

# Technology of Pharmaceutical Industry I

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# Course Description

جامعة /أكاديمية : المعاهد الفنية الصحية التابعة لوزارة الصحة والسكان  
قسم : التصنيع الدوائي

## Course Specifications

توصيف مقرر دراسي

1- بيانات المقرر	
الرمز الكودي :	اسم المقرر :تقنية صناعة المستحضرات الدوائية 1 Technology of Pharmaceutical Industry 1
التخصص : التصنيع الدوائي	عدد الوحدات الدراسية : نظري 3 عملي 10
2- Overall Aim of Course: هدف المقرر:	The prime objective of this course is to provide students with the basic information of different dosage forms. This course focuses on aspects of knowledge, skills and abilities of formulation of solid and semisolid pharmaceutical dosage forms including tablets, capsules, effervescent granules, as well as suppositories, ointments and creams on the production scale.
3- Intended learning outcomes of the course (ILOs): المستهدف من تدريس المقرر- 3	
i. Knowledge and Understanding: ا. المعلومات والمفاهيم :	<u>By the end of this course, students should be able to:</u> 1- Define the different types of pharmaceutical dosage. 2- Recognize the whole production process of different solid and semisolid pharmaceutical products starting from raw materials ending with the finished product. 3- Identify excipients required to prepare different solid and semisolid formulation. 4- Identify different methods to solve problems during manufacturing of solid and semisolid dosage forms.
ii. Intellectual Skills: ب- المهارات الذهنية :	<u>By the end of this course, students should be able to:</u> 1. Determine the role of pharmaceutical excipients in formulations of solid and semisolid pharmaceutical formulation. 2. Estimate and solve problems emerging during technical operations with respect to machine capacity and product quality. 3. Classify different equipments according to its mechanism of action.
III. Professional	<u>By the end of this course, students should be able</u>

<b>Skills:</b> ج- المهارات المهنية الخاصة بالمقرر:	<b>to:</b> 1. Prepare solid and semisolid dosage forms. 2. Practice pharmaceutical terms for different plants used in unit operation. 3. Use the appropriate machines safely and effectively.
<b>IV. General and Transferable Skills:</b> د- المهارات العامة:	<b>By the end of this course, students should be able to:</b> 1. Assess problems. 2. Work efficiently with others. 3. Practice independent learning by using information technology tools.
<b>4- Course content</b> 4- محتوى المقرر:	1. General introduction of different types of pharmaceutical dosage form. 2. Tablets (introduction, tablet components, types of tablets). 3. Tablet preparations, tablet compression machines 4. In process quality control of tablets, tablet production problems, tablet coating and coating problems. 5. Capsules (introduction, capsule types, hard gelatin capsule. 6. Soft gelatin capsules, capsule production problems. 7. Powder and effervescent granules (introduction, production, filling and packaging) 8. Ointments (introduction, ointment bases) 9. Ointments preparation and filling methods. 10. Creams (types, preparation and filling methods). 11. Suppositories (introduction, types, suppository bases). 12. Method of preparation of suppository, suppository problems and suppositories packaging.
<b>5- Teaching and Learning Methods:</b> 5- أساليب التعليم والتعلم	1. Lectures. 2. Group discussions 3. Practical sessions
<b>6- Teaching and learning methods for students with limited abilities</b> 6- أساليب التعليم والتعلم للطلاب ذوي القدرات المحدودة	
<b>7- Student Assessment:</b> 7- تقويم الطلاب :	
<b>a- Assessment methods:</b> أ- الأساليب المستخدمة	<b>a. Class work:</b> 1. Quizzes 2. Midterm theoretical 3. Practical exam

	<p>4. Assignments 5. Participation</p> <p>b. Final exam: Written theoretical</p>
<p>b- Assessment schedule: ب- التوقيت</p>	<p>a. Class work:</p> <ol style="list-style-type: none"> <li>1. Quizzes: <ul style="list-style-type: none"> <li>Quiz I (4<sup>th</sup> week)</li> <li>Quiz II (11<sup>th</sup> week)</li> </ul> </li> <li>2. Midterm theoretical (7<sup>th</sup> week)</li> <li>3. Assignments</li> <li>4. Participation</li> </ol> <p>b. Final exam Practical exam (13<sup>th</sup> week) written theoretical exam (15<sup>th</sup> week)</p>
<p>C-Weight Assessments: ج- توزيع الدرجات</p>	<p>of</p> <ol style="list-style-type: none"> <li>1. Quizzes and class work (13.33%), 20 marks</li> <li>2. Practical (26.67%), 40 marks.</li> <li>3. Final written theoretical exam (60%), 90 marks.</li> </ol> <p>Total percentage 100%</p>
<p>7- List of References: 8- قائمة الكتب الدراسية والمراجع :</p>	
<p>a- Course notes: أ- مذكرات</p>	<p>Lecture and practical notes for Technology of Pharmaceutical Industry 1</p>
<p>b- Essential books (text books) ب- كتب ملزمة</p>	<ol style="list-style-type: none"> <li>1. Ansel, H.C., Popovich, N.G. and Allen, L.V., editors. Pharmaceutical Dosage Forms and Drug Delivery Systems, 10th edition. Philadelphia: Williams &amp; Wilkins. (2014).</li> <li>2. Aulton's Pharmaceutics: The design and manufacture of medicine, Micheal Aulton, 4th Edition, 2013.</li> </ol>
<p>c- Recommended books ج- كتب مقترحة</p>	<ol style="list-style-type: none"> <li>1. Tablet and capsule machine instrumentation. Peter Ridgway and Antony Armstrong. Pharm.Press (2008)</li> <li>2. Pharmaceutical production facilities. Design and applications. Graham C.Cole 2nd edition (2006)</li> <li>3. Handbook of pharmaceutical technology. L.K.Ghosh. CBS Publishers and distributors. (2006)</li> </ol>
<p>d- Periodicals, web sites, دوريات علمية أو نشرات الخ .....</p>	<ul style="list-style-type: none"> <li>• <a href="http://www.pharmamanufacturing.com">www.pharmamanufacturing.com</a></li> <li>• <a href="http://www.pharmaceutical-technology.com">www.pharmaceutical-technology.com</a></li> <li>• <a href="http://www.google.com">www.google.com</a></li> <li>• <a href="http://www.pubmed.com">www.pubmed.com</a></li> <li>• <a href="http://www.biomed.net">www.biomed.net</a></li> </ul>

# Introduction

## Objectives

After reading this chapter, the student will be able to:

1. Describe the general introduction for different solid dosage forms (tablet, capsules, and effervescent granules)
2. know the general introduction for aerosol dosage forms
3. Recognize the general introduction for **Transdermal Drug Delivery**
4. Describe the general introduction for different **liquid dosage forms**

## PHARMACEUTICAL DOSAGE FORMS

A *dosage Form* refers to the gross physical form in which a drug is administered to or used by a patient such as tablet, capsule, injection...etc.

### I. Routes of administration for systemic effects

#### 1. Oral route

The most commonly used route of administration is the oral route. It is convenient for self administration and effective for most drugs except for those that are rapidly inactivated by gastric or intestinal secretions or by passage via the hepatic portal circulation through the liver. The oral route is unsuitable for surgical patients immediately pre- and post- operatively, for patients who are unconscious or vomiting and for those with malabsorption states.

#### 2. Buccal route:

The buccal route is useful for self-administered drugs and may be used to overcome some of the problems of the oral route. Blood flow through the buccal mucosa is high and drug are absorbed into the systemic rather than the hepatic portal circulation, thus avoiding immediate inactivation by the liver. This route may also be used in the unconscious patient.

#### 3. Rectal route

Drugs administered into the rectum are absorbed mainly into the systemic circulation although some entry into the hepatic portal circulation may occur. Absorption from the rectal mucosa is less predictable than from the small intestine following oral administration. However, the rectal route is useful for the systemic administration of drugs known to cause gastrointestinal irritation or to a patient who is unconscious or vomiting.

#### 4. Inhalational route:

The high blood flow through the lungs and the large surface area of the alveolar membrane provide a route for rapid absorption of drugs into the general circulation. Anaesthetic gases, volatile liquids and drugs that can be dispersed in an aerosol form may be administered by inhalation in order to produce a systemic effect. The nasal mucosa may also be used as route of systemic administration.

#### 5. Transdermal route:

Drugs applied to skin surface may be absorbed slowly into the systemic circulation. This route is useful for drugs with a short duration of action after oral administration, particularly those rapidly metabolized by the liver, and may provide a sustained concentration of the drug in the circulation.

#### 6. Parenteral routes:

Drugs may be administration directly into the circulation by the intravenous route. Distribution of the drug throughout the circulatory system is rapid and this route bypasses many biological membranes which may delay absorption into circulation.

### II. Route of administration for local effects:

#### 1. Oral route:

Dosage forms of adsorbents, antimicrobial compounds and antacids may be designed to exert a local effect within the gastrointestinal tract after oral administration.

#### 2. Topical route:

Application of a dosage form to the epithelium covering one of the body surfaces may be used to exert a local effect at the site of application. Examples include preparations applied to the skin, the cornea of the eye, the nasal, rectal, vaginal or urethral mucosa.

## TYPES OF DOSAGE FORMS

**Definition:** Dosage forms are how drug molecules are delivered to sites of action within the body.

### Dosage forms are needed for the following:

1. To obtain accurate dose of the drug.
2. To protect drug from environmental conditions e.g. coated tablets, capsules.
3. To protect drug from gastric juice e.g. coated tablets.
4. To mask bad taste and odor of drug.
5. To place drugs within body tissues.
6. To obtain sustained and controlled release medication.
7. To obtain optimal drug action.
8. For insertion of drugs into body cavities (rectal, vaginal).

### Classification of dosage forms according to route of administration

#### I. Oral dosage forms

##### A. Tablet:

A **tablet** is a hard, compressed medication in round, oval, triangular or square shape.

##### The excipients include:

1. **Diluents:** are substances added to give bulk for drug content to increase tablet size.
2. **Binders:** are substances added to increase cohesiveness between powders to be granules to improve their flowability.
3. **Glidants (flow aids):** are substances added to improve flowability.
4. **Lubricants:** are substances added to powder mass to form a coat around individual particles to ensure efficient tableting.
5. **Disintegrants:** are substances added to ensure that the tablet breaks up in the digestive tract after oral administration.
6. **Anti-adherents:** are substances added to decrease sticking of powder to metal surfaces of tablet machine.

7. **Sweeteners or flavors:** are substances added to mask the taste of bad-tasting active ingredients.
8. **Pigments:** added to make the uncoated tablets visually attractive.

**A coating may be applied to the tablet to:**

1. Hide the taste of the tablet's components.
2. Make the tablet smoother and easier to swallow.
3. Make it more resistant to the environment.
4. Extending its shelf life.

**1.1. Buccal and sublingual tablet:**

- Sublingual and buccal medications are administered by placing them in the mouth either under the tongue (sublingual) or between the gum and the cheek (buccal)
- The medications dissolve rapidly and are absorbed through the mucous membranes of the mouth, where they enter into the bloodstream.
- Avoid the acid and enzymatic environment of the stomach and the drug metabolizing enzymes of the liver.
- Examples of drugs administered by this route: e.g. vasodilators, steroidal hormones.

**1.2. Effervescent tablet:**

- Effervescent tablets are uncoated tablets that generally contain acid substances (citric and tartaric acids) and carbonates or bicarbonates and which react rapidly in the presence of water by releasing carbon dioxide.
- They are intended to be dissolved or dispersed in water before use providing:
  - a. Very rapid tablet dispersion and dissolution.
  - b. Pleasant tasting carbonated drink.

**Chewable tablet:**

- They are tablets that chewed prior to swallowing.
- They are designed for administration to children e.g. vitamin products.
- N.B. No disintegrating agent added to chewable tablets?

## **B. Capsule**

A **capsule** is a medication in a gelatin container (small box). Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. Although development work has been done on the preparation of capsules from other materials, gelatin,

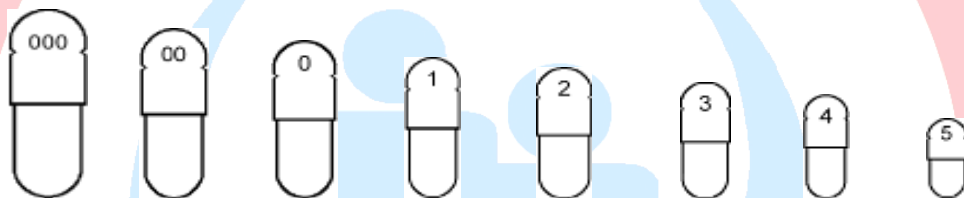
because of its unique properties, remains the primary composition material for the manufacture of capsules. Capsules are tasteless, easily administered, and easily filled either extemporaneously or in large quantities commercially. The industry prepares approximately 23% of its solid dosage forms as hard gelatin capsules and 2% as soft gelatin capsules.

**Advantage:** mask the unpleasant taste of its contents.

The two main types of capsules are:

a. **Hard-gelatin capsules,**

Which are normally used for dry, powdered ingredients, Capsules are supplied in a variety of sizes and colors. The hard, empty capsules are numbered from 000, the largest size that can be swallowed, to 5, which is the smallest. Larger sizes are available for use in veterinary medicine.



**Figure.3. Different sizes of hard gelatin capsules**

b. **Soft-gelatin capsules,**

Soft capsules are formed in a single piece and are more suitable for oils e.g. *Fish oils*, or drugs that need to be dissolved in oils or other liquids to aid the drug to be absorbed in the stomach. In soft capsules, the drug is combined with an appropriate solvent in the centre of the capsule and the capsule shell melts within minutes in the stomach. Drugs are easily absorbed from these mixtures offering two distinct advantages:

- 1) **Quicker effect,** which is good for immediate pain relief
  - 2) **Drug absorbed more effectively,** so lower doses can be used which in turn means the soft capsules can be made smaller, making swallowing easier
- primarily used for oils and for active ingredients that are dissolved or suspended in oil.

### **C. Powder and effervescent granules**

- They are consisting of solid, dry aggregates of powder particles often supplied in single-dose sachets.

- Granules are intended to be dissolved in water before administration.
- Granules may be effervescent or non- effervescent.
- Effervescent granules evolve carbon dioxide when added to water, because they contain effervescent base).

### 1. Powder (Oral):

There are two kinds of powder intended for internal use.

- a. *Bulk Powders:* are multi-dose preparations consisting of solid, loose, dry particles of varying degrees of fineness. They contain one or more active ingredients, with or without excipients and, if necessary, coloring matter and flavoring substances. Usually contain non-potent medicaments such as antacids since the patient measures a dose by volume using a 5ml medicine spoon. The powder is then usually dispersed in water or, in the case of effervescent powders, dissolved before taking.
- b. *Divided Powders:* are single-dose preparations of powder (for example, a small sachet) that are intended to be issued to the patient as such, to be taken in or with water.

### 2. Powders for mixtures:

The mixed powders may be stored in dry form and mixture prepared by the pharmacist or by the patient when required for dispensing, by suspending the powders in the appropriate vehicle e.g Antibiotics for children.

## D. Aerosol dosage forms

### Inhaler:

- Inhalers are solutions, suspensions or emulsion of drugs in a mixture of inert propellants held under pressure in an aerosol dispenser.
- Release of a dose of the medicament in the form of droplets of 50 um diameter or less from the container through a spring-loaded valve incorporating a metering device. The patient then inhales the released drug through a mouthpiece.
- In some types, the valve is actuated by finger pressure, in other types the valve is actuated by the patient breathing in through the mouthpiece.
- It is commonly used to treat asthma and other respiratory problems.

**Nebulizer or (atomizer):**

- A nebulizer is a device used to administer medication to people in forms of a liquid mist to the airways.
- It is commonly used in treating asthma, and other respiratory diseases.
- It pumps air or oxygen through a liquid medicine to turn it into a vapor, which is then inhaled by the patient.
- As a general rule, doctors generally prefer to prescribe inhalers for their patients, because:
  1. These are cheaper
  2. More portable
  3. Carry less risk of side effects.
- Nebulizers are usually reserved only for serious cases of respiratory disease, or severe attacks.

**E. Liquid preparations****a. Oral solution:**

Oral solutions are clear Liquid preparations for oral use containing one or more active ingredients dissolved in a suitable vehicle (usually water).

**b. Oral emulsion:**

Oral emulsions are stabilized oil-in-water dispersions, either or both phases of which may contain dissolved solids.

**c. Oral suspension:**

- Oral suspensions are Liquid preparations for oral use containing one or more active ingredients suspended in a suitable vehicle.
- Oral suspensions may show a sediment which is readily dispersed on shaking to give a uniform suspension which remains sufficiently stable to enable the correct dose to be delivered.

**d. Syrup:**

- It is a concentrated aqueous solution of a sugar, usually sucrose.
- Flavored syrups are a convenient form of masking disagreeable tastes i.e. syrup could be used as a vehicle.

**e. Elixir:**

- It is pleasantly flavored clear liquid oral preparation of potent or nauseous drugs.

- The vehicle may contain a high proportion of ethanol or sucrose together with antimicrobial preservatives which improve the stability of the preparation.
- f. **Oral drops:**
- Oral drops are Liquid preparations for oral use that are intended to be administered in small volumes with the aid of a suitable measuring device. They may be solutions, suspensions or emulsions.
- g. **Gargles and Mouthwashes:**
- They are aqueous solutions used in the prevention or treatment of throat infections.
  - Usually they are prepared in a concentrated solution with directions for the patient to dilute with warm water before use.

## F. **Topical dosage forms**

### Transdermal Drug Delivery

#### 1. **Ointments:**

- Ointments are semi-solid, greasy preparations for application to the skin, rectum or nasal mucosa.
- The base is usually anhydrous and immiscible with skin secretions.
- Ointments may be used as emollients or to apply suspended or dissolved medicaments to the skin.

#### 2. **Creams:**

- Creams are semi-solid emulsions that are mixtures of oil and water.
- They are divided into two types:

**Oil-in-water (O/W) creams:** which are composed of small droplets of oil dispersed in a continuous aqueous phase. Oil-in-water creams are more comfortable and cosmetically acceptable as they are less greasy and more easily washed off using water.

**Water-in-oil (W/O) creams:** which are composed of small droplets of water dispersed in a continuous oily phase.

#### 3. **Gels (Jellies):**

- Gels are semisolid system in which a liquid phase is constrained within a 3-D polymeric matrix (consisting of natural or synthetic gum) having a high degree of physical or chemical cross-linking.
- They are used for medication, lubrication and some miscellaneous applications like carrier for spermicidal agents to be used intra vaginally (a way for contraception).

## Solid Dosage Forms

### i. Tablets

#### Objectives

*After reading this chapter, the student will be able to:*

1. Know the active and excipient used for manufacture of tablet
2. List reasons for the incorporation of drugs into tablet dosage forms
3. Compare and contrast the advantages/disadvantages of solid dosage forms
4. Describe the information needed in preformulation studies to characterize a drug substance for possible inclusion into a dosage form

### Tablets

#### Introduction

1. Why do we need to convert an active pharmaceutical ingredient into a suitable dosage form?
2. What is a tablet?
3. Advantages and disadvantages of tablet as a dosage form

**Why do we need to convert an active pharmaceutical ingredient into a suitable dosage form?**

Active pharmaceutical compounds (drugs) are used for the treatment of a disease or for prophylactic purpose. An Active Pharmaceutical Ingredient (API) may exist in solid, liquid or semisolid form. The API and excipients are suitably processed in

pharmaceutical industry to convert them into dosage forms such as tablet, capsule, suspension, solution.

### **What is a tablet?**

It is a solid dosage form each containing a unit dose of one or more medicament/s. Tablets are solid, flat or biconvex discs prepared by compressing a drug or a mixture of drugs with or without suitable excipients.

### **Advantages of tablet as a dosage form -**

1. Large scale manufacturing is feasible in comparison to other dosage forms.
2. Accuracy of dose is maintained since tablet is a solid unit dosage form
3. Tailor made release profile can be achieved
4. Longer expiry period and minimum microbial spillage owing to lower moisture content
5. As tablet is not a sterile dosage form, stringent environmental conditions are not
6. required in the tablet department
7. Ease of packaging (blister or strip) and easy handling over liquid dosage form
8. Easy to transport in bulk
9. Organoleptic properties (taste, appearance and odor) are best improved by coating of tablet
10. Product identification is easy and markings done with the help of grooved punches and printing with edible ink
11. Different types of tablets are available like buccal, floating, colon targeting, effervescent, dispersible, soluble, and chewable, etc
12. In composition to parenteral dosage form, a doctor or a nurse is not required for administration i.e. self-administration is possible
13. In comparison to capsules, tablets are more tamperproof

### **Disadvantages of tablet as a dosage form**

1. It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use
2. Difficult to formulate a drug with poor wet ability, slow dissolution into a tablet

3. Slow onset of action as compared to parenterals, liquid orals and capsules
4. The amount of liquid drug (e.g. Vitamin E, Simethicone) that can be trapped into a tablet is very less
5. Difficult to swallow for kids, terminally ill and geriatric patients
6. Patients undergoing radiotherapy cannot swallow tablet

### I. Types of tablets

With advancement in technology and increase in awareness towards modification in standard tablet to achieve better acceptability as well as bioavailability, newer and more efficient tablet dosage forms are being developed.

- A. Oral Tablets for Ingestion
- B. Tablets Used in the Oral Cavity
- C. Tablets Administered by other Routes
- D. Tablets Used to Prepare Solution

#### **A. ORAL TABLETS FOR INGESTION**

1. Standard compressed tablet
2. Multiple compressed tablet
  - i. Compression coated tablet
  - ii. Layered tablet
  - iii. Inlay tablet
3. Modified release tablet
4. Delayed action tablet
5. Targeted tablet
  - i. Floating tablet
  - ii. Colon targeting tablet
6. Chewable tablets
7. Dispersible tablets

These tablets are meant to be swallowed intact along with a sufficient quantity

of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

## **B. TABLETS USED IN THE ORAL CAVITY**

1. Lozenges Lozenges and troches
2. Sublingual tablets
3. Buccal tablets
4. Dental cones
5. Mouth dissolved tablet

The tablets under this group are aimed release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity

## **C. TABLETS ADMINISTERED BY OTHER ROUTES**

1. Vaginal tablet
2. Implants

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application

## **D. TABLETS USED TO PREPARE SOLUTION**

1. Effervescent tablet
2. Hypodermic tablet
3. Soluble tablet

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used.

## II. Tablets Formulation

Excipients and their functionalities

Excipients are chosen in tablet formulation to perform a variety of functions like

1. For providing essential manufacturing technology functions (binders, glidants, lubricants may be added)
2. For enhancing patient acceptance (flavors, colourants may be added)
3. For providing aid in product identification (colourants may be added)
4. For Optimizing or modifying drug release (disintegrants, hydrophilic polymers, wetting agents, biodegradable polymers may be added)
5. For enhancing stability (antioxidant, UV absorbers may be added)

### Excipients and their functions

#### a. DILUENT (BULKING AGENT, FILLER

Role: increase bulk of tablet to suitable size.

##### 1. LACTOSE

- Readily soluble in water so quick release of drug.
- Stable and does not react with most medicinal substances.
- Spray-dried form has spherical particles, which flow readily and can be directly compressed without the necessity of adding binders.
- Lactose also is not hygroscopic and readily dries after wet granulation.

##### 2. STARCH

- Used as diluent, binders and disintegrants.
- Derived from wheat, corn, rice & potato.

##### 3. MANNITOL

- Sweet.

- Has a negative heat of solution (cause cooling sensation) so it is used in chewable tablets.

## b. BINDERS

Role & Use; Bind powders together and cause them to form granules.

It may be added:

- a. Dry and then activated by the addition of water or other solvents
- b. Dissolved in a liquid to form a solution and used in the granulation.
- c. Binders added in solution have more binding power than that added dry and then moistened.

## Examples

1. **Acacia:** is a natural gum.
2. **Tragacanth:** Best used dry as it forms heavy mucilage in water, which is difficult to disperse. So it is best used dry
3. **Gelatin:** its solutions must be used warm, since they fall when cold (form viscous gel)
4. **Sucrose:** has good adhesive properties when added dry or as a syrup.
5. **Starch** is a good binder, particularly when the drug is insoluble and in high concentrations.

## Binders used for water sensitive drugs:

- Polyvinylpyrrolidone (PVP): is a binder soluble in alcohols.
- Hydroxypropyl cellulose (HPC): is soluble in chloroform.

## C. ANTIFRICTIONAL AGENTS (LUBRICANT, GLIDANT & ANTIADHERENT)

Three of the problems occur in tablet manufacture:

- a. Flow of granulation
- b. Adhesion of material to the punches and dies
- c. Release of the completed tablet from its mold.

Improve flow characters of granulation

1. Act between surfaces in relative motion to prevent friction and wear.

2. Reduce the friction between the inner die wall and the tablet edge during the ejection.
3. The absence of a lubricant is evidenced by:
  - a. Severe screeching sound.
  - b. Presence of vertical, striation on the edges of the ejected tablets
4. prevent sticking of tablet or granules to punches faces and die walls

**N.B.**

1. Metallic stearate (magnesium, calcium, or potassium) are excellent lubricant but poor antiadherent or glidants.
2. Talc is a poor lubricant but good antiadherent and glidant.
3. A combination of these materials serves to solve many of problems associated with tablet compression.
4. Tablet lubricants are most effective when used in fine particles. (Since their function is related to surfaces, so the greater the degree of subdivision the greater the area they can cover)
5. Lubricants usually passed through 60 mesh before added to granule.
6. Lubricants usually added at last step before compression because:
  - a. They must on surface of the granules.
  - b. Between granules & parts of the tablet press.

**d. DISINTEGRANT**

***Role***

- Break (disintegrate) the tablets when placed in an aqueous medium (gastric fluid).
- It opposes the efficiency of the tablet binder and physical forces of compression.
- Disintegrant swell or expand when wetted with gastric fluid and exert sufficient mechanical pressure from within the tablet to cause it to break apart into small parts.
- The disintegrating force of starch is not due its swelling, but is due to capillary function.

**Examples**

**Starch derivatives:** specially modified starches swell even in cold water. and are more useful as tablet disintegrants e.g. sodium carboxy methyl starch (EXPLOTAB) and sodium starch glycolate (PRIMOGEL).

1. **Gums:** used as disintegrants because of their known capacity to swell in water but excessive amounts make it adhesive and reduce its effectiveness as disintegrants.
2. **Microcrystalline Cellulose (MCC = Avicel):** excellent disintegrant, but only when it is present in concentration of 25% or greater. It is used also as a direct compression vehicle.

e. **COLOURING AGENTS**

1. Added to tablet to distinguish one product from another.
2. The most common way to add a dye to a tablet is to dissolve it in the binder solution.

f. **FLAVOURS AND SWEETENERS**

- They are found in Lozenges and chewable tablets.
- Flavours are never added during wet processing, since the subsequent drying would reduce the concentration of these volatile ingredients.
- Lactose, sucrose, mannitol & dextrose are used as sweetening agent.
- The sweetness of sucrose supplies by itself, but the sweetness of the other may be enhanced by the addition of saccharine.

g. **ADSORBENTS**

**Role**

- Holding quantities of fluids and remain in a dry state.
- Ethereal solution of oils or oil soluble drugs, fluid extracts, and eutectic melts may be mixed with adsorbents and then granulated and compressed into tablets.

**Examples:**

1. **Silicone dioxide:**

- Possesses a great (vast) surface area.

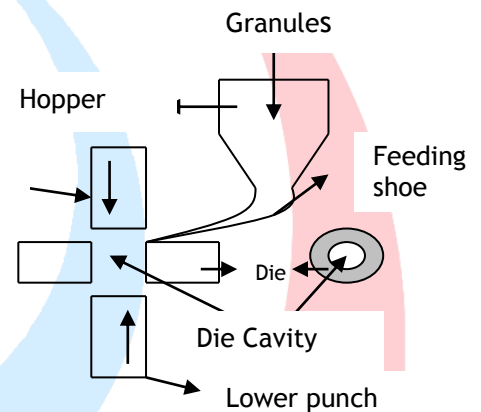
- It can hold up to 50% of its weight in water and still act as a free flowing powder
- It is very useful with hygroscopic materials.
  1. Used with drug extracts, unless the extracts are sensitive to alkali.
  2. The drug is first mixed with the adsorbent and then the rest of the formula is added.

