26. MICROCAPSULES

The microcapsule is a dosage form having a particle size of about 5-500 μm resulting from coating a core material with a shell. Microencapsulation is the process of film-coating solid, liquid or gaseous substances with an inert polymeric substance. In general, the active substance is called the "core" and the coating material is called the "shell".

Purposes and reasons of microencapsulation are;
• To solidify the liquids to ensure easy transport
• Prevent evaporation loss of volatile substances
• Hindering the unwanted taste and smell
• Elimiating the incompatibility
• Protect from atmospheric conditions
• Increasing stability
• Extending the impact period
• Controlled release systems

Core materials can be solid, liquid, gas, emulsion and suspension. Active substances belonging to different pharmacological groups such as antibiotics, analgesics, antihistamines, anticancers, vitamins, peptides-proteins, hormones and enzymes as well as bacteria, antibodies, pesticides, dyes, essences and ink can be microencapsulated.

The shell materials are selected from natural and synthetic, hydrophilic and hydrophobic polymers. Examples of natural polymers used are agar, albumin, alginate, arabic gum, gelatin, dextran, chitosan, collagen, starch, pectin, zein. etc.; Examples of synthetic polymers include acrylic polymers, polyethylene glycol (PEG), aliphatic polyesters, polyorthoesters, polyurethanes, polystyrene, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), cellulose and its derivatives, silicones, shellac and the like.

26.1. Microcapsule Preparation Methods

It is generally examined under three classes.

• Chemical methods:
1. Interfacial polymerization
2. In-situ polymerization
3. Hole method

• Physicochemical methods:
1. Phase separation from aqueous solvent
- Simple coaservation
- Complex coacervation
2. Phase separation from organic solvent
3. Complex emulsion method
4. Fusible dispersion and cooling

• Mechanical methods:
1. Wurster method
2. Spray drying
3. Vacuum coating
4. Electrostatic aerosol method

26.1.1. Coaservation Method

Coaservation is a result of temperature change, addition of non-solvent or salt, addition of another incompatible polymer, or polymer-polymer interaction result. This method is investigated under two groups; phase separation from the aqueous and organic solvent.

The phase separation method from the aqueous solvent:
This method is used to coat water-insoluble solid and liquid substances. Wherein the shell material is dissolved or dispersed in water and the hydrophobic core material is dispersed in this solution. This method is divided into two subsections under the name of simple and complex coacervation.

a) Simple Coaservation: When selected at appropriate rates for temperature, pH, solvent (alcohol) and salt, any aqueous polymer solution will undergo simple coacervation. The added substances cause formation of two phases, one of which is dense from the side of the colloid droplets and the other of which is diluted (Figure 1). The process basically evolves in 4 steps.

b) Complex Coacervation: This method is explained as the interaction of oppositely charged polyelectrolytes interacting with each other to decrease the solubility to achieve complex formation and phase separation. This interaction is due to pH and temperature changes. This method of combination of gelatin and arabic gum at neutral pH is a good example.

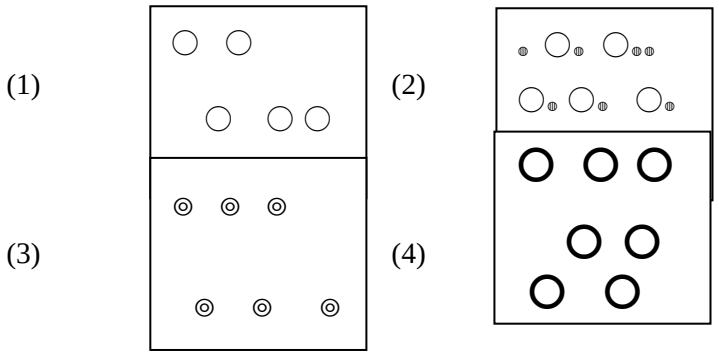

Figure 26.1. Schematic representation of microcapsule formation by simple chelation
(1) The core material (O) is dispersed in the polymer solution.
(2) The solubility of the coating material (•) in the environment is reduced by adding a phase to the solution to provide coservation. Thus, the coating material is separated into a separate phase.
(3) The coating material is deposited on the core material to form a coating (◎).
(4) The coating is hardened (O).

