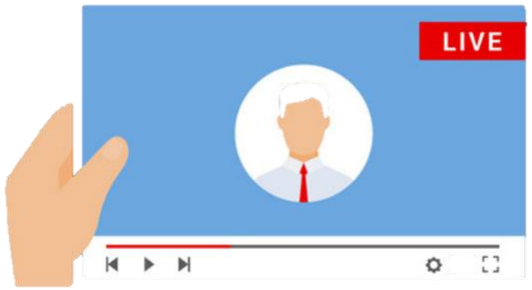


Welcome to GPAT

"Live online class"

Lecture: Pharmaceutics

Oral solid dosage form: Capsules 2

AIC. LMCP Foundation L.M College of Pharmacy Navarangpura, Ahmedabad - 380009

Agenda

Today's Topic: **Capsules 2**

Soft Gelatin Capsule

- Composition
- Manufacture of soft gelatin capsule
- Base absorption
- Important points

Microencapsulation

Solve **6-7 GPAT Questions**

Recap

- Introduction
- Advantages and disadvantages
- Gelatin shell
- Hard Gelatin Capsule

Solve **6-7 GPAT Questions**

Soft gelatin capsule

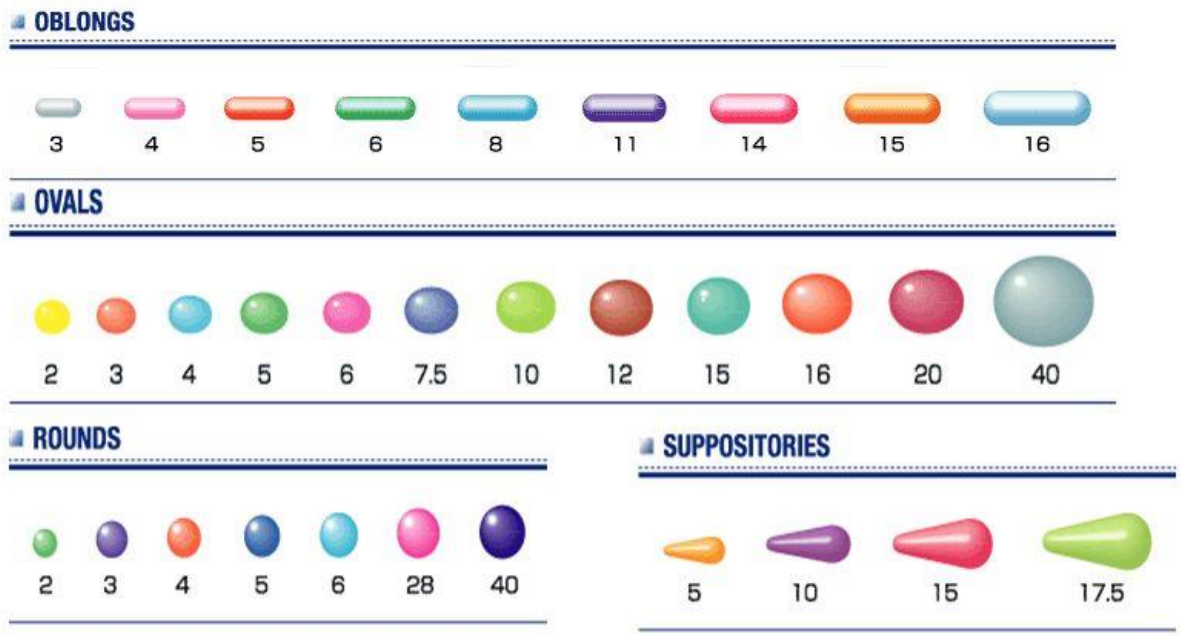
- One piece **hermetically sealed** soft gelatin shell containing a **liquid, a suspension or semisolid**

Advantages

- Soft gelatin capsules are useful when it is desirable to **seal the medication** within the capsule
- The capsules are especially important to contain **liquid drugs or drug solutions**
- **Volatile drug** substances or drug materials especially **susceptible to deterioration** in the presence of air may be **better suited** to a soft gelatin capsule than hard gelatin capsules
- Soft gelatin capsules **are elegant** and are **easily swallowed** by the patients

Shape and size of soft gelatin capsule shell

- The shape of soft gelatin capsule are **round, oval, oblong**
- Maximum capsule size and shape convenient for oral human use is:
  - **20 minim oblong**
  - **16 minim oval**
  - **9 minim round**