**2. Bentonite, kaolin:** are also used as adsorbent.

### Tablet presses

*Machines built to compress tablets consist of:*

1. **Hopper:** for storing the materials for compressing.
2. **Feed frame:** for distributing the materials into the dies.
3. **Dies:** for controlling size & shape of tablet.
4. **Punches:** for compacting the materials within the dies.
5. **Cams:** for guiding the punches.

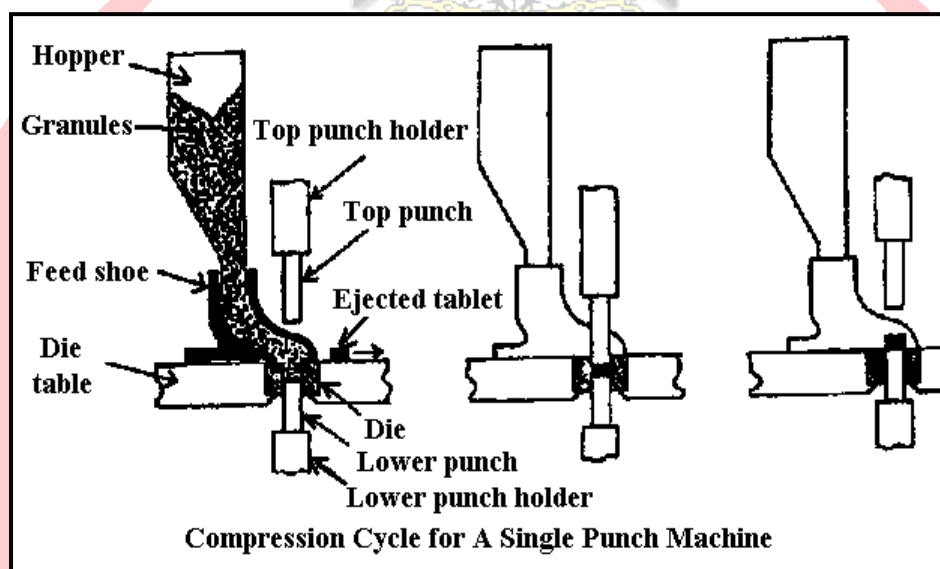


When the die has been filled, the upper punch descends; the machine exerts pressure on the two punches and compact the mass between them.

#### **Operation of single punch machine:**

1. The materials flow through the hopper into the feed shoe, an arm shakes the shoe over the die, causing the material to flow into the die.
2. The amount delivered is determined by the depth of the lower punch (turning clockwise ↓fill - counter clockwise↑).
3. The descent of the upper punch is controlled by the weight adjustment collar
4. The shoe is moved back to permit the upper punch to descend, into the die and compact the material between the faces of the two punches.
5. The lower punch remains stationary at this time.

6. The amount of pressure exerted is controlled by the distance which the upper punch penetrates the die.
7. After compression the upper punch is withdrawn and the lower punch rises bringing the tablet to the top of the die.
8. The shoe again moves forward, removing the tablet off the die while refilling the die.



## PREPARATION OF COMPRESSED TABLETS

### THE GRANULATION PROCESS

#### PREPARATION OF COMPONENTS FOR COMPRESSION:

The techniques for preparing tablets may follow one or a combination of several established methods. These are:

#### 1. Dry methods.

- a. Direct compression.
- b. Granulation by compression.

#### 2. Wet methods.

- a. Wet granulation.
- b. Special procedures.

## Dry methods

### **A- Direct compression**

Direct compression is used when a group of ingredients can be blended, placed onto a tablet press, and made into a perfect tablet without any of the ingredients having to be changed. Powders that can be blended and compressed are commonly referred to as directly compressible or as direct-blend formulations.

Blending the powders, putting them onto a tablet press, and seeing what happens is the most direct way to make a tablet. Sometimes the tablet will fall apart, the active ingredient won't be in all the tablets (no content uniformity), or all the powders won't fit into the die cavity (the place where powders are filled on the tablet press). Simply blending powders does not form a granule.

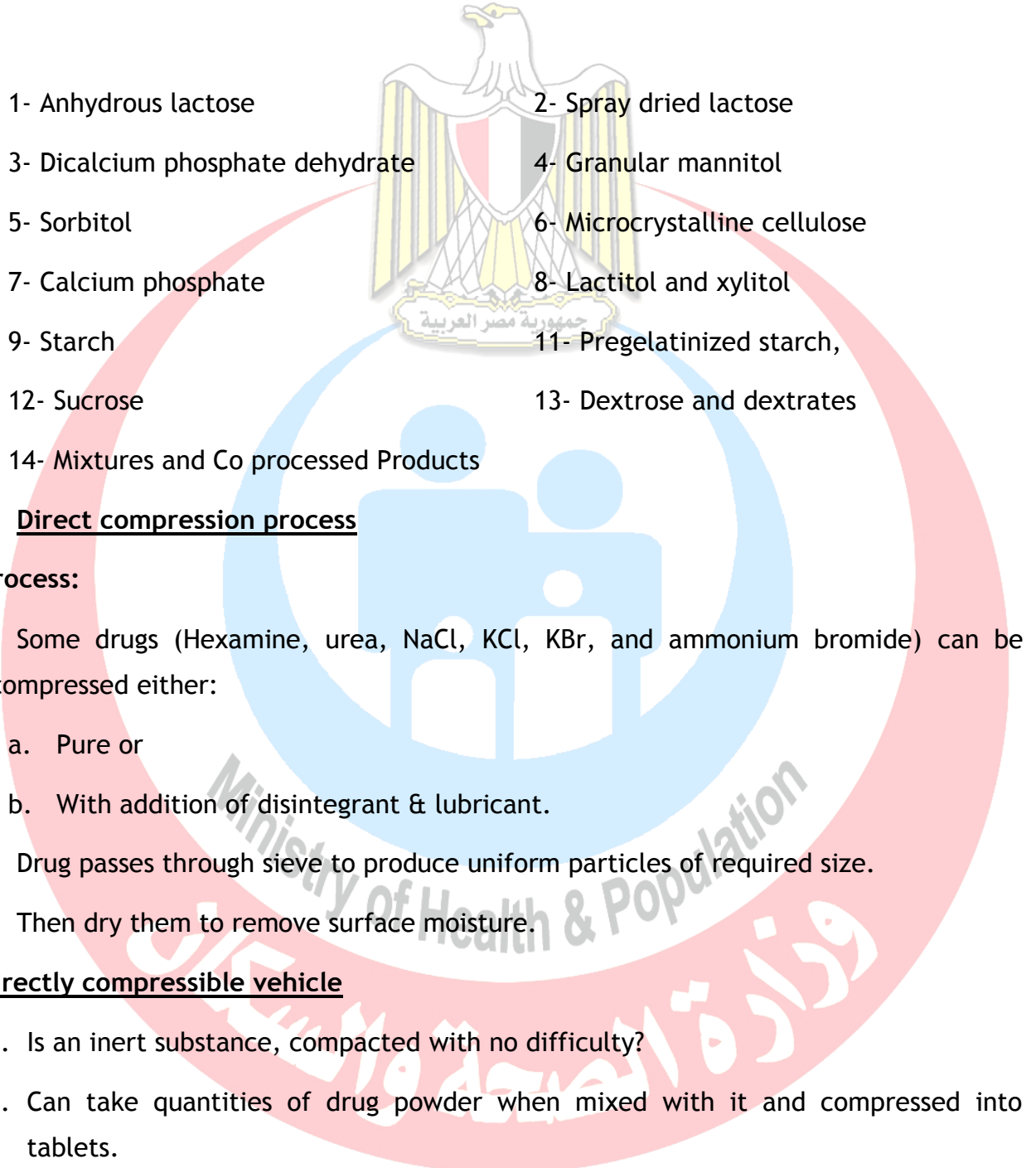
When powders do not compress correctly, they must be granulated. Nevertheless, not all products must be granulated. Many processes are unnecessarily implemented because the objective and reason for choosing a process path were incorrect. Before choosing a means to process a formula, the best course of action is to put the product on the press to see what happens.

#### ***Advantages direct compression process:***

- 1- The direct compression process is its simplicity and hence economy.
- 2- Less equipment is required and the number of stages in the process, each of which will require validation, is greatly reduced.
- 3- There are also lower labor costs, reduced processing time, and lower power consumption.
- 4- The direct compression process is that it is a dry procedure with no need for a drying stage. Thus, exposure to water and the elevated temperatures needed to remove that water are avoided, resulting in a decreased risk of deterioration of the active ingredient.
- 5- A further advantage of direct compression is that tablets disintegrate into their primary particles rather than granular aggregates.
- 6- The resultant increase in surface area available for dissolution should result in faster drug release.

## Directly compressible vehicles:

A directly compressible vehicle is an inert substance which may be compacted with no difficulty and which may do so even when quantities of drugs are mixed with it. It still has this capacity when blended with those other tablet materials necessary to flow, extrusion, and disintegration. Compressible diluents currently available are

- 
- 1- Anhydrous lactose
  - 2- Spray dried lactose
  - 3- Dicalcium phosphate dehydrate
  - 4- Granular mannitol
  - 5- Sorbitol
  - 6- Microcrystalline cellulose
  - 7- Calcium phosphate
  - 8- Lactitol and xylitol
  - 9- Starch
  - 11- Pregelatinized starch,
  - 12- Sucrose
  - 13- Dextrose and dextrates
  - 14- Mixtures and Co processed Products

### Direct compression process

#### Process:

1. Some drugs (Hexamine, urea, NaCl, KCl, KBr, and ammonium bromide) can be compressed either:
  - a. Pure or
  - b. With addition of disintegrant & lubricant.
2. Drug passes through sieve to produce uniform particles of required size.
3. Then dry them to remove surface moisture.

### Directly compressible vehicle

1. Is an inert substance, compacted with no difficulty?
2. Can take quantities of drug powder when mixed with it and compressed into tablets.  
  
e.g. spray dried lactose, anhydrous lactose, calcium phosphate, mannitol, sorbitol and microcrystalline cellulose (Avicel).
3. They rapidly disintegrate, physiologically inert, tasteless, able to be reworked, compress poorly compressible ingredients, and cheap.

### Limitations to the use of these materials:

1. Differences in particle size & bulk density between diluent & drug may lead to variation of drug content of tablets.
2. Drug may interact with vehicle e.g. amine compounds with spray-dried lactose.
3. Static charges developed on drug during grinding & mixing may prevent uniform distribution.
4. It cannot be used for low potency, high dose active ingredients where the inclusion
5. Direct compression tablet diluents are considerably more expensive than conventional diluents such as  $\alpha$ -lactose monohydrate.

### Dry granulation

#### A. Granulation by Precompression or slugging:

1. Used for incompatible materials or which decompose by moistening and heating process used in moist granulation.
2. Powder (drugs and excipients) is compressed by heavy-duty rotary compression machine fitted with punches and dies of about one inch diameter.
3. A very firm pressure is used to form large tablets (slugs).
4. The slugs then broken down to produce small granules suitable for recompression.
5. The disintegrant may:
  - a. All mixed with other ingredients before precompression, or
  - b. A proportion added to granules before they are compressed, so as to give a more rapid initial disintegration.
6. Lubricant is necessary to carry out precompression process, some of it should be reserved for recompression of granules.
7. Tablet produced by precompression tend to be more friable than those obtained by moist granulation.

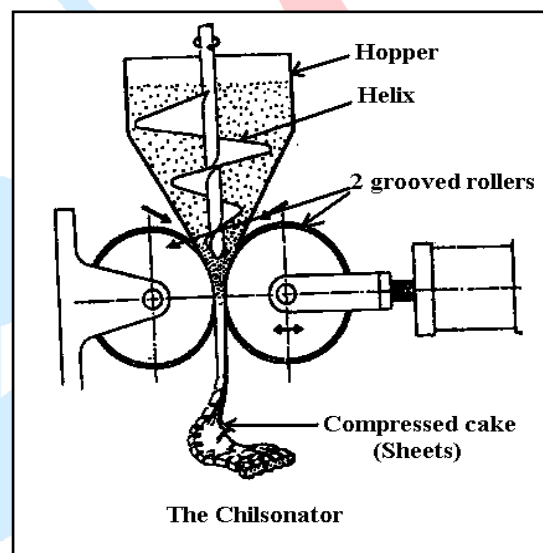
### Advantages:

- a. Elimination of moist granulation & drying of granules save equipment, floor space and

- b. processing time.
- c. Drugs sensitive to heat can be prepared without danger of decomposition.
- d. Tablet disintegration is more rapid **why?** Since disintegration power of starch is not diminished by presence of binder used in moist granulation.
- e. Process is suitable for preparing effervescent tablets.

### Chilsonator:

1. Machine that can turn powder to compact mass at high rate (400 kg/hour) which screened into granules suitable for compression.
2. The machine consists of 2 grooved rollers revolving toward each other. (space between them can be adjusted).
3. Powdered material is fed down between the rollers from a hopper. The aggregate are then screened or milled for production of granules.



### Advantages:

1. Higher production capacity.
2. Greater control of compaction pressure.
3. No need for lubrication of powder.

## Wet Granulation Processes

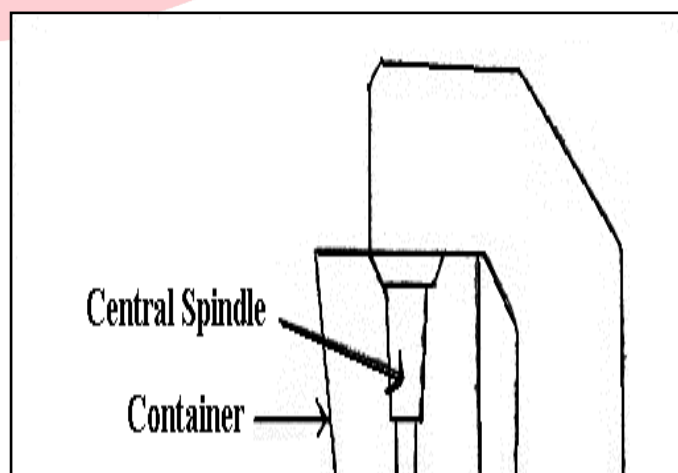
Granulation technique includes wet granulation and dry granulation/slugging wherein binders are added in solution/suspension form and in dry form respectively. In Direct Compression, binders possessing direct compressibility characteristics are used.

### B. Moist Granulation Process:

This most widely used.

#### **Steps:**

1. Sieving the active ingredients and excipients, milling to a



fine powder.

2. Preparation of binder.
3. Weighing ingredients.
4. Dry mixing.
5. Moistening them to form a doughy mass.
6. Sieving mass into coarse granules.
7. Drying granules.
8. Reducing them by sieving to correct size for compression.
9. Adding lubricant, disintegrant.
10. Compression.



#### **Advantages of wet granulation**

- 1- Enhances fluidity and compactibility, suitable for high-dose drugs with poor flow and/or compactibility
- 2- Reduces air entrapment
- 3- Reduces dustiness
- 4- Provides for the addition of a liquid phase (wet granulation) suited to dispersion of low-dose drugs in solution to ensure content uniformity
- 5- Enhances wettability of powders through hydrophilization (wet granulation)
- 6- Permits handling of powders without loss of blend quality

#### **Disadvantages of wet granulation**

- 1- Each unit process brings its own set of complications
- 2- The large number of unit processes increases the chances of problems
- 3- Difficult to control and validate
- 4- Potential adverse effects of temperature, time, and rate of drying on drug stability and distribution during drying

- 5- Overall more costly than direct compression in terms of space, time, and equipment requirements

### Criteria for selection of granulation method

- 1- Use wet granulation WG if the powder is incompressible and use dry granulation DG if the powder is compressible.
- 2- Use WG if API and excipients are wettable, physically, and chemically stable when exposed to moisture or heat.
- 3- Use WG for pressure sensitive materials.
- 4- Use WG if the material is too abrasive, brittle, or elastic.
- 5- Use WG for an easily dissolved product with high porosity - 40%.
- 6- Use DG if the key properties of powder particles need to be retained.
- 7- Use DG for feeds with high bulk density as a result of wide particle-size distribution.
- 8- Do not use DG for particle size below 150 -  $\mu$ m if air entrapment is a problem.

### Special procedures:

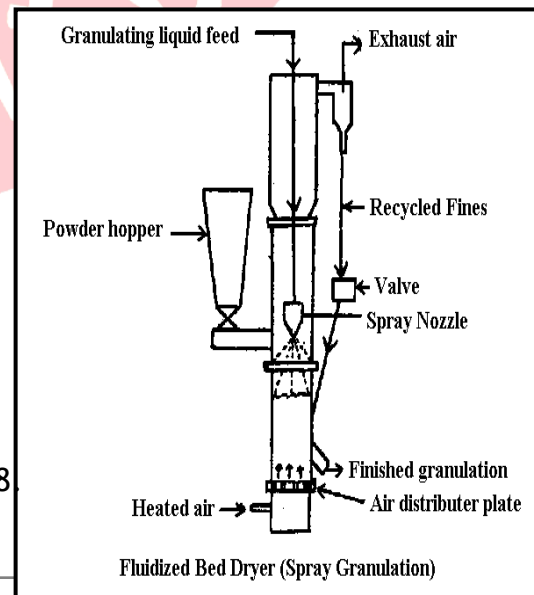
Wetting powder to form granules and drying them in the same piece of equipment.

### Process:

1. Component of formula is suspended &/or dissolved in vehicle (slurry).
2. Slurry sprayed into stream of hot air.
3. Heat dry the material which fall to the bottom of the dryer as a fine spherical granule its size depend on the flow rate of feed.

### Criteria for selection of granulator

- 1- Use pan granulator, high shear mixer granulator, and fluidized bed granulator for wet granulation and roller compactor for dry granulation.
- 2- Use fluidized-bed granulator to obtain granules of low relative density 0.3 - 0.5, pan granulator for medium relative density 0.5 - 0.7, and high shear mixer granulator for high relative density 0.6 - 0.8.



- 3- Use pan granulator only for producing granules larger than 1 mm.
- 4- Use high shear mixer granulator for cohesive materials.
- 5- Use high shear mixer granulator if viscous binder needs to be used.
- 6- Use fluidized-bed granulator if simultaneous drying is desired.

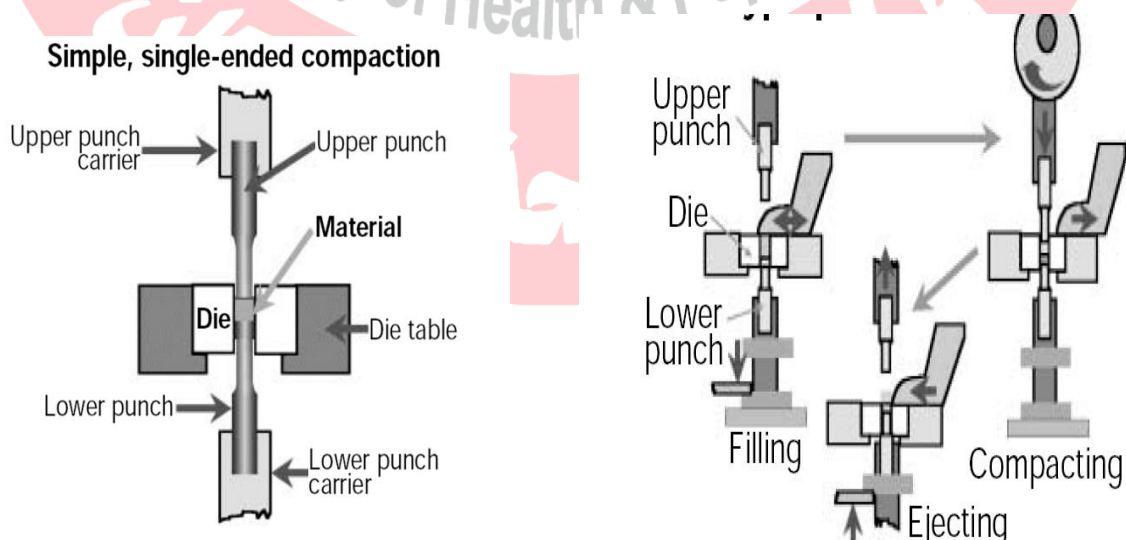
### TABLET COMPRESSION

All tablets are made by a process of compression. Solid, in the form of relatively small particles, is contained in a die and a compressing force of several tonnes is applied to it by means of punches.

The shape of the die governs the cross-sectional shape of the tablet, and the distance between the punch tips at the point of maximum compression governs its thickness. The conformation of the tablet faces, usually flat or convex, is a reflection of those of the punches.

The tip of the lower punch moves up and down within the die, but never actually leaves it. The upper punch descends to penetrate the die and apply the compressive force. It is then withdrawn to permit ejection of the tablet, brought about by an upward movement of the lower punch.

There are two types of tablet press. The excentric press has one die and one pair of punches. The rotary press has a larger number of dies which are fitted, with their corresponding punches, into a rotating turret. Irrespective of the type of press that is used, the process of tablet compression can be divided into three stages.



### **Stage 1, Filling**

The lower punch falls within the die, leaving a cavity into which particulate matter flows under the influence of gravity from a hopper. Though tablets are usually described in terms of weight, the die is filled by a volumetric process. The volume is determined by the depth to which the lower punch descends in the die. Unless this volume is filled reproducibly on each occasion, then the mass of the tablet will vary, and with it the drug content of each tablet. Therefore, uniform filling is essential.

However, it must be borne in mind that the die cavity has a cross-section of only a few millimetres, and only a fraction of a second is available for filling each die. It therefore follows that the particles must flow easily and reproducibly.

### **Stage 2, Compression**

The upper punch descends, and its tip enters the die, confining the particles. The distance separating the punch faces decreases, either by movement of the upper punch alone (as in excentric presses) or by movement of both punches (as happens in rotary presses). The porosity of the contents of the die is progressively reduced, and the particles are forced into ever-closer proximity to each other.

This process is facilitated by the particles fragmenting and/or deforming. Once the particles are close enough together, interparticulate forces then cause the individual particles to aggregate, forming a tablet. The magnitude of the force is governed by the minimum distance separating the punch faces. Therefore, a second essential property of the particles is that they cohere under the influence of a compressive force. It is also essential that this coherence be maintained when the compressing force is removed.

### **Stage 3, Ejection**

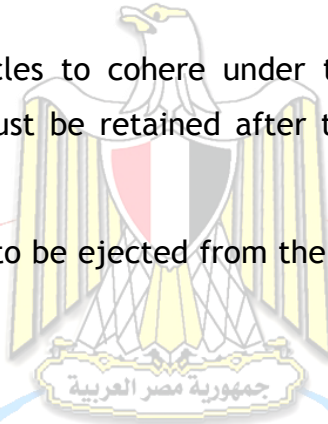
The upper punch is withdrawn from the die, and so the force being applied to the tablet is removed. The effect of this might be to cause the deformed particles to return to their former shape, which would result in a decrease in interparticulate contact and hence tablet strength. It is essential that this does not occur.

As the upper punch leaves the die, the lower punch moves upwards, pushing the tablet before it. During the compression stage, the particles are forced into intimate contact with the interior die wall. It follows that attempts to remove the

tablet will be opposed by frictional forces and so successful ejection demands lack of adhesion between the tablet and the die wall.

Therefore, in summary, for a particulate solid to be successfully transformed into tablets, three key properties need to be present:

1. Good particle flow.
2. The ability of the particles to cohere under the influence of a compressing force. This coherence must be retained after the compressing force has been removed.
3. The ability of the tablet to be ejected from the die after the compressing force has been removed.



### **The effect of manufacturing processes on formulations**

Numerous unit processes are involved in making tablets, including particle size reduction and sizing, blending, granulating, drying, compaction, and (frequently) coating. Various factors associated with these processes can seriously affect content uniformity, bioavailability, or stability. Some of these are given in the following list:

#### **A. Particle Size Reduction**

- 1- Nonuniform particle size can lead to segregation problems
- 2- Development of electrostatic forces inhibits complete blending
- 3- Changing the crystalline state can affect solubility

#### **B. Blending**

- 1- Nonhomogeneous distribution of drug substance is the result of poor blending or unblending
- 2- Overblending of lubricant lowers dissolution rates and affects compactibility

#### **C. Granulation**

- 1- Nonhomogeneous distribution of binder and drug substance gives drug-rich or drug-poor fines
- 2- Decomposition of drug substance due to residual moisture
- 3- Uneven granule size (too many or too few fines) leads to compaction or uniformity problems

#### D. Tableting

- 1- Uneven compaction pressures affect dissolution
- 2- Loss of mix quality in hopper and feed frame gives poor content uniformity
- 3- Additional shearing of lubricant in feed frame lowers dissolution rates

#### E. Coating

- 1- Nonuniform or incomplete coverage of tablets and beads results in different dissolution patterns. When validating new equipment or procedures, the sampling techniques must reflect the quality of the material being tested, the blend of powders, moisture in granulation, or coating integrity.



### Problems occurring in tableting manufacture

#### **1. Binding or sticking in the die**

- The tablet ejected with difficulty & often accompanied by a noise.
- Stop compression otherwise damage of machine occurs

#### Causes of binding:

1. The granules may be insufficiently or unevenly lubricated.
  2. Remixing of the granules or the addition of more lubricant may correct this, (excessive use of lubricant may interfere with disintegration).
  3. Insufficient drying of the granules
  4. Granules absorb moisture while awaiting compression.
  5. The die may be dirty or unpolished.
  6. The die become worn,
- There will be an abnormal amount of clearance between the lower punch and the die wall.

#### **2. Capping**

The top of the tablet or cap becomes detached from the main body, either at the time of compression or after the tablet leaves the die.

#### Causes of capping:

- a. The use of a ringed die: The ring formed by constant friction. This can be smoothed by honing (if it is not too pronounced)

Replacing the worn die

- b. Speed of Compression:

If compression is too rapid lead to air is not given time to escape & remains trapped within the tablet until released by removal of the pressure lead to The air then expands and escapes at the periphery ( the weakest part of the tablet) lead to detaching the cap.

- c. Presence of excessive fines: will prevent air from escaping during compression.

- d. The punches fitting too closely in the die:

Occur with new die, when air in the granule cannot escape between the upper punch and the die wall. corrected by reducing the diameter of the upper punches by grinding

- e. Use of excessive pressure:

Capping occur due to slight expansion of the tablet after the pressure is released.

- f. Influence of the binder:

Binder may be insufficient in amount or unsuitable for a particular drug lead to the granules will be friable and lacking cohesion.

- g. Over drying of granules: granules require a certain moisture content, to assist the action of the binder in producing a firm table.

### 3. Picking

Granules adhere to the punch face after compression; instead of leaving it clean and bright lead to compressed tablet will show a pitted appearance on its surface.

#### Causes of Picking:

- a. Insufficient or uneven lubrication.
- b. The granules may be under dried.
- c. The punch face may be pitted, scratched or unpolished allowing a film of granule on it.

### 4. Weight variation

#### Causes of weight variation:

a. The size of the granules being compressed:

The presence of too many large granules lead to interferes the filling of the void space between them.

The granulation should be ground through a finer screen to produce more small particles.

b. Poor flow:

The granulation does not flow readily lead to some dies are incompletely filled.

So a glidant such as talc is added.

c. Poor mixing:

Lubricant and glidants have not been thoroughly distributed lead to the flow of particles is not uniform and the granules do not moves efficiently into the dies.

d. Punches:

When lower punches are of unequal lengths (in the rotary machine): The fill in each die varies because the fill is volumetric.

### 5. Mottling

It is an unequal distribution of color on the surface of the tablet, with light or dark areas standing out in an otherwise uniform surface. One cause of this imperfection is a drug that differs in color from its excipients or whose degradation products are highly colored. A dye may be used to mask the change. Another cause is migration of a dye during drying of a granulation.