Phase separation method from the organic solvent:
In this method, the shell material is hydrophobic and the core material is hydrophilic. The water-soluble liquid or solid substance is coated with a phase separation resulting from the addition of a second non-solvent polymer to the organic solvent-soluble shell material.

26.2. Controls for Microcapsules

26.2.1. Microscopic studies:

Optical microscope and scanning electron microscope (SEM) are used to determine the surface properties of the microcapsules.

26.2.2. Quantity of microcapsule content:

The content is quantified using two main methods based on the core material and the solubility of the coating polymer. If both materials are soluble in lipophilic solvents, the microcapsules are dissolved in an organic solvent and the active substance is determined using the appropriate analytical method. Only when the core material dissolves in water, microcapsules are disintegrated in water using high speed disintegrants / mixers or ultrasonic baths. The amount of active substance released from the microcapsules is determined using appropriate methods.

Calculation of yield:

% Product yield: [Total amount of microcapsules obtained (mg) / Total amount of solids in the formulation (mg)] x 100

Calculation of active substance loading capacity:

Active substance loading capacity%: [Amount of active substance loaded in microcapsules (mg) / Amount of active substance in the formulation (mg)] x 100

26.2.3. Examination of micromeritic properties

Since the particle size of the core material affects the properties of the resulting microcapsules, particle distribution analysis of the core material and the resulting microcapsules is performed using methods such as optical microscopy or Coulter counter.

26.2.4. Active substance release from microcapsules

The release of the active substance from the microcapsules varies depending on the concentration of the polymer used, the size of the microcapsule and the wall thickness. The capsule wall shows rapid degradation due to thermal, mechanical, chemical effects and slow degradation with dissolution.

26.2.5. Determination of microcapsule wall thickness

Practice 26.1.

I. Active substance and coating polymer solution

Paracetamol (250-354 μm)	25 g
Polyisobutylene	6 g
Eudragit RS 100	8 g
Chloroform q.s.	100 g
Prepare 20 g	

II. Non-solvent solution

Polyisobutylene	6 g
Cyclohexane q.s.	100 g
Prepare 60 g	

Preparation:

Place 20 mL chloroform solution containing 1.2 g polyisobutylene (PIB) and 1.6 g Eudragit RS in a three necked balloon (250 mL) in a thermostatted water bath set at 25 ^{o}C. Add paracetamol (250-354 μm) with the particle size preset. While the contents in the flask are constantly stirred with a magnetic stirrer (300 rpm), 60 g of cyclohexane solution with 3.6 g of PIB is added dropwise with a rate of 0.9 g per minute by means of a dropping funnel. The microcapsule formation is completed after a period of addition processing is over. The microcapsules are washed 2 times with cyclohexane in portions of 100 ml to separate the PIB residue remaining on the surface of the microcapsule and the free polymer residues. Finally, 50 ml of cyclohexane are added to the microcapsules and vacuum filtered. The obtained microcapsules are dried at room temperature.

Controls:
Amount determination: The amount of paracetamol is determined spectrophotometrically in methanol at a wavelength of 246 nm.
Dissolution rate determination: The dissolution rate is carried out using a continuous flow method in a pH 5.8 phosphate buffer. The content of paracetamol in the samples taken at specific time intervals over 7 hours is determined spectrophotometrically at a wavelength of 240.5 nm.