Composition of soft gelatin capsule shell

- Gelatin
- **Plasticizer** – glycerin, sorbitol, Propylene Glycol
- **Water or Moisture Content (6 to 10%)** (Moisture Content is determined by **Toluene Distillation Method or Azeotropic Distillation**)
- **Preservatives -** Methyl and Propyl Paraben (4:1)
- **Colourants** – FD and C, Certified Lakes
- **Opacifier** – Titanium Dioxide **(0.2 to 1.2%)**
- **Flavouring Agent – Ethyl Vanillin (0.1%)**
- **Fumaric acid is added to aid solubility and to reduce aldehyde tanning of gelatin**

Manufacture of soft gelatin capsule

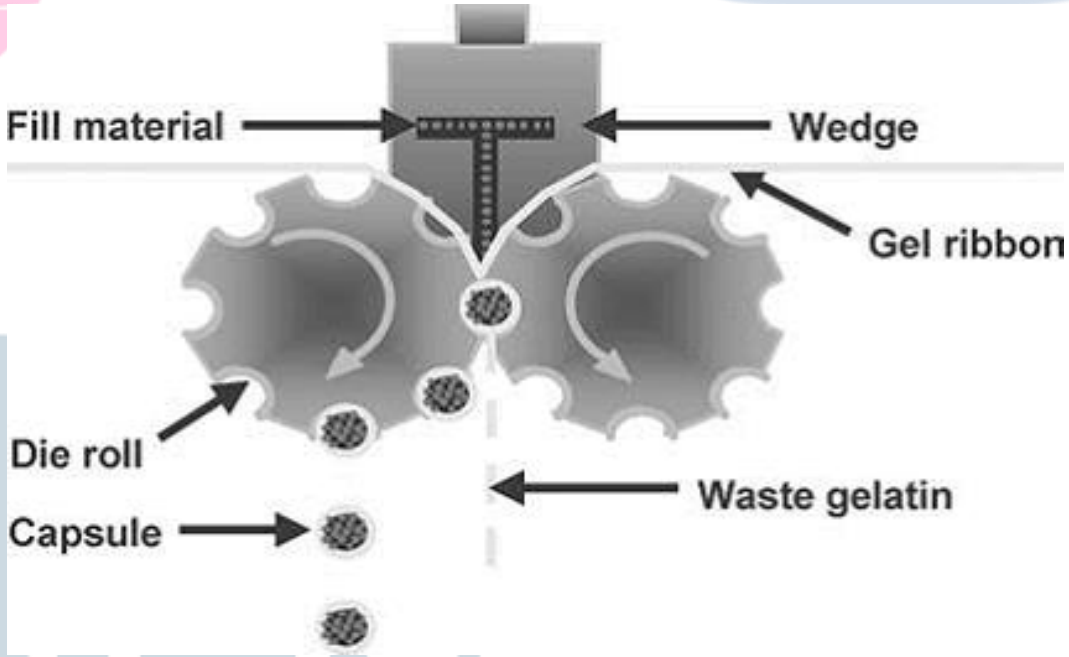
- Is manufactured by four methods
  - Plate process (Oldest process)
  - **Rotary die process (Mostly used in large Scale)**
  - Reciprocating die (developed process for rotary die)
  - Accogel machine (unique equipment that accurately fills powdered dry solids into S.G.C.)

Plate process

- Gelatin sheet is placed over a die plate containing numerous die pockets.
- Application of vacuum to draw the sheet in to the die pockets,
- Fill the pockets with liquid or paste
- Place another gelatin sheet over the filled pockets, and
- Sandwich under a die press where the capsules are formed and cut out.

Rotary die process

- The material to be encapsulated flows **by gravity**.
- **Two plasticized gelatin ribbons** are continuously and simultaneously fed with the **liquid or paste fill between the rollers** of the rotary die mechanism where the **capsule are simultaneously filled, shaped, hermetically sealed and cut from the gelatin ribbon.**
- The sealing of the capsule is achieved by mechanical pressure on the die rolls and the **heating(37-40°C)** of the ribbons by the wedge.



Accogel

- Accogel machine 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 gelatin linked pockets of the die roll
- The continued rotation of the filled die converges with the rotating sealing roll where a second gelatin 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

GPAT QUESTION

_____ is added to aid solubility and to reduce aldehyde tanning of gelatin.

A. Formalin

B. Fumaric acid

C. Shellac

D. All of above

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GPAT QUESTION

Maximum capsule size convenient for oral human use is _____ minim oblong, _____ minim oval and _____ minim round.