To overcome this difficulty, the formulator may change the solvent system, reduce the drying temperature, or grind to a smaller particle size. Colored adhesive solutions sometimes are not distributed well because they must be added hot to much cooler powder mixtures. The adhesive then comes out of solution and carries most of the color with it.

### 6. Hardness variation

#### Hardness depends on:

1. The weight of material filled in the die
  2. The space between the upper and lower punches at the moment of compression.
- If the material varies or the distance between punches, hardness variation occurs.

- Hardness increase with normal storage of the tablets.

## 7. Double impression

This involves only lower punches which have a monogram or other engraving on them. Now of compression, the tablet receives the imprint of the punch. On some machines, the punch is free to drop and then travel uncontrolled for a short distance before it rises up the ejection cam to push the tablet out of the die. During its free travel, it rotates. At this point the punch may make a new, although lighter, impression on the bottom of the tablet, result, a double imprint.

### Evaluation of tablets

1. Weight variation tolerances
2. Tablet hardness:
3. Friability:
4. Tablet disintegration
5. Dissolution rate
6. Content Uniformity
7. Tablet Thickness

### Methods

1. Sugar coating
2. Film coating
3. Compression coating

### 1. Sugar Coating

#### It is used to:

- mask unpleasant tastes and odours
- Protect an ingredient from decomposition as a result of exposure to air or moisture.

- Improve tablet appearance.

**Characteristics of tablets used for sugar-coating:**

- An optimum convexity
- Hard enough to withstand coating process
- Not absorb solvent used in coating.
- have a dissolution rate as required in vivo testing
- dust free

**Process of coating**

**(Seal coat + Subcoat + Syrup coat + Polishing coat)**

<p><b>1.Seal coat</b></p>	<ul style="list-style-type: none"> <li>- Used to separate the core from the water that is used the coating process.</li> <li>- This by the use of cellulose acetate phthalate or shellac.</li> <li>- dusting powder (talc) prevent adherence of tablet to pan and to each other</li> <li>- At least two seal coats are necessary to make the tablet waterproof</li> <li>- Six seal coats can be applied, depending upon:             <ul style="list-style-type: none"> <li>o Tablet shape</li> <li>o Hygroscopicity of the core</li> <li>o Sensitivity of the core to water.</li> </ul> </li> <li>- Too many seal coat would retard disintegration and dissolution.</li> <li>- Insufficient seal affect core stability by permitting water to enter the core during the coating process.</li> </ul>
<p><b>2.Sub-coating</b></p>	<ul style="list-style-type: none"> <li>o to round off tablet surface rapidly</li> <li>o to improve bonds between seal coat and sugar coat</li> </ul>

	<ul style="list-style-type: none"> <li>- This is done by solution of gelatin and or acacia beside dusting powder (Talc or titanium dioxide).</li> <li>o The table surface can become rough during subcoating.</li> </ul> <p><b><u>Roughness occur due to:</u></b></p> <ol style="list-style-type: none"> <li>1. Excess dust that remains after the dusting process.</li> <li>2. Rolling of tablets too long after the dusting powder has been applied.</li> <li>3. Application of insufficient amount of subcoating solution to wet all the tablets.</li> </ol> <ul style="list-style-type: none"> <li>- Tablets that become rough during subcoating often can be recovered by application of a number of syrup coats.</li> </ul>
3.syrup coat	<p>involves <b><u>three phases:</u></b></p> <ul style="list-style-type: none"> <li>- Application of <u>grossing syrup</u> (a syrup solution with subcoating powder dispersed in it).</li> </ul> <p><u>N.B:</u> Dyes are added during grossing since one of the primary objectives of this step is to develop a colour.</p> <ul style="list-style-type: none"> <li>- Application of <u>heavy syrup</u></li> <li>- Application of <u>regular syrup</u></li> </ul>
4.polishing coat	<p><u>This is done in polishing pan.</u></p> <ul style="list-style-type: none"> <li>- Polishing solution (Carnuba wax, white bees wax, paraffin wax and naphtha in petroleum ether) is applied</li> <li>- The tablets can roll on until the naphtha odour disappears.</li> <li>- no air is used during the polishing step</li> </ul>

**N.B.:**

- Mottling or spotting of the finished tablets can occur due to migration of moisture to the surface of the tablet.
- This can be avoided by drying the tablets during the various stages of the syruing process.

## 2. Film Coating

### Advantages

- Reduction in coating time and coating material.
- No significant increase in tablet weight.
- No undercoat or waterproof coat.
- Durable and resist chipping and cracking.
- Protect against light, air and moisture.
- Not prolong disintegration time.
- Pharmaceutically elegant.

### Properties of Film-Coating Materials

1. Soluble in organic solvents.
2. Soluble in all or at selective pH in the G.I.T.
3. Produce a smooth and elegant continuous film.
4. Stable in the presence of heat, light, moisture, air and drugs being coated.
5. Have acceptable or no taste, colour and odour.
6. Can hold pigments and other coating additives.
7. Resist crack and protect from moisture, light, odour or drug sublimation.

Film formers can be classified into non enteric and enteric materials.

Type	Materials used	Characters of materials
Non	Hydroxy Propyl Methyl Cellulose (HPMC)	<ul style="list-style-type: none"> <li>- excellent film forming ability</li> <li>- stable to light, heat, air and moisture</li> <li>- tasteless, odourless and resist chipping</li> <li>- soluble in GIT juices and organic solvents</li> </ul>
	Ethyl Cellulose	<ul style="list-style-type: none"> <li>- non toxic, tasteless &amp; stable</li> <li>- insoluble in water and GIT fluids, so not suitable by itself for tablet coating (can be</li> </ul>

enteric coating		made permeable by mixing with soluble HPMC)
	polyvinyl pyrrolidone (Povidone)	<ul style="list-style-type: none"> <li>- Hygroscopic, tacky so use a glidant (talc) or plasticizer during coating.</li> <li>- sol. in water, GI fluids and organic solvents</li> <li>- form clear glossy hard coat</li> </ul>
	polyethylene glycol(PEG)	<ul style="list-style-type: none"> <li>- sol. in water, GI fluids</li> <li>- good barrier for controlling drug odor</li> <li>- Used with CAP &amp; waxes to form GIT soluble film</li> </ul>
Enteric coating	Cellulose Acetate Phthalate (CAP)	<ul style="list-style-type: none"> <li>- Hygroscopic, susceptible to hydrolysis by high temp. and humidity</li> <li>- insoluble in H<sub>2</sub>O and acidic solutions but dissolve at pH 6</li> </ul>
	Shellac	<ul style="list-style-type: none"> <li>- insol. in slightly acidic PH</li> <li>- disintegration and drug release may be delayed in slightly acidic intestinal fluid</li> </ul>

#### Properties of an ideal enteric coating material:

- Impermeable to gastric juices.
- Susceptible to intestinal juices.
- Stable during storage.
- Form continuous non-interrupted coating.
- Non toxic.
- Inexpensive.
- Easy to apply with minimum equipment.

#### Additives of film coating solution

Additive	characters
plasticizers	<ul style="list-style-type: none"> <li>- Plasticizers are liquids of low volatility added to film-forming materials to increase the flexibility of the resulting film &amp; improve its quality.</li> <li>- Examples: Castor oil, propylene glycol and polyethylene glycol 200 and 400</li> </ul>
surfactant	<ul style="list-style-type: none"> <li>- Improve spreading of the coat solution over the tablets</li> <li>- Allow the use of immiscible or insoluble ingredients in coating</li> <li>- Aid in dissolving the coat upon ingestion.</li> </ul>
colouring agents (colorant)	<p><u>Colorants</u> provide elegance &amp; provide product distinction</p> <p><u>Choice of colorant depends upon:</u></p> <ol style="list-style-type: none"> <li>1. Particle size</li> <li>2. Solubility</li> <li>3. Fastness to light</li> </ol> <ul style="list-style-type: none"> <li>- Coloring agents may be dissolved or suspended in solvent systems for film coating.</li> <li>- To make the color uniform and aid rapid and complete covering of the tablet: <ol style="list-style-type: none"> <li>1. Use insoluble dyes</li> <li>2. Use opaquing extenders</li> <li>3. Use lakes</li> </ol> </li> <li>- Water-soluble dyes precipitated with bases such as alumina or talc.</li> <li>- This insoluble pigment has good covering power and better light and solvent stability.</li> </ul>
Opaquing extender (Opacifant)	<ul style="list-style-type: none"> <li>- Used when transparent films are not required.</li> <li>- <u>Titanium dioxide</u> is best because of its extreme whiteness and stability.</li> </ul>
flavor or sweetener	Improve the taste

### Film defects

Defect	Characters
1. Blistering	<p>The solvent forced from the coat surface cause blister</p> <p><u>Causes:</u></p> <ol style="list-style-type: none"> <li>1. Rapid drying force solvent to the surface at a rate too fast for the film to hold.</li> </ol>

	<p>2. Reduced adhesion between film and tablet surface.</p> <p><b><u>Treatment:</u></b></p> <p>1. Reduce drying temperatures                      2. More prolonged drying time.</p>
2. Wrinkling	<p><b>Presence of many wrinkles on the surface of the coat</b></p> <p><b><u>Causes:</u></b></p> <p>1. The film is too thick.                      2. Improper drying of the film</p>
3. Bridging	<p><u>Film shrinks during the drying process.</u></p> <p><b><u>Cause:</u></b> lack of adhesion of the film to the tablet surface.</p> <p><b><u>Treatment:</u></b></p> <p>1. Add materials that impart a degree of tack.                      2. Increase the porosity of the tablet surface</p> <p>3. Addition of a plasticizer to increase cohesiveness of the coat</p>
4. Sweating	<p><u>The presence of an oily film or droplets of liquid on the surface of the coat</u></p> <p><b><u>Cause:</u></b> Plasticizers and surfactants are exuded from the film</p> <p><u>This is due to:</u></p> <p>1. Incompatibilities between ingredients in the film.</p> <p>2. Strong cohesive forces of the polymer                      3. High drying temperatures.</p> <p><b><u>Prevention:</u></b></p> <p>0 Proper choice of the types and amounts of additives</p> <p>0 Proper drying conditions.</p>
5. Orange Peel	<p><u>The surface of the coat resembles the peel of an orange.</u></p> <p>Coating solution not spread and not forms a smooth coat.</p> <p><b><u>Cause:</u></b></p> <p>1. Rapid drying of the coat</p> <p>2. Insufficient solution distribution after each application of coating solution</p> <p>3. Coats applied with spray cause small amounts of coating material dry suddenly.</p> <p><b><u>Prevention:</u></b></p> <p>f. Control the evaporation rate of the solvent.</p> <p>g. Continue to apply additional coating solution before previous coat are completely dry</p>
	<p><u>The coat is easily removed from outer layer in sheets</u></p> <p><b><u>Cause:</u></b> lack of adhesion of tablet surface and coat due to rapid drying between coating applications.</p>

6. Flaking	<p><b><u>Prevention</u></b></p> <p>h. Produce one continuous coat rather than individual layers.</p> <p>i. sufficient coating material should be applied at one time to dissolve a small portion of the previous coat in order to increase bonding between old layer and new one</p>
7. Bloom	<p><b>Dull film or bloom developing on the surface of the coat</b></p> <p><b><u>Cause:</u></b></p> <p>1. Coating done under high humid conditions → partial solvation of the outer layer of the film and colouring material by moisture.</p> <p>2. Plasticizers migrate to the surface of the coat</p>
8. Spotting	<p><b>The presence of mottled or spotting areas on the coat.</b></p> <p><b><u>Causes:</u></b></p> <p>1. Plasticizers migrate to the surface → dissolve dyes and cause spots.</p> <p>2. Solvent carries soluble material to the surface during the drying process.</p> <p><b><u>Prevention:</u></b></p> <p>- Dry the coated products at a slower rate in air-conditioned areas.</p>

**Rework:**

Film-coated tablets can rework when show a defects.

This by.

1. The coat is washed off by rapid dipping in solvent.
2. The tablets are ground in a mill, and the resulting granules are recompressed

**OTHER TYPES OF COATING**

**3. Compression coating:**

**Advantages:**

- The process is entirely without moisture
- Coating materials is rapidly soluble → high physiologic availability.
- Surface and size of coated tablets is uniform.
- Separate incompatible ingredients.
- The coating may be enteric or delayed release substance

**Disadvantages:**

- Needs large equipment
- Complex operation

### **Definition of IPQC for in Process Quality Control.**

These are checks that are carried out before the manufacturing process is completed. The function of in-process controls is monitoring and if necessary adaption of the manufacturing process to comply with the specifications. this may include control of equipment and environment too. In-process materials should be tested for identity, strength, quality and purity as appropriate and approved or rejected by the quality control unit during the production process. Rejected in-process materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing. Written procedure should be established and followed that describe the in-process controls and tests as specified.

$\frac{3}{4}$  Tablet or capsule weight variation.  $\frac{3}{4}$  Disintegration time.  $\frac{3}{4}$  Content uniformity and homogeneity.  $\frac{3}{4}$  Dissolution time and rate.  $\frac{3}{4}$  Clarity, Completeness or pH of solutions.

### **In-process quality control tests for various dosage forms (Tablet)**

1. Drug contents determination.
2. Moisture contents of granules.
3. Assay of active ingredients.
4. Weight variation of uncoated tablets.
5. Hardness test.
6. Disintegration test.

#### **Drug Content Determination**

A physically sound tablet may not produce the desired effects. To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch, and a measure of the tablets ability to release the drug needs to be ascertained.

#### **Moisture Content of granules**

Granules should possess sufficient strength to withstand normal handling and mixing

processes without breaking down and producing large amounts of fine powder. On the other hand, some size reduction during compaction into tablets is desirable to expose the areas of clean surface necessary for optimum bonding to take place so moisture content is the very important factor for producing good pharmaceutical product.

### **Assay of active ingredient**

In a tablet an active ingredient is present which is called active pharmaceutical ingredient (A.P.I). So to prepare the tablet assay has to be done to produce good finished product.

### **Hardness test**

The monitoring of tablet hardness is especially important for drug products that possess real or potential bioavailability problems that are sensitive to altered dissolution release profiles as a function of the compressive force employed. One of the earliest testers to evaluate tablet hardness was the Monsanto hardness tester to evaluate tablet hardness tester.

### **Disintegration test**

A generally accepted maximum is that drug to be readily available to the body, it must be in solution. For most tablets, the first important step towards solution is break down of the tablet into smaller particles or granules, a process known as disintegration. The U.S.P device to test disintegration uses 6 glass tubes that are 3 inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly. To test for disintegration time, one tablet is placed in each tube, and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid and at  $37^{\circ} \pm 2^{\circ} \text{C}$ , such that tablet remains 2.5cm below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. A standard motor driven device is used to move the basket assembly containing the tablets up and down through distance of 5 to 6cm at a frequency of 28 to 32 cycles per minute.



## Solid Dosage Forms

### ii. Capsules

#### Objectives

*After reading this chapter, the student will be able to:*

1. Differentiate between hard gelatin and soft gelatin capsules.
2. Compare and contrast advantages and disadvantages of hard gelatin and soft gelatin capsules.
3. List categories of inert ingredients, with examples, which are employed in the manufacture of hard or soft gelatin capsules.
4. Define and differentiate weight variation from content uniformity.

### CAPSULES

#### **Definition**

Capsules are officially Solid dosage forms in which the drug is enclosed within a hard or soft soluble shell made from a suitable form of gelatin.

- Capsules are not suitable for liquids that dissolve gelatin like aqueous or alcoholic solutions.
- They are administered mainly by swallowing orally.

#### **Advantages of capsules**

1. Granules, powder, liquids, semi-solid formulation and mini tablet can easily be filled alone or in combination in the capsules.

2. Ideal for controlled release formulation in particular pellets.
3. Requires fewer excipients
4. Reduced stability problems with sensitive drug
5. Easily disintegrated and rapidly release of the drug.
6. Capsules are easily swallowed by almost any adult personal with a drink
7. Capsules may be administered rectally or vaginally with dipped in warm water to facilitate insertion.
8. Unique colour and shape configurations enhance product identity

### ***Disadvantages***

1. No possibility of fractioning dosage form
2. More prone of adherence to oesophagus
3. Sensibility to temperature and humidity during storage
  - Moisture shell content (13 - 15)
  - If less brittle
  - If softer and sticky
4. Not adequate for highly hygroscopic drug
5. Problems with high amount of bulky materials

### **Types of capsules**

1. **Hard gelatin capsules** (two-piece) consists of two pieces in the form of cylinders closed at one end: the shorter piece, called the 'cap', fits over the open end of the longer piece, called the 'body'.
2. **Soft gelatin capsules** (one-piece) Capsules are solid dosage forms in which the medicaments are contained within gelatin shells.

### **Composition of hard gelatin capsules**

The capsule shells are usually made from mixture of either type of gelatin and water.

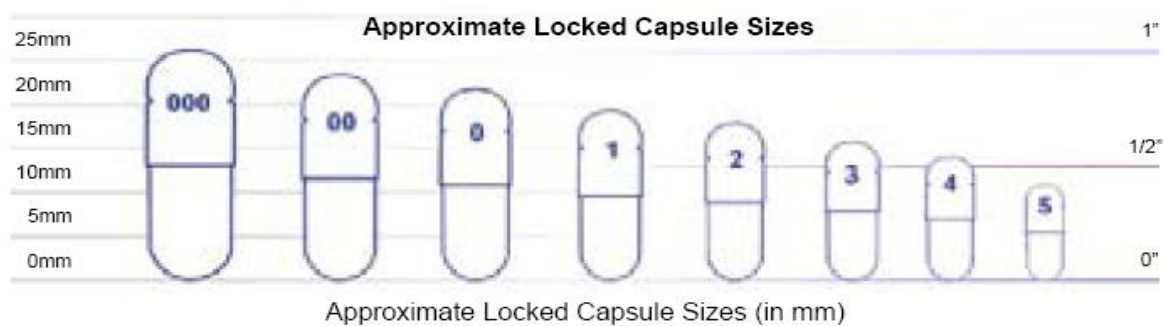
### **They may also contain**

- Coloring agents such as various iron oxides,

- Opaque-producing agent e.g titanium dioxide,
- Dispersing agents such as HPMC
- Hardening agents such as sucrose
- Preservatives such as sulfur dioxide.

### 1. Sizes of hard gelatin capsules:

- Hard gelatin capsules "tended for human use are available in sizes ranging from No. 5, the smallest, to No. 00 which, is the largest size. The capacity of the capsule is mainly depend upon the bulk density show in figure and tablet 3.1.



Capsule Volume size	ml	Capacity in mg powder density			
		0.6	0.8	1.0	1.2 g/ml
000	1.37	822	1096	1370	1644
00	0.91	546	728	910	1092
0	0.68	408	544	680	816
1	0.50	300	400	500	600
2	0.37	222	296	370	444
3	0.30	180	240	300	360
4	0.21	126	168	210	252

Figure and Table 3.1 Examples for hard gelatin capsule dimensions and filling capacities

### **Preparation and types of gelatine**

Animal skins and bones are the raw materials used for the manufacture of gelatin. It is prepared by the partial hydrolysis of collagen, which is the main protein constituent of connective tissues, skin and bones.

### **Procedures for production of hard gelatin capsules:**

Fully automated machines are used for production of hard gelatin capsules. The production process involves the following steps:

- 1- **Dipping:** Plates holding various number of manganese bronze or stainless-steel pins are dipped into melted gelatin mixture, maintained at constant temperature to provide the desired viscosity.
- 2- **Spinning:** pins are carefully removed from the gelatin path
- 3- **Drying:** The gelatin on the pins is gently dried by a flow of hot air.
- 4- **Trimming:** The dried shells are mechanically trimmed to the desired length by stationary knives
- 5- **Stripping:** The shells are then ejected from the pins
- 6- **Joining of capsules:** The body and cap pieces are joined and ejected

The quality and the exact geometry of the capsules are usually controlled by:

- Pins dimensions.
- Viscosity of the gelatin mixture.
- Dipping period.
- Depth to which the pins are submerged.
- Spinning speed.
- Drying program.
- Trimmer setting.

### **Capsule-filling machines:**

Two types of capsule filling machines are available:

### 1- Hand-operated capsule filling machines:

These machines are available in capacities up to 144 capsules and can produce up to 2000 capsules per hour.

### 2- Industrial capsule-filling machines:

They are fully automatic machines.

They are very efficient and can fill hundreds of thousands (165,000)/hr./unit.

### Components of capsule formulation:

a. **Diluents:** Generally; hard gelatin capsules capacities approximately ranged from -65 mg to -1000g including drug and diluents if necessary.

- Lactose and starch are commonly utilized diluents in capsule filling.

b. **Lubricant:**

They are used to facilitate the flow of the drug are used. a magnesium stearate is an example of the commonly used lubricant.

c. **Wetting agents:** They are commonly added where the active ingredient is hydrophobic PEG.

d. **Disintegrants:** They also may be added in powder formulations to prevent aggregation and dispersal of capsule in the gut.

### Sealing and finishing operation:

Finishing operation in hard gelatin production involves three steps:

#### 1. Closer or Sealing of hard gelatin capsules:

Hard gelatin capsules can be closed or sealed by any of the following techniques:

a. **Grooving:** In this technique, grooves molded in the cap and the body portions to provide a positive closure when they are fully engaged.

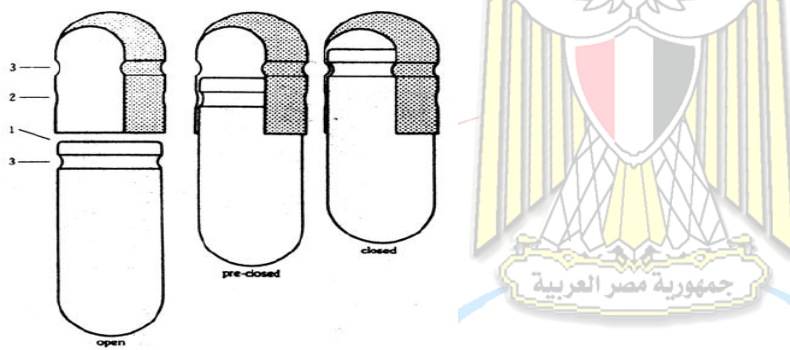
b. **Welding:** In this process, positive closure also may be obtained by spot fusion of the cap and body pieces together through thermal means or by application of ultrasonic energy.

c. **Banding:** It is a process in which one or more layers of gelatin are applied over the stem of the cap and body.

d. **Liquid fusion process:** It the process in which the filled capsules are wetted with a hydro-alcoholic solution, which penetrates the space where

the cap overlaps the body, and then dried. N.B. The last two techniques are usually employed to completely seal the hard shell capsules in large-scale production and they have the following advantages:

- They improve the stability of the contents by limiting oxygen penetration.
- They are employed when semi-solids or liquids are encapsulated to prevent leakage.



## 2. Cleaning and polishing:

This can be done by one of the following techniques;

- Vacuum cleaning: In large scale, many capsule-filling machines are equipped with a cleaning vacuum that removes extraneous materials from the capsule shells.
- Salt polishing: In this process the filled capsules and sodium chloride are rotated in a container similar to tablet coating pan.
- Imprinting: It can be done on either empty or filled capsules using various types of machines.

### Problems encountered in hard gelatin capsules formulation:

#### 1. Eutectic mixture:

They are mixtures of two or more substances which has a lowest melting point known as the eutectic point. Camphor-salicylic acid are examples of eutectic mixtures.

- Eutectic mixture can be dispensed in three methods:
  - Each of the mixture ingredients is kept separately and mixed with inert absorbent powder such as kaolin, light magnesium oxide or magnesium carbonate.

#### 2. Deliquescent powder:

Capsules containing deliquescent or hygroscopic materials should be dispensed in tight container with an absorbent such as magnesium carbonate, colloidal silicon dioxide or other suitable adsorbent.

### 3. Separation of incompatible materials:

Separation of two mutually incompatible drugs can be achieved placing one in small capsule and then enclose it with the second drug in a larger capsule.

### 4. Accuracy in weighing potent drugs:

Adding an inert powder to the drug will increase the bulk to be weighed and increase accuracy of the weighed materials.

## II. Soft Gelatin Capsules (Softgels)

Soft gelatin (also called softgel or soft elastic) capsules consist of one piece of gelatin (40%) hermetically-sealed soft shells. Soft gelatin capsules are prepared by gadding a plasticizer (20-30%), such as glycerin or polyhydric alcohol (., sorbitol), to gelatin.

- The plasticizer makes gelatin elastic.
- Soft gelatin capsules come in various shapes such as spherical, elliptical, oblong, and special tube shapes with and without twist off. Soft gelatin capsules (elastic capsules) normally contain from 5-8 % water.
- Similar to hard gelatin capsules, the shell composition may contain colorant such as dyes, opaquing agent such as titanium dioxide and preservative.
- Flavoring agents and up to 5% sucrose as sweetening agent may be included to soft gelatin shells.

### Types of softgels according to models of drug delivery

1. Orally administered softgels containing solutions or suspensions that release their contents in the stomach.
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*, designed with a tag to be twisted or snipped off, thereby allowing access to the fill material. This type of softgel is very useful for unit dosing of topical medication, inhalations, or for oral dosing of a pediatric product.
5. Meltable softgels, designed for use as 'patient friendly' pessaries or suppositories.

#### Advantages of Soft Gelatin Capsules

1. Ease of swallowing
2. Improved drug absorption: introduction of the drug in solution form lead to higher absorption rates than solid oral dosage forms.
3. Increased bioavailability:
4. Decreased plasma variables: often noticed for solid dosage forms for drugs of low bioavailability. Administering the drug as solution in softgels will increase the absorption and maintain plasma concentration. Ex: cyclosporin A in premicroemulsion formulations.
5. Portability: highly portable for consumers/patients.
6. Safety for potent and cytotoxic drugs:
7. Oils and low melting point drugs: if oils of melting points  $<75^{\circ}\text{C}$  or those difficult to compress, or If drug is oily and can be filled without additives.
8. Dose uniformity of low dose drugs: liquid dosing avoid powder poor flowability and so give good content uniformity.
9. Product stability: low oxygen permeability, low moisture content

#### Disadvantages of Softgels:

1. Substances that soften, dissolve, or easily migrate through the capsule shell cannot be formulated as softgels. These materials include volatile organic compounds such as alcohols, esters,, low molecular weight water-soluble materials.
2. In liquid-filled capsules the contact between the shell and its liquid contents is more intimate than exist with dry-filled capsules and this may increase the chances of for undesired interactions.
3. The necessary to contract out the filling operations to one of the very small number of companies with the necessary equipment and expertise.

**Application of soft gelatin capsules:**

They can contain non-aqueous liquids, suspensions, pasty materials, or dry powders. They are especially important to contain volatile drug substances or drug materials susceptible to deterioration in the presence of air

**Production of soft gelatin capsule:**

The Rotary Die Process developed by Robert P. Scherer in 1933 to prepare softgels. In this process the following steps are involved:

1. Metered volumes of the fill matrix are injected from the wedge into the space between the gelatin ribbons as they pass between the die rolls.
2. The gel then expands into the pockets of the dies.
3. The two softgel halves are sealed together by the application of heat and pressure.
4. Finally, the capsules are cut automatically, dried and packed. Each ribbon provides one half of the softgel. In this way it is possible to make bicoloured softgels.
5. The produced capsules are then washed through a series of naphtha bath, dried and kept in refrigerating tanks which prevent the capsules from adhering to one another

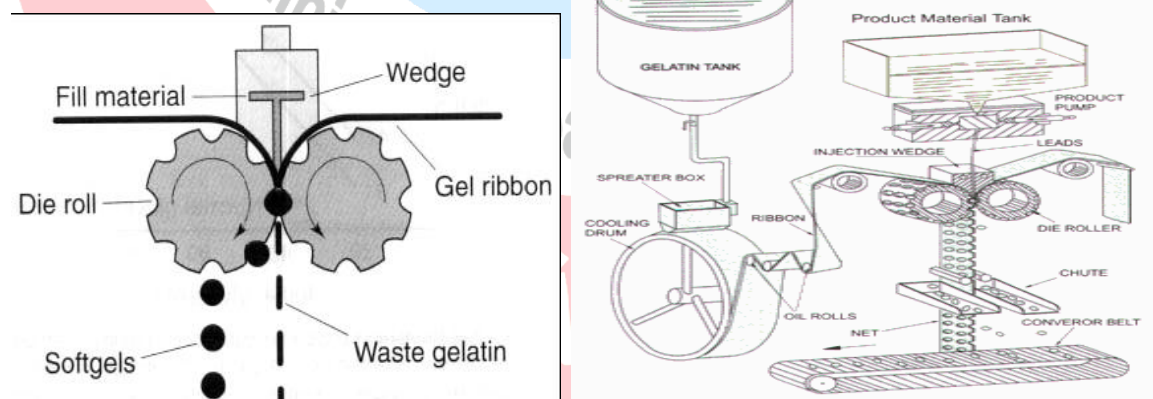


Figure 3-3: Diagrammatic representation for the rotary die process.