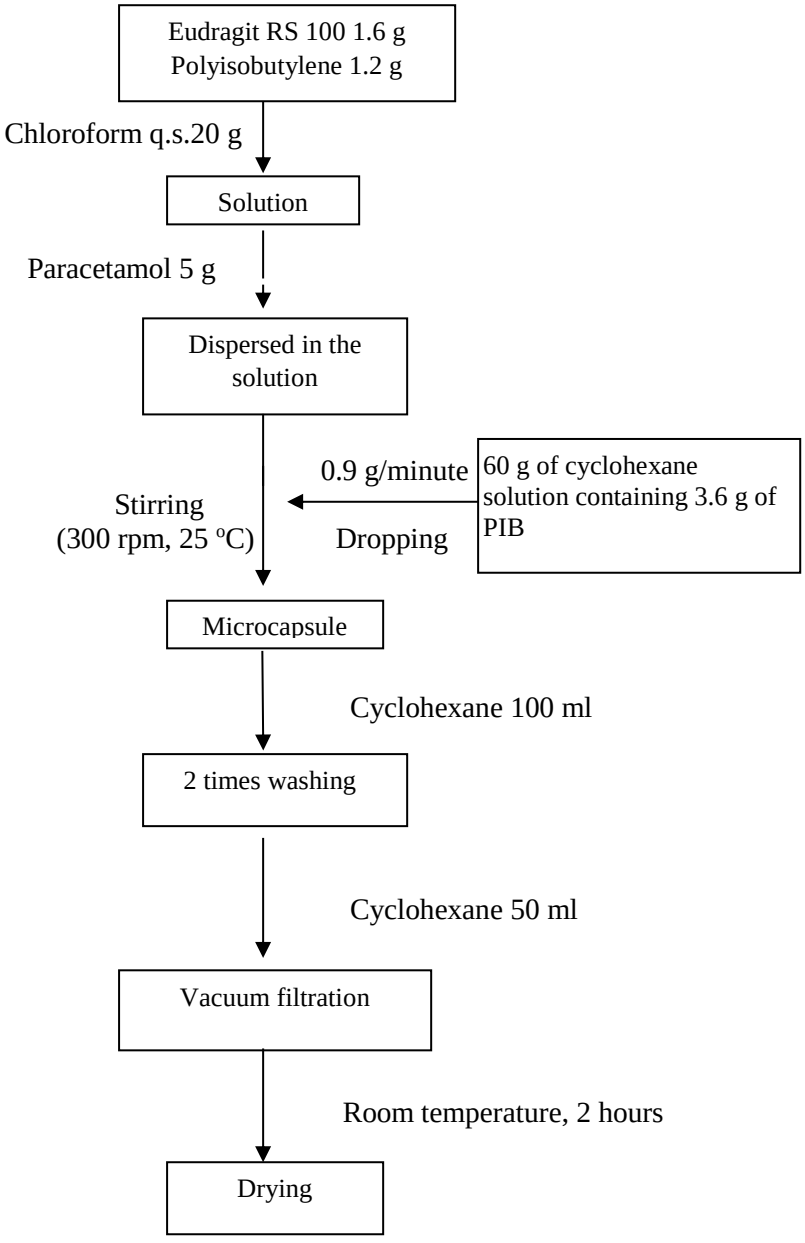

Figure 26.2. Microcapsule preparation flow diagram

Questions
1. By which method did you prepare microcapsules? Why?
2. Analyze the microcapsules you have prepared under an optical microscope and make comments on the result.
3. Determine the amount of active substance in the microcapsules and record the results.
4. What are the factors that affect product yield in microcapsules? Interpret the results of product yield and active substance loading you have found.

27. MICROSPHERES

Microspheres are microcarrier systems that can be prepared in different surface and bulk structures which are porous or non-porous, disintegrating or non-disintegrating in various sizes, from a few micrometers to millimeters. As a drug delivery system, they are usually applied as a dispersion. These systems are taken orally for sustained and delayed drug release. They can be implanted by s.c., i.m. or i.p. routes for delivering the drug locally or to the systemic circulation at a controlled rate. The microspheres are also adminestered by injection into the blood stream for targeted drug delivery to the desired cells, tissues or organs physically or chemically.

Microspheres have a wide range of applications. For example; marking in agglutination tests, marking for flow monitoring and other rheological investigations, separation processes, carrier in bioaffinity chromatography, immobilization of biologically activity substances, calibration in particle and cell counters with electron and light microscopes, marker in cell studies, carrier in cell cultures, column filler in chromatography columns, filler in plastic materials and radioimmunoassay and other immunological tests and researches. In in vivo applications, the microspheres are produced from biodegradable polymers to eliminate the difficulty of removal of the non-biodegradable carriers after use.