A. 9, 20, 16

B. 20, 16, 9

C. 16, 9, 20

D. None

APOMiNd

Formulation of suspension for soft gelatin capsule

- **Except for Accogel process** (which is primarily concerned with the capsulation of dry powders), **solids are filled into soft capsules in the form of either solution or suspension**
- The preparation of a **solution** of a solid medicament should be the **first goal**; usually the **solution is easily capsulated and exhibit better uniformity, stability and biopharmaceutical properties than suspension**
- For oral products, the medicament should have sufficient solubility in the solvent system so that the necessary dose is contained in a maximum fill volume
- **Solids are not soluble in the solvent system are capsulated as suspension**
- The **choice of suspension medium** are directed toward producing **the smallest size capsule**

Base adsorption (of solids to be suspended)

- Base adsorption (BA) is **number of grams of liquid base** required to produce a capsutable **mixture with 1 gram of solid**

BA = weight of the base/weight of the solid

- The base adsorption of solid is influenced by :
  - **The solid particle size and shape**
  - **Its physical state (fibrous, amorphous or crystalline)**
  - **Its density, moisture content, oleophilic or hydrophilic nature**

Minim per gram factor

- M/G is volume in minim that is occupied by one gram of solid (S) plus weight of liquid base required to produce a capsutable mixture.
- **The minim per gram factor is calculated by dividing the weight of base (BA) plus the gram of solid (S) by the weight of mixture (W) per cubic centimeter or 16.23 minims (V).**

$$(BA + S)\frac{V}{W} = \frac{M}{g}$$

- The **lower the BA** of the solid and **the higher the density of the mixture**, the **smaller the capsule.**
- Most widely used Suspending agents are-
  - **Oily base – Wax mixture**
  - **For Non-Oily base – PEG4000 and PEGG6000**

Example

The minim per gram factor for a SGC prepared containing 2 mg mixture made up using 1 mg of drug X and 0.75 mg vegetable oil was 25. Find the volume (in mL) filled in SGC.

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SOLUTION:

M/g = 25; **BA** = 0.75 mg; **S** = 1mg; **V**= ?; W= 2 mg

$$(BA + S)\frac{V}{W} = \frac{M}{g}$$

V= 28.57 minims

16.23 minims = 1mL

So 28.57 = **1.76 mL**

Weight Variation Test

1. 20 intact capsules are individually weighed, and the average weight is determined → None of the individual weights are less than 90%, or more than 110%, of the average.
2. Fail in Step 1 → the individual net weights are determined → averaged, and differences are determined between each individual net content and the average. The test requirements are met
    1. if not more than two of the individual differences are greater than 10% of the average, or
    2. if in no case any difference is greater than 25%.
3. If more than 2 but less than 6 net weights determined by the test deviate by more than 10% but less than 25%, the net contents are determined for an additional 40 capsules, and the average is calculated for the entire 60 capsules

Weight Variation Test

- **Rotoweigh –** It measures the **reflected energy (backscatter) of low power X-ray beam**.
- **Vericap 1200 –** It measures the change in **dielectric constant** or **capacitance variation**.

Content Uniformity

1. 30 capsules are selected, 10 of which are assayed by the specified procedure → 9 of the 10 are within the specified potency range of 85 to 115%, and the tenth is not outside 75 to 125%
2. If more than 1, but less than 3, of the first 10 capsules fall outside the 85 to 115% limits, the remaining 20 are assayed → all 30 capsules are within 75 to 125% of the specified potency range, and not less than 27 of the 30 are within the 85 to 115% range

Special techniques

Solubility limits for empty capsules as follows:

1. **water resistance -** fails to dissolve in water at 20 to 30°C in 15 min;
2. **acid solubility -** dissolves in less than 5 min in 0.5% aqueous HCl (w/w) at 36 to 38°C

Reduction in solubility

Formalin treatment → decrease in solubility of the gelatin film → cross-linkage of the gelatin molecule initiated by the aldehyde

Coatings → **S**alol, shellac, cellulose acetate phthalate, and certain resins

Alternative: starch, Hydroxypropyl methylcellulose and pullulan

Hydroxypropyl methylcellulose (HPMC) capsules

- HPMC capsules are **odorless and flexible,** and their appearance corresponds to that of gelatin capsules, except that surface of HPMC capsules is matt.
- HPMC capsules have several advantages including **low moisture content (2–5%),** chemically inert and stable under very low moisture conditions.
- HPMC is a **plant derived material**, whereas gelatin is of swine or bovine (animal) origin. This eliminates the problem related to religious and vegetarian dietary restrictions.

