PHARMACEUTICS II

صيدلانيات 2
محاضرة رقم 1
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INTRODUCTION

DEFINITIONS OF SOME PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS.

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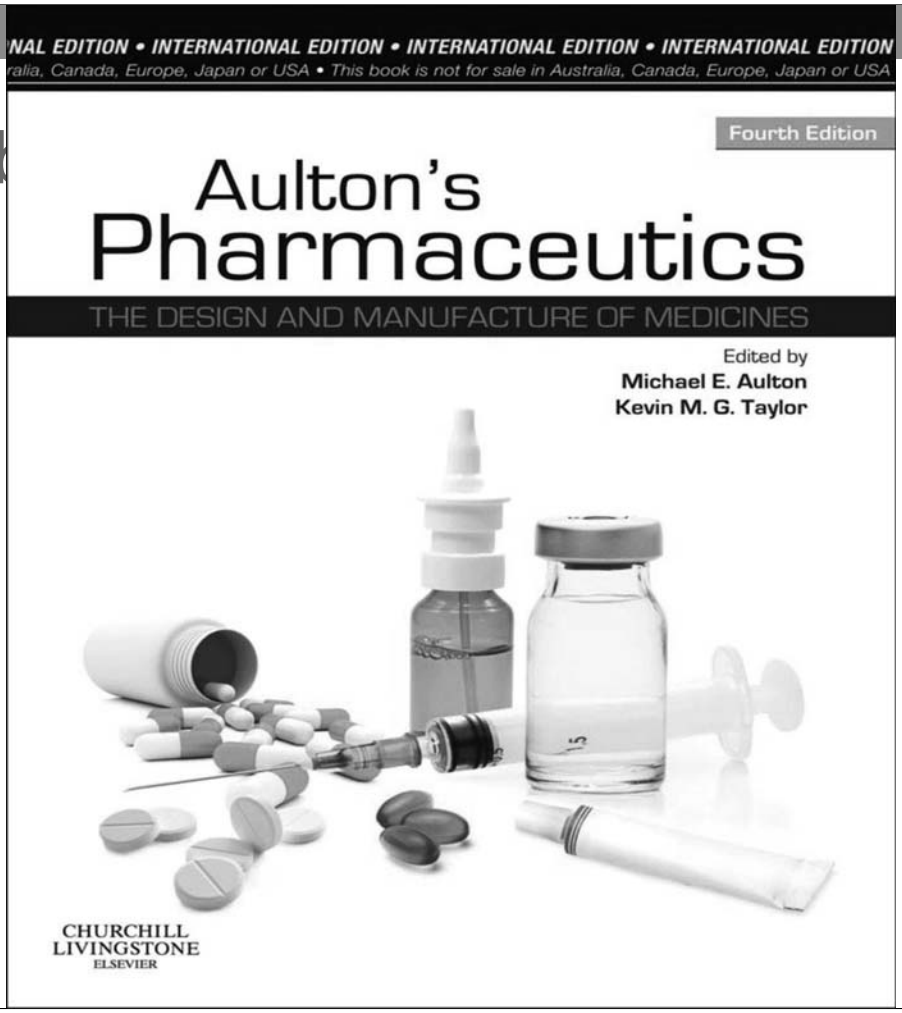
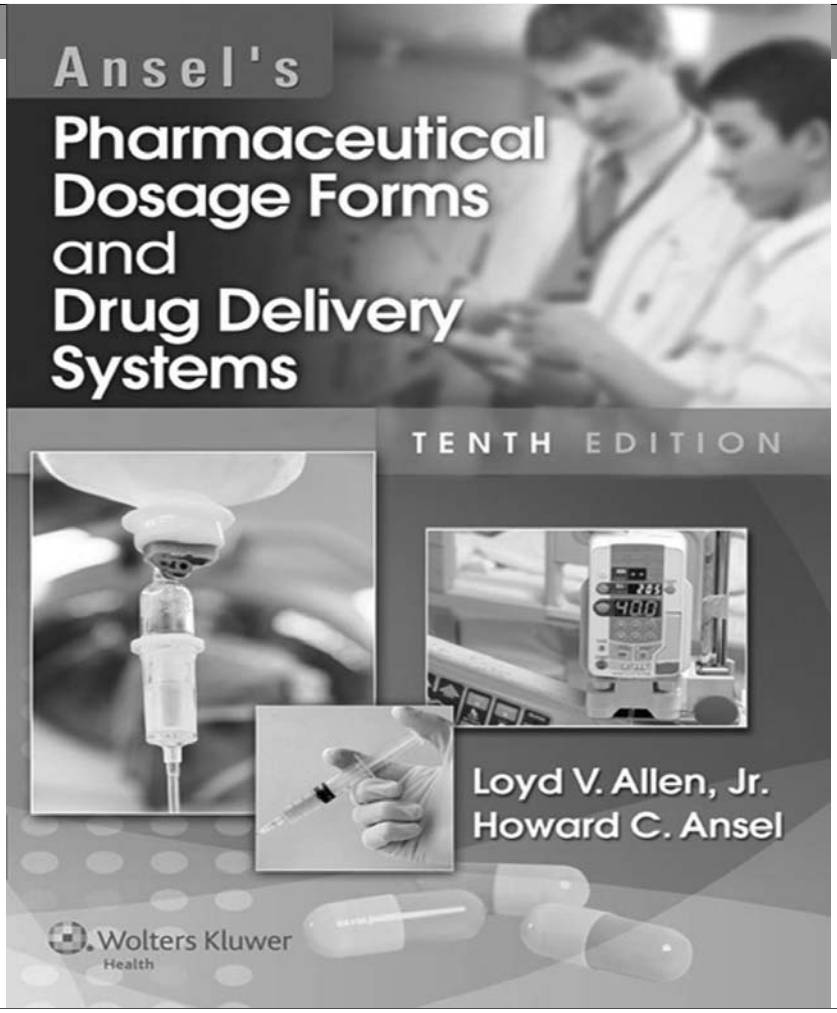
References and Textbooks