The methods used in the preparation of microspheres can be listed as follows;
• Polymerization: Emulsion polymerization, suspension polymerization, micelle polymerization,
• Coaservation: Simple coacervation, complex coacervation,
• Emulsion formation / solvent evaporation: s / w emulsion, o / o emulsion, w / o / w emulsion,
• In-situ method,
• Polycondensation: Suspension polycondensation, emulsion polycondensation,
• Spray freezing,
• Spray drying,
• Hole = Orifice method,
• Gelling and cross-linking in the disperse phase.

In the identification and use of microspheres; Size and surface properties, amount of active substance loaded, the release of active substance, biological compliance and toxicity, storage and sterilization criteria are examined and taken as a basis.

Application areas of microspheres in clinical applications; anticonvulsant drugs, antiinflammatory drugs, local anesthetics, orthopedic applications, chemoembolization, implantation to the brain, tissue, targeting to the cell or organ, binding to peptides and proteins and vaccines.

Practice 27.1

Ethylcellulose	2.0 g
Aluminum stearate	1.5 g
Potassium chloride	2.0 g
Acetone	100 ml
Liquid paraffin	100 ml
n-Hexane	50 ml

Preparation:

In a 200 ml beaker, ethylcellulose is completely dissolved in 100 ml of acetone. Then aluminum stearate and potassium chloride are dispersed in this solution. The mixture is stirred in a 25°C water bath for 10 minutes (150-350 rpm) and poured into 100 ml liquid paraffin at 25 °C. Acetone is evaporated by heating the emulsion to 45 °C and stirring continuously. It is then washed with n-hexane and dried at 40 °C.

27.1. Controls on Microspheres

• Quantification of active substance: Weigh out a little bit from the formula. Dissolve in a solvent which is the common solvent of the polymer and active substance. After the microspheres are completely dissolved, strain and complete with a certain volume of solvent in the balloon. Measure the absorbance of the solution by the UV spectrophotometer at the wavelength at which the active substance gives maximum absorbance.

• Particle size and distribution: Sieve analysis or microscope method can be applied for this purpose. Operate the unit with the mini sieve set in accordance with ASTM standards (DIN 4188) for 10 minutes at 100 settings. Weigh the fraction on each sieve to% and plot the graph.

• Viscosity - Stack angle: Place a glass funnel with an upper diameter of 10 cm, a width of 0.9 cm neck and a length of 1 cm neck, 10 cm from the mouth point. Put 10 g of micropellet into this funnel and allow free flow to the bottom paper. Determine the stack angle as described in the micromeritic section.

• Cluster volume and density (in measuring cylinder): Take 10 ml of microspheres. Measure the volume by doing 20 tapping. Calculate the density by dividing the weight of the known powder set by the volume of the weight.

• Dissolution rate test: Apply the dissolution rate test to the desired amount of the active substance by placing the weighed microspheres in the 900 ml dissolution medium using a pallet or basket method. If the palette method is applied, you can add 0.01-0.03% Tween 60 to the environment to increase the contact surface of the microspheres with the dissolution medium. Calculate the concentration of the active substance from the calibration equation by reading the absorbance at the determined wavelength spectrophotometer by taking 5 ml of sample at the determined intervals (add the fresh solution to the dissolution medium as the sample volume taken from the medium each time).

- Other Controls That Can Be Applied
    Operation activity
    Determination of swelling degree

Questions

1. Which method do you use in the laboratory for the production of microsphere? What other methods are available for this purpose?
2. What are the advantages and disadvantages of preparing microspheres of active substances?
3. Examine the dry microspheres obtained by microscopy and show the differences between what you observed before drying and during their formation.

30. AEROSOLS

They are single or multi-phase systems which are sprayed in dispersion of liquid or solid particles in a gas phase. They are preparations used in the field of pharmacy and medicine either by inhalation or externally.

They work in two ways because they show pressure sprays;

• They give their contents with the energy given from outside, which are usually given the names of nebuliser and atomizer,

• They contain energy carriers such as compressed and / or liquefied propellant, in which aerosol or spray names are often used.