**Control of the rotary die process**

Temperature: control the heat available for capsule seal formation.

Timing: the time available for dosing unit quantities of fill matrix is critical.

Pressure: the pressure exerted between the two rotary dies controls the soft gel shape and the final cut-out from gel ribbon.

### Enteric-coated capsules (Delayed-release capsules):

Capsules can be coated to resist releasing the drug in the gastric secretions of the stomach and releases it in the intestine because of one or more of the following purposes:

- a. To avoid gastric disorders such as nausea and irritation from some drugs such as non-steroidal anti-inflammatory drugs (NSAD's), aminophylline, and iron salts.
- b. To avoid drug degradation via gastric secretions such as erythromycin
- c. To obtain delayed, controlled or sustained drug release .
- d. To exert an intended local action such as intestinal antiseptics and anthelmintics.
- e. To prevent drugs from being interfered with the food digestion process such as tannins and salts of heavy metals.

### ***Enteric coating is usually prepared with several ingredients including:***

1. **Formaldehyde solutions:** In the early time of coating technology, the main technique being used was to dip the sealed capsules into formaldehyde solutions, Enteric capsules should be resist bursting in the gastric secretions for at least 5 hours, and soluble or disintegrate in the pancreatic solutions within 2 hours.

### ***N.B. For capsules made enteric with formaldehyde solution***

- The rate of disintegration in pancreatic fluid is inversely proportional with the dipping time of the capsule in formaldehyde solution. Therefore, capsules intended to disintegrate in the duodenum (upper part of intestine) should be immersed for longer time,
- While those are intended to disintegrate in lower part of the intestine should be immersed for shorter time.
- Capsules dipped for 5 minutes in formaldehyde solution dissolved in about 3 hours.

Capsules dipped for 15 minutes in formaldehyde solution dissolved in about 1 hr.

2. **Synthetic polymers;** Now enteric coatings are usually prepared from materials that have acidic groups such as cellulose acetate phthalate (is widely used in

commercial coated products), ammoniated shellac which are insoluble at low pH but dissolve when the pH increases to about 5.7.

3. **Other materials;** Ethylcellulose, hydroxypropylene methylcellulose, fat-derivatives, combination of vegetable fibers with carnauba wax and stearic acid.

**N.B.** Community pharmacist may extemporaneously prepare enteric-coated capsules by dipping them from 4-5 times in a 10 % solution of cellulose acetate phthalate

#### **Mechanisms For the removal of an enteric coating:**

- 1- **Ionization;** For synthetic polymer containing acidic group e. g. cellulose acetate phthalate, it will be unionized (insoluble form) at the low pH of the stomach. As the pH increase along with-the GIT, the acidic polymer is ionized to a more soluble form. The coating then dissolves and release the drug.
- 2- **Hydrolysis and or Emulsification;** In this mechanism, the enteric ingredients either hydrolyzed via intestinal enzymes or emulsified and dispersed by the bile salts or both. Ethylcellulose, fatty-derivative coatings are removed by this mechanism. The ester butyl stearate is hydrolyzed by esterase enzyme to butanol and stearic acid.
- 3- **Length of contact time with moisture;** In this mechanism, the removal of the enteric coating depends upon the time period in which it will be in contact with moisture. The time required for disintegration depends mainly upon the thickness of the coating and the ratio of its constituents.

#### **Quality control of capsules**

##### **1. Content uniformity**

###### **a. Weight variation;**

###### **b. Hard capsules:**

- Weight accurately 10 intact capsules individually to obtain the gross weight.
- Remove carefully and fully the contents of each capsule by suitable means.
- Weight accurately the empty shells individually.

- Calculate the net weight for each capsule by subtracting the weight of the shell from the gross weight of the respective intact capsule.
- From the result of Assay available in the individual monograph, calculate the contents of the active ingredient in each of the capsules, assuming the uniformity of the content.

**c. Soft gelatin capsules:**

- Weight accurately 10 intact capsules individually to obtain the gross weight.
- Carefully cut open the capsule using clean, dry suitable cutting instrument such as sharp blade.
- Remove the contents by washing with suitable solvent.
- Allow the solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking care to avoid gain or loss of moisture.
- Weight accurately the empty shells individually.
- Calculate the net contents for each capsule by subtracting the weight of the shell from the weight of the respective intact capsule.
- From the result of the assay available in the individual monograph, calculate the contents of the active ingredient in each of the capsules, assuming the uniformity of the content.

**2. Disintegration test**

**3. Dissolution test**



## Solid Dosage Forms

### iii. Effervescent Granules

#### Objectives

*After reading this chapter, the student will be able to:*

1. Provide examples of medicated powders used in prescription and nonprescription products.
2. Differentiate between the fusion method and wet method for the preparation of effervescent granulated salts.

### Effervescent Granules

#### Definition:

Effervescent Granules are mixtures of citric acid and tartaric acids with sodium bicarbonate and occasionally sugar, and usually some medicament is incorporated.

#### Advantages of Effervescent Granules:

It is a good way of masking taste of unpalatable drugs, e.g., MgSo<sub>4</sub>, iron salts or bitter drugs since CO<sub>2</sub> effervescent action causes numbness to the tongue.

- Effervescent action is preferred psychologically.
- Effervescent promotes gastric reaction, so it acts as a digestant.

Citric acid : tartaric : sod. bicarbonate

1 : 2 : 3

#### N.B:

- If the amount of citric acid is more than the stated amount, the granules become very sticky.
- If the amount of tartaric acid is more than the stated amount, the granules become very chalky and friable.

- We use sodium bicarbonate which is a weak alkali so that if any part of the alkali did not react, it won't harm the mucous membrane of the esophagus.
- Citric acid used should be crystalline, as we need the water of crystallization to help to bind particles together to form granules.

**Methods of preparation of effervescent granules:**

**I. Fusion method:**

1. Finely powder all ingredients.
2. Mix the powders in a porcelain dish, transfer it into a boiling water bath.
3. Triturate while on water bath. When the mass seems doughy , turn over so as to allow for the release of all water of crystallization of citric acid .
4. Remove from the water bath, force the mass through the sieve No.10 . The collected granules are dried in a hot oven at 40 °c .
5. The dried granules are shaken gently over sieve No. 20 and non-passed granules are collected.

**II- Wet method :**

1. In a mortar, separately grind each ingredient of the effervescent base into fine powder.
2. Start adding alcohol portion wise till a dough mass is produced.
3. Force the mass through sieve No.10 on a piece of paper.
4. Leave the granules to dry.
5. Then the collected granules are shaken gently over sieve No. 20.
6. Collect the granules retained inside the sieve.

**I - Plain effervescent granules**

Send 20g. of effervescent granules sodium citro tartarate granules.

Rx,

Sodium bicarbonate .....510 g

Citric acid ..... 180g

Tartaric acid .....270g

**Calculation:**

- The total weight of the above formula is 960 g. This will be approximated to about 1000 g.
- The quantity required is 20g. An excess of 25% is required to counteract loss during operation, therefore 25 g. are prepared.
- So, multiply each ingredient by a factor of 25/1000.

**II-Anti -spasmodic Effervescent Granules**

Send 20g . of effervescent granules containing 5% liquid extract of belladonna.

Rx ,

Sodium sulphate .....220 g.

Sodium bicarbonate .....477 g

Tartaric acid .....252g

Citric acid .....162g.

Fiat:Granules

Sig.:1 tsp. q6h

**Calculation:**

Base =25 g.

Belladonna =  $\frac{5 \times 25}{100} = 1.25$

100

**Procedure :**

- 1- Evaporate the extract in a test tube to  $\frac{1}{4}$  of its volume .
- 2- Add to the powders and mix using alcohol.
- 3- Then complete using the wet method.

**II. Vitamin C supplement**

Send 20 g of effervescent granules containing ascorbic acid.

R<sub>x</sub>

Sodium bicarbonate	8 g
Ascorbic acid	16 g
Sucrose	26 g

Fiat: granules

Sig; 1 tsp prn



**\*\*Procedure:**

1. In a mortar, grind the ascorbic acid to fine powder.
2. Then grind the sucrose.
3. Grind portion of the sucrose with sodium bicarbonate, then add all the grinded powders together.
4. Start adding the alcohol quantity sufficient to form a damp compact mass.
5. Complete for granulation.



# Pharmaceutical Aerosol

## Objectives

*After reading this chapter, the student will be able to:*

1. Definition, advantage and disadvantage of Different type of aerosol dosage forms.
2. Explain how a drug's powder particle size influences the pharmaceutical dosage forms which will be used to administer it.
3. know the different types of aerosol dosage forms
4. Compare and contrast the various types of medicated powders

## Pharmaceutical Aerosol

### Definition

Pharmaceutical dosage forms containing drug (therapeutic agent) and a propellant, it may be applied topically, by inhalation or to any body cavity

### Advantages

1. Completely closed so no contamination and offer stability of O<sub>2</sub> and moisture sensitive
2. Rapid onset of action
3. Applied topically without mechanical action so cause no irritation C.F. ointments
4. Avoid degradation in GIT and avoid 1<sup>st</sup> pass effect
5. Minimize side effects of drugs as it contains smaller dose with more efficiency
6. Drug targeting to site of action e.g. Inhalations
7. Bioavailability of drugs is not affected by meals C.F oral administration of Cyclosporine give higher bioavailability after fatty meals which enhance oral absorption

### Substances which must be present in aerosol system

1. Active constituent (concentrate)

2. **Propellant:** responsible for expelling drug out of container (bottle) when valve is opened
3. **Container:** plastic, metal or glass
4. **Valve:** continuous spray valve or metered dose valve (one press give single dose)

### Types of aerosols

#### 1. Inhaler

#### 2. Topical aerosols include

- a) Local anaesthetics: used in emergency in sports championship
- b) Shaving cream: foamy consistency, valve have wide openings
- c) Vaginal spray

#### 3. Body cavities Sprays: nose (Intranasal), lungs (through mouth), oral cavity (sublingual e.g. Nitrolingual)

#### 4. Spray (Space) aerosols: small particle size thus remains suspended in air for long time include many products not related to pharmaceuticals e.g. Deodorants, Insecticides (Pyrosol) and Room freshener

#### 5. Surface aerosols: larger particle size than spray aerosols so they are deposited on surfaces e.g. Paints for cars or hair sprays for coating of hair where it form a styling film on hair thus it keep hair in certain style

#### 6. Semisolid aerosols: used for lotions and creams

### Components of aerosole

- 1- Concentrate
- 2- Propellant
- 3- Valve
- 4- Container

#### 1- Concentrate

It may be solution, suspension, emulsion or semisolid

a. **Solution**

- Easiest method to prepare an aerosol formulation
- It is preferred as the AC is soluble in propellant system (single propellant or mixture of propellants)
- If AC is insoluble in propellant we should add certain solvent e.g. **ethyl alcohol** to dissolve the drug but it must be miscible with the propellant used as in spray aerosols
- Each drop contain propellant with AC and solvent, thus when propellant expand (evaporate) when out of container (higher temp.) it will disperse the droplet into smaller particles
- **Droplet size of solution aerosol depend on**
  - Amount of propellant
  - Nature of propellant
  - Amount of concentrate
  - Nature of concentrate
  - Valve design (Actuator opening)

b. **Suspension**

- AC is insoluble in solvent
- No cosolvent is used

Problems of formulation of suspensions	How to avoid these problems
1) Caking during storage and Particle size growth	1) Use drug in <b><u>anhydrous form</u></b> as wet particles may aggregate
2) Blocking of openings of valve by solid particles	2) <b><u>Density</u></b> of AC and propellant should be similar otherwise sedimentation of drug may occur thus use a mixture of propellants
3) Clogging of dip tube by solid particles	3) <b><u>Reduction of particle size</u></b> by ball milling or jet pulverizer
	4) Use <b><u>SAA as suspending</u></b> (dispersing agent)

which may be **lecithin, oleic acid, oleyl alcohol** (for oral suspensions) or **isopropyl myristate** (for topical suspensions)

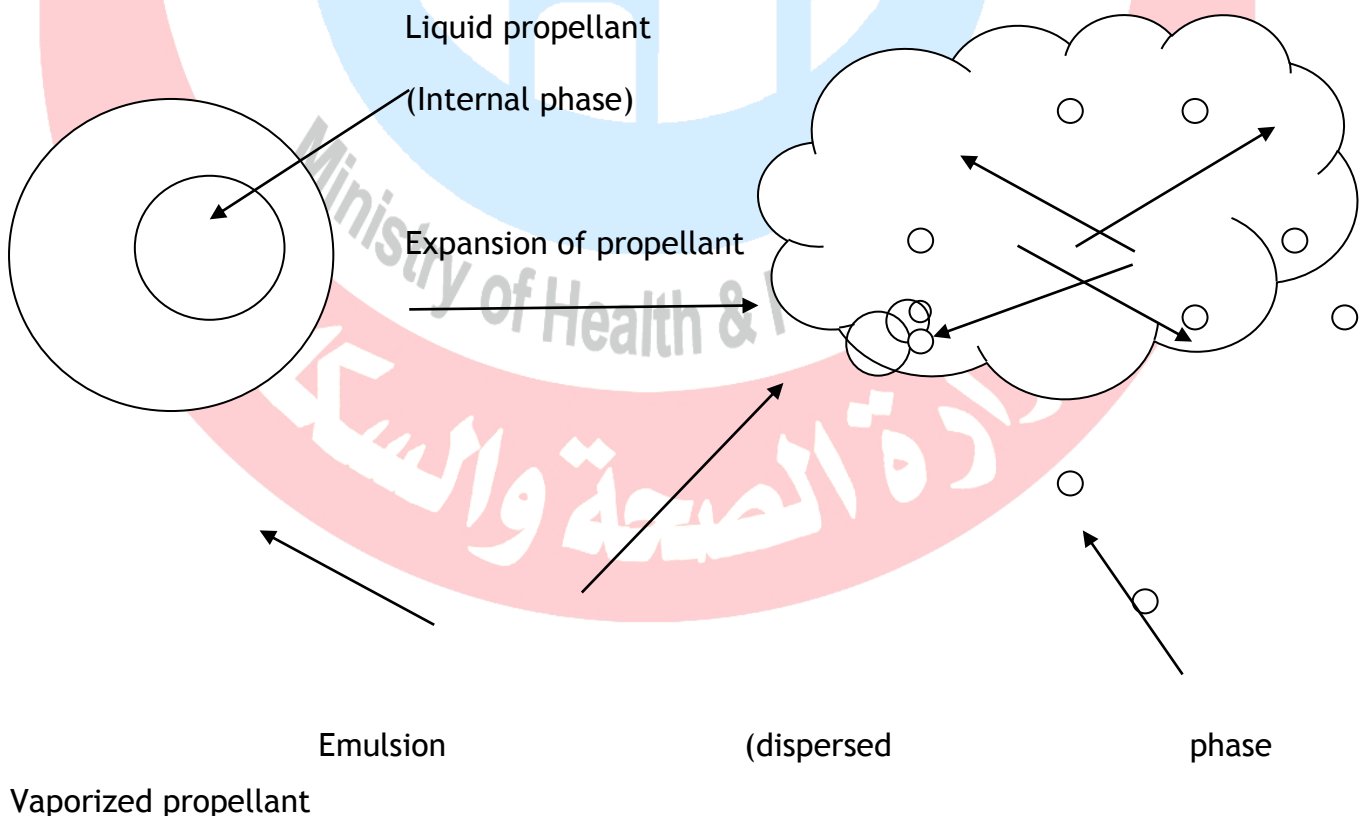
5) Solubility of AC in propellant must be minimal, **Why?** As stated by **Ostwald Ripening Phenomena** “small particles dissolve first faster than large particles then precipitate on larger ones” thus may cause particle size growth

c. **Emulsion**

- Contain drug + emulsifying agent + propellant + aqueous or non-aqueous phase
- When emulsion get out of container it forms 2 types of foams

i. **Stabilized foam**

- Part of the Propellant become part of internal oily phase (7-10%) but if it is a hydrocarbon (3-4% only) and the remaining emulsion in external phase thus when the product get out of container, propellant will vaporize and expand forming a matrix to develop foam



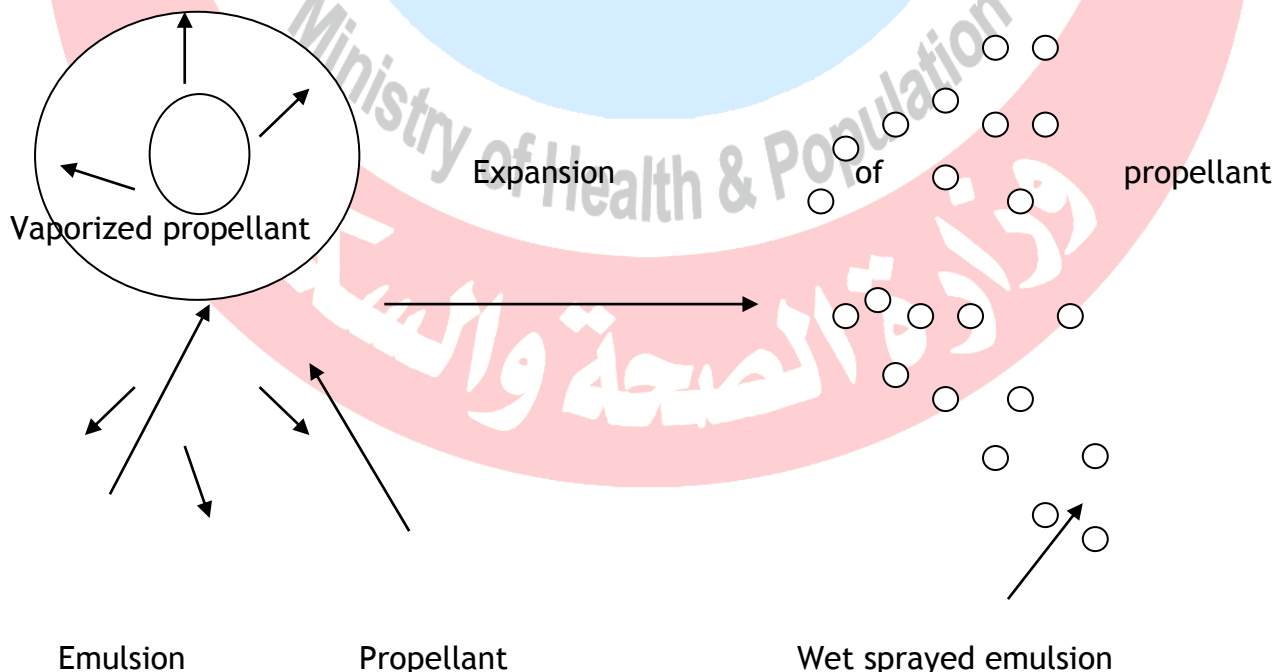
- The remaining propellant occupy the head space of the container creating a pressure 40 - 50 psig (psia)
- Foam reach required site in stable form

ii. **Quick - breaking foam**

- Contain **ethyl alcohol** + water + **surfactant** (must be soluble in alcohol or water but not in both otherwise it may form **stable foam**)
- Foam collapse before reaching affected area
- It is O/W emulsion

**N.B.**

- **If propellant exists in external phase**, thus it will vaporize rapidly leaving behind very small droplets as Wet spray
- Type of emulsion is **W/O**, it has to be shaken before use
- Amount of propellant is higher **25-30%**, it is hydrocarbon or fluorocarbon propellant as they have specific gravity < 1 (water) thus float on aqueous phase (external phase)
- It must be shaken before use



## 2. propellant

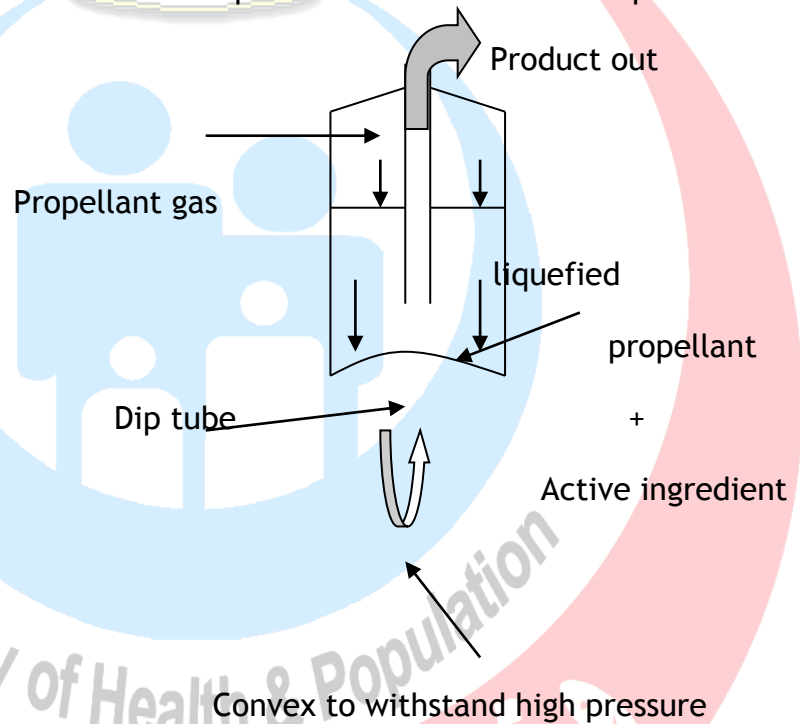
### a. Liquefied gas propellant

#### Principle

- Produce pressure inside container by its vapor pressure & does not depend on its concentration i.e. its action continues and maintain constant pressure inside the container till end of system (if present in small amount)
- Driving force is Expansion ratio

$$\text{Expansion ratio} = \frac{\text{Final volume of vaporized propellant}}{\text{Initial volume it occupy inside container before vaporization}}$$

Increase expansion ratio lead to increase dispersion of aerosol into fine particles



#### Principle

1. Propellant ( $\downarrow$  B.P,  $\uparrow$  V.P) equilibrate itself between vapor phase above product and liquid phase mixed with active ingredient
2. Vapor propellant produce  $\uparrow$  pressure in all directions mostly over surface of product thus expel product out once valve is opened up the dip tube because pressure inside  $>$  atmospheric pressure
3. As product is dispensed, space above solution  $\uparrow$  so slight drop in pressure occur which is restored again by vaporization of some propellant existing as liquid (reservoir) with the drug as its B.P is less than room temperature

4. By this way pressure inside the package is kept constant till all products is dispensed

### Types of Liquefied gas propellants

#### 1. Trichloromonofluoro methane (Propellant 11)

- It is non polar solvent
- Good solvent power for most drugs (hydrophobic)
- Not used for aqueous solutions, it hydrolyze in water

#### 2. Dichlorodifluoro methane (Propellant 12)

- Good solvent power
- Very high vapor pressure 84.9 psia thus is mixed with propellant 11 to give the required dispersion
- Very stable

#### 3. Dichlorotetrafluoro ethane (Propellant 114)

- Poor solvent power for drugs
- Low vapor pressure 27.6 psia
- Stable
- Used for metered dose inhalers
- When we add ethyl alcohol to liquefied gas propellants, according to Raoult's law vapor pressure should decrease BUT with Chlorofluoro carbons (positive deviation occur) where attraction between propellant molecules and ethyl alcohol molecules is less than attraction between propellant molecules themselves or ethyl alcohol molecules themselves thus increase escaping tendency and ↑ vapor pressure of the propellant

### 2. Hydrofluoro carbons (propellant 134) and (propellant 227)

- Used for replacement of propellant 12 in metered dose inhalers
- Contain no Cl atoms, but have 1 or more H atoms
- They break down in atmosphere faster than Chlorofluoro carbons, so they have a less destructive effect on ozone layer
- They have very high vapor pressure 70 psia

- Tests are still done to determine their safety

3. **Other liquefied gas propellants** (propellant 22, 142 and 152 a)

4. **Hydrocarbons** e.g. Butane, isobutene and propane

- Replace Chlorofluoro carbons in all products except metered dose inhalers
- Non-reactive, non toxic, inexpensive

**B. Compressed gas propellants** e.g. Nitrogen, CO<sub>2</sub> and Nitrous oxide

**3. Valve**

**Functions**

1. Control flow of product from container in accurate dose
2. Affect (together with propellant) properties of product; deliver it in the required form

- Types**
1. Continuous spray valve
  2. Metered dose valve

**(1) Continuous spray valve**

- Used for topical preparations
- Formed of 7 components

**Valve components**

**a. Actuator**

Usually called button, Fitted over the valve it contain one opening on its side to deliver the product

**Types:** according to diameter of the orifice

1. **Spray actuator:** narrow orifice
2. **Foam actuator:** wide orifice
3. **Semisolid actuator:** wide orifice

**b. Mounting cup**

- Attach valve to container properly

- Made of stainless steel or Al, coated from underside (contact with product) by epoxy or vinyl layer to protect against O<sub>2</sub> in head space
- If the product will come out through the mounting cup which have a narrow opening (less than 1 inch diameter) the mounting cup is called Ferrule as in metered dose inhalers
- It is better coated with Brass to ↓ interaction with the product

### c. Housing

- Made from Nylon or Derlin, contain openings to pass the product out

**Stem** Made from Nylon, contain one or more tubes to transfer the product from dip tube to housing act as expansion chamber to disperse liquid into proper type of spray

### d. Gasket

Made of neoprene rubber, should be compatible with other ingredients, close stem openings when valve is in closed position

### e. Spring

Made of stainless steel, hold gasket in place and when actuator is depressed and released will return valve to closed position

## (2) Metered dose valve

- Used only in pharmaceutical products
- To deliver accurate dose of drug each time in a reproducible way not only from specific container but from any container to which it is fitted
- Deliver a dose 25 -75 μl (commercially available)
- Have very narrow opening i.e. not contain mounting cup but a Ferrule
- May be used in upright position (dip tube is required for solution aerosols) or in inverted position (no dip tube in case of suspension and emulsion)

## Advantages of metered dose valves

- 1) Portable
- 2) Low cost
- 3) Disposable
- 4) One container contain up to 200 doses

- 5) Deliver reproducible doses
- 6) It is hermetically sealed so drug is highly protected

### Disadvantages of metered dose valves

#### 1) Oropharyngeal deposition of dose instead of passing to lung, why?

Upon 1<sup>st</sup> actuation the product droplet (large up to 40  $\mu$ ) will exit at high velocity about 30 m/s without sufficient dispersion into smaller droplets (2 - 6  $\mu$  required for good penetration into lung without impaction in throat), this occur because propellant 11 ( $\downarrow$  VP) which represent 25% of the formulation does not vaporize sufficiently to disperse the droplet

#### 2) Inspiration of large amount of propellants cause bronchoconstriction and certain types of arrhythmia

3) Initial doses for prophylaxis of asthma are too large (> 1 mg) to be delivered and contained in a metered dose inhaler because dose that can be delivered is limited by size of the metering chamber (< 1 mg) and diameter of the orifice

4) Most patients (children and elderly) can't synchronize deep inspiration with actuation of the inhaler thus only 20% of the dose reaches the lung successfully. So it is advisable to take a deep inspiration followed by small period of breath holding to achieve maximum retention of the drug in lungs

### Dry Powder Inhaler (Breath actuated device)

➤ It is a system in which drug is administered as very fine cloud of powder

1) **Powder**: to be loaded in the device

2) **Capsule**: loaded into device and contain powdered drug, gelatin fragments may affect inhalation of solid drug from device

3) **Disc**: loaded into device and contain powdered drug, no gelatin fragments

### Types of dry powder inhalers

1) Unit dose device e.g. Spinhaler

2) Multidose inhaler

### Advantages of dry powder inhalers

1. Require no synchronization of actuation and deep inspiration
2. No propellant is used (No side effects of propellants)
3. No loss in dose, 100% of dose may reach lung

### Disadvantages of dry powder inhalers

1) As drug must be micronized in very small size, thus suffer very **poor flowability** and electrostatic charge may develop on surface of solid particles leading to lumpness????

