INHALED DRUG DELIVERY

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Drugs are generally delivered to the respiratory tract for the treatment or prophylaxis of airways diseases. The administration of a drug at its site of action can result in a rapid onset of activity, which may be highly desirable, for example when delivering bronchodilating drugs for the treatment of asthma. Additionally, smaller doses can be administered locally compared to delivery by the oral or parenteral routes, thereby reducing the potential incidence of adverse systemic effects and reducing drug costs. The pulmonary route is also useful where a drug is poorly absorbed orally, e.g. sodium cromoglycate, or where it is rapidly metabolized orally, e.g. isoprenaline. The avoidance of first-pass metabolism may also be advantageous.

The lung may be used as a route for delivering drugs having systemic activity, because of its large surface area, the abundance of capillaries and the thinness of the air-blood barrier. This has been exploited in the treatment of migraine with ergotamine, and studies have demonstrated the potential for delivering proteins and peptides such as insulin and growth Hormone via the airways.
To deliver a drug into the airways it must be presented as an aerosol. In pharmacy this is defined as a two-phase system of solid particles or liquid droplets dispersed in air or other gaseous phase, having sufficiently small size to display considerable stability as a suspension.

The deposition of a drug/aerosol in the airways is dependent on four factors: the physicochemical properties of the drug, the formulation, the delivery/liberating device and the patient (breathing patterns and clinical status).

The most fundamentally important physical property of an aerosol for inhalation is its size.

The particle size of an aerosol is usually standardized by calculation of its aerodynamic diameter, $da$, which is the physical diameter of a unit density sphere which settles through air with a velocity equal to the particle in question. Therapeutic aerosols are heterodispersed (polydispersed), and the distribution of sizes is generally represented by the geometric standard deviation (GSD).
The influence of environmental humidity on particle size

As a particle enters the respiratory tract, the change from ambient to high relative humidity (approximately 99%) results in condensation of water on to the particle surface, which continues until the vapour pressure of the water equals that of the surrounding atmosphere. For water-insoluble materials this results in a negligibly thin film of water; however, with water-soluble materials a solution is formed on the particle surface. As the vapour pressure of the solution is lower than that of pure solvent at the same temperature, water will continue to condense until an equilibrium between vapour pressures is reached, i.e. the particle will increase in size.

Particle deposition in the airways

The efficacy of a clinical aerosol is dependent on its ability to penetrate the respiratory tract. To penetrate to the peripheral (respirable) regions, aerosols require a size less than about 5 or 6 µm, with less than 2 µm being preferable for alveolar deposition. Larger particles or droplets are deposited in the upper respiratory tract and are rapidly cleared from the lung by the mucociliary action, with the effect that drug becomes available for systemic absorption and may potentially cause adverse effects. Steroid aerosols of sufficiently large size may deposit in the mouth and throat, with the potential to cause oral candidiasis.
The size of aerosolized drug may be especially important in the treatment of certain conditions where penetration to the peripheral airways is particularly desirable, for instance the treatment and prophylaxis of the alveolar infection *Pneumocystis carinii pneumonia*.

There are three main mechanisms responsible for particulate deposition in the lung: gravitational sedimentation, impaction and diffusion.

**Breathing patterns**

Patient-dependent factors, such as breathing patterns and lung physiology, also affect particle deposition. For instance, the larger the inhaled volume the greater the peripheral distribution of particles in the lung, whereas increasing inhalation flow rate enhances deposition in the larger airways by inertial impaction. Breath-holding after inhalation enhances the deposition of particles by sedimentation and diffusion.

Optimal aerosol deposition occurs with slow, deep inhalations to total lung capacity, followed by breath-holding prior to exhalation. It should be noted that changes in the airways resulting from disease states, for instance airways' obstruction, may affect the deposition profile of an inhaled aerosol.

There are currently three main types of aerosol generating device for use in inhaled drug therapy:

- **metered-dose inhalers**,  
- **dry powder inhalers** and  
- **nebulizers**.
**Metered-dose inhalers**

Metered-dose inhalers are the most commonly used inhalation drug delivery devices. In MDIs, drug is either dissolved or suspended in a liquid propellant mixture together with other excipients, including surfactants, and presented in a pressurized canister fitted with a metering valve (see the figure). A predetermined dose is released as a spray on actuation of the metering valve. When released from the canister the formulation undergoes volume expansion in the passage within the valve and forms a mixture of gas and liquid before discharge from the orifice. The high speed gas flow helps to break up the liquid into a fine spray of droplets.

**Containers**

Pharmaceutical aerosols may be packaged in tinplated steel, plastic-coated glass or aluminium containers. In practice, MDIs are generally presented in aluminium canisters, produced by extrusion to give seamless containers with a capacity of 10-30 mL. Aluminium is relatively inert and may be used uncoated where there is no chemical instability between container and contents. Alternatively, aluminium containers with an internal coating of a chemically resistant organic material, such as an epoxy resin, can be used.
Propellants

The propellants used in MDI formulations are liquefied gases, traditionally chlorofluorocarbons (CFCs) and increasingly hydrofluoroalkanes (HFAs). At room temperature and pressure these are gases, but they are readily liquefied by decreasing temperature or increasing pressure. The head space of the aerosol is filled with propellant vapour, producing the saturation vapour pressure at that temperature. On spraying, medicament and propellant are expelled and the head volume increases. To re-establish the equilibrium, more propellant evaporates and so a constant pressure system with consistent spray characteristics is produced.

Formulations generally comprise blends of CFC-11 and CFC-12 or CFC-11, CFC-12, and CFC-114, together with a surfactant such as a sorbitan ester, oleic acid or lecithin, which acts as a suspending agent and lubricates the valve. CFCs and HFAs are numbered using a universal system. The first digit is the number of carbon atoms minus 1 (omitted if zero), the second is the number of hydrogen atoms plus 1, and the third is the number of fluorine atoms.
In the European Union, all ozone-depleting CFCs had been banned by the end of 1995. Pharmaceutical aerosols are currently exempted. Propellants HFA-134a (trifluoromonofluoroethane) and HFA-227 (heptafluoropropane) are non-ozone depleting, non-flammable HFAs, also called hydrofluorocarbons (HFCs), which have been widely investigated as alternatives to CFC-12. HFA-134a and HFA-227 have some physical properties, including density, which are similar to those of CFC-12 and, to a lesser extent, CFC-114.

However, HFCs present major formulation problems: in particular they are poor solvents for the surfactants commonly used in MDI formulation and no alternative to CFC-11 is currently available. Ethanol is approved for use in formulations containing HFAs to allow dissolution of surfactants, and is included in marketed non-CFC MDI products. However, ethanol has low volatility and may consequently increase the droplet size of the emitted aerosols.
**Metering valve**

The metering valve of an MDI permits the reproducible delivery of small volumes (25-100 \( uL \)) of product. Unlike the non-metering continuous-spray valves of conventional pressurized aerosols, the metering valve in MDIs are used in the inverted position (Fig. 31.3). Depression of the valve stem allows the contents of the metering chamber to be discharged through the orifice in the valve stem and made available to the patient. After actuation, the metering chamber refills with liquid from the bulk and is ready to dispense the next dose.

MDI valves are complex in design and must protect the product from the environment, while also protecting against product loss during repeated use. The valve stem fits into the actuator, which is made of polyethylene or polypropylene. The dimensions of the orifice in the actuator plays a crucial role, along with the propellant vapour pressure, in determining the shape and speed of the emitted aerosol cloud.
**Formulating metered-dose inhalers**

Pressurized aerosols may be formulated as either solutions or suspensions of drug in the liquefied propellant. Solution preparations are two-phase systems. However, the propellants are poor solvents for most drugs. Cosolvents such as ethanol or isopropanol may be used, although their low volatility retards propellant evaporation. In practice, pressurized inhaler formulations have been almost exclusively suspensions. These three-phase systems are harder to formulate and all the problems of conventional suspension formulation, such as caking, agglomeration, particle growth etc. must be considered.

Careful consideration must be given to the particle size of the solid (usually micronized to between 2 and 5 um), valve blockage, moisture content, the solubility of active compound in propellant (a salt may be desirable), the relative density of propellant and drug, and the use of surfactants as suspending agents, e.g. lecithin, oleic acid and sorbitan trioleate (usually included at concentrations between 0.1 and 2.0% w/w).

These surfactants are very poorly soluble in HFAs, and so either ethanol must be used as a cosolvent or alternative surfactants such as fluorinated polymers must be developed.
**Filling metered-dose inhaler canisters**

Canisters are filled by liquefying the propellant at reduced temperature or elevated pressure.

In **cold filling**, active compound, excipients and propellant are chilled and filled at about -30°C. Additional propellant is then added at the same temperature and the canister sealed with the valve.

In **pressure filling**, a drug/propellant (CFC-11) concentrate is produced and filled at effectively room temperature and pressure (in fact, usually slightly chilled to below 20°C). The valve is crimped on to the canister and additional propellant (e.g. CFG-12) is filled at elevated pressure through the valve, in a process known as gassing.

Pressure filling is most frequently employed for inhalation aerosols. Once filled, the canisters are leak tested by placing them in a water bath at elevated temperature, usually 50-60°C. Following storage to allow equilibration of the formulation and valve components, the containers are weighed to check for further leakage, prior to spray testing and insertion into actuators.
Advantages and disadvantages of MDI

Advantages of MDIs:
portability, low cost and disposability. Many doses (up to 200) are stored in the small canister and dose delivery is reproducible. The inert conditions created by the propellant vapour, together with the hermetically sealed container, protects drugs from oxidative degradation and microbiological contamination.

