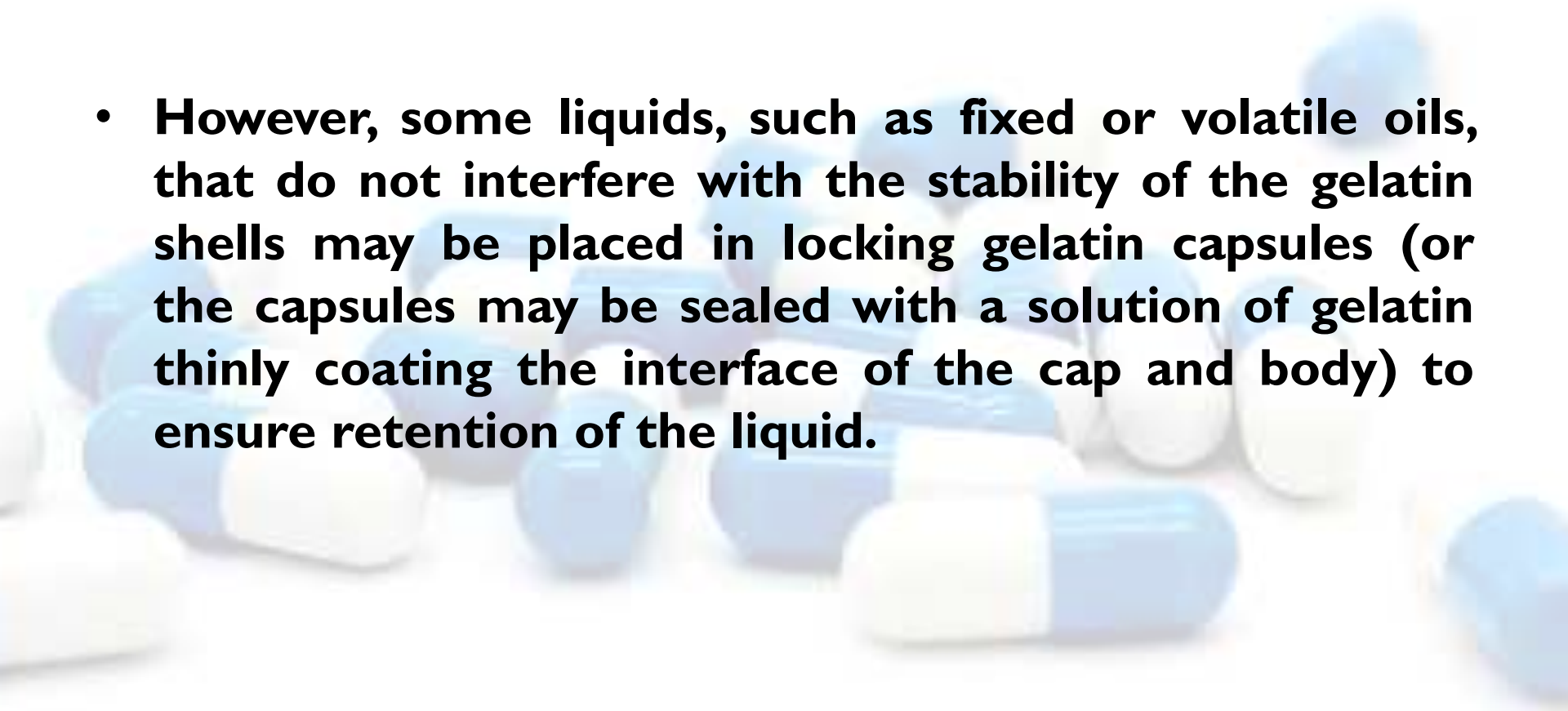
Examples of fill in hard gelatin capsules. 1, powder or granulate; 2, pellet mixture; 3, paste; 4, capsule; and 5, tablet. (Courtesy of Capsugel Division, Warner-Lambert.)