### Flowability depend on

1. Particle size
2. Particle shape
3. Surface roughness
4. Density
5. Moisture content
6. Hardness

### Solution

- Drug is mixed with larger inert carrier e.g. **lactose** (30 - 60 $\mu$ ) to improve flowability and prevent lumpness of micronized drug and also ensure uniformity of dose.
- Lactose will remain in oropharyngeal area and drug pass rapidly to lung, success of this system depends on ability of patient to create a sufficient air stream with turbulent flow to deaggregate and desorb drug particles from lactose particles

2) Liberation of powder from device is limited by ability of patient to inhale rapidly to produce sufficient air stream to deaggregate solid particles and withdraw them into lung but this is difficult in case of patients with respiratory problems and bronchospasm

3) Drug is exposed to environmental conditions which may affect its stability e.g. elevated humidity which may cause powder to lump

### Success of dry powder inhaler formulation depend on

- Adhesion of drug and carrier (lactose) during mixing to be filled into hard gelatin capsule
- Ability of the patient to inhale strongly to produce turbulent air stream to deaggregate and desorb drug from carrier where drug pass to lung (2 - 6  $\mu$ ) but the carrier will impact in oropharyngeal area ( 30 - 60  $\mu$ )

### Evaluation of aerosols

#### A- Flammability and combustibility:

1. Flame extension
2. Flash point
3. Closed drum test

**B- Physicochemical characteristics:**

1. Vapor pressure
2. Density
3. Moisture content
4. Identification of the propellant

**C- Performance:**

1. Aerosol valve discharge rate
2. Spray pattern
3. Dosage with metered valves
4. Net contents
5. Foam stability
6. particle size determination

**D- Biological:**

1. Therapeutic activity
2. Toxicity



# Transdermal Drug Delivery Systems

## Objectives

*After reading this chapter, the student will be able to:*

1. Explain the physical-chemical properties of drugs which determine their ability to be incorporated into a transdermal dosage form.
2. Describe physiological factors of the skin which influence percutaneous absorption.
3. Define a chemical permeation enhancer and describe physical methods used to facilitate the percutaneous absorption of drugs.
4. Differentiate between the various types of systems used for transdermal delivery.

## Transdermal drug delivery systems

### Introduction

For many decades the skin has been commonly used as the site for the administration of dermatological drug to achieve localized pharmacologic action in the skin tissue. In this case the drug molecule is considered to diffuse to a target tissue in the proximity of drug application to produce its effect before it distributed to the blood circulation for elimination (**Error! Reference source not found.**). The use of hydrocortisone for dermatitis, benzoyl peroxide for acne and neomycin for superficial infection are few examples.

Nowadays, there is increasing recognition that the skin can serve as a port of administration of systemically acting drugs. In this case the drug applied topically will be absorbed first into blood circulation and then to be transported to target tissue, which could be remote from the site of drug application, to achieve its therapeutic response (**Error! Reference source not found.**). Examples are transdermal controlled administration of nitroglycerin for the treatment of angina pectoris, scopolamine for prevention of motion sickness, and estradiol for the medication of post-menopause.

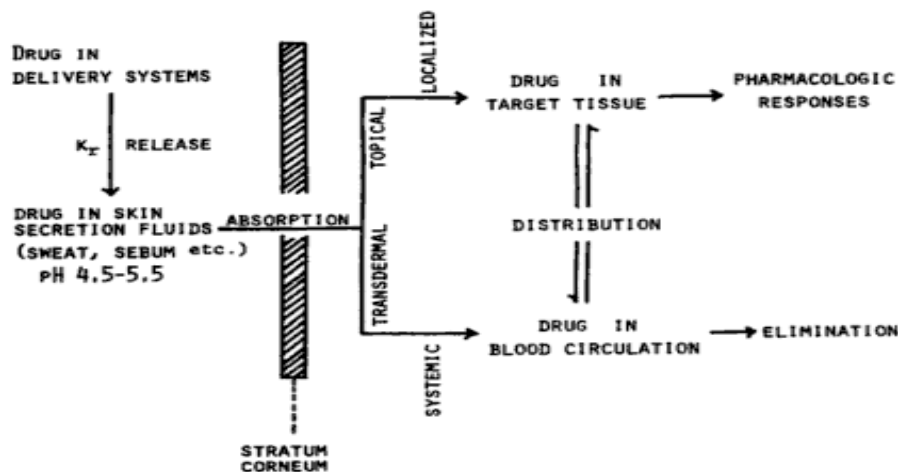


Figure 1: Percutaneous absorption of drugs for localized therapeutic actions or for systemic medications away from the site of topical application.

### Advantages over traditional DDS (oral and parenteral)

1. Minimize and avoid Peak and Valley phenomenon i.e. fluctuations in plasma drug levels and not rendering sustained effect , while the TDDS provides a prolonged delivery of drug, in a steady-state profile.
2. Reduces the prospects of peak-associated side effects, and ensures that the level of the drug is above the minimal therapeutic concentration.
3. Avoid the hepatic first-pass effect observed during oral administration by allowing the permeation of drugs across the skin and into the systemic circulation.
4. Avoiding the inconvenience of frequent parenteral administration.

### Anatomy of the skin

The skin has an average surface area of  $2 \text{ m}^2$ . It is one of the most extensive and readily accessible organs in the body. With a thickness of only a fraction of a millimeter, (1) the skin separates the underlying blood circulation network from the outside environment, (2) serves as a barrier against physical, chemical and microbial attacks, (3) acts as a thermostat in maintaining body temperature and (4) protects against penetration of ultraviolet rays.

- The skin is a multilayered organ composed of three major tissue layers; the epidermis, the dermis and the hypodermis (Error! Reference source not found.).
- The stratum corneum is the outermost layer of the epidermis exposed to the external environment.
- They are keratinized dead cells converted to proteins and continuously shed. The water content of the stratum corneum is about 20% as compared to 70% in the

physiologically active stratum germinativum (regenerative layer of the epidermis).

- An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts per cm<sup>2</sup> of the skin surface.

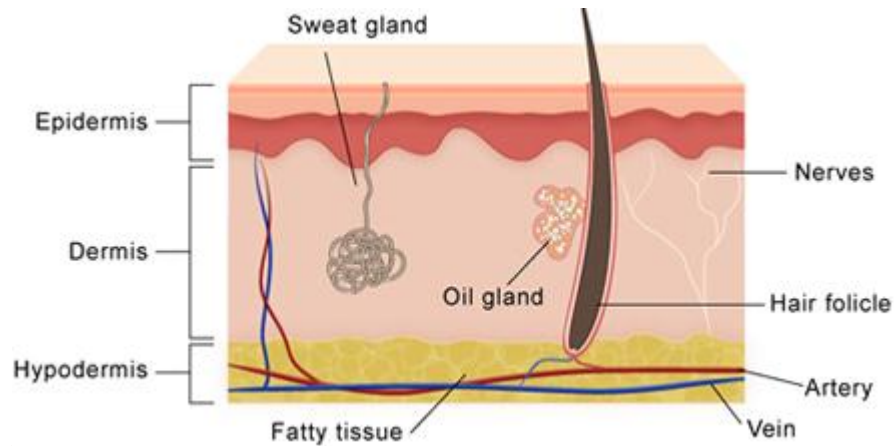


Figure 2: Cross-section of human skin, showing various layers and appendages.

- Even though foreign agents, especially water soluble ones, may be able to penetrate through the skin via these skin appendages, at a rate which is faster than through the intact area of the stratum corneum, this trans-appendageal route of percutaneous absorption has a very limited contribution to the overall kinetic profile of transdermal permeation.
- The **transdermal permeation** of most neutral molecules can be considered as primarily a process of **passive diffusion** through intact stratum corneum.

### Basic components of transdermal drug delivery systems

- Protective liner.
- Adhesive formulation.
- Drug release membrane.
- Drug reservoir.
- Pigmented packing.

#### A. Protective liner

During storage the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. Since the liner is in intimate contact with the TDDS, the liner should be:

- Chemically inert
- Non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) with a release coating layer made up of silicon or Teflon.

## **B. Adhesive formulation**

The adhesion of TDDS is one of the critical factors to the safety, efficacy and quality of the product. It is related to drug delivery and therapeutic effect.

In other words, poor adhesion results in improper dosing of patients. Secondly, patches that fail to adhere for their prescribed time phase must be replaced more frequently, thereby increasing the patient's cost.

## **C. Drug release membrane**

The elementary way to control the release of a drug is to disperse through an inert polymeric matrix. In this system, the drug is physically blended with polymeric powder (either hydrophilic or lipophilic), and the medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. An inverse relationship is observed between the release rate and membrane thickness.

## **D. Drug reservoir**

### **a. Drug**

Suitable candidates are:

- Drugs used in low doses,
- Drug molecule having a small molecular weight of  $<1000$  Da,
- with adequate solubility in the vehicle,
- Log P value of  $< 5$ ,
- melting point of  $200$  °C,
- and appropriate lipophilicity.

## **E. Penetration enhancer**

Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin. Thus, allow the drug to penetrate to the viable tissues and enter the systemic circulation. They should be **inert, non-irritant, non-sensitizing, non-phototoxic, non-comedogenic, and ideally work rapidly.**

### **a. Plasticizers**

Plasticizers have also been used in many formulations ranging from 5 to 20% (w/w, dry basis). Along with the **brittleness and ductility** of the film, it is also responsible for **adhesiveness** of the film. Some of its examples are **glycerol or sorbitol**, at **15%w/w**, and glycol derivatives such as **PEG 200**, and

PEG 400.

**b. Pigmented packing.**

Backings are chosen for **appearance, flexibility and need for occlusion.**

Examples of backings are polyester film, polyethylene film and polyolefin film, and aluminum vapor coated layer.

Approaches to development of transdermal therapeutic systems

Several technologies have been developed to provide rate control over the release and transdermal permeation of drugs. These approaches can be classified into four categories:

- I. Membrane-permeation controlled systems.
- II. Adhesive diffusion-controlled systems.
- III. Matrix dispersion-type systems.
- IV. Microreservoir systems.

**I. Membrane-permeation controlled systems**

In this system, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane. The drug molecules are permitted to release only through the rate controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous solid medium, e.g. silicon fluid forms a paste like suspension. The rate controlling membrane can be micro-porous or non-porous membrane, e.g. ethylene-vinyl acetate polymer, with a defined drug permeability property.

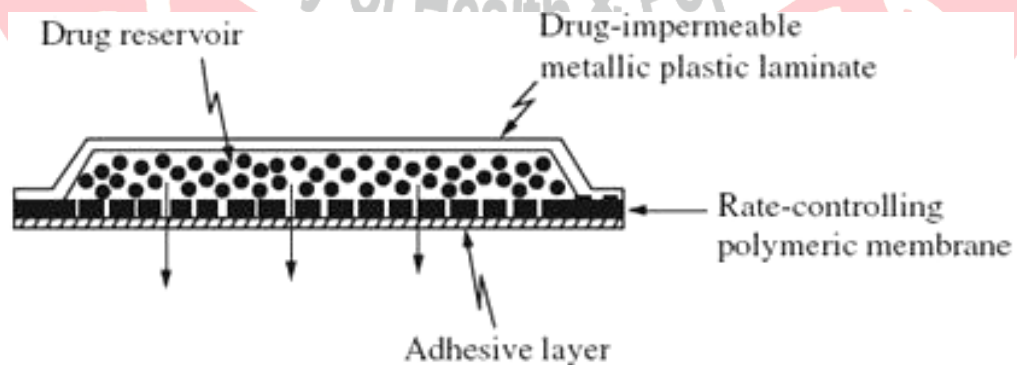


Figure 3: Cross-sectional view of membrane-permeation controlled TDDS.

The rate of drug release can be tailored by varying polymer composition, permeability coefficient and/or thickness of the rate controlling membrane and adhesive.

**Example 1:** nitroglycerin-releasing TDDS (Transderm-Nitro system/ Ciba) for once a day medication of angina pectoris.

**Example 2:** scopolamine-releasing TDDS (Transderm-Scop system/Ciba) for 3-day protection of motion sickness

**Example 3:** clonidine-releasing TDDS (Catapres-TTS/ Boehringer Ingelheim) for weekly treatment of hypertension.

## II. Adhesive diffusion-controlled systems

In this system the **drug reservoir** is formulated by directly **dispersing the drug in an adhesive polymer** then spreading the medicated adhesive, by solvent casting, onto a flat sheet of drug impermeable metallic plastic **backing** to form a thin drug reservoir layer. On the top of the drug reservoir layer, layers of non-medicated, **rate controlling adhesive polymer** of constant thickness are applied to produce an adhesive diffusion-controlled drug delivery system (**Error! Reference source not found.**).

**Example:** Nitroglycerin-releasing TDDS (Deponit-system/Parma Schwartz) in Europe.

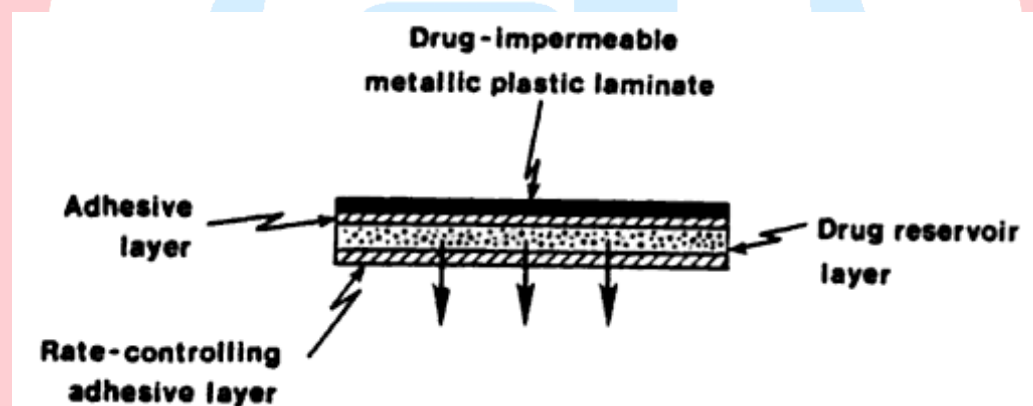


Figure 4: A cross-sectional view of adhesive diffusion-controlled TDDS.

## III. Matrix dispersion type systems

In this system the drug reservoir is formed by homogeneously dispersing the drug in a hydrophilic or lipophilic polymer matrix and the medicated polymer is then molded into medicated disc with a defined surface area and controlled thickness. This drug reservoir-containing polymer disc is then glued onto an occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. Instead of applying the adhesive polymer directly on the surface of the medicated disc as in the first two transdermal therapeutic system, the adhesive polymer is spread along the circumference to form a strip of adhesive rim around the medicated disc.

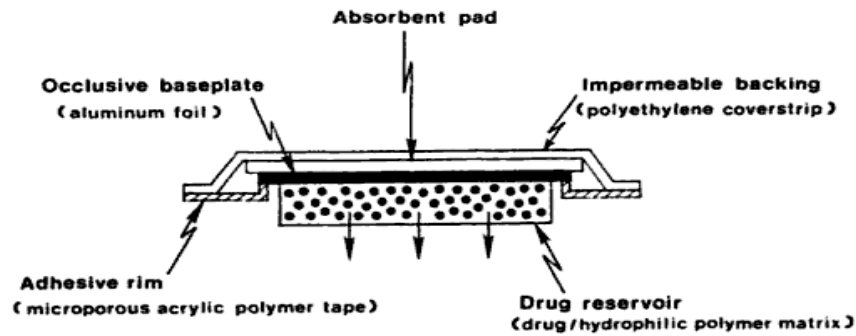


Figure 5: A cross-sectional view of matrix dispersion-type TDDS

**Example:** Nitroglycerin-releasing TDDS (Nitro-Dur system/Key) which has been approved by the FDA for once-a-day medication of angina pectoris.

#### IV. Microreservoir systems

A combination of the reservoir and matrix dispersion-type drug delivery system. In this approach, the drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer then dispersing homogeneously the drug suspension in a lipophilic polymer, by high shear mechanical force, to form microscopic spheres of drug reservoirs.

This thermodynamically unstable dispersion is quickly stabilized by immediately crosslinking the polymer chains, which produces a medicated polymer disc with constant surface area and a fixed thickness. A transdermal therapeutic system is produced in which the medicated disc is positioned at the center and surrounded by an adhesive rim. (Error! Reference source not found.).

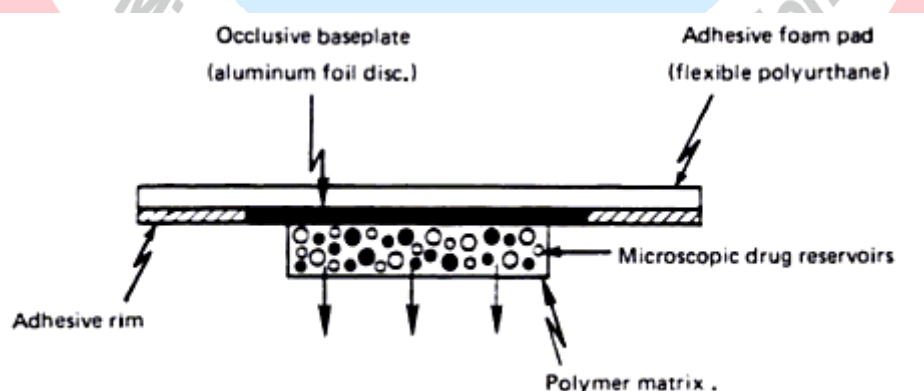


Figure 6: A cross-sectional view of micro-reservoir type TDDS

New approaches for drug permeation through skin barrier

One challenge in designing of transdermal drug delivery system is to overcome the skin's formidable barrier function.

## **A. Passive penetration enhancement techniques**

Recent technologies ranging from chemical enhancers which either increase the diffusivity across the skin or increase the drug solubility in the skin to newer innovative approaches which involve the design of super loaded formulations, micro emulsion and vesicular systems.

The penetration enhancers can either be used singly or mixtures of chemical permeation enhancers can be used giving synergistic effect. These synergistic systems include eutectic mixtures, nanoparticle complex self-assembled vesicles.

### ***a) Microemulsion***

It can be formed by numerous oil, surfactant, co-surfactant, and aqueous constituents. It was found that microemulsions acted as:

1. An effective vehicle for the solubilization of both lipophilic and hydrophilic drugs.
2. A protecting medium for the entrapped drugs from degradation, hydrolysis, and oxidation.
3. It can also provide prolonged release of the drug.
4. Prevents irritation.

### ***c) Vesicles and Nanoparticles***

Vesicles can be prepared by a wide variety of lipids and surfactants. Most commonly, they are composed of phospholipids or non-ionic surfactants (such as Spans 80) and are referred to as liposomes and niosomes.

Nanoparticles are an alternative system not requiring the permeation enhancers or temporary skin digestion, both of which can increase the possibility of irritation.

Vesicles act as:

1. Drug carriers to deliver entrapped drug molecules into or across the skin.
2. Penetration enhancers.
3. A depot for sustained release of dermally active compounds.
4. A rate-limiting membrane barrier for the modulation of systemic absorption.

### ***d) Inclusion complexes***

Cyclodextrins (Cyds) influences the percutaneous absorption basically by the two mechanisms. Firstly, by solubilizing the drug thereby increasing its accessibility at the absorption site, and secondly by an interaction with the free lipids present in the SC.

#### e) *Coacervation effect*

Coacervation is a form of ion pairing in which the paired complexes aggregate to form a separate hydrophobic phase. Ion pair transport across membranes has been studied as a means of facilitating the permeation of ionizable drugs.

#### f) *Eutectic mixtures*

Melting point of a drug is inversely proportional to its solubility and lipophilicity. As a consequence, lowering the melting point exhibits increased transdermal permeation. These systems serve two mechanisms; Firstly, the formation of a low-melting mixture with the drug which improves its partitioning across the skin. Second is the direct disruption of the skin structure which further enhances drug permeation. By selecting the right permeation enhancer to be combined with the drug synergy in permeation can be obtained.

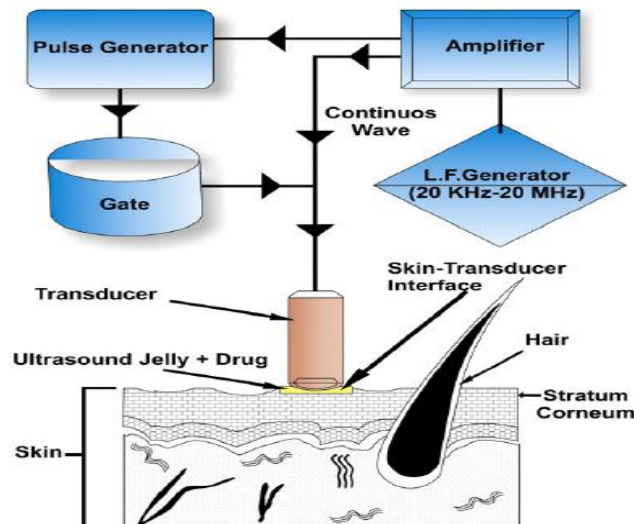
### **I. Active penetration enhancement technique**

#### **a) *Iontophoresis***

Iontophoresis is the facilitated movement of ions across a membrane under the influence of an externally applied small electrical potential difference ( $0.5 \text{ mA/cm}^2$  or less), which has proved to enhance the skin penetration and the release rate of a number of drugs having poor absorption/permeation profile. The mechanisms of transdermal iontophoresis include electroosmosis (electric field induced solvent flow) and electroporation (increasing the porosity of skin due to electric field). The technology has been used successfully to accelerate the permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins and oligonucleotides) including biopharmaceuticals with molecular weights greater than 7 KDa.

#### **b) *Sonophoresis***

The applicability of ultrasound to deliver therapeutic compounds through the skin is generally referred to as sonophoresis (also known as phonophoresis) . Dermal exposure on ultrasound may include: (i) Cavitation (generation and oscillation of gas bubbles). (ii) Thermal effects (temperature increase). (iii) Induction of convective transport. (iv) Mechanical effects (occurrence of stresses due to pressure variation induced by ultrasound). In this technique, the drug is blended with a coupling agent usually a gel but sometimes cream or ointment is used which transfers ultrasonic energy from the device to the skin through this coupling agent (**Error! Reference source not found.**).

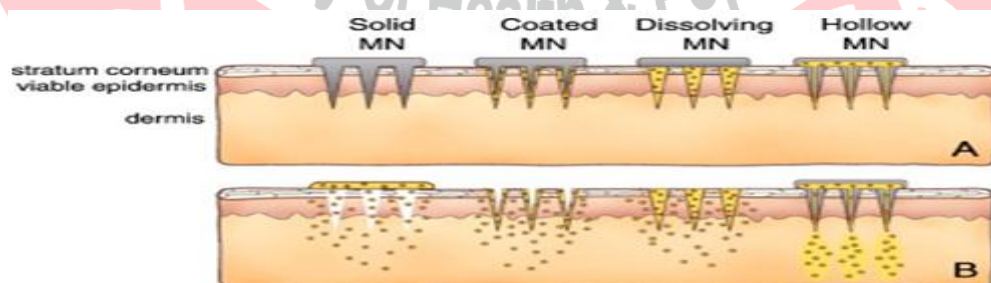


Application of Sonophoresis: Drug is mixed with Coupling (Jelly like) agent for the transfer of ultrasonic energy which is produced by frequency generator (either high or low).

### c) Microneedles

Microneedles (MNs) are small micron-sized needles which when applied on the skin breaches the SC to create microchannels through the skin thereby assisting drug delivery.

1. Piercing an array of solid microneedles into the skin followed by application of a drug patch at the treated site.
2. Coating drug onto microneedles and inserting them into the skin for subsequent dissolution of the coated drug within the skin.
3. Encapsulating drug within biodegradable, polymeric microneedles followed by insertion into the skin for controlled drug release.
4. Injecting drug through hollow microneedles.



Various modes of microneedles for TDDS

The microchannels thus created help topically applied drug molecules to bypass the SC which is the major rate limiting barrier for transdermal permeation. Moreover microneedles are minimally invasive and painless as they do not penetrate up to the

papillary dermis where nerve endings are situated. The main reasons that MN-based TDDS is yet not commercialized are their poor safety and inconvenience for self-administration.

**d) Magnetophoresis.**

**e) Photomechanical waves.**

**f) Electron beam irradiation.**



# Pharmaceutical Liquid Dosage Forms

## i. Solution

### Objectives

*After reading this chapter, the student will be able to:*

1. Define the various types of oral and topical liquid dosage form.
2. List the advantages and disadvantages of using liquid dosage forms
3. Compare and contrast liquid dosage forms to traditional oral dosage forms.
4. Define solubility and describe how different factors increase or decrease solute solubility in a given solvent.
5. Evaluate and select a proper solvent and delivery system for a given solute, purpose, and/or patient population.

## Pharmaceutical Liquid Dosage Forms

### Solution

A solution is a homogenous mixture that is prepared by dissolving a solid, liquid, or gas in another liquid and represents a group of preparations in which the molecules of the solute or dissolved substance are dispersed among those of the solvent. Pharmaceutical solution's use, it may be classified as oral, otic, ophthalmic, topical and Certain solutions prepared to be sterile and pyrogen free and intended for parenteral "injections".

Aqueous solutions containing a sugar are classified as "syrups", sweetened hydroalcoholic (combinations of water and ethanol) solutions are termed "elixirs", solutions of aromatic materials are termed "spirits" if the solvent is alcoholic or "aromatic waters" if the solvent is aqueous.

Solutions prepared by extracting active constituents from crude drugs dissolve in alcohol or in a hydro alcoholic solvent are termed "tinctures" or "Fluid extracts", depending on their method of preparation and concentration.

## Advantages and Disadvantages of Solutions as an Oral Dosage Form

### Advantages

1. A solution is a homogenous system and therefore the drug will be uniformly distributed throughout the preparation. In suspension or emulsion formulations uneven dosage can occur because of phase separation on storage.
2. Young children and some adults have difficulty in swallowing tablets and capsules. Thus, liquids are easier to swallow than solids.
3. Drug administered in the form of a solution, the drug is immediately available for absorption. Therefore, the therapeutic response is faster than if using a solid dosage form.
4. Some drugs, including aspirin and potassium chloride in tablet form, can irritate and damage the gastric mucosa. Irritation is reduced by the administration of a solution of a drug because of the immediate dilution by the gastric contents.

### Disadvantages

1. Drugs in aqueous solution are poorly stable rather than if they were formulated as a tablet or capsule.
2. Liquids are bulky and therefore inconvenient to transport and store.
3. Solutions often provide suitable media for the growth of microorganisms and may therefore require the incorporation of a preservative.
4. The taste of a drug, which is usually unpleasant, is always more pronounced when in solution than when in solid form. Solutions can, however, easily be sweetened and flavored to make them more palatable.
5. Accurate dosage usually depends on the ability of the patient to use a spoon or, more rarely, a volumetric dropper.