Disadvantages.
They are inefficient at drug delivery. On actuation, the first propellant droplets exit at a high velocity, which may exceed 30 m/s. Consequently, much of the drug is lost through impaction of these droplets in the oropharyngeal areas. The mean emitted droplet size typically exceeds 40 um, and propellants may not evaporate sufficiently rapidly for their size to decrease to that suitable for deep lung deposition.

An additional problem with MDIs, which is beyond the control of the formulator and manufacturer is their incorrect use by patients. Reported problems include:
• Failure to remove the protective cap covering the mouthpiece;
• Failure to shake the canister;
• Failure to inhale slowly and deeply;
• Inadequate breath-holding;
• Poor inhalation/actuation synchronization.
**Spacers and breath-actuated metered-dose inhalers**

Some of the disadvantages of MDIs, namely inhalation/actuation coordination and the premature deposition of large propellant droplets high in the airways, can be overcome by using extension devices or 'spacers' positioned between the MDI and the patient.

The dose from an MDI is discharged directly into the reservoir prior to inhalation. This reduces the initial droplet velocity, permits efficient propellant evaporation and removes the need for actuation/inhalation coordination. The disadvantage of spacers is that they may be bulky.

**Techniques for use of MDI devices:**

- **Two finger width from mouth**
- **Use of space or holding chamber**
- **Placement of inhaler in mouth (not for use with steroids)**

**Fig. 31.4** The Nebuhaler spacer device, fitted with a face mask for use by a child. Courtesy of AstraZeneca
Dry powder inhalers

In dry powder inhaler (DPI) systems, drug is inhaled as cloud of fine particles. The drug is either preloaded in an inhalation device or filled into hard gelatin capsules or foil blister discs which are loaded into a device prior to use.

DPIs have several advantages over MDIs. DPI formulations are 1-propellant free and 2-do not contain any excipient, other than a carrier, which is almost invariably lactose. 3-They are breath actuated, avoiding the problems of inhalation/actuation coordination encountered with MDIs, and consequently they are particularly useful for young children. 4-DPIs can also deliver larger drug doses than MDIs, which are limited by the volume of the metering valve and the maximum suspension concentration that can be employed without causing valve clogging.

Dry Powder Inhalers (DPI)

• **Breath activated**
• **Micronized drug particles blended with an excipient (e.g., glucose or lactose)**
• **Physical properties of drug and excipient critical (i.e., particle size, shape, surface morphology, etc)**
DPIs have several disadvantages:
Liberation of powders from the device and the deaggregation of particles are limited by the patient's ability to inhale, which in the case of respiratory disease may be impaired.
An increase in turbulent air flow created by an increase in inhaled air velocity increases the deaggregation of the emerging particles, but also increases the potential for inertial impaction in the upper airways and throat, and so a compromise has to be found. Further, DPIs are exposed to ambient atmospheric conditions, which may reduce formulation stability. For instance, elevated humidity may cause powders to clump.
Finally, DPIs are less efficient at drug delivery than MDIs, twice the dose is usually required for delivery from a DPI than from the equivalent MDI.

Classification of Dry Powder Inhalers, Based on Design and Function

<table>
<thead>
<tr>
<th>Single-Dose Devices</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerolizer</td>
<td>formoterol capsule</td>
</tr>
<tr>
<td>HandiHaler</td>
<td>tiotropium capsule</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple Unit-Dose Devices</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diskhaler</td>
<td>fluticasone blister</td>
</tr>
<tr>
<td></td>
<td>zanamivir blister</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple-Dose Devices</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Turbuhaler</td>
<td>budesonide</td>
</tr>
<tr>
<td>Turbuhaler</td>
<td>budesonide/formoterol</td>
</tr>
<tr>
<td>Diskus</td>
<td>salmeterol</td>
</tr>
<tr>
<td>Diskus</td>
<td>salmeterol/fluticasone</td>
</tr>
</tbody>
</table>

1- Unit-dose devices with drug in hard gelatin capsules

The first DPI device developed was the Spinhaler for the delivery of sodium cromoglycate. Each dose, contained in a hard gelatin capsule, is loaded individually into the device.
2- Multidose devices with drug in foil blisters

I- Diskhaler (Glaxo SmithKline). In this system, drug is mixed with a coarse lactose carrier and filled into an aluminium foil blister disc which is loaded, by the patient, into the device on a support wheel. Each disc contains four or eight doses of drug and the blisters are pierced with a needle as a result of mechanical leverage on the lid. Air flow through the blister causes the powder to disperse.

II- The Turbohaler (AstraZeneca), has overcome the need for both a carrier and the loading of individual doses. The device contains a large number of doses (up to 200) of undiluted, loosely aggregated micronized drug, which is stored in a reservoir from which it flows on to a rotating disc in the dosing unit. The fine holes in the disc are filled and the excess drug is removed by scrapers. As the rotating disc is turned, by moving a turning grip back and forth, one metered dose is presented to the inhalation channel, and this is inhaled by the patient.
The Turbohaler requires a higher inspiratory effort than the Diskhaler, owing to its higher internal resistance, and is more sensitive to humidity if not closed quickly after each use.

**Nebulizers**

Nebulizers deliver relatively large volumes of drug solutions and suspensions and are frequently used for drugs that cannot be conveniently formulated into MDIs or DPIs, or where the therapeutic dose is too large for delivery with these alternative systems.

Nebulizers also have the advantage over metered dose and dry powder systems in that drug may be inhaled during normal tidal breathing through a mouthpiece or face-mask, and thus they are useful for patients such as children, the elderly and patients with arthritis, who experience difficulties with MDIs.

There are two categories of commercially available nebulizer: jet and ultrasonic.

**Jet nebulizers**

Jet nebulizers (also called air-jet or air-blast nebulizers) use compressed gas (air or oxygen) from a compressed gas cylinder, hospital air-line or electrical compressor to convert a liquid (usually an aqueous solution) into a spray.

**Ultrasound nebulizers**

In ultrasonic nebulizers the energy necessary to atomize liquids comes from a piezoelectric crystal vibrating at high frequency. At sufficiently high ultrasonic intensities a fountain of liquid is formed in the nebulizer chamber.
Manufacturing consideration

Aside from the active ingredient, water is usually the most important constituent in a liquid product. It should meet the USP requirements for purified water. It may be obtained by distillation or ion-exchange treatment. In recent years, manufacturers have devoted considerable effort to upgrading the microbial purity of the water supply used in oral liquids. Techniques employed include reverse osmosis purification, ultraviolet sterilization, membrane filtration, and constant circulation in piping systems that have no “dead ends” where microorganisms can thrive. In general, the most difficult microbes to remove from a purified water system are the pseudomonads. Figure 15-10 shows a purified water system designed to minimize microbial growth.
The ion-exchange resin used in the water system are important to the successful maintenance of low bacteria counts. Ex a quaternary ammonium anion-exchange resin is effective for a wide range of flow rates and for many different bacterial strains. Amberlite IR-120 is a strongly acidic, cation-exchange resin that balances the chemical equilibrium of the water.

**Equipment**

The type of equipment used in the manufacturing of oral solutions consist of mixing tanks equipped with a means of agitation, measuring devices for large and small amount of solids and liquids, and a filtration system for the final polishing and/or sterilization of the solution. In addition most product facilities are equipped with systems for bulk material handling, such as discharging equipment.
All equipment must be thoroughly cleaned and sanitized (sterilized if possible) before use. Appropriate disinfectants include dilute solutions of hydrogen peroxide, phenol derivatives, and peracetic acid. Equipment and lines can be sterilized by such methods as alcohol, boiling water, autoclaving, steam, or dry heat.

Tanks are usually constructed of polished stainless steel and are usually jacketed to allow for heating or cooling of the contents. They can be obtained in a number of different sizes, and are completely covered and equipped with see-through charging ports and illumination for easy observation of the contents. If tanks are used for the compounding of the bulk liquid, they have a built-in agitation system.

Water condensate that forms on the lid of mixing tanks and similar processing equipment during heating and chilling steps may provide a source of microbial contamination that is often overlooked.

The liquid is then clarified by cycling through a filtration system, and the polished solution is stored in an adjacent tank until released by the quality control department. The liquid may then be transported to the filling line, either manually by filling into portable transport tanks or by pumping (or gravity flow) through a suitable liquid delivery conduit.
The distance the product travels between the holding tank and the filling line should be held to a minimum to reduce the chance of microbial contamination. All lines should be easy to disassemble, clean, and sanitize.

A major source of microbial contamination is often the processing operators. Head covering should be worn at all times. Gloves and face masks should be worn as necessary.

An ongoing education program is recommended to maintain operator interest and concern for good work habits.