Starch capsules

- The starch capsules are made of **potato starch** and represents direct alternative to hard gelatin capsules.
- Compared to gelatin capsules, starch capsules feature several advantages: **their dissolution is pH independent; they are suitable for enteric coating, they are stable due to bound moisture and capsules are tamper evident, preservative free and produced from non animal derived material.**
- The starch capsule is odour-less, rigid and exhibits dissolution behaviour similar to the gelatin capsules.
- The moisture content of starch capsule ranges between **12 and 14 % w/w**, with more than 30% being tightly bound. The presence of bound moisture suggests that starch capsules may provide better stability

Some more important points

pH of encapsulated preparation should in between 2.5 to 7.5.because more acidic pH causes hydrolysis of gelatin shell. More alkaline pH cause tanning of gelatin shell (Reduce the solubility)

Weight Variation test–20 Capsules

Weight	Allowed variation
Less than 300 mg	10%
Equal or More than 300 mg	7.5%

Disintegration Test

Type	Time
Soft Gelatin Capsule	60 min
Hard Gelatin Capsule	30 min

Some more important points

Equipment	Use
Rotoshort	A unfilled, loose capsule sorting machine
Rotofill	Fill Pellet in Hard Gelatin Capsule
Accofill	Fill Powder in Hard Gelatin Capsule
Accogel	Fill Powder in Soft Gelatin Capsule
Rotoweigh	A High speed Capsule Weighing Machine
Seidinader	Capsule Polishing machine

GPAT QUESTION

_____ works on the principle of dielectric constant and removes the unfilled capsules.

A. Rotoweigh

B. Vericap

C. Accofil

D. Rotofil

GPAT QUESTION

More alkaline product in soft gel capsule can cause _____.

A. Leakage

B. Tanning

C. Roughness

D. All of above

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Microencapsulation

- Microencapsulation involves the coating of particles ranging dimensionally from several tenths of a micron to 5000 microns in size
- Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection, and of controlling the release characteristics or availability of coated materials

Microencapsulation

Advantages

- Masking of bitter taste drugs
- Conversion of liquid to pseudo solid
- Environmental protection
- Reduction of hygroscopicity .Eg: NaCl
- Reduction of vaporization of volatile drugs
- Prevention of incompatibilities among drugs

Disadvantages

- Possible cross reaction between core and shell material
- Difficult to achieve continuous and uniform film
- Shelf life of hygroscopic drugs is reduced
- More production costs

Formulation considerations

Core

- The core material, defined as the specific material to be coated, can be liquid or solid in nature
- The **liquid core** can include dispersed and/or dissolved material
- The **solid core** can be a mixture of active constituents, stabilizers, diluents, excipients, and release-rate retardants or accelerators

Formulation considerations

Coating Materials

- The coating material should be capable of forming a film that is cohesive with the core material; be chemically compatible and nonreactive with core material; and provide the desired coating properties, such as strength, flexibility, impermeability, optical properties, and stability
- **Water soluble resins:** Gelatin, Gum Arabic, Starch, Polyvinylpyrrolidone, Carboxymethylcellulose, Hydroxymethylcellulose, Methylcellulose, Arabinogalacton, Polyvinyl alcohol, Polyacrylic acid
- **Water-insoluble resins:** Ethylcellulose, Polyethylene, Polymethacrylate, Polyamide (nylon), Poly (ethylene-vinyl acetate), Cellulose nitrate, Silicones, Poly (lactide-co-glycolide)
- **Waxes and lipids:** Paraffin, Carnauba, Spermaceti, Beeswax, Stearic acid, Stearyl alcohol, Glyceryl stearates
- **Enteric resins:** Shellac, Cellulose acetate phthalates, Zein

TECHNIQUES TO MANUFACTURE MICROCAPSULES

Physical Methods

- Air Suspension
- Coarcervation Phase Separation
- Pan Coating
- Spray Drying & Spray Congealing