Solutions can be classified according to the type of solvent used;

#### A. Aqueous Solutions

#### B. Non- Aqueous Solutions.

## A. Aqueous Solutions

Water is the most widely used solvent for use as a vehicle for pharmaceutical products due to:

1. Lack of toxicity.
2. Physiological compatibility.
3. Ability to dissolve a wide range of materials.

### ***Types of pharmaceutical water***

Purified Water BP, which has been freshly boiled and cooled immediately before use to destroy any vegetative microorganisms that might be present. Purified Water must, however, be used on all occasions where the presence of salts - often dissolved in potable water - is undesirable. Purified Water is normally prepared by the distillation or deionization of potable water, or by the process of reverse osmosis. Water for Injections must be used for the formulation of parenteral solutions and is obtained by sterilizing pyrogen-free distilled water immediately after its collection. For the formulation of aqueous solutions of drugs, such as phenobarbitone sodium or aminophylline, which are sensitive to the presence of carbon dioxide, Water for Injections free from carbon dioxide must be used. Similarly, drugs which are liable to oxidation, such as apomorphine and ergotamine maleate, require Water for Injections BP free from dissolved air to be used.

These are both obtained from a pyrogenic distilled water in the same way as before, but are then boiled for at least 10 minutes, cooled, sealed in their containers while excluding air, and then sterilized by autoclaving.

### **B. Non-Aqueous Solutions**

It is not possible to ensure complete solution the ingredients at all storage temperatures or if the drug is unstable in aqueous systems, it may be necessary to use an alternative solvent. The use of non-aqueous systems may also have other Advantages. For example, the intramuscular injection of solutions of drugs in oils is often used for depot therapy. The oily solution remains as a discrete entity within the muscle tissue, releasing the drug slowly into the surrounding tissue whereas similar aqueous solution would diffuse readily, and being miscible with tissue fluid, would cause the drug to be released quickly.

It must be taken in mind that, in choosing a suitable solvent, its toxicity, irritancy

and sensitizing potential must be considered as well as its flammability, cost, stability and compatibility with other excipients. It will be obvious that a greater choice of solvent will be available for inclusion into products for external application than those for internal use, while for parenteral products the choice is even further limited.

**The following is a classification of some of the most widely used non-aqueous solvents in pharmaceutical preparations.**

**1. Fixed oils of vegetable origin:**

These are non-volatile oils which consist mainly of fatty acid esters of glycerol. For example, Almond oil which consists of glycerides mainly of oleic acid, is used as a solvent for oily phenol injection BP, water being unsuitable because of the caustic nature of aqueous phenol solutions, also, olive oil, sesame oil, maize oil, cotton seed oil, soya oil and castor oil, are all suitable for parenteral use. Some fixed oils are sufficiently tasteless and odorless to be suitable for oral use as solvents for such materials as vitamins (A) and (D). Fractionated coconut oil is used as the solvent for phenoxymethyl penicillin which would otherwise hydrolyse rapidly if present in an aqueous system. Oils tend to be unpleasant to use externally, however, unless presented as an emulsion. Arachis oil is one of the few examples and is used as the solvent in Methyl Salicylate liniment B.P.

**2. Alcohols:**

Next to water, alcohol is the most useful solvent in pharmacy. It is used as primary solvent for many organic compounds. Together with water, it forms a hydroalcoholic mixture that dissolves both alcohol-soluble and water-soluble substances, a feature especially useful in the extraction of active constituents from crude drugs.

Alcohol has been well recognized as a solvent and excipient in the formulation of oral pharmaceutical products. Alcohol is often preferred because of its miscibility with water and its ability to dissolve many water-insoluble ingredients, including drug substances, flavorants and antimicrobial preservatives. It is also used in liquid products as an antimicrobial preservative alone or with parabens, benzoates, and other agents.

However, aside from its pharmaceutical advantages, as a solvent and preservative, concern has been expressed over the undesired pharmacologic and potential toxic effects of alcohol when ingested in pharmaceutical products, particularly by children. Thus, the U.S. Food and Drug Administration (FDA) has proposed the recommended alcohol content

limit of 0.5% for OTC oral products intended for children under 6 years of age, 5 % for products intended for children 6 to 12 years of age and 10% for children over 12 years of age.

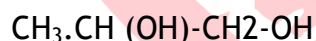
Diluted alcohol is prepared by mixing equal volumes of alcohol and purified water. The final volume of such mixtures is not the sum of the individual volumes of the two components, because the liquids contract upon mixing, the final volume is generally about 3 % less than what would otherwise be expected. It is for this reason that the strength of diluted alcohol is not exactly half that of the more concentrated alcohol but slightly greater.

Rubbing alcohol contains about 70% ethyl alcohol by volume, the remainder consisting of water, denaturants, with or without color additives, perfume oils and stabilizers. The use of this denaturant mixture makes the separation of ethyl alcohol virtually impossible with ordinary distillation apparatus. This denaturant mixture is composed of 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutylketone, and 100 parts by volume of ethyl alcohol. The product is volatile and flammable and should be stored in tight containers. It is employed as rubefacient and soothing externally, a germicide for instruments and a skin cleanser prior to injection. It is also used as a vehicle for topical preparations.

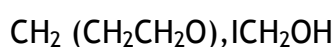
Isopropyl rubbing alcohol is about 70% by volume isopropyl alcohol, the remainder consisting of water with or without color additives, stabilizers and perfume oils. It is used externally as a rubefacient and soothing rub and as a vehicle for topical products.

### 3. Polyhydric alcohols:

Alcohols containing two hydroxyl groups per molecule are known as glycols but due to their toxicity are rarely used internally. One important exception to this is propylene glycol which is often used in conjunction with water or glycerol as cosolvent.



The lower molecular weight polyethylene glycols (PEG) or macrogols having the following general formula can be used as cosolvents with alcohol or water-although their main use is in the formulation of water- miscible ointment bases. OH



Glycerol, an alcohol possessing three hydroxyl groups per molecule, is also widely used particularly as a cosolvent with water for oral use. Glycerin has preservative qualities, it can be used externally at higher concentrations, for example in phenol Ear

Drops.

**4. Dimethyl sulphoxide :**

This is a highly polar compound and is thought to aid the penetration of drugs through the skin.

**5. Ethyl ether:**

This material is widely used for the extraction of crude drugs. It is, however, used as a cosolvent with alcohol in some collodions.

**6. Liquid paraffin:**

The oily nature of this material makes it unpleasant to use externally, although it is often used as a solvent for the topical application of drugs in emulsion formulations. When used internally, it is indigestible and absorbed only to a limited extent, it is an example of emollient cathartic when given internally in the, form of emulsion.

**7. Miscellaneous solvents:**

Isopropyl myristate and isopropyl palmitate are oily materials used as solvents for external use particularly in cosmetics, where their low viscosity and lack of greasiness make them pleasant to use.

Xylene is present in some ear drops to dissolve ear wax. As with aqueous systems, it may be possible to improve the solubility of a drug in a particular vehicle by the addition of a cosolvent. For example, nitrocellulose is poorly soluble in both alcohol and ether but soluble in mixture of both. The formulation of Digoxin injection is best achieved by the inclusion of both ethyl alcohol and propylene glycol.

**Other Formulation Additives**

**I. Buffers:**

These are materials which, when dissolved in a solvent, will enable it to resist any change in pH when an acid or an alkali is to be added. The choice of suitable buffer depends on the pH and buffering capacity. required. It must be compatible with other excipients and have low toxicity.

Most pharmaceutically acceptable buffering systems are based on carbonates citrates, gluconates, lactates, phosphates or tartarates. Borates can be used for external application but not to mucous membranes or to abraded skin.

As the pH of most body fluids is 7.4, such as injections, eye drops and nasal drops should be buffered at this value. Many body fluids themselves, however, have a buffering capacity and when formulating low volume intravenous injections or eye drops a wider pH range can be tolerated. There must be a compromise between a pH which is physiological and a pH of maximum stability and solubility and optimum bioavailability.

Examples illustrating the use of buffers include benzyl penicillin injection. The optimum pH range for the stability of penicillin solutions is 6-7. Hydrolysis readily occurs in aqueous solutions with the formation of inactive benzyl penicilloic acid, this is accompanied by, a fall in, pH which further catalyses hydrolysis leading to progressively greater acidity and more rapid hydrolysis until the antibiotic has been destroyed. Decomposition can be retarded by buffering the pH of the solution to 6-7 with 45% W/V sodium citrate.

## II. Flavors and perfumes:

The simple use of sweetening agents may not be sufficient to render palatable a product containing a drug with a particularly unpleasant taste. In many cases, therefore, a flavouring agent can be included. This is particularly useful in pediatric formulation to ensure patient compliance.

Flavouring and perfuming agents can be obtained from either natural or synthetic sources. Natural products include fruit juices, aromatic oils such as peppermint and lemon oils, herbs and spices. They are available as concentrated extracts, alcoholic or aqueous solutions, syrups or spirits. Artificial perfumes and flavours are of purely synthetic origin, they tend to be cheaper, more readily available, less variable in chemical composition and more stable than natural products. They are usually available as alcoholic or aqueous solutions or as powders.

In some cases there exists a strong association between the use of a product and its flavour or perfume content. For example, products intended for the relief of indigestion are often mint flavoured as mint has been used for its carminative effect.

Other suitable materials for the masking of unpleasant tastes include menthol, peppermint oil and chloroform. In addition to their own particular tastes and odours, they also act as desensitizing agents by the exertion of a mild anaesthetic effect on the sensory taste receptors. Flavour-enhancing agents such as citric acid and glycine or monosodium glutamate are widely used in solutions.

Taste of product	Suitable masking flavour
Salty	Apricot, butterscotch, liquorice, peach, vanilla
Bitter	Anise, chocolate, mint, passion fruit, wild cherry
Sweet	Vanilla, fruits, berries
Sour	Citrus fruits, liquorice, raspberry

### III. Colours:

Once a suitable flavour has been chosen, it is often useful to include a colour which is associated with that flavour to improve the attractiveness of the product. There is available range of both natural and synthetic colours. The former, which tend to be more widely acceptable than synthetic ones. However, they exhibit the usual problems associated with natural products, namely variations in availability and in chemical composition, both of which may cause formulation difficulties.

Synthetic dyes tend to give brighter colours and are generally more stable than natural materials.

### IV. Preservatives:

There are essentially two strategies to be adopted in the preparation of microbiologically acceptable pharmaceutical preparations. The first, and most important, is to minimize the access of microorganisms from the sources, and the second is to formulate the final product with inclusion of preservatives. Certain syrups may contain preservatives. The preservatives used may be the following:

Preservative	pH	Concentration (%)
Benzoic acid	Less than 6	0.1 - 0.2
Sodium benzoate	Less than 6	0.1 - 0.2
Butyl paraben	3 - 9	0.02
Propyl paraben	3 - 9	0.05
Methyl paraben	3 - 9	0.1
Sorbic acid	Less than 6	0.1
Alcohol	3 - 9	15 - 20
Glycerin	3 - 9	45

Benzoates, parabens and sorbic acid are most effective in acid syrups and are ineffective in alkaline syrups.

### **Sources of contamination of solutions**

#### **1. Equipment:**

The equipment should be as simple as possible for the purposes required with a minimum of junctions, valves and pumps, to allow cleaning in place.

#### **2. Raw materials:**

Raw materials, particularly those of natural origin, and water are a rich source of microorganisms.

#### **3. Personnel:**

The procedures adopted to control contamination, will be of little importance unless the personnel involved understand and appreciate the problems and significance of microbial contamination. This requires education in hygiene to minimize the introduction of microorganisms by staff. A full range of appropriate clothing must be available to protect the product from body surfaces such as hood, mask, overall protective gloves and boots.

### **Some examples of antimicrobial agents**

#### **1. Phenolics:**

Various distillation fractions of coal tar yield phenolic compounds including cresols, xylenols and phenol, all of which are toxic and caustic to skin and tissues. Modification of the phenol molecule by the introduction of chlorine and methyl groups as in chlorocresol and chloroxylenol has the dual effect of eliminating toxic and corrosive properties and at the same time enhancing and prolonging antimicrobial activity. Thus, chlorocresol is used as bactericide in injections.

#### **2. Alcohols, acids and esters:**

Ethyl alcohol, has long been used as preservative. The effect of aromatic substitution is to produce a range of compounds which are less volatile and less rapidly active, e.g. phenylethanol for eye drops and contact lens solutions, benzyl alcohol in injections.

The organic acids, sorbic and benzoic and their esters, by their low toxicity, are well established as preservatives.

The formulation pharmacist must be aware of chemical interactions between the various components of a solution that may alter the preparation's stability and/or

potency. For instance, esters of p-hydroxybenzoic acid (methyl- ethylpropyl and butyl parabens), frequently used preservatives in oral preparations, have a tendency to partition into certain flavoring oils. This partitioning effect could reduce the effective concentration of the preservatives in the aqueous medium of a pharmaceutical product below the level needed for preservative action.

### 3. Quaternary ammonium compounds:

These cationic surface-active compounds, they are derivatives of an ammonium halide in which the hydrogen atoms are substituted by at least one lipophilic group (Alkyl group). In contrast to phenol cresols, these compounds are mild in use and active at high dilutions as to be virtually non-toxic. They are active as actions. thus, alkaline conditions promote activity. One effect of the detergent properties of these compounds is to interfere with cell permeability such that susceptible bacteria, mainly the gram-positive groups, leak their contents and eventually undergo lyses. Gram negative bacteria are less susceptible. Mixtures of quaternary ammonium compounds with other antimicrobial agents can be used.

### V. Reducing agents and antioxidants:

The decomposition of pharmaceutical products by oxidation can be controlled by the addition of reducing agents or antioxidants.

### VI. Sweetening agents:

Low molecular weight carbohydrates and in particular sucrose are the most widely used sweetening agents. Sucrose has the advantage of being colourless, very soluble in water, stable over a pH range of about 4-8. Polyhydric alcohols such as sorbitol, mannitol and to a lesser extent glycerol also possess sweetening power and can be included in preparations for diabetic use where sucrose is undesirable.

Artificial sweeteners can be used both in conjunction with sugars and alcohols to enhance the degree of sweetness or on their own in formulations for patients who must restrict their sugar intake.

They are sweeter than sucrose and therefore rarely required at a concentration greater than about 0.2%. The most widely used is the sodium or calcium salt of saccharin, exhibiting high water solubility and are chemically and physically stable over a wide pH range.

### VII. Isotonicity modifiers:

Solutions for injection, for application to mucous membranes and large volume solutions for ophthalmic use must be made iso-osmotic with tissue fluid to avoid pain and irritation.

### VIII. Viscosity enhancement

It may be difficult for aqueous-based topical solutions to remain in place on the skin or in the eyes for any significant time because of their low viscosities. To counteract this effect, low concentrations of gelling agents can be used to increase the apparent viscosity of the product. Examples include povidone, Hydroxyethylcellulose (HEC) and carbomer.

#### Preparation of solutions

Some chemical agents in a given solvent require an extended time for dissolving. To hasten dissolution a pharmacist may employ one of several techniques, such as applying heat, reducing the particle size of the solute, using a solubilizing agent, or subjecting the ingredients to vigorous agitation.

Most chemical agents are more soluble at elevated temperatures than at room temperature or below because an endothermic reaction between the solute and the solvent uses the energy of the heat to enhance dissolution.

Pharmacists must be careful not to exceed the minimally required temperature, for many medicinal agents are destroyed at elevated temperatures, and the advantage of rapid solution may be completely offset by drug deterioration. If volatile solutes are to be dissolved or if the solvent is volatile (as alcohol), the heat would encourage the loss of these agents and must therefore be avoided.

Finally, for both small and large-scale manufacture of solutions, the only equipment necessary is suitable mixing vessels as, a means of agitation and a filtration system to ensure clarity of the final solution. Solute present in low concentrations, are often predissolved in a small volume of the solvent and then added to the bulk. Volatile materials such as flavours and perfumes are, where possible, added at the end of the process and after cooling to reduce loss by evaporation.

## STABILITY OF SOLUTIONS

Both the chemical and physical stability of solutions in their intended containers is important. A solution must retain its initial clarity, odour, colour, taste and viscosity over its shelf life.

Clarity can easily be assessed by visual examination or by a measurement of its optical density after. Colour too may be assessed both visually spectrophotometrically. The stability of flavours and perfumes must be also assessed by chromatographic methods.

## TYPES OF SOLUTIONS

Solutions can be classified according to their route of administration into:

### **I. Oral Solutions:**

As discussed before most solutions intended for oral administration contain flavorants and colorants to make the medication more attractive and palatable. When needed, they may also contain stabilizers to maintain the chemical and physical stability of the medicinal agents and preservatives to prevent the growth of microorganisms in the solution.

Liquid pharmaceuticals for oral administration are usually formulated such that the patient receives the usual dose of the medication in a conveniently administered volume, as 5 ml (one teaspoonful), 10 ml, or 15 ml (one tablespoonful). A few solutions have unusually large doses, for example magnesium citrate oral solution, with a usual adult dose of 200 ml. On the other hand, many solutions for children are given by drop with a calibrated dropper.

#### **1. Syrups**

Syrups are concentrated aqueous preparations of a sugar or sugar substitute with or without flavoring agent and medicinal substances.

Syrups containing flavoring agents but not medicinal substances are called non medicated or flavored syrups. These syrups are intended to serve as pleasant tasting vehicles for medicinal substances to be added in the compounding of prescriptions.

Medicated syrups are commercially prepared from the starting materials, by combining each of the individual component of the syrup, such as sucrose, purified water, flavoring agents, coloring agents, therapeutic agent and other necessary and desirable ingredients. Examples of medications administered as medicated syrups are antitussive and antihistamines.

Syrups provide a pleasant means of administration of a liquid form of a disagreeable tasting drug. They are particularly effective in the administration of drugs to youngsters.

Any water-soluble drug that is stable in aqueous solution may be added to a flavored syrup. However, care must be exercised to ensure compatibility between the drug substance and the other components of the syrup. Also, certain flavored syrups have an acidic medium, whereas others may be neutral or slightly basic, and the proper selection must be made to ensure the stability of any added medicinal agent.

### Components of syrups

Most syrup contains the following components in addition to the purified water, and any medicinal agents.

- a. The sugar, usually sucrose, or sugar substitute used to provide sweetness and viscosity.
- b. Antimicrobial preservatives.
- c. Flavorants and colorants.

Also, many syrups, especially those prepared commercially, contain special solvents, solubilizing agents, thickeners, or stabilizers.

#### a. **Sucrose and non-sucrose-based syrups:**

Sucrose is the sugar most frequently employed in syrups, although, it may be replaced by other sugars and substances as sorbitol, glycerol and propylene glycol. In some instances, all glycogenetic substances (materials converted to glucose in the body), including the above-mentioned agents, are replaced by non glycogenetic agents, such as methyl cellulose or hydroxyl ethyl cellulose. Those substances are best used for patients whose diet must be controlled and restricted to non glycogenetic substances as well as diabetic patients. The viscosity resulting from the use of these cellulose derivatives is much like that of sucrose syrup.

Most syrup contains a high proportion of sucrose, usually 60 to 80%, not only because of the desirable sweetness and viscosity of such solutions, but also because of their inherent stability in contrast to the unstable character of dilute sucrose solutions. The aqueous dilute sucrose solutions are an efficient nutrient medium for the growth of microorganisms, particularly yeast and molds. On the

other hand, concentrated sugar solutions are quite resistant to microbial growth because of the unavailability of the water required for the growth of microorganisms. This aspect of syrups is best demonstrated by the simplest of all syrups, simple syrup, which is prepared by dissolving 85 g sucrose in enough purified water to make 100 ml of syrup.

In cool storage, some sucrose might crystallize from solution and, by acting as nuclei, initiate a type of chain reaction that would result in separation of an amount of sucrose. The syrup would then be very much unsaturated and probably suitable for microbial growth; therefore, preservatives are employed to prevent microbial growth and to ensure stability during their period of use and storage.

A further with the storage and use of syrups involves the crystallization of the sugar within the screw cap used to seal the containers. This can be avoided by the addition of the polyhydric alcohols (sorbitol- glycerol or propylene glycol) or by the inclusion of invert sugar which is a mixture of glucose and fructose.

**b. Antimicrobial preservative:**

The amount of preservative required to protect syrup against microbial growth varies with the proportion of water available for growth. Among the preservatives commonly used in syrups with the usually effective concentrations are benzoic acid 0.1-0.2 %, sodium benzoate 0.1-0.2% and various combinations of methyl parabens, propyl parabens and butyl parabens for about 0.1%. Frequently alcohol is used in syrups to assist in dissolving alcohol soluble ingredients, but normally, it is not present in the final product in amounts that would be considered to be adequate for preservation (15 to 20%).

**c. Flavorant:**

Most syrups are flavored with synthetic flavorants or with naturally occurring materials, such as volatile oils (e.g. orange oil), to render the syrup pleasant tasting. Because syrups are aqueous preparations, these flavorants must be water soluble. However, sometimes a small amount of alcohol is added to syrup to ensure the complete solution of a poorly water-soluble flavorant.

**d. Colorant:**

To enhance the appeal of the syrup, a coloring agent that correlates with the flavorant employed (e.g. green with mint, brown with chocolate) is used. The colorant is generally water soluble, non reactive with other syrup components and

color stable at the pH range and under the intensity of light that syrup is likely exposed during its shelf life.

### Preparation of syrups

Syrups are mostly frequently prepared by one of four general methods:

- a. Solution by agitation without the aid of heat
- b. Addition of sucrose to a medicated or flavored liquid. percolation.
- c. Solution with the aid of heat:

#### **a. Solution with the aid of heat**

Syrups are prepared by this method when it is desired to prepare the syrup as quickly as possible and when the syrup's components are not damaged or volatilized by heat. In this method, the sugar is generally added to the purified water, and heat is applied until the sugar is dissolved. Then other heat stable components are added to the hot syrup, the mixture is allowed to cool, and its volume is adjusted to the proper level by addition of purified water. If heat labile agents or volatile substance such as volatile flavoring oils and alcohol, are to be added, they are generally added to the syrup after cooling to room temperature.

Caution must be taken to overcome the use of excessive heat as sucrose, a disaccharide, may be hydrolyzed into monosaccharides, dextrose (glucose), and fructose (levulose). This hydrolytic reaction is inversion, and the combination of the two monosaccharide products is invert sugar. The speed of inversion is greatly increased by the presence of acids, the hydrogen ion acting as catalysis to the reaction. The sweetness of the syrup is altered after inversion, because invert sugar is sweeter than sucrose, and the normally colorless syrup darkens because the effect of heat on the levulose portion of the invert sugar. Because of the effect of decomposition by heat, syrups can not be sterilized by autoclaving. The use of purified water and the addition of preservative agents can protect the syrup during its shelf-life.

#### **b. Solution by agitation without the aid of heat:**

To avoid heat-induced inversion of sucrose, syrup may be prepared without heat by agitation. This process is more time consuming than use of heat, but the product has maximum stability.

#### **c. Addition of sucrose to a medicated or flavored liquid:**

Occasionally a medicated liquid, such as tincture or fluid extract, is employed as the source of medication in the preparation of syrup. Many such tinctures and fluid extracts are prepared with alcoholic or hydroalcoholic vehicles. If the alcohol-soluble components are desired medicinal agents, some means of rendering them water soluble is employed. However, if the alcohol-soluble components are unnecessary, they are generally removed by mixing the tincture or fluid extract with water, allowing the mixture to stand until the separation of water-insoluble agents is complete, filtering them from the mixture. The filtrate is the medicated liquid to which the sucrose is added. If the tincture or fluid extract is miscible with aqueous preparations, it may be added directly to simple syrup or flavored syrup.

**d. Percolation:**

In the percolation method, either sucrose may be percolated to prepare the syrup, or the source of the medicinal component may be percolated to form an extractive to which sucrose or syrup may be added. When preparing percolated sucrose, purified water or an aqueous solution can pass slowly through a bed of crystalline sucrose, where cotton is, placed in its neck, thus dissolving sucrose and forming syrup.

**2- Elixirs:**

They are clear, sweetened hydroalcoholic solutions intended for oral use and are usually flavored to enhance their palatability. Compared with syrups, elixirs are usually less sweet and less viscous because they contain a lower proportion of sugar and consequently are less effective than syrups in masking the taste of medicinal substances. However, because of their hydroalcoholic character, elixirs are better able than aqueous syrups to maintain both water-soluble and alcohol-soluble components in solution.

The proportion of alcohol in elixirs varies widely, since the individual components of the elixirs have different water and alcohol solubility characteristics. For elixirs containing agents with poor water solubility, the proportion of alcohol required is greater than for elixirs prepared from components having good water solubility. In addition to alcohol and water, other solvents, such as glycerin and propylene glycol, are frequently employed in elixirs as adjunctive solvents. Although many elixirs are sweetened with sucrose or with sucrose syrup, some use sorbitol, glycerin and/or artificial sweeteners. Elixirs having a high alcoholic content usually use an artificial sweetener, such as saccharin, which is required only in small amounts rather than

sucrose, which is only slightly soluble in alcohol and requires greater quantities for equivalent sweetness.

All elixirs contain flavorings to increase their palatability, and most elixirs have coloring agents to enhance their appearance. Elixirs containing more than 10 to 12% of alcohol are usually self-preserving and do not require the addition of an antimicrobial agent.

A disadvantage of elixirs for children and for adults who choose to avoid alcohol is their alcoholic content.

### Types of Elixirs

Elixirs may be Non-medicated or medicated elixirs.

#### **A) Non Medicated Elixirs:**

Those elixirs may be useful to the pharmacist in the filling of prescriptions involving:

- a. The addition of a therapeutic agent to a pleasant tasting vehicle.
- b. Dilution of an existing medicated elixir.

In selecting a liquid vehicle for a drug substance, the pharmacist should be concerned with the solubility and stability of the drug substance in water and alcohol. If a hydroalcoholic vehicle is selected, the proportion of alcohol should be only slightly above the amount needed to effect and maintain the drug's solution. When dealing with dilution of an existing medicated elixir, the non-medicated elixir should have approximately the same alcoholic concentration as the elixir being diluted. Also, the flavor and color characteristics of the diluents should not be in conflict with those of the medicated elixir, and all components should be chemically and physically compatible. Examples of non medicated elixirs are: Aromatic elixir, Compound benzaldehyde elixir, and Isoalcoholic elixir.

#### **B) Medicated Elixirs**

They are employed for the therapeutic benefit of the medicinal agent. Examples of medicated elixirs are: Phenobarbital elixir used as sedative and hypnotic, Acetaminophen elixir used as analgesic, antipyretic and Diphenhydramine Hcl elixir used as antihistaminic.

### Preparation of Elixirs

Elixirs are usually prepared by simple solution with agitation and/ or by admixture of two or more liquid ingredients. Alcohol- soluble and water- soluble components are

generally dissolved separately in alcohol and in purified water, respectively. Then the aqueous solution is added to the alcoholic solution, rather than the reverse, to maintain the highest possible alcoholic strength at all times so that minimal separation of the alcohol-soluble components occur. When the two solutions are completely mixed, the final mixture will be cloudy, because of separation of some of the flavoring oils by the reduced alcoholic concentration. If this occurs the elixir is usually permitted to stand for a prescribed number of hours to permit the oil globules to coalesce so, that they may be more easily removed by filtration. Talc, is a frequent filter aid in the preparation of elixirs, absorbs the excessive amounts of oils and therefore assists in their removal from the solution. The presence of glycerin, syrup, sorbitol and propylene glycol in elixirs generally contributes to the solvent effect of the hydroalcoholic vehicle, assists in the dissolution of the solute, and enhances the stability of the preparation.

### 3- Tinctures

Tinctures are alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances. They vary in method of preparation, strength of the active ingredient and alcoholic content. When they are prepared from chemical substances (e.g. iodine, thiomersal) tinctures are prepared 'by simple solution of the chemical agent in the solvent. Depending on the preparation, tinctures contain alcohol in amounts ranging from approximately 15 to 80%. The alcohol content protects against microbial growth and keeps the alcohol soluble extractives in solution. Because of the alcoholic content, tinctures must be tightly stoppered and not exposed to excessive temperatures. Also, because many of the constituents found in tinctures undergo a photochemical change upon exposure to light, many tinctures must be stored in light-resistant containers and protected from sunlight.