**Compounding procedure**

Dilute solutions, prepared from rapidly dissolving materials are simply prepared by charging the solute to the solvent and agitation until the solution is homogeneous. When more concentrated sol are being made, or when the solute is slowly dissolving, it may advantageous to employ heat. The syrup formula and manufacturing method presented in next table illustrate some of the steps involved in compounding a complex liquid formulation.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Per ml</th>
<th>Per batch (5000 L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>2.00 mg.</td>
<td>10.0 kg</td>
</tr>
<tr>
<td>Sodium benzoate USP</td>
<td>1.00 mg.</td>
<td>5.0 kg</td>
</tr>
<tr>
<td>Menthol. USP</td>
<td>0.10 mg.</td>
<td>0.5 kg</td>
</tr>
<tr>
<td>Alcohol. USP</td>
<td>0.05 ml. (40.8 mg.)</td>
<td>250.0 liters (204.0 kg.)</td>
</tr>
<tr>
<td>Flavor</td>
<td>0.005 ml. (4.5 mg.)</td>
<td>25.0 liters (22.5 kg.)</td>
</tr>
<tr>
<td>Dye FD&amp;C Yellow No. 6</td>
<td>0.10 mg.</td>
<td>0.5 kg</td>
</tr>
<tr>
<td>Glycerin</td>
<td>0.05 ml. (62.45 mg.)</td>
<td>250.0 liters (312.250 kg.)</td>
</tr>
<tr>
<td>Sorbitol solution, USP</td>
<td>0.10 ml. (128.5 mg.)</td>
<td>500.0 liters (642.5 kg.)</td>
</tr>
<tr>
<td>Standard granulated sugar</td>
<td>550.00 mg.</td>
<td>2750.0 kg</td>
</tr>
<tr>
<td>Purified water, USP q.s. 10</td>
<td>1.0 ml.</td>
<td>5000 liters</td>
</tr>
</tbody>
</table>
1. Charge 2000 L of purified water through the water meter into the compounding tank. Check the volume against the outage chart. Heat to approximately 50°C.

2. To the water in the compounding tank, charge the following materials in the amounts specified in the batch sheet. Dissolve each one, with agitation, before adding the next: (a) drug, (b) sodium benzoate, (c) standard granulated sugar. Agitate the contents of the compounding tank until homogeneous, and then cool to 30°C.

3. Charge the specified amount of glycerin to the compounding tank. Agitate until the batch is homogeneous.

4. Charge the specified amount of sorbitol solution to the compounding tank. Agitate until the batch is homogeneous.

5. Measure 20 L of alcohol into a suitable stainless steel container. Add and dissolve the specified charge of menthol. Add and dissolve the specified charge of flavor.

6. Charge the alcoholic solution of menthol and flavor to the batch in the compounding tank. Agitate until homogeneous.

7. Charge the balance of the specified amount of alcohol to the batch. Agitate until homogeneous.

8. Charge 10 L of purified water to a clean stainless steel container. Add to the water and dissolve the specified amount of FD&C Yellow No. 6.

9. Charge the dye solution to the batch in the compounding tank, and agitate until homogeneous.

10. Add to the compounding tank sufficient purified water to bring the batch volume to 5000 L.

11. Weigh out 2.5 kg of filter aid, and charge it to the contents of the compounding tank. Agitate for 10 min. The batch is now ready to filter.

12. Cycle the batch through the filter and back to the compounding tank until the filtrate is clear. At this point, the filtrate may be discharged and collected in the designated holding tank.

13. Sample the batch, and submit for testing in accordance with standard procedure.
Packaging

The specific method used for filling a pharmaceutical liquid varies greatly depending on the characteristics of the liquid (e.g. viscosity, surface tension, foam-producing qualities and compatibility with the materials used in the construction of the filling machine), the type of package into which the liquid is placed, and the required product output. Three basic filling methods: gravimetric, volumetric, and constant level are used for most liquid filling operation.

The last two methods are used most frequently in filling of pharmaceutical liquids. Filling containers to a given weight (gravimetric filling) is limited to large containers or to highly viscous products. Volumetric filling is usually accomplished by positive displacement piston action. Each filling station is equipped with a measuring piston and cylinder.

Constant-level filling uses the containers as the means for controlling the fill of each unit. The fill amount is varied by adjusting the height to which the container is filled. Any dimensional variations in the container result in comparable variation in the net filling per unit.

A problem that is common to all types of liquid filling machines, but that is particularly bothersome with high-speed automatic equipment, is excessive foam. Foaming during the filling operation often can be decreased by filling equipment that minimise product turbulence, closed-system filling to limit the introduction of air or other gases that participate in the formation of foam, mechanical defoaming devices, and reduction in the speed of filling line.
Manufacturing of suspension

Preparative Techniques

The actual preparation of suspension involve choosing the ingredients and determining the type of manufacturing equipment to be used. If the susp is made by dispersion process, it is best to achieve pulverisation of the solid by a micronisation technique. This involves subjecting the particles to a turbulent air chamber in which they collide with each other and fracture. Particles under 5 microns are readily obtained. Although it is not widely used for this purpose, spray drying also can be considered a method of comminution to produce a finely divided solid phase.

If the susp is made by controlled crystalization, a supersaturated sol should be formed and then quickly cooled with rapid stirring. This cause the formation of many nuclei and hence many crystals.

At some times during sus extension, it is likely that shearing will be desired. This homogenization can be accomplished by the conventional stator-rotor colloid mills. Ultrasonic equipment also can be used to effect high intensity mixing, but usually, this technique is not applied commercially.
Excessive shearing (or high temperature) may irreversibly damage polymeric materials such as gums, so that viscosity loss is suffered. Instead of trying to hydrate gums and clays by massive shearing, it is often better to give the material the necessary time to hydrate under condition of mild shearing.

An alternate procedure is to mix with, or preferably spray the gum with aceton or alcohol solution of wetting agent (e.g. sodium dioctyl sulfosuccinate). About 0.4% (based on the gum weight) of the wetting agent should be added to the gum. This technique can produce a marked beneficial effect, as wetting of the gum and hence hydration is greatly accelerated.

**Formulation example**

**Aluminum hydroxide suspension**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide</td>
<td>326.8 g</td>
</tr>
<tr>
<td>Sorbitol solution</td>
<td>282.0 mL</td>
</tr>
<tr>
<td>Syrup</td>
<td>93.0 mL</td>
</tr>
<tr>
<td>Glycerin</td>
<td>25.0 mL</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.9 g</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>0.3 g</td>
</tr>
<tr>
<td>Flavor</td>
<td>q.s.</td>
</tr>
<tr>
<td>Purified water, to make</td>
<td>1000.0 mL</td>
</tr>
</tbody>
</table>
The parabens are dissolved in a heated mixture of the sorbitol solution, glycerin, syrup, and a portion of the water. The mixture is then cooled and the aluminum hydroxide added with stirring. The flavor is added and purified water to the volume. The suspension is then homogenized, using a hand homogenizer, homomixer, or colloid mill. A high-speed industrial-size mixer used to prepare dispersions of various types, including suspensions and emulsions, is shown in Figure 14.5. A large storage holding tank with a liquid filling unit in the process of filling large-mouth suspension bottles is shown in Figure 14.6.
Equipment for emulsification

- Mechanical stirrers
- Homogenizers
- Ultrasonifiers
- Colloid mills

**Mechanical Stirrers.** An emulsion may be stirred by means of various impellers mounted on shafts, which are placed directly into the system to be emulsified. Simple top-entering propeller mixers are adequate for routine development work in the laboratory and for production purposes, if the viscosity of the emulsion is low. If more vigorous agitation is required, or if the preparation has moderate viscosity, turbine type mixers are employed both in the laboratory and in production. Other mixers, provided with paddle blades, counter rotating blades, or planetary action blades, are available for special requirements. The degree of agitation is controlled by the speed of impeller rotation, but the patterns of liquid flow and the resultant efficiency of mixing are controlled by the type of impeller, its position in the container, the presence of baffles, and the general shape of the container (Chaps. 5
the use of stirrers for the formation of emulsions is often limited when vigorous agitation of viscous systems is required, when extremely fine droplets are needed, or when foaming at high shear rates must be avoided.

**Homogenizers**

In a homogenizers, the dispersion of two liquids is achieved by forcing their mixture through a small inlet orifice at high pressures.

Homogenisers are useful for liquids or pastes, however, homogenisation rise the temp of the emulsion and cooling is required.

**Ultrasonifier**

These devices have limited output and are expensive. They usually used in lab for fluid emulsion of moderate viscosity and extremely low particle size.

**Colloid mills**

Homogenizers and ultrasonic equipment depend on sudden changes in pressure to effect the dispersion of liquids. By contrast, colloid mills operate on the principle of high shear, which is normally generated between the rotor and the stator of the mill. Colloid mills are used primarily for the comminution of solids and for the dispersion of susp containing poorly wetted solids but are useful for the preparation of relatively viscous emulsion.

**Example**

1. Oral Emulsion (o/w)

| (A) Cottonseed oil, winterized | 460.0 g |
| Sulfadiazine                    | 200.0 g |
| Sorbitan monostearate          | 84.0 g  |
| (B) Polyoxyethylene (20) sorbitan monostearate | 36.0 g |
| Sodium benzoate                | 2.0 g  |
| Sweetener                      | qs     |
| Water, potable                 | 1000.0 g |
| (C) Flavor oil                 | qs     |
To develop a smooth product it is necessary to reduce the particle size of sulfadiazine. For this purpose, the blend of the drug, the oil and the oleophilic emulsifier is warmed slightly and passed through a colloid mill. The emulsion itself is formed by adding the drug susp to the aqueous phase, but in contrast to usual emulsion tech, the two phases are blended at different temp. Presumably, heating of the drug susp at 65 C would materially lower its viscosity and cause excessive settling of the drug particles unless specialized stirring equipment were employed.