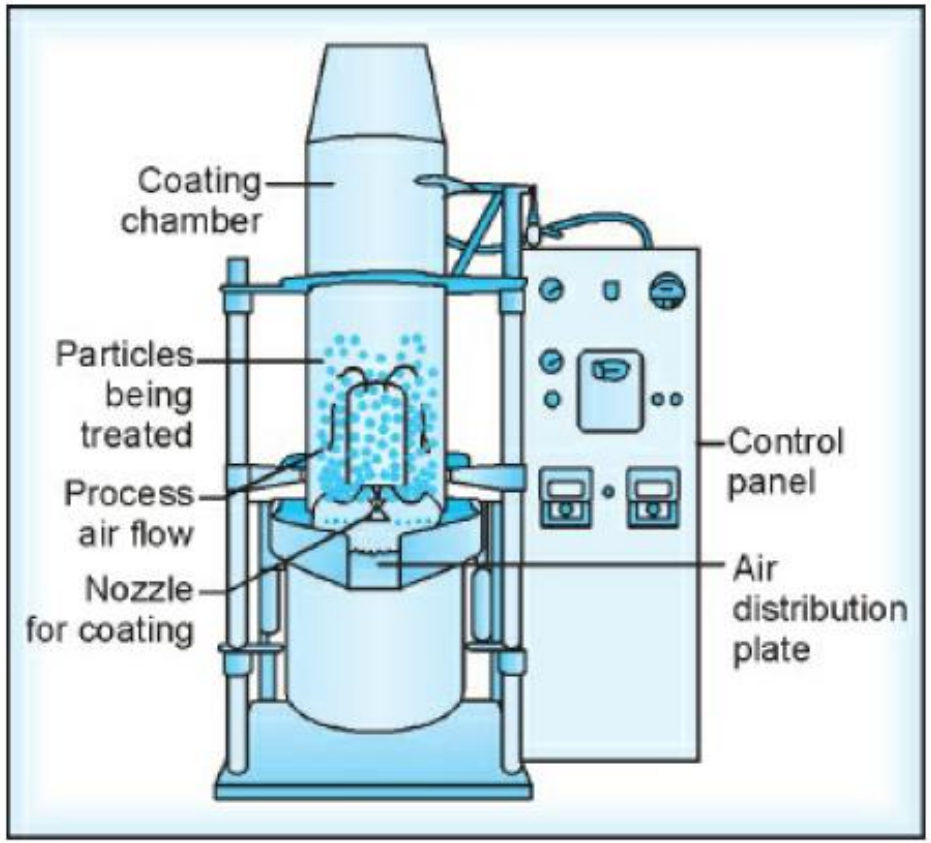
Chemical Methods

- Solvent Evaporation
- Polymerization

TECHNIQUES TO MANUFACTURE MICROCAPSULES

Air Suspension

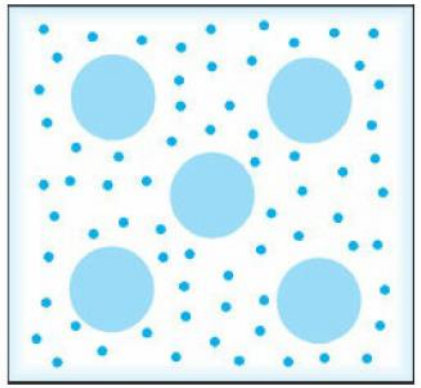
1. Fine solid core materials are suspended by a vertical current of air
2. Evaporation of the solvent
3. The encapsulating material is deposited onto the core material
4. Achieved the desired film thickness
5. The encapsulated product is dried by passing the stream air



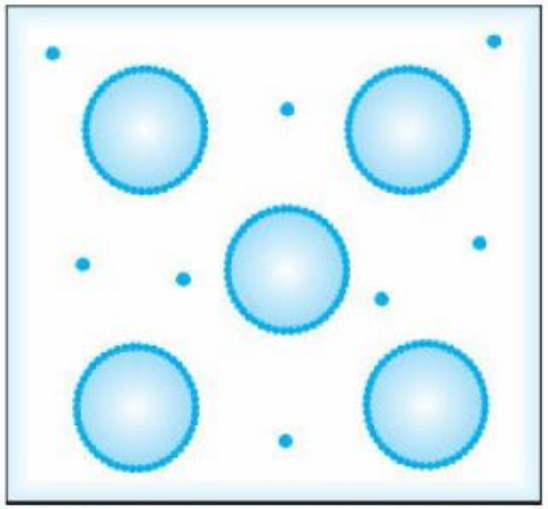
TECHNIQUES TO MANUFACTURE MICROCAPSULES

Coacervation Phase Separation

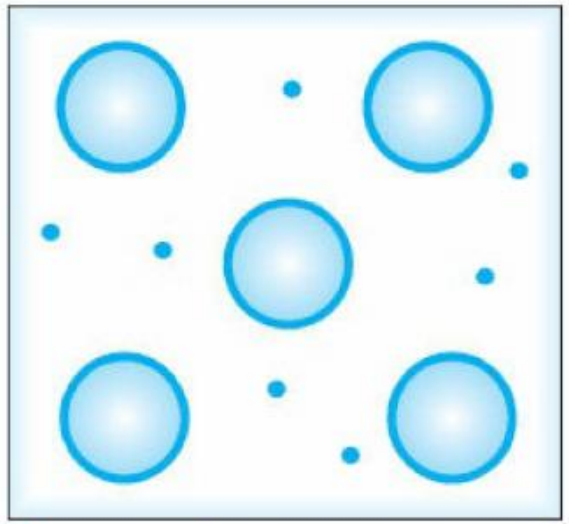
1. Core material phase is dispersed in the solution of coating polymer
2. Solvent of polymer is vehicle the phase
3. Deposition of polymer solution onto the core material
4. Deposition of liquid polymer occurs when the polymer is absorbed
5. Microcapsule