## II. Topical solutions and tinctures

Generally, the topical solutions employ an aqueous vehicle, whereas the topical tinctures employ an alcoholic vehicle.

Most topical solutions and tinctures are prepared by simple dissolving. However, certain solutions are prepared by chemical reaction, others are prepared by maceration of the natural components in the solvent as in compound benzoin tincture.

Because of the nature of the active ingredients or the solvents, many topical

solutions and tinctures are self-preserved. Those that are not may contain suitable preservatives. Topical solutions and tinctures should be packaged in containers that make them convenient to use. Those that are used in small volume, such as the anti-infective, are usually packaged in glass or plastic bottles with an applicator tip as a part of the cap or in plastic squeeze bottles that deliver the medication in drops. Many of the anti-infective solutions and tinctures contain a dye to delineate the area of application to the skin.

### 1. Liquids for cutaneous application Lotions, liniments, paints and collodions

**a- Lotions** Can be formulated as solutions, and are designed to be applied to the skin without friction. They may contain humectants, so that moisture is retained on the skin after application of the product, or alcohol, which evaporates quickly, imparting a cooling effect and leaving the skin dry.

**b- Liniments**, Are intended for massage into the skin and can contain such ingredients as methyl salicylate or camphor as counterirritants. are often termed

**c- paints**, Liquids for application to the skin or mucous membranes in small amounts and are usually applied with a small brush. The solvent is normally alcohol, acetone or ether, which evaporates quickly leaving a film on the skin that contains the active agent. A viscosity modifier such as glycerol is often added to ensure prolonged contact with the skin.

**d- Collodions** Are similar preparations which, after evaporation of the solvent, leave a tough, flexible film that will seal small cuts or hold a drug in intimate contact with the skin. The film former is usually pyroxylin (nitrocellulose) in an alcohol/ether or alcohol/acetone solvent blend. Often a plasticizer such as castor oil and an adherent such as colophony resin are included.

### 2. Ear preparations

Also known as otic or aural products, these are simple solutions of drugs in either water, glycerol, propylene glycol or alcohol/water mixtures for local use, and include antibiotics, antiseptics, cleansing solutions and wax softeners. They are applied to the external auditory canal as drops, sprays or washes.

### 3. Eye preparations

These are small-volume sterile liquids designed to be instilled on to the eyeball or within the conjunctival sac for a local effect.

#### 4. Irrigations

Irrigations are sterile, large-volume aqueous-based solutions for the cleansing of body cavities and wounds. They should be made isotonic with tissue fluid.

#### 5. Mouthwashes and gargles

Aqueous solutions for the prevention and treatment of mouth and throat infections can contain antiseptics, analgesics and/or astringents. They are usually diluted with warm water before use.

#### 6. Nasal products

These are formulated as small-volume solutions in an aqueous vehicle, oils being no longer used for nasal administration. Because the buffering capacity of nasal mucus is low, formulation at a pH of 6.8 is necessary. Nasal drops should also be made isotonic with nasal secretions using sodium chloride, and viscosity can also be modified using cellulose derivatives if necessary.

### III. Vaginal and rectal solutions

#### 1- Vaginal douches

Vaginal douches may be prepared from: powders (Douche powders) or from liquid solutions or liquid concentrates.

Powders are used to prepare solutions for vaginal douche, that is, for irrigation cleansing of the vagina. The powders themselves may be prepared and packaged in bulk or as unit packages. A unit package is designed to contain the appropriate amount of powder to prepare the specified volume of douche solution. The bulk powders are used by the teaspoonful or tablespoonful in the preparation of the desired solution. The user simply adds the prescribed amount of powder to the appropriate volume of warm water and stirs until dissolved. In using liquid concentrates, the patient is instructed to add the prescribed amount of concentrate (usually a teaspoonful or cupful) to a certain amount of warm water (frequently a quart). The resultant solution contains the appropriate amount of chemical agents in proper strength,

Among the components of vaginal douche powders are the following:

1. Boric acid or sodium borate.
2. Astringents, e.g., potassium alum, ammonium alum, zinc sulfate.

3. Antimicrobials, e.g., oxyquinoline sulfate, povidone iodine.
4. Quaternary ammonium compounds, e.g., benzethonium chloride.
5. Detergents, e.g., sodium lauryl sulfate.
6. Oxidizing agents, e.g., sodium perborate.
7. Salts, e.g., sodium citrate, sodium chloride
8. Aromatics, e.g., menthol, thymol, eucalyptol methyl salicylate, phenol.

Douche powders are used for their hygienic effects. A few douche powders containing specific therapeutic anti-infective agents against monilial and trichomonal infections.

## 2- Enemas:

They are aqueous or oily solutions, as well as emulsions and suspensions, are available for the rectal administration of medicaments for cleansing, diagnostic or therapeutic reasons.

Enemas are of two types

- a. Retention Enemas.
- b. Evacuation Enemas.

### a. *Retention Enemas:*

A number of solutions are administered rectally for local effects (e.g., hydrocortisone) or for systemic absorption (e.g., aminophylline). In the case of aminophylline, rectal administration minimizes the undesirable gastrointestinal reactions associated with oral therapy. Clinically effective blood levels of the agents are usually obtained within 30 minutes followed rectal instillation. Corticosteroids are administered as retention enemas as adjunctive treatment of some patients with ulcerative colitis.

### b. *Evacuation Enemas:*

They are used to cleanse the bowel. Many enemas are available in disposable plastic squeeze bottles containing a premeasured amount of enema solution. The agents are solutions of sodium phosphate and sodium biphosphate, glycerin and docusate potassium, and light mineral oil.

#### IV. Topical oral (Dental) solutions

A variety of medicinal substances are employed topically in the mouth for a number of purposes and in a wide range of dosage forms. Some of these products, such as teething lotions and toothache drops are medicated, whereas others are used for hygienic purposes, such as dentifrices, denture products, and many of the mouth washes.

##### **1- Mouth Washes:**

Mouth washes are hydroalcoholic solutions. A mouth wash can be used for two purposes therapeutic and cosmetic. Therapeutic, rinses or washes can be formulated to reduce plaque, gingivitis, dental caries and stomatitis. Cosmetic mouth washes may be formulated to reduce bad breath through the use of antimicrobial and/ or flavoring agents.

Mouth washes generally contain the following groups of excipients:

##### **a. Alcohols:**

Alcohol is often present in the range of 10-20%. It enhances the flavor Aids in masking the unpleasant taste of active ingredients, functions as a solubilizing agent for some flavoring agents and may function as preservative.

##### **b. Humectants:**

They can be used is 5-20% of the mouthwash. These agents such as glycerin and sorbitol increase the viscosity of the preparation and enhance the sweetness of the product and together with ethanol, may improve the preservative action.

##### **c. Surfactants:**

They are used in concentration range of 0.1-0.5%. Surfactants are used because they aid in the solubilization of flavors and in the removal of debris. They are usually of the nonionic class as cationic surfactants impart a bitter taste although they provide antimicrobial properties.

##### **d. Flavors:**

They are used to overcome the disagreeable taste. Examples of flavors are: peppermint, cinnamon, menthol or methyl salicylate.

##### **e. Coloring agents:**

They are also used in mouth washes to make the product more palatable and

attractive.

## V. Miscellaneous solutions

### 1. Aromatic waters:

Aromatic waters are clear, aqueous solutions saturated with volatile oils or other aromatic or volatile substances. Aromatic waters are prepared from a number of volatile substances, including orange flower oil, peppermint oil, rose oil, anise oil, spearmint oil, camphor and chloroform. Naturally, the odors and tastes of aromatic waters are of the volatile substances from which they are prepared. Most of the aromatic substances in the preparation of aromatic waters have very low water solubility, and even though water may be saturated, its concentration of aromatic material is still rather small. They are used as perfuming and/or flavoring vehicles. Aromatic waters will deteriorate with time and should, therefore, be made in small quantities and protected from intense light and excessive heat storing in air tight, light resistant containers. Deterioration may be due to volatilization, decomposition or mould growth.

Examples of aromatic waters include peppermint water and anise water which also have carminative properties and chloroform water which also acts as preservative.

### Preparation of Aromatic waters

#### a. Distillation process:

For fresh drugs, the proportion of drug to distillate is about (1:2), or (2:1). For dried drugs such as cinnamon, anise, the proportion is (1:10) drug: distillate. For dried leaf drugs such as peppermint, the proportion is (3:10) drug: distillate. After the distillation, any excess of oil in the distillate is removed filtration. Multiple distillation may be applied if the volatile principle in the water is present in small quantities, thus the distillate is returned several times to the still with fresh portions of drug. This process is called "cohobation".

#### b. Solution process:

Aromatic waters may be prepared by shaking 2 g or 2 ml of the volatile substance with 1000 ml of purified water. The mixture is set aside for 12 hours, filtered through wetted filter paper, and made to volume (1000 ml) by adding purified water through the filter.

Aromatic waters are usually manufactured as concentrated waters and are then

diluted, traditionally 1 to 40 in the final preparation.

## 2. Spirits:

Spirits are alcoholic or hydroalcoholic solutions of volatile substances. Generally, the alcoholic concentration of spirits is rather high, usually over 60%. Because of the greater solubility of aromatic or volatile substances in alcohol than in water, spirits can contain a greater concentration of these materials. Than the corresponding aromatic waters. When mixed with water or with an aqueous preparation, the volatile substances present in spirits generally separate from solution and form a milky preparation.

Spirits may be used pharmaceutically ad flavoring agents and medicinally for the therapeutic value of the aromatic solute. As flavoring agents, they are used to impart the flavor of their solute to other pharmaceutical preparations. For medicinal purposes, spirits may be taken orally, applied externally, or used by inhalation, depending upon the particular preparation. When taken orally, they are generally mixed with a portion of water to reduce the pungency of the spirit.

Examples of spirits are: aromatic ammonia spirit, camphor spirit, compound orange spirit and peppermint spirit.

### Preparation of spirits

Depending on the materials, spirits may be prepared by simple solution, solution by maceration, or distillation.

#### a. **Simple solution:**

This is the method by which the majority of spirits are prepared. By this method, aqueous ingredients are dissolved in water, oils are dissolved in alcohol, and the aqueous solution is added gradually to the alcoholic one. Set aside for 24 hours in a cool place, with occasional shaking, then filter.

#### b. **Solution with maceration:**

In this procedure, the leaves of the drug are macerated in purified water to extract water soluble matter. The moist macerated leaves are added to a prescribed quantity of alcohol.

#### c. **Distillation:**

Same as mentioned above in aromatic waters.

# Practical Part

## تقنية صناعة المستحضرات الدوائية 1

### Technology of pharmaceutical industry I

#### Practical part

#### Granulation

#### Definition

**Size enlargement** It is the process in which powder particles are made to adhere to form larger, multiparticle entities called granules

#### Objectives of Size Enlargement

1. Reduction of dust losses.
2. Minimization of the hazards of some dusts such as irritation and static accumulation.
3. Reduction of surface area of hygroscopic substances, thus minimizing water absorption lead to increase the stability.
4. Preparation of materials having good flow properties that are required for pass the quality-controlled test.
5. Increasing the bulk density of the material, thus facilitating storage and transportation.
6. Retardation of reaction rates through decreased surface area.
7. Particles of a material can be transformed into larger units by granulation, compression and coating.

#### Mechanisms of granuler formation

**In the dry methods** particle adhesion takes by applied pressure. A compact or sheet is produced which is larger than the granule size required, and therefore the required size can be obtained by milling and sieving.

**In wet granulation methods**, liquid added to dry powders has to be distributed

through the powder by the mechanical agitation created in the granulator. The particles adhere to each other with further agitation and liquid addition causes more particles to adhere.

### The main processes used for granulation

#### a. Wet granulation,

- This involves adding a liquid binder to a fine powder mixture and mixing until a coherent paste is obtained.
- The paste is then granulated by forcing it through a sieve to produce wet granules which are then dried

#### Desirable Granule Properties

- Controlled size distribution
- Specific granule with intragranular porosity
- Specific bulk density

#### Disadvantages of wet granulation:

1. it is not applicable to materials that are affected by moisture or heat.
2. The method is also time-consuming and requires both space and energy.

#### Equipment used for wet granulation include:

1. Low shear granulation
2. High shear mixture granulation
3. Fluid bed granulation
4. Spray drying

#### 1. Low shear granulation

In the traditional granulation process a planetary mixer is often used for wet massing of the powders,

The mixed powders are fed into the bowl of the planetary mixer and granulating liquid is added as the paddle of the mixer agitates the powders.

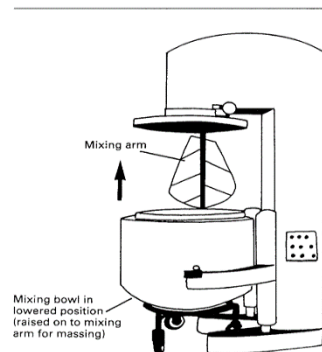
The planetary action of the blade when mixing is similar to that of a household mixer.

The moist mass has then to be transferred to a granulator, such as an oscillating

granulator

### Disadvantages of shear granulator

1. Its long duration
2. The need for several pieces of equipment
3. The high material losses that can be incurred
4. because of the transfer stages.



## 2. High shear mixture granulation

This type of granulator (e.g. Diosna, Fielder) is used extensively in pharmaceuticals.

### Granulation Process Parameters

#### Impeller Speed

Higher Impeller speeds (200-600 rpm) generally, results in denser and smaller granules. Low impeller speeds generally, result in more porous, large granules.

#### Chopper Speed

Generally chopper speed has significant effect on uniformity of granule size (1500-6000 rpm)

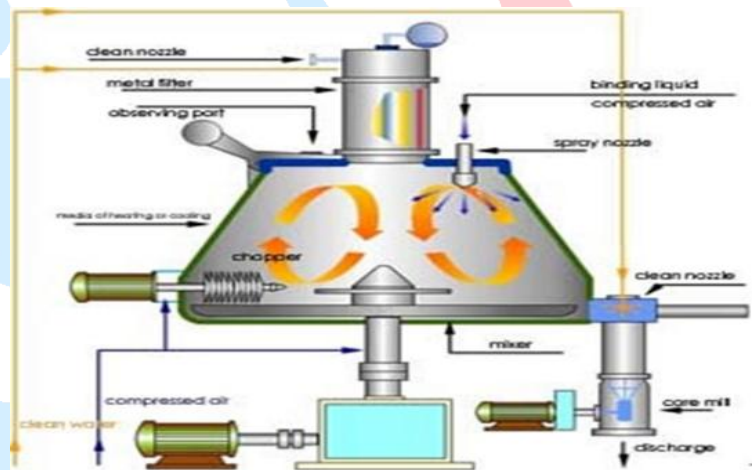
#### Water Addition Rate and Method

Water Addition Rate is critical to granule quality (2-5 min)

#### Massing Time

Massing time is normally in the order of 1 to 10 minutes. Long massing times (> 20 mins) may lead to increased disintegrant lead to decreased dissolution rates due to the formation of denser granules.

### Advantages High-shear granulation



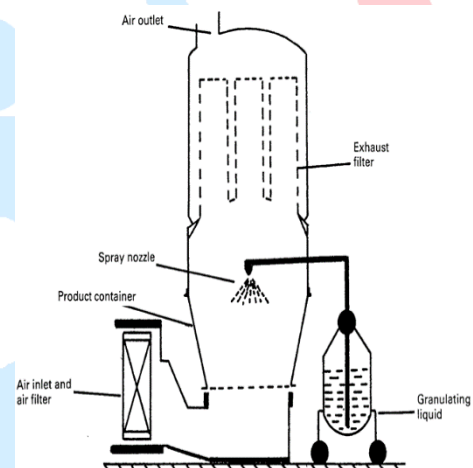
- Short processing time
- Less amount of liquid binders required compared with fluid bed.
- Highly cohesive material can be granulated
- Good compliance with GMP & small technical space required for granule production
- It is a contained process

### 3. Fluid bed granulation

Fluidized-bed granulators (e.g. Aeromatic, Glatt) have a similar design and operation to fluidized-bed driers, i.e. the powder particles are fluidized in a stream of air, but in addition granulation fluid is sprayed from a nozzle on to the bed of powders

Granulating fluid is pumped from a reservoir through a spray nozzle positioned over the bed of particles.

The fluid causes the primary powder particles to adhere when the droplets and powders collide. Sufficient liquid is sprayed to produce granules of the required size, at which point the spray is turned off but the fluidizing air continued.



- The wet granules are then dried in the heated fluidizing air stream.
- The material processed by fluid bed granulation are finer, free flowing and homogeneous drying granules.

#### Advantages of fluidized-bed granulation

1. Fluidized bed granulation has many advantages over conventional wet massing. All the granulation processes are performed in one unit, saving labour costs, transfer losses and time.
2. The process can be automated once the conditions affecting the granulation have been optimized.

**Disadvantages of fluidized-bed granulation**

1. The equipment is initially expensive
2. Optimization of process (and product) parameters affecting granulation needs extensive development work, not only during initial formulation work but also during scale-up from development to production.

**Granulation by Fusion**

- This method is used in the preparation of granular effervescent salts.
- When a mixture of sodium bicarbonate and citric acid is heated, the citric acid releases its water of crystallization which causes adhesion of the particles of the solids.
- The resulting coherent mass is pressed through a sieve or any of the mechanical granulators already described.
- The granules are then dried to remove the remainder of the water of crystallization at a temperature not exceeding 54°C.

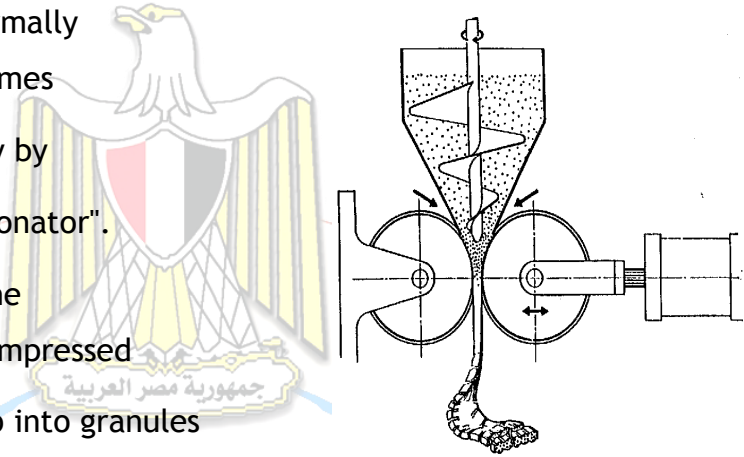
**Dry Granulation**

Here, the material in a fine powder is first aggregated by using

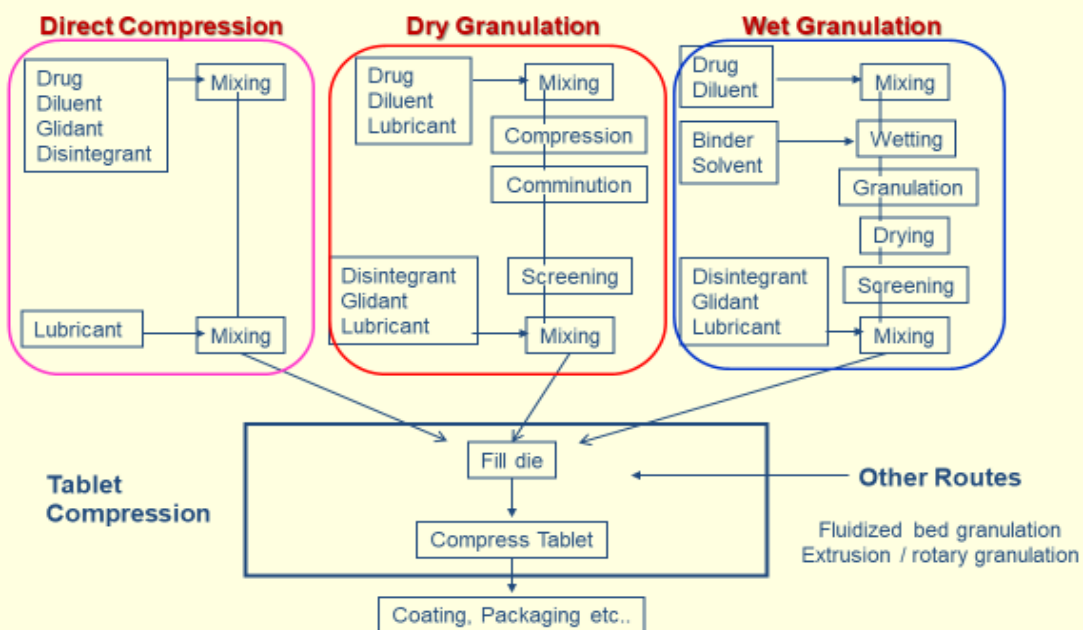
1. heavy-duty tablet presses known as slugging machines to form large flat-faced tablets called slugs.
  2. by passage between rollers in a machine known as the "Chilsonator", to give compressed sheets.
- The slugs or sheets are then broken up into the required granular size in a suitable milling machine.
  - Dry granulation is recommended for handling materials that are sensitive to heat and moisture. The method, however, subjects the drug to compression twice, which may affect its stability.
  - Slugging Machines: These are heavy-duty tablet presses that are fitted with punches and dies of about one inch in diameter. Pressures up to 20,000 p.s.i. can be exerted by such machines.

## 1. Chilsonator

- This is named after its inventor, Francis Chilson.
- It consists of a pair of specially grooved rolls, which rotate toward each other.
- The material is fed in between these rolls at a controlled rate, and the pressure Pressure up to 100,000 p.s.i. can be exerted if required.
- Therefore, materials that normally require slugging two or more times can be granulated satisfactorily by a single pass through the "Chilsonator".
- The product obtained from the Chilsonator is in the form of compressed sheets, which can be broken up into granules of the desired size.



## Processing routes



## Tablet Compression

Tablet machines can be divided into:

1. **Single-station, or single punch**” presses (For small-scale production).
2. **Multi-station or rotary press**” (for Large-scale industrial production).

### Basic components of Tablet Presses:

- Hopper for holding and feeding granules or powder to die be compressed.
- Dies that define the size and shape of the tablet.
- Punches for compressing the granules within the dies.
- Cam tracks for guiding the movement of the punches.
- A feeding mechanism for moving granules from the hopper into the dies.

### Stages of Tablet Formation

#### (Compaction Cycle)

##### Die filling

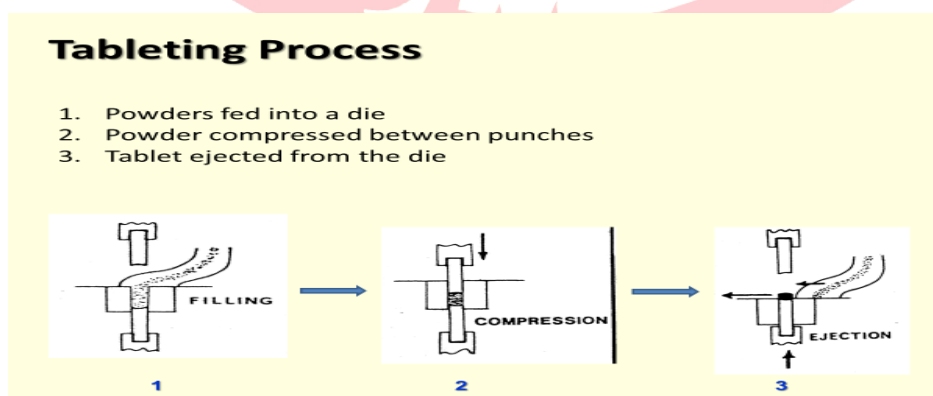
- Gravitational flow of the powder from hopper via the die table into the die. (The die is closed at its lower end by the lower punch).

##### Tablet formation

- The upper punch descends, enters the die, the powder is compressed until a tablet is formed. after maximum applied force is reached, the upper punch leaves the powder i.e. compression phase.

##### Tablet ejection

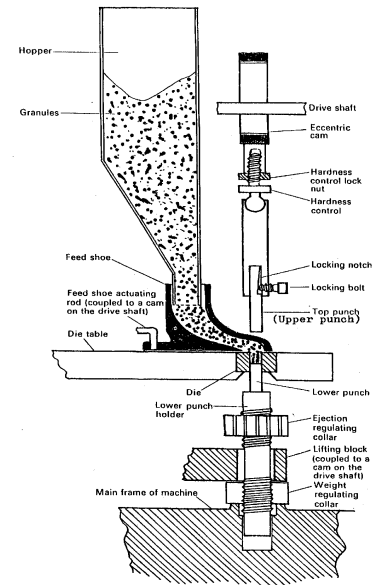
- The lower punch rises until its tip reaches the level of the top of the die. The tablet is subsequently removed from the die and die table by a pushing device.



## Single-Punch Tablet Machine

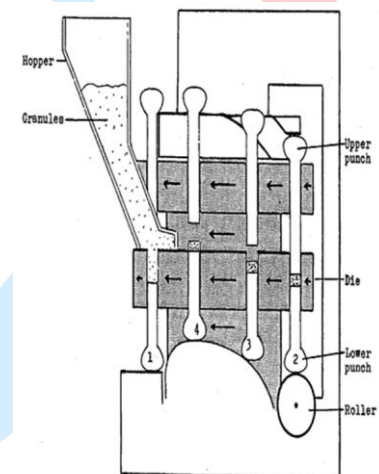
A single-punch tablet machine consists fundamentally of a **die fitted** with an **upper and lower punch** as shown in Figures.

1. when the upper punch is out of the die, **Lower punch drop** to the desired position in the die cavity.
2. **Feed shoe filled** with granulation from the hopper comes over the die & fills it.
3. The **feed shoe then retracts** to level the layer of granulation in the die.
4. The **upper punch lowers & compresses** the material into tablet.
5. The upper punch **retracts**.
6. **Lower punch rises** to lift the tablet to be ejected by the feed shoe, which moves over the die again to repeat the process.



## Rotary Tablet Machine

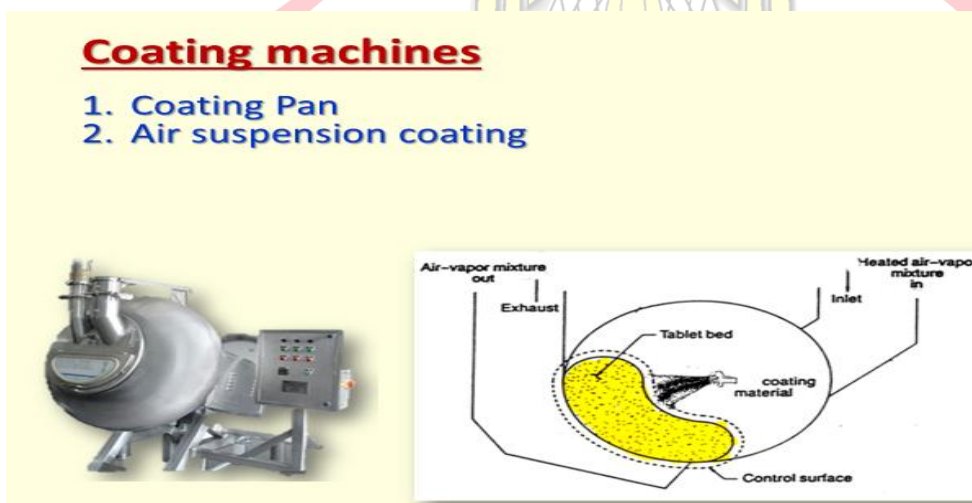
- 1- At the beginning of the cycle the **upper punch** is in **raised position** and the **lower punch** drops to the **lowest position**. The die is filled with granules.
- 2- The upper punch lowers to enter the die and the upper and lower punches pass between rollers, and granules are compressed to a tablet.
- 3- The upper punch is in raised position.
- 4- The lower punch rises to completely eject the tablet.