Whichever type of energy is applied, aerosol systems are all physically applied. Generally, inhalation aerosols are used by inhalation and spray aerosols are used externally.

They have different structure and properties according to usage area and purpose. Real aerosols contain more than 80% of the propellant, and the size of the spraying particles is less than 5 μm. The ratio of liquefied propellant used externally and defined as surface spray ranges from 40 to 70%, and the size of the spraying particles is between 50 and 250 μm. If the spray gas ratio falls below 30%, preparations are defined as wet spray, where the spraying granules are in the form of droplets in the size of 250-1000 μm, not in the form of a bundle. If the active substance emulsifies with liquefied atomizing gas, foam aerosols arise where the amount of atomising gas is between 10 and 20%. If the active substance is spraying in solid form, aerosols are formed, called powder sprays, in which the propellant ratio is between 5-20%.

An aerosol system consists mainly of the main container, the valve assembly, the atomizer (propellant or impeller) and the concentration of the active substance in the gas.

The main container is made of metal (aluminum, steel, tin), glass or plastic and is in one piece (monoblock), two pieces or three pieces (bodymaker). The selection of the cabinet structure varies depending on the method of use, the formulation of the contents, and the commercial point of view. Although glass containers are transparent compared to other types of containers, their use remains limited due to the lack of mechanical and thermal resistance, although the risk of interaction with the contents appears to be minimal, thus being advantageous. The corrosion rate is high in metal containers, against which inner surfaces are coated with an inert layer (storage, plastic coating, etc.). They are resistant to mechanical shocks and higher internal pressures. Plastic containers are very inert but can only carry low pressure contents, they are preferred in nebuliser systems, which take more pressure energy from the outside.

The valve set determines the spraying and spraying of the system. They are of two types as continuous (continuous) and metered (specific dose) spraying. Continuous sprayers perform spraying on a continuous basis as long as the activator head on the valve hold pressed while metered dose sprayers are sprayed at a specific dose only once, regardless of how long they are pressed. The valve assembly consists of several parts, two of which are the spray chamber and the spray hole. These parts determine the spraying properties and size distribution of the particles sprayed together with the propellant in the contents of the aerosol system.

The sprayer contained in the aerosols carrying the pressure energy consists of compressed and / or liquefied propellants (propellants). Compressed gases are used without liquefaction are nitrogen, nitrogen oxides, argon, carbon dioxide. Liquefied hydrocarbons such as propane, butane, isobutane or halogenated hydrocarbons such as chlorine-fluorine hydrocarbons such as vinyl chloride, methyl chloride, ethyl bromide, Frigen or Freon. Spray pressures vary according to types and mixing ratios, usually used in medicine and pharmaceuticals to provide internal pressures of between 1 and 10 atm. In

general, it is desirable that the pressure should be about 3-4 atm in the aerosols to be sprayed on the air, the pressure should be around 3-5 atm in the aerosols to be sprayed on the skin, and even lower in the inhalation aerosols. The relationship of pressure / particle size is very important in inhalation aerosols. Particles that are 20-30 μm in size remain in the trachea, while those in the 10-20 μm reach the bronchioles and those in the 5-10 μm reach the bronchioles. Those of smaller size will descend into the alveoli.

The part defined as a concentrate in an aerosol system consists of the active substance, solvent and co-solvent (cosolvent) and other auxiliaries (such as surface active substances) required in the formulation. If a concentrate containing active substance dissolves in the phase of liquefied propellant to form a homogeneous mixture, a two-phase aerosol system will emerge. In such a system, there is vaporized propellant at the top and all the remaining mixture in the liquid phase at the bottom. On the other hand, if the evaporated propellant is in the upper part and the active substance phase is in the form of two separate phases and the liquefied propellant phases are present, a three-phase aerosol system is formed. These should be used with thorough shaking.