Step 1: Core and liquid coating in manufacturing vehicle



Step 2: Deposition of liquid coating material

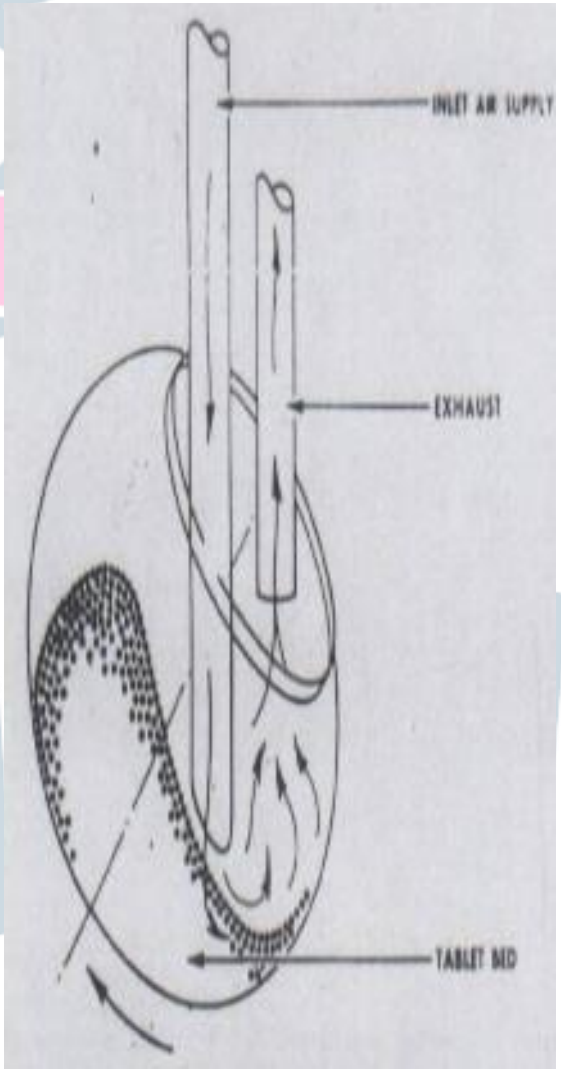


Step 3: Completed capsules in manufacturing vehicle

TECHNIQUES TO MANUFACTURE MICROCAPSULES

Pan Coating

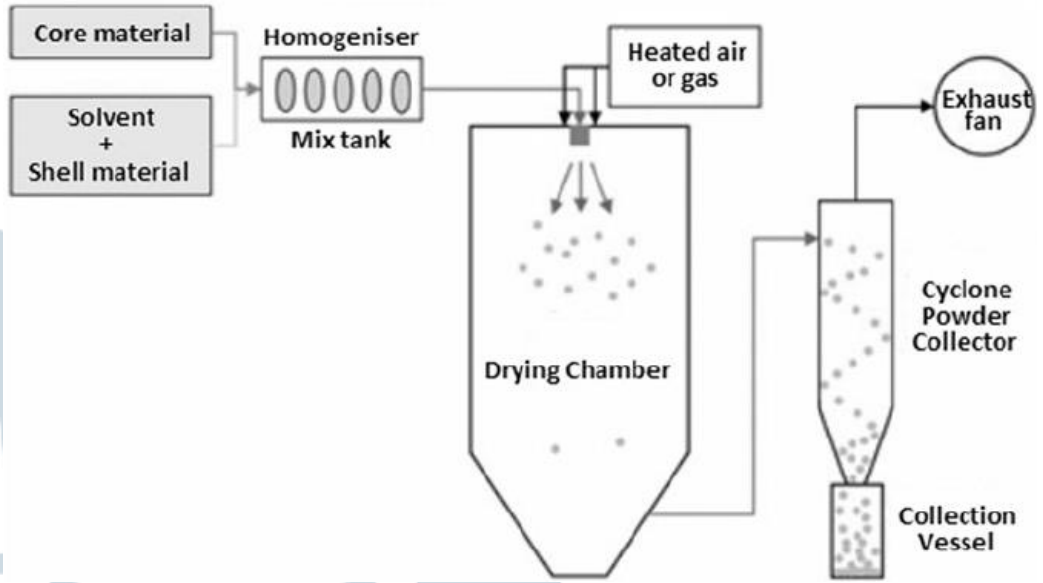
1. Solid particles are mixed with a dry coating material
2. Temperature is raised
3. The coating material melts and encloses the core particles
4. Then is solidified by cooling
5. Microcapsule