Notes: The addition of the flavoring oil at a lower temp prevents loss due to volatility. The emulsion should be protected against microorganisms, sodium benzoate used for this purpose. The absence of an antioxidant in this emulsion suggests the presence of such additive in the cottonseed oil.
Microencapsulation

Is a mean of applying relatively thin coatings to small particles (from 1 to 1000 µm) of solids or droplets of liquids and dispersions.

Applications

• This technique can be used for converting liquid drugs in a free flowing powder.
• The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation.
• Incompatibility among the drugs can be prevented by microencapsulation.
• Vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil can be prevented by microencapsulation.
• Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl.
• Alteration in site of absorption can also be achieved by microencapsulation.
• Toxic chemicals such as insecticides may be microencapsulated to reduce the possibility of sensitization of factorial person.
Core material
The core material, defined as the specific material to be coated, can be liquid or solid in nature. The composition of the core material can be varied, as the liquid core can include dispersed and/or dissolved materials. The solid core can be active constituents, stabilizers, diluents, excipients, and release-rate retardants or accelerators.

Coating materials
The selection of appropriate coating material decides the physical and chemical properties of the resultant microspheres. While selecting a polymer, the product requirements ie. Stabilization, reduced volatility, release characteristics, environmental conditions, etc. should be taken into consideration. The polymer should be capable of forming a film that is cohesive with the core material. It should be chemically compatible, non-reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability.

Generally hydrophilic polymers, hydrophobic polymers (or) a combination of both are used for the microencapsulation process.

A number of coating materials have been used successfully; examples include gelatin, polyvinyl alcohol, ethyl cellulose and cellulose acetate phthalate. The film thickness can be varied considerably depending on the surface area of the material to be coated and other physical characteristics of the system.

The microcapsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions, and other dosage forms.
Table 1: Core material and its characteristics

<table>
<thead>
<tr>
<th>Core Material</th>
<th>Characteristic Property</th>
<th>Purpose of Encapsulation</th>
<th>Final Product Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Slightly water-soluble solid</td>
<td>Taste-masking</td>
<td>Tablet</td>
</tr>
<tr>
<td>Activated Charcoal</td>
<td>Adsorbent</td>
<td>Selective sorption</td>
<td>Dry Powder</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Slightly water-soluble solid</td>
<td>Taste-masking, sustained release, reduced gastric irritation, separation of incompatibles</td>
<td>Tablet or capsule</td>
</tr>
<tr>
<td>Islet of Langer-Hans</td>
<td>Viable cells</td>
<td>Sustained normalization of diabetic condition</td>
<td>Injectable</td>
</tr>
<tr>
<td>Insorbide dinitrate</td>
<td>Water-soluble solid</td>
<td>Sustained release</td>
<td>Capsule</td>
</tr>
<tr>
<td>Liquid crystals</td>
<td>Liquid</td>
<td>Conversion of liquid to solid, stabilization</td>
<td>Flexible film for thermal mapping of anatomy</td>
</tr>
<tr>
<td>Menthol/methyl salicylate/camphor mixture</td>
<td>Volatile solution</td>
<td>Reduction of volatility, sustained release</td>
<td>Lotion</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Slightly water-soluble solid</td>
<td>Sustained release</td>
<td>Varied</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>Highly water-soluble solid</td>
<td>Reduced gastric irritation</td>
<td>Capsule</td>
</tr>
<tr>
<td>Urease</td>
<td>Water-soluble enzyme</td>
<td>Perme selectivity of enzyme, substrate, and reaction products</td>
<td>Dispersion</td>
</tr>
<tr>
<td>Vitamin-A Palmitate</td>
<td>Nonvolatile liquid</td>
<td>Stabilization to oxidation</td>
<td>Dry powder</td>
</tr>
</tbody>
</table>

**Examples on improved stability**

**FIG. 13-32.** Stability of a microencapsulated vitamin A palmitate corn oil prepared by phase-separation/coacervation technique, compared with an unencapsulated control. (From Bahan.)

**FIG. 13-34.** Stability enhancement of incompatible aspirin mixture by microencapsulation. A, Aspirin hydrolysis of chlorpheniramine maleate-aspirin mixture; B, aspirin hydrolysis of microencapsulated mixture; and C, hydrolysis of aspirin control. (From Bahan.)
Example on release property

Release of aspirin accomplished by a diffusion mechanism from the PH-insensitive ethylcellulose polymer.

Fig. 13-35. In vitro release patterns of crystalline aspirin coated with various amounts of ethylcellulose using phase-separation/coacervation techniques. A, 52% coating; B, 29% coating; C, 16% coating; D, 13% coating. (From The NCR Corporation.)

MICROENCAPSULATION TECHNIQUES

I-Physical methods

1- Air-suspension coating

Microencapsulation by air suspension technique consist of the dispersing of solid, particulate core materials in a supporting air stream and the spray coating on the air suspended particles. Within the coating chamber, particles are suspended on an upward moving air stream. The design of the chamber and its operating parameters effect a recirculating flow of the particles through the coating zone portion of the chamber, where a coating material, usually a polymer solution, is spray applied to the moving particles.

During each pass through the coating zone, the core material receives an increment of coating material. The cyclic process is repeated depending on the purpose of microencapsulation, the coating thickness desired or whether the core material particles are thoroughly encapsulated.
The supporting air stream also serves to dry the product while it is being encapsulated. Drying rates are directly related to the volume temperature of the supporting air stream.

2- Coacervation

The first commercial microparticle product based on the complex coacervation method was carbonless copy paper. This process consists of three Steps:

**Step-1: The first step of coacervation phase separation involves the formation of three immiscible chemical phases:**
a liquid vehicle phase, a coating material phase and a core material phase. The three phases are formed by dispersing the core material in a solution of coating polymer, the vehicle phase is used as a solvent for polymer.
The coating material phase consists of a polymer in a liquid phase, is formed by using one of the phase separation-coacervation method, i.e., by changing the temperature of the polymer solution, by adding a salt, or by inducing a polymer-polymer interaction.

**Step-2:** It involves the deposition of the liquid polymer coating upon the core material. This is done by controlled mixing of liquid coating material and the core material in the manufacturing vehicle. The liquid coating polymer deposited on the core material if the polymer is adsorbed at the interface formed between the core material and liquid phase.

**Step-3:** In the last step rigidizing of the coating material done by the thermal, cross linking desolvation techniques, to forms a self supporting microcapsule.

![Diagram](image.png)

Fig. 4: Coacervation process: (a) Core material dispersion in solution of shell polymer; (b) Separation of coacervate from solution; (c) Coating of core material by micro droplets of coacervate; (d) Coalescence of coacervate to form continuous shell around core particles.
3- Pan coating

Relatively large particles can be encapsulated by pan coating. Size of solid particles should be greater than 600 um to achieve effective coating using this method.

Medicaments are usually coated onto various spherical substances such as nonpareil seeds and then coated with protective layers of various polymers.

The coating is apply as a solution or or as an atomised spray to the desired solid core materials in the coating pan.

To remove the coating solvent, warm air is passed over the coated materials as the coating are being applied in the coating pan. In some cases, final solvent removal is conducted in a drying oven.

4-Spray Drying

Spray drying is a single-step, closed-system process applicable to a wide variety of materials. The drug is dissolved or suspended in a suitable (either aqueous or non-aqueous) solvent containing polymer materials. The solution or suspension is atomized into a drying chamber, and microparticles form as the atomized droplets are dried by heated carrier gas. The result of the spray drying process is heavily dependent on the material properties: The instrument settings, such as inlet temperature, rate of feed flow, spray air flow, and aspirator flow, can together influence the product parameters such as particle size, yield, temperature load, and content of residual solvents.
II-Chemical methods
1- Solvent evaporation
The processes are carried out in a liquid manufacturing vehicle.

2- Polymerization
Oral Modified Release Dosage Forms

Modified release dosage forms are drug delivery systems whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenient objectives not offered by conventional forms.

Several types of modified-release drug products are recognized:

1. **Extended-release drug products.** A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

2. **Delayed-release drug products.** A dosage form that releases a discrete portion or portions of drug at a time other than promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

3. **Targeted-release drug products.** A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

The USP considers that the terms controlled release, prolonged release and sustained release are interchangeable with extended release.

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**Diagram 1:**
- Immediate release
- Delayed release
- Plasma concentration over time

**Diagram 2:**
- Rapid release
- Sustained release
- Concentration (μg/mL) over time (hours)
**Advantages of sustained release dosage forms:**
1. Control of drug therapy is achieved.
2. Rate and extent of drug absorption can be modified
3. Frequency of drug administration is reduced.
4. Patient compliance can be improved.
5. Maximizing the availability of drug with minimum dose.
6. The safety margin of high potency drug can be increased.

**Disadvantages of sustained release dosage forms:**
1. It not permits rapid termination of therapy.
2. Less flexibility in dose adjustment.
3. These dosage forms are designed on the basis of average biological half life.
4. MR formulations cost more per unit dose than conventional dosage form.

**DRUG CANDIDATES FOR EXTENDED-RELEASE PRODUCTS**

1- The drug suited for ex-release should exhibit neither very slow nor very fast rates of absorption and excretion. Drugs with slow rates of absorption and excretion are usually inherently long-acting. Drugs with very short half-lives, i.e., less than 2 hours, are poor candidates for extended release because of the large quantities of drug required for such a formulation. Also, drugs that act by affecting enzyme systems may be longer acting than indicated by their quantitative half-lives because of residual effects and recovery of the diminished biosystem.