The production of aerosols is carried out without using pressure in the cold or under normal temperature with pressure. In cold filling, the concentrate and liquefied propellant cooled to -40 ° C are filled separately into the container and the valve system is closed by fitting in the container. When filling with normal pressure, first put the active substance concentrate in the container, install the valve system and pressurize the liquefied atomizing gas valve through the opening of the valve. This method is also applied to the use of non-liquefied propellant.

Aerosol systems that do not contain spraying energy are in the form of a flexible plastic container which is sprayed with the contents of the container or is sprayed with a pendant switch attached to the container and does not contain propellant. They spray the droplet in the form of fog in varying sizes and quantities according to the squeeze pressure and the degree of the injection hole.

Practice 30.1.

Production of Antimycotic Active Compound Bearing Aerosol

Oxiconazole	250 g
Ethyl alcohol (96%)	10.5 g
Freon	12 15.9 g

Preparation:
Oxyconazole is dissolved in ethyl alcohol and filled into pre-cleaned aerosol tubes at 13 ml. The immersion tube of the valve is adjusted according to the cuff to be used and the tube valve is installed in the aerosolization device. Then the propellant gas is filled in the tubular aerosol filling device as necessary. Labeled appropriately.

Practice 30.2.

Controls on Aerosols

1. Spray rte control
At least four aerosol containers are prepared. The cap and guard are removed. Each is sprayed for two to three seconds and weighed accurately. The containers are immersed in the water bath at 25 ° C until the internal pressures are balanced. Whether the internal pressure has come to the balance is measured as described in Article 2. Containers with balanced internal pressures are removed from the water tank, dried and sprayed for 5 seconds (timer is used to detect the time). Weigh each container again. The containers are re-immersed in the water bath set temperature and the spraying and weighing process is repeated three times. The average spray rate in grams per second is calculated.

2. Pressure test
At least four aerosol containers are prepared. Remove the cap and guard and keep in the 25°C water until the internal pressure is constant. After the containers are taken from the water tank, they are thoroughly shaken. The sprayer head is removed and dried if wet. Each container is held upright and the pressure gauge is tightly connected to the valve. The pressure gauge should be tightly connected with the adapter fitted to the valve, which should be pre-set to the approximate expected pressure. The pressure is read directly from the manometer display.

3. Determination of the droplet size in two-phase aerosols
This method is based on the principle that it is stained by spraying a piece of paper treated with a dye-talc mixture. For this purpose, a special device is used to measure the jetting differential shown by different series and different sprayer heads.
The test is carried on by adding oil or water-soluble paints to the formulation according to the nature of the contents. Particles are absorbed when hit to paper, and this paper is used for comparison.

In the special device, the paper is fixed just behind the rotating disc. The aerosol container is inserted into the device. Spray for one or two seconds and examine whether the paper is removed and homogeneous drop distribution is observed. The number and size of droplets in a given area are calculated as % using appropriate magnifying devices (eg microscope).

The results are shown on the log-probability graph. The mean droplet size and standard deviation are calculated by using this graph.

4. Determination of particle size in aerosols carrying solid particles
The aerosol container is thoroughly shaken and fixed. The effective spray distance is determined by spraying the aerosol for two to three seconds. At halfway of this distance, the aerosol is sprayed onto a thoroughly cleaned glass slide vents on the same plane as the sprayer head. Powders adhering to the glass slide are dispersed using a suitable sieve. The dimensions of the solid particles are determined by microscopy. It is classified according to its dimensions by counting at least 1200 particles. The results are shown on the log-probability graph to calculate the average particle size and standard deviation.

5. In the case of unit dose spraying aerosols,
The density of the aerosol formulation is determined. The aerosol container is thoroughly dried and weighed and tared. Spraying is carried on by pressing the actuator valve. The container is cleaned again, dried and weighed. Weight loss is detected sensitively. This process is applied at least ten times. Averaged results are taken. The density of the formulation is divided by the average weight loss to find the spray volume. The result is compared to the valve specification.

6. Leakage test

7. Net weight determination

8. Checking the corrosion resistance of the container

Questions
1. What type of content should be used with which type of aerosol containers, why?
2. How much pressure should the aerosols have and how much pressure can they hold?
3. Describe the importance of quantitation in unit dose spray aerosols.