TECHNIQUES TO MANUFACTURE MICROCAPSULES

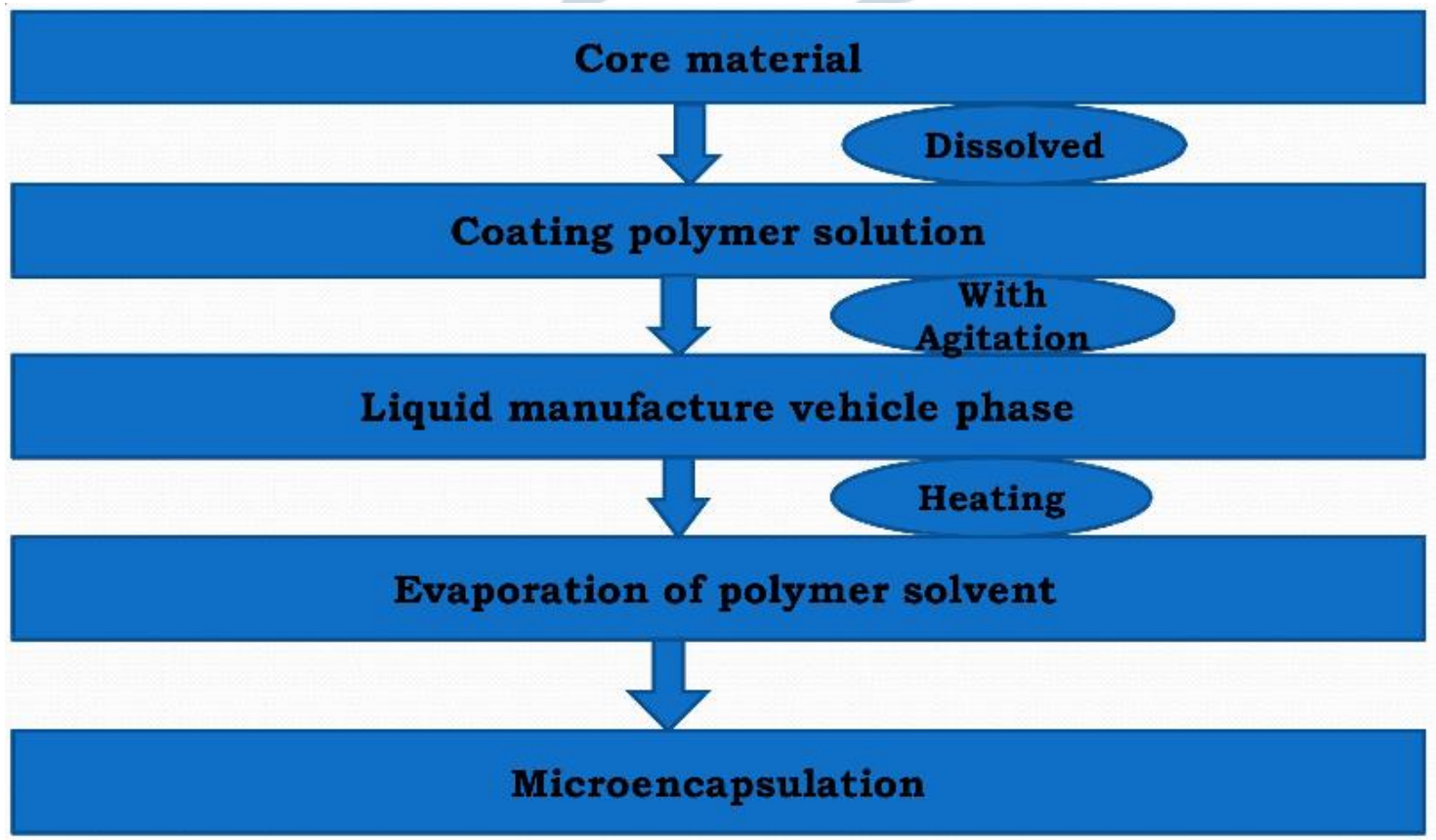
Spray Drying & Spray Congealing

1. Core particles are dispersed in a polymer solution
2. Sprayed into a hot chamber
3. Shell material solidifies onto the core materials
4. Solvent evaporates
5. Microcapsule