2- They are uniformly absorbed from the gastrointestinal tract. Drugs prepared in extended-release forms must have good aqueous solubility and maintain adequate residence time in the gastrointestinal tract. Drugs absorbed poorly or at varying and unpredictable rates are not good candidates for extended-release products.
3-They are administered in relatively small doses. Drugs with large single doses are not suitable for extended release because the tablet or capsule needed to maintain a sustained therapeutic blood level of the drug would be too large for the patient to swallow easily.

4-They possess a good margin of safety. The most widely used measure of the margin of a drug's safety is its therapeutic index. Drugs that possess very narrow therapeutic indices are poor candidates for formulation into extended-release formulations because of technologic limitations of precise control over release rates and the risk of dose dumping due to a product defect. Patient misuse (e.g., chewing dosage unit) also could result in toxic drug levels.

5- They are used in the treatment of chronic rather than acute conditions. Drugs for acute conditions require greater adjustment of the dosage by the physician than that provided by extended-release products.

APPROACHES TO SUSTAIN RELEASE DRUG DELIVERY SYSTEM
1. Dissolution controlled release systems
2. Diffusion controlled release systems
3. Ion exchange resin- drug complexes
4. Osmotic pressure controlled systems
5- Mucoadhesive system

I-Dissolution controlled Systems

In dissolution systems, the release rate functions through dissolution and not diffusion. Various methods attempt to decrease the dissolution rate of the drug, especially highly soluble drugs, through using slow-dissolving polymers. The dissolution systems can be achieved through two approaches:
A. **Matrix dissolution controlled release system**

Matrix dissolution system is known as monolithic because the drug present in the matrix is completely dissolved in the medium (usually polymer). As the polymer dissolves, the drug will be released as polymer is dissolving simultaneously. In this case, instead of the drug being entrapped inside of the membrane, the drug is blended with the polymer in a matrix. They are mostly made of waxes like beeswax, carnauba wax, hydrogenated castor oil, etc. and play important role to control the drug release rate by controlling the rate of dissolution.

Examples on matrix dissolution product. Repetab tablets, chlor-Trimeton (chlorpheniramie maleate).

B. **Reservoir dissolution controlled release system**

In reservoir system, the drug particles are coated by polymers that dissolving at a given rate; normally, slow release rate is achieved through using slow-dissolving polymers. As the membrane surrounding the drug dissolves, the drug will slowly be released and available for dissolution.

<table>
<thead>
<tr>
<th>Table 47-4. Encapsulated Dissolution Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRODUCTS</strong></td>
</tr>
<tr>
<td>Spansule capsules</td>
</tr>
<tr>
<td>Dexedrine</td>
</tr>
<tr>
<td>Hispiril</td>
</tr>
<tr>
<td>Thorazine</td>
</tr>
<tr>
<td>Sequel capsules</td>
</tr>
<tr>
<td>Artrane</td>
</tr>
<tr>
<td>Diamox</td>
</tr>
<tr>
<td>Ferro-sequels</td>
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</tbody>
</table>
Diffusion systems rely on diffusion for the drug release rate. There are two types of diffusion systems – reservoir device and matrix device.

**A- Reservoir device**

In a reservoir device, the core of the drug is surrounded by a polymeric membrane, which determines the rate of drug release based on Fick’s first law. Therefore, the drug release mechanism primarily involves diffusion. The release rate is variable with polymer type and thickness of the membrane, as well as drug concentration and partition coefficient of the drug. Zero order delivery is possible with this system, but it can have the potential for toxicity if the system fails.
B-matrix device
In a matrix device, the drug is mixed homogenously with the polymer matrix. Solid drug on the surface of the dosage form that is exposed to the aqueous solution will dissolve first and diffuse out of the matrix. Then the drug will dissolve layer by layer.

The matrix device is ideal for giving a bolus dose coupled with sustained release. Compared with the reservoir device, the matrix device releases drug quicker because no rate controlling membrane exists.

- Many different insoluble materials can be used to create a matrix device. These include insoluble plastics, such as polyvinyl chloride or polyethylene. Hydrophilic polymers with high molecular weights such as methylcellulose and sodium carboxymethylcellulose can also be employed. Lipid compounds like wax or glyceryl tristearate are other common examples of matrix materials.

<table>
<thead>
<tr>
<th>Table 47-3. Matrix Diffusion Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRODUCTS</strong></td>
</tr>
<tr>
<td>Gradumet tablets</td>
</tr>
<tr>
<td>Desoxyn</td>
</tr>
<tr>
<td>Ferro-Gradumet Tral</td>
</tr>
<tr>
<td>Lontab tablets</td>
</tr>
<tr>
<td>PBZ-SR</td>
</tr>
<tr>
<td>Procan SR</td>
</tr>
</tbody>
</table>

Drugs release through diffusion
Least complicated approaches to manufacture sustained release dosage form involves the direct compression of drug, materials & additives to form a tablet.
III-Osmotic Systems

These types of system are also known as oros, which follows the mechanism of osmotic pressure where the drug is released at constant zero order rate. The reservoir is made up of the drug and osmotic agent like mannitol or KCl, which is surrounded by semi-permeable membrane. A small orifice is present in the dosage form, which allows the entry of water in the reservoir and helps the dissolved drug to pumped out at the determined rate due to osmotic pressure. The release of the drug from the reservoir is unaffected by the conditions of the GIT. The release of drug is depended on factors like size of orifice, thickness of semipermeable membrane, permeability of membrane, osmotic properties of core and stability of the drug. The OROS System is the main osmotic system owned by Alza Corporation.
Another osmotic oral drug product is the "push–pull" system called Gastrointestinal Therapeutic System (GITS), developed by Alza Corporation for nifedipine (Procardia XL) and other drugs. The system consists of a semipermeable membrane and a two-layer core of osmotic ingredient and active drug. As water enters the system, the osmotic pressure builds up from the inner layer, pushing the drug out through a laser-drilled orifice in the drug layer. An example of GITS uses acetazolamide for the treatment of ocular hypertension in glaucoma. The drug was delivered from the system at zero-order rate for 12 hours at 15 mg/hr, as shown in.

**Pellet-Type Sustained-Release Products**

The pellet type of sustained-release drug product is also often referred to as a bead-type dosage form. In general, the beads are prepared by coating drug powder onto preformed cores called *nonpareil seeds*. The nonpareil seeds are made from slurry of starch, sucrose, and lactose. Preparation of the cores is tedious. The rough core granules are rounded for hours on a coating pan and then classified according to size. The drug-coated beads generally provide a rapid-release carrier for the drug depending on the coating solution used.
Coatings may be aqueous or nonaqueous. Aqueous coatings are preferred. Nonaqueous coatings may leave residual solvents in the product, and removal of solvents during manufacture presents danger to workers and the environment. Cores are coated by either sprayed pan coating or by air-suspension coating. Once the drug beads are prepared, they may be further coated with a protective coating to allow a sustained or prolonged release of the drug.

The use of various amounts of coating solution can provide beads with various coating protection. A careful blending of beads may achieve any release profile desired. Alternatively, a blend of beads coated with materials of different solubility may also provide a means of controlling dissolution of the drug.

Some products take advantage of bead blending to provide two doses of drug in one formulation. For example, a blend of rapid-release beads with some pH-sensitive enteric-coated material may provide a second dose of drug release when the drug reaches the intestine.

The pellet dosage form can be prepared as a capsule or tablet. When pellets are prepared as tablets, the beads must be compressed lightly so that they do not break. Usually, a disintegrant is included in the tablet, causing the beads to be released rapidly after administration.
Formulation of a drug into pellet form may reduce gastric irritation, because the drug is released slowly over a period of time, therefore avoiding high drug concentration in the stomach. Dextroamphetamine sulfate timed-release pellets (Dexedrine Spansule) is an early example of a beaded dosage form.

Another older product is a pellet-type extended-release product of theophylline. The frequency of adverse reactions after theophylline is administered as solution is higher than the case when theophylline administered as pellets. Some side effects may be attributed to the high concentration of theophylline. Pellet dosage form allows drug to be absorbed gradually, therefore reducing the incidence of side effects by preventing a high $C_{\text{max}}$.

A major advantage of the pellet dosage form is that the pellets are less affected by the effect of stomach emptying. Because numerous pellets are within a capsule, some pellets will gradually reach the small intestine each time the stomach empties, whereas a single extended-release tablet may be delayed in the stomach for a long time as a result of erratic stomach emptying.
Prolonged-Action Tablets

An approach to prolong the action of a drug is to reduce the aqueous solubility of the drug, so that the drug dissolves slowly over a period of several hours. The solubility of a drug is dependent on the salt form used, and an examination of the solubility of the various salt forms of the drug should be the first step in drug development. In general, the base or acid form of the drug is usually much less soluble than the corresponding salt. For example, sodium phenobarbital is more water soluble than phenobarbital, the acid form of the drug. Diphenhydramine hydrochloride is more soluble than the base form, diphenhydramine.