## Coating

A coating can be applied to a solid dosage form (a tablet, a pill, a granule or a capsule) to;

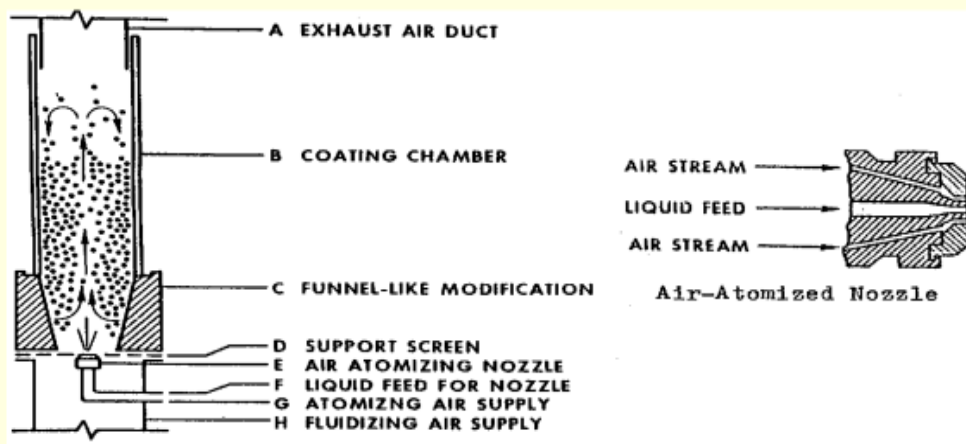
- to increase the stability, if the drug is affected by atmospheric moisture or oxygen,
- to mask an unpleasant taste,
- to retard loss of volatile ingredients,
- to improve the appearance of the solid form or
- to identify the finished product as being manufactured by a particular pharmaceutical firm.
- A coating may control the site and release of action, as with enteric coating,



## 2. Fluidized Bed (Air Suspension) Coater

- Fluidized bed coaters are also highly efficient drying systems.
- The airflow is controlled so that more air enters the center of the column, causing the tablets to rise in the center.
- The movement of tablets is upward through the center of the chamber. They then fall toward the chamber wall and move downward to re-enter the air stream at the bottom
- Coating solutions are continuously applied from a spray nozzle located at the bottom of the chamber
- Tablet cores that are friable and prone to chipping and edge abrasion may be difficult to coat even under optimum conditions in the fluidized bed systems owing to the relatively rough tablet-to-tablet impact and tablet-chamber contact.
- Specific for pellets and granules (not preferred for tablets)

## The Fluidized Bed (Air Suspension) Coater



### Example of Film Former Materials:

#### Non-enteric materials

- HPMC
- EC
- HPC
- PVP
- PEG

#### Enteric materials

- They are **pH- dependent** and **pH-sensitive** materials.
- Resist gastric fluid.
- Ready to permeability to intestinal fluid.
- **Ex.**
- 1- **Cellulose Acetate Phthalate (CAP).**
- 2- **Acrylate Polymers (Eudragit L , S)** as they resist gastric fluid and soluble in intestinal fluid of pH 6.

## Mixing

### A. Mixing is defined

It is the process of combining different materials to produce a homogeneous mixture.

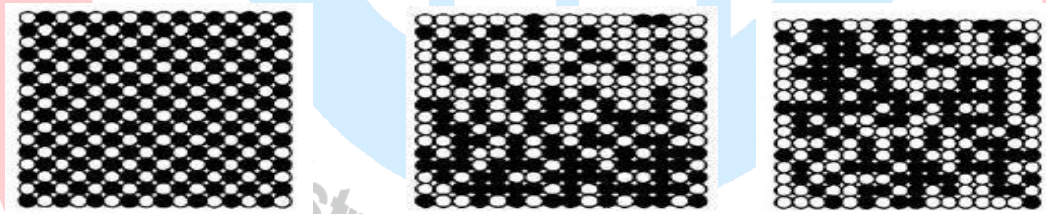
### B. Types of mixing process

- I. Solid-solid mixing
- II. Liquid-liquid mixing
- III. Solid-liquid mixing

### Solid-Solid Mixing and Powder mixing

#### Mixing Process

1. **Perfect mix.** would be produced when each particle is as closely as possible in contact with a particle of the other component. This is shown in (Fig. 1).
2. **Random mix**, which is defined as a mix where the probability of selecting a particle is the same at all positions in the mix.
3. **Powder mixing** is a neutral type of mixing. It is one of the most common operations employed in pharmaceutical industries for the different types of formulations, e.g. powders, capsules.



**Fig.1 Perfect mix      Segregating mix      Random mix**

### Mixing occur due to

- convective effect of the ribbons
- shearing.

### **Shear mixing**

- The use of an agitator arm will create shear forces in the powders leading to mixing.
- This mechanism predominates in High shear mixer.

- Mixing by using agitator arm or a blast of air.

### **Diffusive mixing**

- During this mixing, the materials are tilted so that the gravity forces → slipping and diffusion of upper layers which lead to mixing of the powders. HOW?
  - By changing its path
  - By trapping in the voids by other layer of particle
- This predominates in tumbling mixers
- Diffusive is also referred to as Micromixing.
- Redistribution of particles by random motion

### **Factors affecting Perfect Mixing of Powder**

1. Material density: It is difficult to mix two powders having different density. This is due to dense material always move downwards & settles down at the bottom.
2. Particle size: Variation of particle size can lead to separation, because small particles move downward through the space between the bigger particles.
3. Particle shape: The ideal particle shape is Spherical for uniform mixing.
4. Particle attraction: Some particles exert attractive forces due to electrostatic charges on them. This can lead to separation. The effect increases as particle size decreases.
5. Proportions of materials: The best result can be achieved if two powders are mixed in equal proportions by weight or by volume.

**N.B. For potent drugs, geometric dilution method is used**

### **Condition of Good Mixing**

- Mixer volume: allow sufficient space (50%) for dilation of the bed. Overfilling reduces the efficiency and may prevent mixing entirely.
- Mixing mechanism: The mixer must apply suitable shear forces to bring about local mixing
- Mixing time: there is an optimum time for mixing for any particular situation,
- Handling the mixed powder the powder should be handled in such a way that segregation is minimized (Minimized vibration)

Machines used for solid-solid mixing**1. Ribbon mixer**

- \* Mixing is achieved by the rotation of helical blades in a hemispherical trough.
- \* 'Dead spots' are difficult to eliminate in this type of mixer
- \* it mixes poorly flowing material and is less likely to cause segregation than a tumbling mixer.
- \* Not suitable for granular material.



Two helical blades rotate opposite to each other at different speeds, one of them moves the material in one direction and the other in the opposite direction.

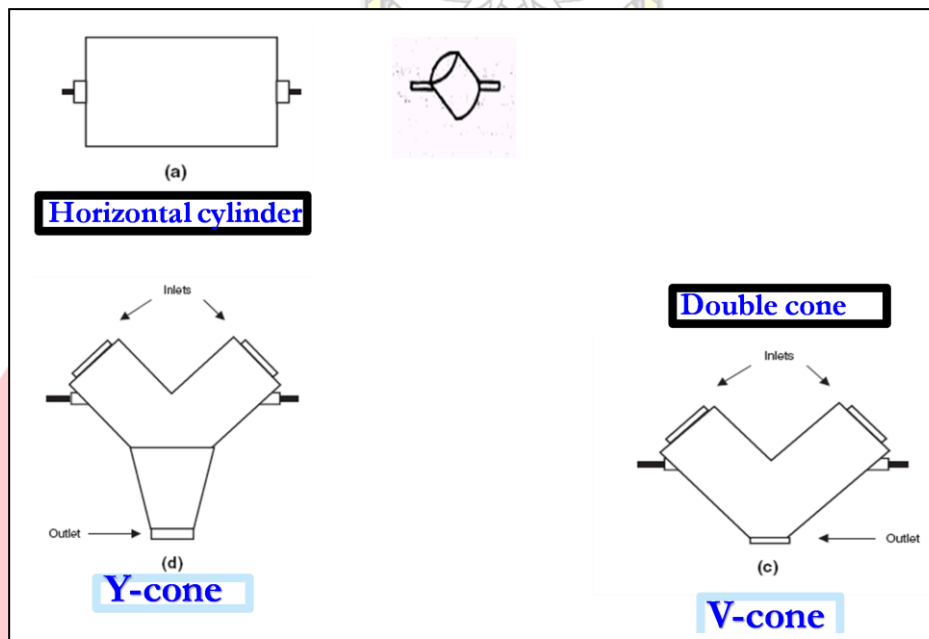
**2. Tumbling mixers**

- They operate by tumbling the material in a partially filled container rotating around a horizontal axis.
- These mixers use the gravity to give a flow.
- Diffusive mixing mechanism is the predominant.
- The tumbling mixer is used for
  1. Free flowing powder
  2. Granular material.
- Tumbling mixer is Poor for cohesive/poorly flowing powders, because the shear forces generated are usually insufficient to break up any aggregates.
- Movement to the materials by tilting powder → slipping and diffusion of upper layers which lead to mixing of the powders (diffusive mixing)
- Shear forces are low and end-to-end movement is slight. This may be overcome by:
  - including baffles

- the shape of the vessel may be altered to avoid symmetry.

**N.B.** the tumbling mixer preferable where differences in density for particle size occur

- When V shape is inverted, the material splits into two portions. This process of dividing and recombining continuously yields ordered mixing by mechanical means.



- an intensifier bar can be utilized to impart the shear
- The agitator bar not only can provide additional shear force, but can also provide a milling functionality to the agglomerates
- the particles hit against the wall and are deflected, causing considerable velocity and acceleration gradients.
- The repeated reversal of the direction of flow makes the tumbling mixer preferable where differences in density for particle size occur.

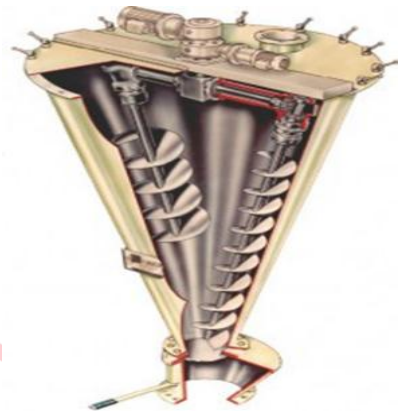
#### Advantages and disadvantages of Tumbling mixers

1. suitable for mixing friable materials because they produce mild forces → gentle mixing.
2. Used when there is a difference density and particle size... WHY?

**Because** the particles in a tumbler mixer hit against the walls and are then deflected to give good mixing.

### 3. Agitator Mixers Nautamixer

- \* It consists of a conical vessel fitted at the base with a rotating screw
- \* The screw conveys the material to near the top, where it cascades back into the mass.
- \* In this design the three mechanisms of mixing are utilized:
  1. Diffusive mechanism due to its conical vessel.
  2. Convective due to helical conveyer.
  3. Shear mixing due to rotating arm.



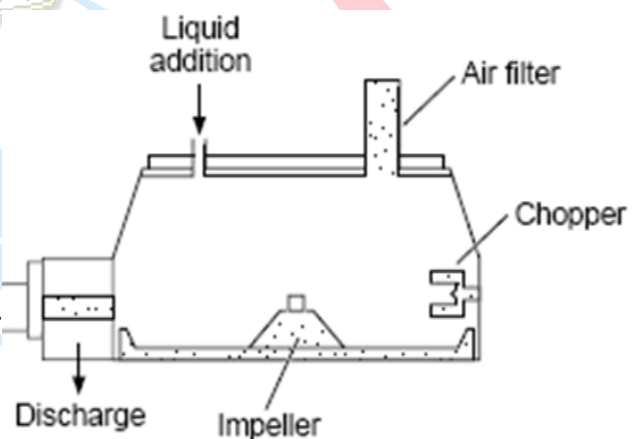
#### Advantages of Nautamixer

- No dead points.
- Can be used for drying under vacuum.

#### Development of Nautamixer

- Double jacketed.
- Can be used as hopper for tablet machine.

**Disadvantage:** expensive



### 3. High Shear Granulator

It can be used for mixing, granulation and drying à so ↓ waste products and ↓ number of workers required for these processes.

1. Mixing
2. Granulation by adding binder à wet mass à use a chopper to cut the mass into granules.
3. Drying à by the hot air or a heated jacket

**Centrally mounted impeller blade at the**

bottom of the mixer rotates at high speed, throwing the material towards

the mixer bowl wall by centrifugal force

then dropping back down towards the center of the mixer. The particulate movement within the bowl tends to mix the components quickly owing to high

shear forces (arising from the high velocity) and the expansion in bed volume that allows diffusive mixing.

**Diosna** → Mixing, Granulation and Drying

**Zanchetta** → Mixing, Granulation, Drying and size reduction

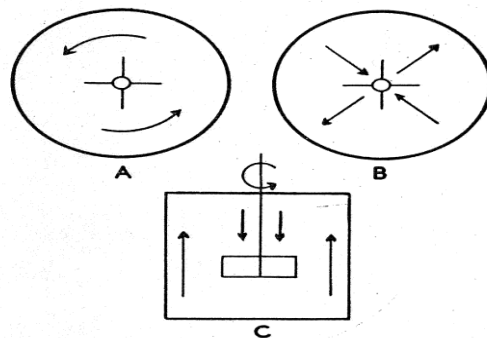
### Liquid Mixing

Liquid mixing is usually performed with a rotational device (impeller) which provides the necessary shear forces. The movement of the liquid at any point in the vessel will have three velocity components and the complete flow pattern will depend upon variations in these three components in different parts of the vessel.

The three velocity components are:

- **Radial components**, acting in a direction vertical to the impeller shaft.
- **A longitudinal component or axial**, acting parallel to the impeller shaft.
- **A tangential component**, acting in a direction that is a tangent to the circle of rotation round the impeller shaft.

A satisfactory flow pattern depends on the correct balance of these components.



**A: tangential - B: radial - C: axial**

#### Disadvantage of vortex formation

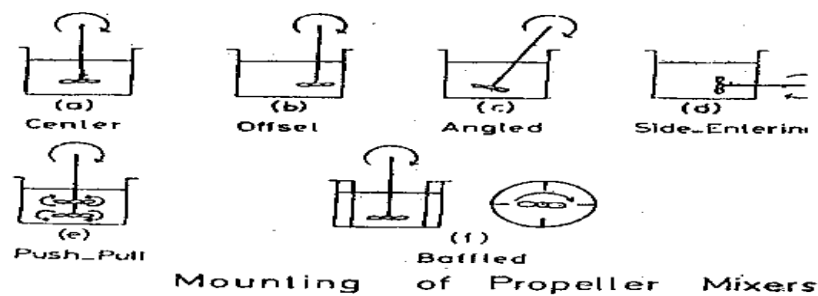
- No good mixing due to swirling of the liquid layers.
- Centrifugal force will throw the particles (suspension) towards the wall of tank then downward to the bottom of tank.
- Air enters into the material, which decompose readily oxidized substances. Air

foaming which affect accurate filling of tank.

### Suppressing of vortex

In general, tangential flow should be minimized by:

- Moving the impeller to an off-center position, thus destroying mixer symmetry (small tanks).
- Modifying the flow pattern with baffles (large tanks). Tanks with vertical agitators may be baffled by one, two, or more strips mounted vertically on, or just away from, the vessel wall.
- Impeller is mounted in the side of the tank (very large tanks).



## Equipment for Mixing of Miscible Liquids and Suspensions

### 1. Propeller mixers

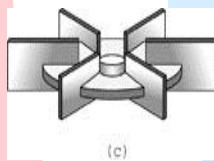
- Propellers are commonly used for mixing miscible and immiscible liquids of low viscosity and in suspension manufacturing. The marine propeller is typical of the group.
- High speed rotation provides high shear rates in the vicinity of the impeller
- Flow pattern with mainly axial and tangential components.
- In large-scale operations, horizontal mounting in the side of the vessel is frequently used.



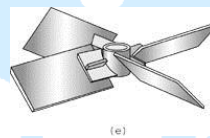
3-blade marine propeller Weedless Guarded stator ring

## 2. Turbines

- Turbines are effective mixers over a wide viscosity range
- Intermediate speed rotation.
- Pitched-blade turbines are sometimes used to increase axial flow.
- Baffles must be used to limit swirling unless the turbine is shrouded.
- The blades occupy 30-50% of diameter vessel



Disk turbine



Pitched-blade

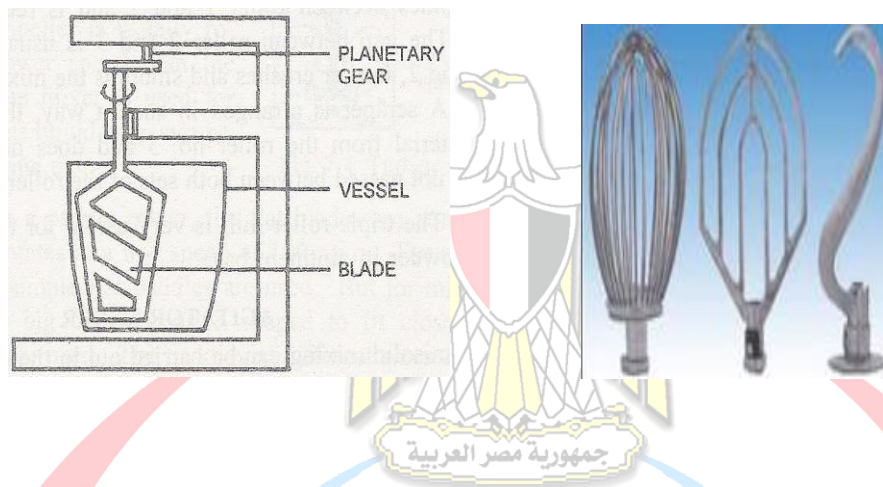
### Mixers for semi-solids

may be divided into:

- Agitator mixers: Planetary mixers
- Colloidal mill and triple roller mill

1. **Planetary mixers** are used for mixing and beating for viscous and pasty materials, the planetary mixer is still often used for basic operations of mixing and blending in pharmaceutical industry. Mechanism of mixing is shear. Shear is applied between moving blade and stationary wall. Mixing arm moves around its

own axis and around the central axis so that it reaches every spot of the vessel. Figure 5-a and b shows planetary mixer and its different blade attachment.



**Planetary mixer and different blade attachment**

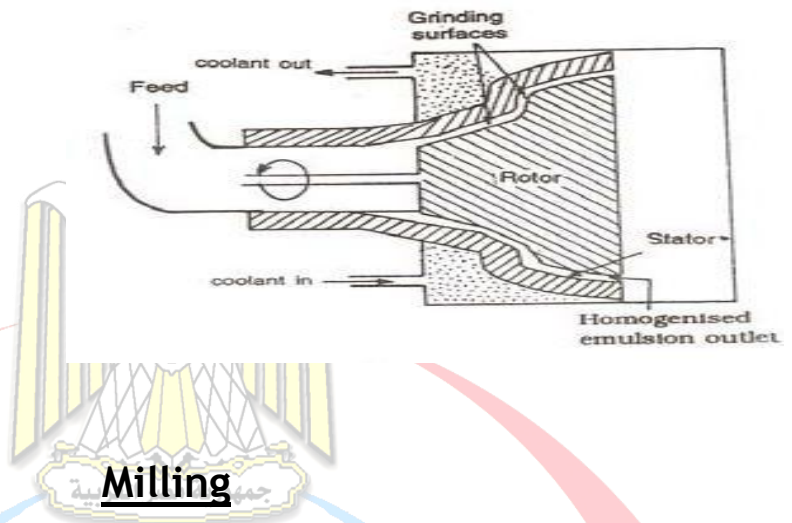
### Colloid Mill

- The colloid mill is useful for milling, dispersing, homogenizing and breaking down of agglomerates in the manufacture of pastes, emulsions ointment, cream, gels and high viscous fluids. The main function of the colloid mill is to ensure a breakdown of agglomerates or in the case of emulsions to produce droplets of fine size around 1 micron.
- The material to be processed is fed by gravity to the hopper or pumped so as to pass between the rotor and stator elements where it is subjected to high shearing and hydraulic forces. The faces of the rotor stator may be completely smooth or may be roughened by series concentric or radial corrugations in order to impart a mechanical shear action to the material. Material is discharged whereby it can be recirculated for a second pass.
- Rotational speed of the rotor varies from 3,000-20,000r.p.m. with the spacing between the rotor and stator capable of very fine adjustment varying from 0.001 inch to 0.125 inch depending on the size of the equipment.
- In these mills almost all the energy supplied is converted to heat and the shear forces can excessively increase the temperature of the product. Hence, most colloid mills are fitted with water jackets and it is also necessary to cool the

material before and after passing through the mill.

- The materials must be supplied at such a rate that the space between the rotor and stator is kept entirely filled with liquid.

### Two Stage Colloid Mill



### Definition

Size reduction is the process of reducing the particle size of a substance to a finer state of subdivision, to smaller pieces, to coarse particles or to powder. Size reduction process is also referred to as comminution and grinding. When the particle size of solids is reduced by mechanical means it is known as milling.

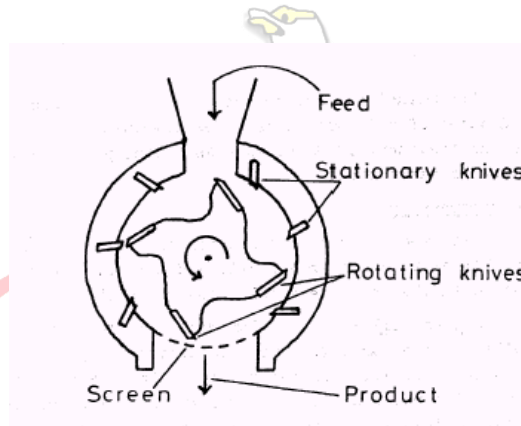
### Objectives

- Size reduction increases the surface area of drugs that help in rapid solution formation in the case of chemical substance.
- The extraction from animal glands such as liver and pancreas and from crude vegetable drugs is facilitated
- To increase the therapeutic effectiveness of certain drugs by reducing the particle size e.g., the dose of griseofulvin is reduced to half than that of originally required.
- The mixing of several solid ingredients is easier and more uniform if the ingredients are reduced to same particle size.
- The stability of emulsions is increased by decreasing the size of the oil globules.
- The physical appearance of ointments, pastes and creams can be improved by reducing its particle size.

**Machines for milling**

**Equipment based on the mechanism of Cutting**

**Cutter mill:** Cutting machinery is simple, consisting of rotating knives in various arrangements. The knives are kept sharp so that they cut rather than tear.



**Cutter mill**

**Equipments based on the mechanism of Attrition**

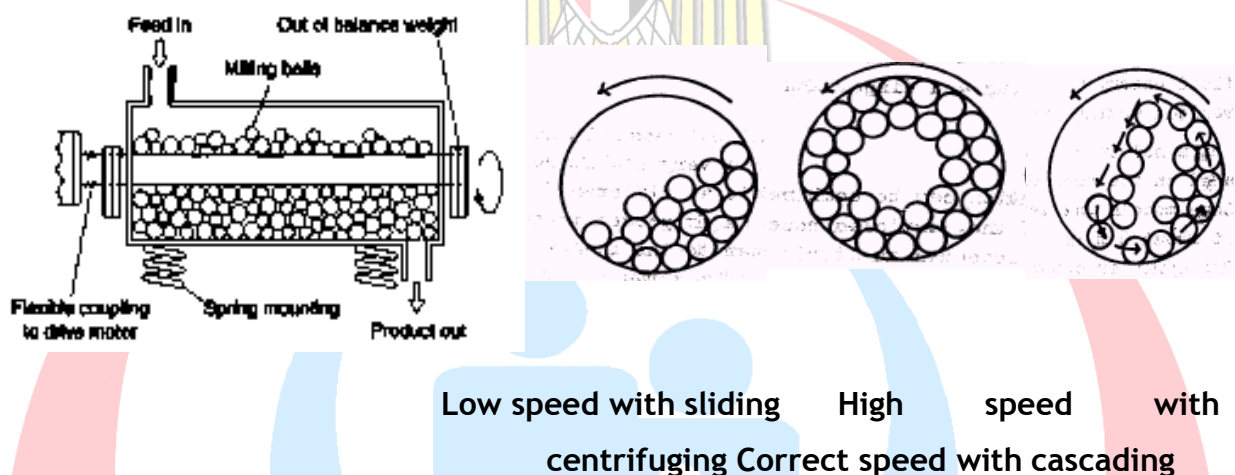
**Roller mills:** Two or three rolls, usually in metal or in porcelain, are mounted horizontally with a very small, but adjustable, gap in between (fig. 3). The rolls rotate at different speeds, so that the material is sheared as it passes through the gap and is transferred from the slower to the faster roll, from which it is removed by means of a scraper. : The roller mills are useful for the size reduction of solids in suspensions, pastes, or ointments.

**Equipment based on the Combined Impact and Attrition**



## Ball mill

Ball mill is cylindrical device that rotates around a horizontal axis, partially filled with the material to be ground plus the grinding medium (figure 4). Different materials are used for media, including ceramic balls, flint pebbles and stainless-steel balls. The shell is rotated at a speed which will cause the pellets to cascade, thus reducing particle sizes by impact. The optimum speed of rotation is about 75% of the critical speed, which is defined as the speed which causes the steel balls to centrifuge.



**Fig. 4- Ball mill with examples of operating speed**

Ball mills are very effective for grinding smooth, aqueous or oily dispersions by wet grinding since it will give particles of 10 microns or less. Input variables that affect product size; milling time, powder load, size and quantity of milling media, and rotation speed

### **Advantages:**

1. Ball mill can grind a wide variety of materials of differing character and of different degrees of hardness.
2. It can be used in a completely enclosed form, which makes it especially suitable for use with toxic materials.
3. It can produce very fine powders.

### **Disadvantages**

1. Wear occurs, principally from the balls, but partially from the casing and this may result in the product being contaminated, with abrasive materials this may exceed

2. Soft or sticky materials may cause problems by caking on the sides of the mill or by holding the balls in aggregates.

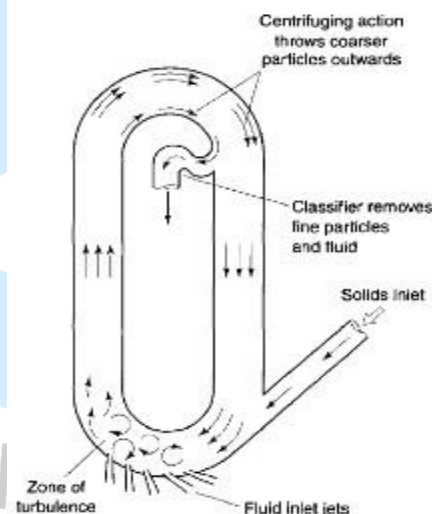
### Fluid energy mill

1. It consists of a loop of a pipe, which has a diameter of 20 to 200 mm, depending on the overall height of the loop which may be up to about 2 meters, a fluid, usually air, is injected at high pressure through nozzles at the bottom of the loop, giving rise to a high velocity circulation in a very turbulent condition, as shown in Fig.5.

Solids are introduced into the stream and, as a result of the high degree of turbulence, impact and attritional forces occur between the particles.

A classifier is incorporated in the system, so that particles are retained until sufficiently fine.

The feed to the mill needs to be pre-treated to reduce the particles size to the order of 100 mesh, enabling the process to yield a product as small as 5 micrometers or less.



**Fig. 5 - Fluid energy mill**

#### **Advantages:**

1. The particle size of the product is smaller than that produced by any other method of size reduction.
2. Expansion of gases at the nozzles leads to cooling, counteracting the usual frictional heat which can affect heat-sensitive materials.
3. Since the size reduction is by inter-particulate attrition there is little or no

abrasion of the mill and so virtually no contamination of the product.

4. For special cases with very sensitive materials it is possible to use inert gases.
5. Having a classifier as an integral part of the system permits close control of particle size and of particle size distribution.



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