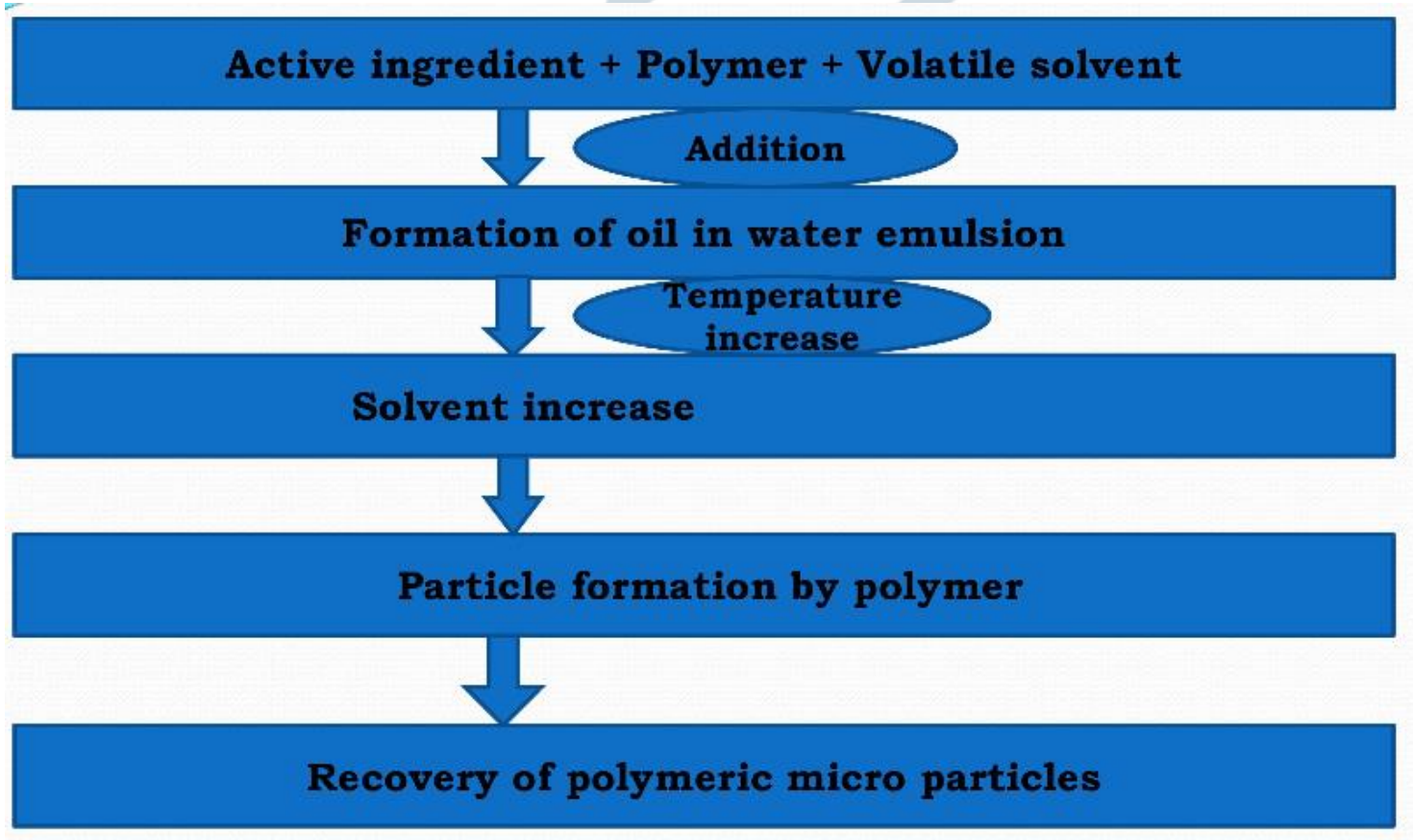
TECHNIQUES TO MANUFACTURE MICROCAPSULES

Solvent Evaporation



TECHNIQUES TO MANUFACTURE MICROCAPSULES

Polymerization



Some more important points

Microencapsulation process	Applicable core material	Approximate particle size (Micron)
Air suspension	Solids	35 – 5000
Coacervation-Phase separation	Solids and liquids	2 – 5000
Multiorifice centrifugation	Solids and liquids	1 – 5000
Pan coating	Solids	600 – 5000
Solvent evaporation	Solids and liquids	5 – 5000
Spray drying and spray congealing	Solids and liquids	600

GPAT QUESTION

Which of the following technique is used for microencapsulation of liquids?

A. Pan coating

B. Coacervation-Phase Separation

C. Air suspension

D. Both A and C

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THANK YOU

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