Many of the lubricants used in tableting may also be used as lipophilic agents to slow dissolution. For example, magnesium stearate and hydrogenated vegetable oil (Sterotex) are actually used in high percentages to cause sustained drug release in a preparation. The major disadvantage of this type of preparation is the difficulty in maintaining a reproducible drug release from patient to patient, because oily materials may be subjected to digestion, temperature, and mechanical stress, which may affect the release rate of the drug.
Manufacture of semisolids

Manufacture of semisolid emulsion

Time, temp and mechanical work are three variables in the manufacture of emulsified semisolids. The three factors are interrelated and must be carefully controlled if the same high-quality batches are to be manufactured repeatedly.
Preparation of oil and aqueous phases

- The components of the oil or fat mixture are placed into a stainless steel steam-jacketed kettle melted, and mixed.
- Some of the solid components (e.g. stearic acid, cetyl alcohol) are available in many different forms: cakes, flakes, or powder. The flakes are preferable because of the convenience of handling. The powder may have occasional fine metal contaminants from the pulverising equipment. Petrolatum is inconvenient to handle unless it is melted and transferred by pumping or pouring from its drum. Transfer of large quantity of petrolatum is expedited by heating the petrolatum in the steel drum in which it is received from the supplier by means of immersion heaters, or by placing the drums in a hot room (60 to 62 °C) until the petrolatum is fluid.
liquified petrolatum can then be transferred to the mixing kettle by metering pump through metal-reinforced inert plastic hoses and insulated pipes. The oil phase is then strained through several layers of cheese cloth to remove any foreign matter. Alternatively, the petrolatum can be passed through a filter medium, particularly for an ophthalmic preparation. The oil phase is transferred by gravity or pump to the emulsion mixing kettle whose walls have been heated to the temp. of the oil phase to prevent some of its higher-melting components from congealing. The components of the aqueous phase are dissolved in the purified water and filtered. A soluble drug may be added to the aqueous phase at this time, provided the high temperature does not degrade the active substance or the emulsion is not adversely affected; otherwise, the soluble drug may be added in solution after the emulsion has formed and has cooled.
Mixing of Phases. The phases are usually mixed at a temperature of 70 to 72°C, because at this temperature intimate mixing of the liquid phases can occur. The phase mixing temperature can be lowered a few degrees if the melting point of the fat phase is low enough to prevent the premature crystallization or congealing of its components. Decreasing the temperature at which the phases are mixed decreases the cooling time, which is a significant factor when the batch size is large. The properties of some emulsions (borax-beeswax type) depend on the temperature at which the phases are mixed. The initial mixing temperature must be raised above 70 to 72°C, because intimate mixing of the components at monolayer levels cannot occur, since the emulsion that forms immediately has a high Viscosity.
The phases can be mixed in one of three ways:

1- Simultaneous blending of the phases
2- Addition of the dispersion phase to the continuous phase
3- Addition of the continuous phase to the dispersion phase
Cooling the semisolid emulsion

Following the addition of phases, the rate of cooling is generally slow to allow for adequate mixing while the emulsion is still liquid. The temp of the cooling medium in the kettle jacket should be decreased gradually and at a rate consistent with the mixing of the emulsion and scraping of the kettle walls to prevent formation of congealed masses of the ointment or cream, especially when the semisolid contains a large percentage of high-melting substances.
• If perfume is to be added to an O/W emulsion, it is best done while the mixture is at a temp of 43 to 45 C to avoid chilling the emulsion and to facilitate the dissolution of the perfume oil in the still incompletely congealed oil phase.

• The perfume may be added near room temp to a W/O emulsion, since dissolution of the perfume oil is to occur in the outer phase of the system.

• The drug is added in sol form, if not already incorporated, or as crystals, provided it is soluble in the external phase. An insoluble powder should be dispersed in the continuous phase prior to removing the semisolid from the kettle for homogenization and/or storage.
Soft gelatin capsules

SGC are capsules in which the mechanical properties of gelatin have been manipulated by the addition of a plasticiser (most notably glycerol or other polyhydric alcohols, e.g. sorbitol), resulting in a more flexible capsule. Softgels consist of a liquid or semisolid matrix inside a one-piece outer gelatin shell. Ingredients that are solid at room temperature can also be encapsulated into softgels, provided they are at least semisolid below approximately 45°C. The drug compound itself may be either in solution or in suspension in the capsule-fill matrix. The characteristics of the fill matrix may be hydrophilic (for example polyethylene glycols) or lipophilic (such as triglyceride vegetable oils).

The softgel capsule shell consists of gelatin, water and a plasticizer. It may be transparent or opaque, and can be coloured and flavoured if desired. Preservatives are not required owing to the low water activity in the finished product.

Although virtually any shape softgel can be made, oval or oblong shapes are usually selected for oral administration.
Softgels can be formulated and manufactured to produce a number of different drug delivery systems:

1-Orally administered softgels containing solutions or suspensions that release their contents in the stomach in an easy to swallow, convenient unit dose form.

2- Chewable softgels, where a highly flavoured shell is chewed to release the drug liquid fill matrix.

3- Suckable softgels, which consist of a gelatin shell containing the flavoured medicament to be sucked and a liquid matrix or just air inside the capsule.

4- Twist-off softgels, which are designed with a tag to be twisted or snipped off, thereby allowing access to the fill material. This type of softgel can be very useful for unit dosing of topical medication or inhalation.

5- Meltable softgels, designed for use as 'patient friendly' pessaries or suppositories.

**RATIONALE FOR THE SELECTION OF SOFTGELS AS A DOSAGE FORM**

1-Improved drug absorption

Softgel formulations address particular drug absorption issues by presentation of the drug to the g.i.t in the form of a solution from which it can be rapidly absorbed. With the solution-softgel approach, the shell ruptures within minutes to release the drug solution, which is usually in a hydrophilic or highly dispersing vehicle that aids the rate of absorption. This may be a valuable attribute for (a-) therapeutic reasons, such as the treatment of migraine or acute pain, or (b) where there is a limited absorptive region or 'absorption window' in the g.i.t.
2- Increased bioavailability

Softgels may also improve the extent of absorption. This can be particularly effective for hydrophobic drugs with a relatively high molecular weight. E.g. the protease inhibitor saquinavir, a solution-softgel product exhibits around three times the bioavailability of saquinavir hard capsule formulation.

In some cases a drug may be solubilized in a vehicle that is capable of spontaneously dispersing into an emulsion on contact with g.i.t fluid. This is known as a self-emulsifying system. In other cases a drug may be dissolved in an oil/surfactant vehicle that produces a microemulsion or a nanoemulsion on contact with gastrointestinal fluids e.g. A nanoemulsion of progesterone.

3- Decreased plasma variability

High variability in drug plasma levels is a common characteristic of drugs with limited bioavailability. The cyclic polypeptide drug cyclosporine (Sandimmun Neoral®) benefits from such an approach by using a microemulsion preconcentrate in a softgel.

4- Patient compliance and consumer preference
Consumers expressed their preference for softgels in terms of (a) ease of swallowing, (b) absence of taste and (c) convenience. In addition due the high BA of drug in softgel it is possible to reduce the capsule size, which will further improve patient compliance.
5- Safety for potent and cytotoxic drugs
The processes used in preparing tablets and hard-shell capsules can generate a significant quantity of airborne powders. This can be of great concern for highly potent or cytotoxic compounds in terms of the operator and environmental protection required for satisfactorily safe product manufacture.

By preparing a solution or suspension of drug, where the active component is essentially protected from the environment by the liquid, such safety concerns can be significantly reduced.

Oils and low melting-point drugs
Other low melting-point drugs may be formulated with a diluent oil in order to ensure satisfactory liquid flow and dosing into softgels.

6- Dose uniformity of low-dose drugs
In pharmaceutical manufacture liquid dosing avoids the difficulties of poor powder flow and therefore poor content uniformity.

Improved homogeneity is achieved by dissolving the drug in a liquid and then encapsulating the liquid matrix in a softgel.

Product stability
If a drug is subject to oxidative or hydrolytic degradation, the preparation of a liquid-filled softgel may prove beneficial. The liquid is prepared and encapsulated under a protective nitrogen atmosphere and the subsequently dried shell has very low oxygen permeability. By formulating in a lipophilic vehicle and packaging in well designed blister packs using materials of low moisture transmission, the drug can be protected from moisture. Conversely, it is well accepted that, in a solution, the drug may be more reactive than in the dry state and therefore potentially less stable.
MANUFACTURE OF SOFTGELS

The method of manufacture was improved using a process that involved sealing two sheets of gelatin film between a pair of matching flat brass dies. The pressure between the two plates enabled individual capsules to be cut out from the die mould, and these capsules were subsequently dried.

In old machine of liquid-fill capsules, the rotary die process involves the continuous formation of a heat seal between two ribbons of gelatin, simultaneous with dosing of the fill liquid into each capsule.

Although the speed and efficiency of the manufacturing process have improved greatly in recent years, the basic manufacturing principle remains essentially unchanged. Before the encapsulation process takes place, there are two subprocesses that are often carried out simultaneously, yielding the two components of a softgel. These are (a) the gel mass which will provide the softgel shell, and (b) the fill matrix for the contents.
The gel mass is prepared by dissolving the gelatin in water at approximately 80°C and under vacuum, followed by the addition of the plasticizer. Once the gelatin is fully dissolved then other components, such as colours, opacifier, flavours and preservatives, may be added.

The hot gel mass is then supplied to the encapsulation machine through heated transfer pipes by a casting method that forms two separate gelatin ribbons, each approximately 150 mm wide. During the casting process the gelatin passes through the sol-gel transition and the thickness of each gel ribbon is controlled to ± 0.1 mm, in the range of about 0.5-1.5 mm. The thickness is checked regularly during the manufacturing process.

The liquid fill matrix containing the active drug substance is manufactured separately from preparation of the molten gel. Manufacture of the active fill matrix involves dispersing or dissolving the drug substance in the non-aqueous liquid vehicle using conventional mixer-homogenizers.