- **Rather than weighing a potent drug, a pharmacist may choose to insert a prefabricated tablet of the desired strength in each capsule.**
- **Other less potent agents and diluents may then be weighed and added.**
- **On an industrial scale, coated pellets designed for modified release drug delivery are also commonly placed in capsule shells**





- **Gelatin capsules are unsuitable for aqueous liquids because water softens gelatin and distorts the capsules, resulting in leakage of the contents.**
- **However, some liquids, such as fixed or volatile oils, that do not interfere with the stability of the gelatin shells may be placed in locking gelatin capsules (or the capsules may be sealed with a solution of gelatin thinly coating the interface of the cap and body) to ensure retention of the liquid.**



- **Rather than placing a liquid as such in a capsule, the liquid may be mixed with an inert powder to make a wet mass or paste, which may then be placed in capsules in the usual manner.**
- **Eutectic mixtures of drugs, or mixtures of agents that have a propensity to liquefy when admixed, may be mixed with a diluent or absorbent such as magnesium carbonate, kaolin, or light magnesium oxide to separate the interacting agents and to absorb any liquefied material that may form.**

## The Feton capsule- filling machine.

**A.** With empty capsules in the loader tray, the tray placed on top of the filler unit.

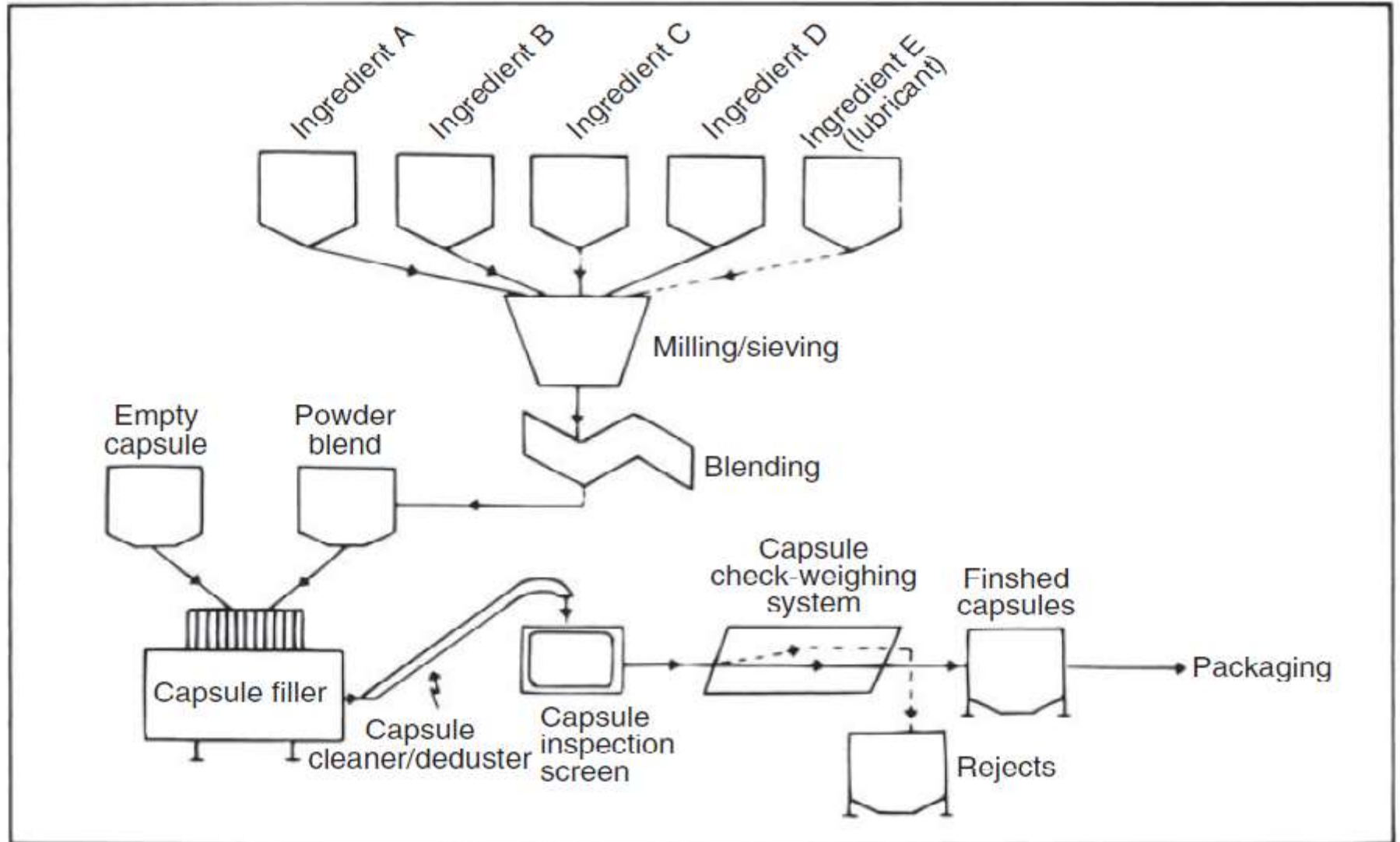
**B.** The loader inserts the capsules into the filling unit and is removed, and the top plate is lifted to separate the caps from the bodies.