A number of different parameters are controlled during the preparation of the active fill matrix, depending on the properties of the drug substance. For example, oxygen-sensitive drugs are protected by mixing under vacuum and/or inert gas; and in some cases an antioxidant component may be added to the formulation. Also, if the drug substance is present as a suspension in the liquid fill matrix then it is important to ensure that particle size of the drug does not exceed approximately 200 µm.
The process involves careful control of three parameters:
1. Temperature. This controls the heat available for capsule seal formation.
2. Timing. The timing of the dosing of unit quantities of fill matrix into the softgel during its formation is critical.
3. Pressure. The pressure exerted between the two rotary dies controls the softgel shape and the final cut-out from the gel ribbon.

FORMULATION OF SOFTGELS

Gelatin shell formulation
Typical softgel shells are made up of gelatin, plasticizer and materials that impart the desired appearance (colourants and/or opacifiers), and sometimes flavours.

**Gelatin**
A large number of different gelatin shell formulations are available, depending on the nature of the liquid fill matrix. Most commonly the gelatin is alkali- (or base-) processed (type B) and it normally constitutes 40% of the wet molten gel mass. Type A acid-processed gelatin can also be used.

**Important specification of gelatin**
- Bloom strength
- Viscosity
- Iron content
Plasticizers
Plasticizers are used to make the softgel shell elastic and pliable. They usually account for 20-30% of the wet gel formulation. The most common plasticizer used in softgels is glycerol, although sorbitol and propylene glycol are also used, often in combination with glycerol.

The amount and choice of the plasticizer contribute to the hardness of the final product and may even affect its dissolution or disintegration characteristics, as well as its physical and chemical stability. Plasticizers are selected on the basis of their compatibility with the fill formulation, ease of processing, and the desired properties of the final softgel, including hardness, appearance, handling characteristics and physical stability.

One of the most important aspect of softgel formulation is to ensure that there is minimum interaction or migration between the liquid fill matrix and the softgel shell.

Water
Water usually accounts for 30-40% of the wet gel formulation and its presence is important to ensure proper processing during gel preparation and softgel encapsulation. Following encapsulation, excess water is removed from the softgels through controlled drying. In dry softgels the equilibrium water content is typically in the range 5-8% w/w, which represents the proportion of water that is bound to the gelatin in the softgel shell. This level of water is important for good physical stability, because in harsh storage conditions softgels will become either too soft and fuse together, or too hard and embrittled.
Colourants/opacifiers

Colourants (soluble dyes, or insoluble pigments or lakes) and opacifiers are typically used at low concentrations in the wet gel formulation. Colourants can be either synthetic or natural, and are used to impart the desired shell colour for product identification. An opacifier, usually titanium dioxide, may be added to produce an opaque shell when the fill formulation is a suspension, or to prevent photodegradation of light-sensitive fill ingredients.

Titanium dioxide can either be used alone to produce a white opaque shell or in combination with pigments to produce a coloured opaque shell.

Modified-release capsules

- They are hard or soft capsules in which the contents or the shell or both contain excipients or are prepared by special procedures such as microencapsulation which, separately or together, are designed to modify the rate, place or time of release of the active ingredient(s) in the gastrointestinal tract.
• **Sustained-release capsules**
  *(Extended- or Prolonged-release capsules)* are designed to slow the rate of release of the active ingredient(s) in the gastrointestinal tract.

• **Delayed-release capsules**
  *(gastro-resistant/enteric capsules)* are hard or soft capsules prepared in such a manner that either the shell or the contents resist the action of gastric fluid but release the active ingredient(s) in the presence of intestinal fluid.
Manufacture of suppositories

Four methods are used in preparing supp, namely molding by hand, compression, pour molding, and compression on regular tablet press.

Pour molding

The most commonly used method for producing supp on both a small a large scale is the molding process. First, the base material is melted, preferably on a water or steam bath to avoid local overheating, and then active ing. Are either emulsified or suspended in it. Finally, the mass is poured into cooled metal molds, which are usually chrome-or nickle-plated.

Automatic molding machine

The molding operations (pouring, cooling, and removal) can be performed by machine. All filling, ejecting and mold-cleaning operations are fully automated. The output of a typical rotary machine ranges from 3500 to 6000 supp per hour.

In the rotary molding machine, chrome-plated brass molds are installed radially in the cooling turntable. First, the prepared mass is fed into a filling hopper where it is continuously mixed and maintained at constant temperature. The supp mold is lubricated by brushing or spraying and then filled to a slight excess. After the mass solidifies, the excess material is scraped off and collected for re-use. All pumping and scraping units are heated electrically at controlled temperatures.
After cooling, the solidified supps are moved to the ejecting station, where the mold is opened and the supps are pushed out by steel rods. The mold is closed, and then moved on to the spraying station for lubrication and a repeat of the cycle. Temp and output speeds are regulated to create optimal conditions for continuous, automatic production.

Molds must be kept clean to prevent any deposition of mass from interfering with their proper closure. Incomplete closure of the molds results in overweight supps with mold marks.

On the straight-line machine, molds are arranged for increased productivity (up to 10,000 supps per hour).

Packaging of molded suppositories
Suppositories must be packaged so that each supp is overwrapped or they must be placed in a container in such a manner that they do not touch each other. Staining, breakage or deformation by melting caused by adhesion can result from poorly wrapped and packaged supps.

Supps in direct contact with one another are spoiled by fusion resulting from changes in ambient temp. Partially melted supp stain the outer package unless they are overwrapped or are packaged with some other barrier that prevents contact with the outer container. Supps usually are foiled in tin or aluminum; paper and plastic strips are also used.

In-package molding
This involves an automated methods for molding supps directly in their wrapping material. This is accomplished with either plastic or aluminum foil. Machine utilizing plastic either thermoform the mold and fill the mold in sequence, or simply fill the mass into previously thermoformed molds.
Machine using aluminum foil/ polypropylene lacquer laminates emboss two parallel strips of foil so that when they are sealed together, molds are formed.

In both plastic and aluminum approaches, the tops of the molds are left open for the entrance of filling nozzles. After the mass has been injected, usually by means of small, variable-throw piston pumps, the tops are sealed. The strips are then passed in an upright position through a cooling station. Using these technique, one machine can make 12000 to 20000 supp per hour. The advantages of in-package molding include high production rates, no generation of scrapings, no bulk handling or storage of unwrapped supp and maintenance of strict temp control.

Disadvantages of in-package molding
1- Dependence on the shape of the formed mold and seal completeness for the shape of the supp.
2- depression formation in the rear of the supp since no scraping take place.
Disposable molds have the additional advantage of being suited for supp intended for tropical climates. If the mass should melt at the high storage temperatures, the mold still retains it in its proper shape, so that upon cooling it can be dispensed without distortion.

An approach to formulating supp.
The first consideration of the formulator are:
1- Is the medication intended for local or systemic use?
2- Is the site of application rectal, vaginal or urethral?
3- Is the desired effect to be quick, or slow and prolonged?
Evaluation of suppository

Testing of suppositories: Finished. suppositories are routinely inspected for:
• Appearance. Content uniformity. Melting range. test Drug release test.
  Fragility test. Disintegration test. Breaking test (Hardness)

Melting range test
• Macro-melting range is a measure of the time it takes for the entire suppository to melt when immersed in a constant-temperature (37°C) in water bath. USP tablet disintegration apparatus is used

In-vitro drug release
• In-vitro drug release pattern is measured by using the same melting range apparatus.
  • Aliquots of the release medium were taken at different time intervals within the melting period.
  • The drug content in the aliquots was determined.
  • The drug release pattern was plotted (time versus-drug release curve).

Rectal formulations other than suppositories

Apart from suppositories, many formulations can be used for the rectal administration of drugs. For the treatment of local disturbances, such as haemorrhoids, fatty ointments are widely used. In the treatment of rectocolitis large-volume enemas are used, e.g. 100 mL. This enables the drug to reach the upper part of the rectum and the sigmoid colon.

Capsules used to achieve a systemic effect are usually filled with a solution or suspension of the drug in vegetable oil or paraffin. Such capsules are mostly of the soft-shell type. Limited experience has been obtained with this dosage form, but it seems that there are no striking differences between the bioavailability from rectal capsules and that from fatty suppositories.
**Microenemas** are solutions or dispersions of the drug in a small volume (approximately 3 mL) of water or vegetable oil. This form is supplied in a small plastic container equipped with an application tube. After insertion of the tube, the container is emptied by compressing the bulb. The advantage of this delivery system is obvious, as no melting and dissolution process is necessary before drug release can start, if water is used as a vehicle.

For the systemic administration of drugs, delivery forms such as tablets, capsules and microenemas are used. Tablets are not very attractive because they cannot disintegrate rapidly, owing to the small amount of water present in the rectum. Tablets that release CO₂ after insertion can be used, thereby stimulating defecation. Many good results have been obtained with drugs delivered in microenemas, but this form is still of limited applicability because of its relatively high cost, administration cannot be performed easily by patients themselves and it is rather difficult to deliver the total content of the plastic container.
Ind Ph II

Tablet coating

Dr. Myasar Alkotaji
Tablet Coating

Tablet coatings functions:
1- mask the taste of unpalatable drugs,
2- protect the drug from deterioration due to light, oxygen or moisture,
3- separate incompatible ingredients,
4- control the release of medicament in the gastrointestinal tract (functional coating),
5- provide an elegant or distinctive finish to the tablet.
6- Coloured coatings aid in the rapid identification of product.
7- facilitates tab handling on high speed automatic filling and packaging equipment.
8- Cross contamination is also reduced in the manufacturing plant, as 'dusting' from tablets is eliminated by coating.
The materials used for coating may largely comprise sucrose (sugar coating), water-soluble film-forming polymers (film coating) or substances which are soluble in the intestinal secretions but not in those of the stomach (enteric coating).

These types of coating can all be applied by the pan or fluid-bed processes; the compression coating technique is suitable for sugar and enteric coatings, but not for film coating.

**Sugar Coatings**

This traditional coating imparts a smooth, rounded, elegant appearance to the tablet.

**Advantages:**
1. It gives a smooth and shining surface
2. It masks the bitterness and sweetness in taste
3. It increases the elegance of the product.

**Disadvantage:** It increases the weight of the tablet and it is hygroscopic.
Sugar coating

Description of tablets: Smooth, rounded and polished to a high gloss.

Process: Multistage Process involving 6 separate operations

1. Seal tablet core
2. Sub coating
3. Smoothing
4. Colouring
5. Polishing
6. Printing

Example of sugar coated tablets
1- **Sealing**. This involved the application of one or more coats of a waterproofing substance in the form of alcoholic spray, such as pharmaceutical Shellac (traditionally) or synthetic polymers, such as CAP.

The amount of the sealing coat applied should be carefully calculated so that there is no negative effect on the drug release characteristics in case of immediate release product.
2-Subcoating

Large quantities of sugar-coatings are usually applied to the tablet core (typically increasing the tablet weight by (50-100%) in order to round off the tablet edge. Much of this material build-up occurs during this stage and is achieved by adding a bulking agent such as Calcium carbonate, to the sucrose solution.

Antiadherents e.g. Talc may be added after partial drying to prevent sticking of the tablets together.

Generally two methods are used for subcoating: i) The application of gum (acacia, gelatin or PVP) based solution followed by dusting with powder and then drying (warm air). This routine is repeated until the desired shape is achieved.

ii) The application of a suspension of dry powder in gum/sucrose solution followed by drying. Thus subcoating is a sandwich of alternate layer of gum and powder. It is necessary to remove the bulk of the water after each application of coating syrup.
3- Smoothing

The subcoating stage results in tablets with rough surfaces. To facilitate the color application (which requires smooth surface), subcoated tablets are smoothed out by a thick sucrose syrup coating. Smoothing usually can be accomplished by the application of a simple syrup solution (approximately 60-70 % sugar solid). This syrup generally contains pigments, starch, gelatin, acacia or opacifier if required.

Small quantities of colour suspension can be applied to impart a tint of the desired colour when there are irregularities in coating. Polishing accomplished by 5-10 coats and warm air is applied to speed up the drying time of each coat.
4- **Coloring**
Color coatings usually consist of thin sucrose syrup containing the requisite coloring materials. (water-soluble dyes or water-insoluble pigments) This step must be done into a clean pan deprived of any residues from the previous operations. The most efficient process for color coating involves the use of a predispersed opacified lake suspension.

5- **Polishing**
After the coloring step, the tablet surfaces tend to be smooth but somewhat dull in appearance. To achieve glossy finish, final stage involving application of waxes; beeswax and carnauba wax is employed. Wax can be added in three ways:

1- pan can be lined with wax and tablets polish as tumble in the pan.
2- Piece of wax may placed in pan and tablet polished while tumbled.
3- Wax may dissolved in non aqueous solvent and sprayed on tablets during tumbling
6- Printing

Different tablets could be identified by manufacturer's logo, product name, dosage strength or other appropriate code. For sugar-coated tablets, such identification could be only achieved by printing process using special edible inks.
A. Pan Coating
In this process the tablets are tumbled in a bowl or pan which rotates about an axis tending about 30° to the horizontal. With the correct pan load a three dimensional circulation is established and sufficient coating solution is added to wet the tablet surfaces. Internal baffles or hand manipulation of the wetted tablets ensures that the solution is evenly distributed and a satisfactory tumbling action maintained while the coating is dried by a stream of warmed air. Small amounts of dusting powder may be applied to reduce tackiness and cohesion of the tablets during the drying stage. The volume of coating solution for each application is critical; inadequate wetting leads to irregular coating, whereas with too large a volume the tablets agglomerate and do not tumble well. The cycle of alternate wetting and drying is continued to build up a coating of the required properties. Initially, the tablets are subject to considerable abrasive action and for this reason should be more highly compressed than the corresponding uncoated tablets.
Control of the coating process is obtained by modifying the following:

- rotation rate of the drum/pan
- airflow rate
- temperature of the air
- concentration of sugar/polymer within the coating solution/emulsion.

More recently, pan coaters have been developed in which the pan is perforated. In these systems the warmed air is passed into the drum and through the tablet bed before being exhausted (with the solvent from the coating solution) via the perforated drum.
2- Fluidised bed coating

Air suspension coaters are highly efficient coating systems in which the coating solution is sprayed on to tablets (or granules) that have been suspended in a positive (warmed) airflow. Typically the tablets are initially suspended in the centre of the chamber and then move to the periphery of the chamber before falling to the bottom, at which stage the process is continuously repeated. The coating solution is fed into the fluidisation chamber as an atomised spray.
Problems of sugar coating

1- Surface roughness
One of the major problems of tablet coating is the production of tablets that exhibit a rough surface. This phenomenon is often associated with drying of the coating droplets prior to reaching the surface of the tablet. To correct this problem the spray rate may be increased and the inlet air temperature decreased.

2- Cracking:
The formation of cracks in tablet coatings is principally due to the use of an inappropriate coating formulation
3-Twinning or building multiple
This is due to the high viscosity of coating solution or due to unevenly distribute of coating solution

4-Uneven color
This is due to:
1- improper mixing of the colour within the coating formulation
2- uneven coating process, resulting in regional differences in the thickness of the applied coating
3- migration of coloured components within the tablet core into the coating
Film Coating

Film coating involves the deposition, usually by a spray method, of a thin film of polymer surrounding the tablet core.

Coating materials and formula

- polymers or film formers
- plasticizers
- solvents
- coloring agents

Polymer

Characteristics of a film coating

Solubility, viscosity, permeability and mechanical properties.

- Polymers for conventional coating
  1- cellulose ether
    - soluble in water except ethyl cellulose (EC)
    - hydroxy propyl methyl cellulose (HPMC) is the most commonly used
2- Acrylate polymers

aminoalkyl methacrylate copolymers soluble in acid, protective coating
e.g. Eudragit E

Film coating can be functional:

Enteric coating: This technique is used to protect the tablet core from disintegration in the acid environment of the stomach for one or several reasons.

Some examples of enteric coating polymers (pH dependent polymer)
· Polyvinyl acetate phthalate, Cellulose acetate phthalate,
· Polymethacrylates e.g. Eudragit L, Eudragit S

Sustained release coating: (polymers are water insoluble)
- Acrylate polymers e.g. Eudragit RS
- Wax (bee wax, carnauba wax, stearyl alcohol)
- Ethylcellulose
2- Plasticizers are simply relatively low molecular weight materials which have the capacity to alter the physical properties of the polymer to render it more useful in performing its function as a film-coating material e.g. PEG and glycerol.

3- Solvent
Water or organic solvent (alcohol or acetone).

4- Coloring agent (iron oxide pigments, titanium dioxide, aluminium Lakes).

5- Other materials like antiadherent (talc), surfactant and preservatives.
Film coating Process details
The vast majority of film-coated tablets are produced by a process which involves the atomization (spraying) of the coating solution or suspension on to a bed of tablets.

Basic process requirements for film coating
1. adequate means of atomizing the spray liquid for application to the tablet cores.
2. adequate mixing and agitation of the tablet bed.
Spray coating relies upon each core passing through the area of spraying.
3. sufficient heat input in the form of drying air to provide the latent heat of evaporation of the solvent.
4. good exhaust facilities to remove dust- and solvent-laden air.
Film coating machine
• Film coating process variables
• Tablet size / shape
• Pan loading
• Pan rotation speed
• Baffle arrangement

• Suspension spray rate
• Suspension viscosity
• Spray nozzle size

• Inlet air temperature → tablet bed temperature
Monitoring the film coating process

1- Tablet appearance (Colour coverage and depth)

2- Weight gain of tablets
(Weigh 20 tablets at the start and every 15 minutes) • Calculate weight gain • May get some dehydration of tablets initially

3- Weight of suspension used
Normally assume 10 to 30% excess suspension

4- Tablet bed temperature
5- Exhaust air temperature
Coating faults
These arise from two distinct causes:
1. Processing: for example, inadequate drying conditions will permit coating previously deposited on the tablet surface to stick against neighbouring tablets.
2. Formulation faults: film cracking or 'bridging' of break lines are examples of this type, reformulation will almost certainly be successful in overcoming the problem.

STANDARDS FOR COATED TABLETS
The European Pharmacopoeia has similar requirements for coated and uncoated tablets, the differences being:
   Film-coated tablets comply with the disintegration test for uncoated tablets except that the apparatus is operated for 30 minutes. The requirement for sugar coated tablets is modified to include a 60-minute operating time. Furthermore, the test may be repeated using 0.1 N HC1 in the event that any tablets fail to disintegrate in the presence of water.
Sealing

Subcoating
Polishing