**C.** The powder is placed on the unit and the capsule bodies are filled.

**D.** The top plate is returned to the unit and the caps are placed on filled capsule bodies.



# Process of automated capsule filling



# Filling hard gelatin capsules

- **The various types of machines have capacities ranging from 24 to 300 capsules and, when efficiently operated, are capable of producing about 200 to 2,000 capsules per hour.**
- **Machines developed for industrial use automatically separate the caps from empty capsules, fill the bodies, scrape off the excess powder, replace the caps, seal the capsules as desired, and clean the outside of the filled capsules at up to 165,000 capsules per hour.**
- **The formulation must be such that the filled body contains the accurate drug dosage.**
- **This is verified through the use of automated in-process sampling and analysis**


# Capsule Sealing

- Tamper-evident capsules can be prepared by sealing the joint between the two capsule parts.
- Parke-Davis makes distinctive-looking capsules by sealing them with a colored band of gelatin (Kapseals). If removed, the band cannot be restored without expert resealing with gelatin.
- Capsules may also be sealed through a heat-welding process that fuses the capsule cap to the body through the double wall thickness at their juncture.
- The process results in a distinctive ring around the capsule where heat welded.



- **Still another process uses a liquid wetting agent that lowers the melting point in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures (40°C–45°C).**
- **Industrial capsule-sealing machines are capable of producing 60,000 to 150,000 gelatin-banded, heat-welded, or thermally coupled capsules per hour.**
- **Although it is difficult and tedious, extemporaneously prepared capsules may be sealed by lightly coating the inner surface of the cap with a warm gelatin solution immediately prior to placement on the filled capsule body.**

## Cleaning and polishing capsules

- **Small amounts of powder may adhere to the outside of capsules after filling.**
  - **The powder may be bitter or otherwise unpalatable and should be removed before packaging or dispensing.**
  - **On a small scale, capsules may be cleaned individually or in small numbers by gauze or cloth.**
- 
- A collection of blue and white capsules scattered on a white surface. The capsules are of various sizes and orientations, some showing the blue and white halves. The background is a soft-focus white surface.



- **On a large scale, many capsule filling machines are affixed with a cleaning vacuum that removes any extraneous material from the capsules as they exit the equipment.**
- **Industrial cleaning and polishing of filled hard capsules using the Accela-Cota apparatus. rubbing them with a clean.**



A collection of blue and white capsules scattered on a white background. The capsules are arranged in a loose, horizontal cluster across the middle of the frame. The text "THANK YOU" is overlaid in the center in a bold, red, serif font.

**THANK  
YOU**