Textb





What is Pharmaceutics?

Pharmaceutics converts a drug into a medicine

- The word '**Pharmaceutics**': the stages that **FOLLOW** on from the **discovery** or **synthesis** of the drug, its isolation and purification, and testing for advantageous pharmacological effects and absence of serious toxicological problems.

What is drug?!!

- Pharmacologically active ingredient
- ‘Pharmacological agent’, ‘active principle’, ‘active ingredient’, or increasingly ‘active pharmaceutical ingredient (API)’, etc.

What is medicine?!!

- Medicines are drug-delivery systems.
- That is, they are a means of administering drugs to the body in a safe, efficient, accurate, reproducible and convenient manner.

Three major considerations in the design of dosage forms

1. The physicochemical properties of the drug itself.

2. Biopharmaceutical considerations, such as how the administration route of a dosage form affects the rate and extent of drug absorption into the body.

3. Therapeutic considerations of the disease state and patient to be treated.

Principles of dosage form design

- **The principal objective of dosage form design**

is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large-scale manufacture with reproducible product quality.

Table 1.1 Dosage forms available for different administration routes

Administration route	Dosage forms
Oral	Solutions, syrups, suspensions, emulsions, gels, powders, granules, capsules, tablets
Rectal	Suppositories, ointments, creams, powders, solutions
Topical	Ointments, creams, pastes, lotions, gels, solutions, topical aerosols, foams, transdermal patches
Parenteral	Injections (solution, suspension, emulsion forms), implants, irrigation and dialysis solutions
Respiratory	Aerosols (solution, suspension, emulsion, powder forms), inhalations, sprays, gases
Nasal	Solutions, inhalations
Eye	Solutions, ointments, creams
Ear	Solutions, suspensions, ointments, creams

Drug factors in dosage form design

Drug factors can have profound effects on the physiological availability and physical and chemical stability of the drug.

Examples:

1. Dissolution,
2. Crystal size
3. Polymorphic form
4. Solid-state stability
5. Particle size
6. Ionization state

Table 1.3 Properties of drug substances important in dosage form design and potential stresses occurring during processes, with range of manufacturing procedures

Properties	Processing stresses	Manufacturing procedures
Particle size, surface area	Pressure	Precipitation
Particle surface chemistry	Mechanical	Filtration
Solubility	Radiation	Emulsification
Dissolution	Exposure to liquids	Milling
Partition coefficient	Exposure to gases and liquid vapours	Mixing
Ionization constant	Temperature	Drying
Crystal properties, polymorphism		Granulation
Stability		Compaction
Organoleptic		Autoclaving
Molecular weight		Crystallization
		Handling
		Storage
		Transport

Dosage form design: Biopharmaceutical aspects

- Biopharmaceutics can be regarded as the study of the relationship between the physical, chemical and biological sciences applied to drugs, dosage forms and drug action.
- Understanding the principles of this subject is important in dosage form design, particularly with regard to drug absorption, as well as drug distribution, metabolism and excretion.`

Dosage form design: Biopharmaceutical aspects

- In general, a drug substance must be in solution before it can be absorbed via absorbing membranes and epithelia of the skin, gastrointestinal tract and lungs into body fluids.
- Drugs are absorbed in two general ways: by **passive diffusion** and by **carrier mediated transport mechanisms**.
- In passive diffusion, the process is driven by the concentration gradient existing across the cellular barrier.
- Lipid solubility and degree of ionization of the drug at the absorbing site influence the rate of diffusion.

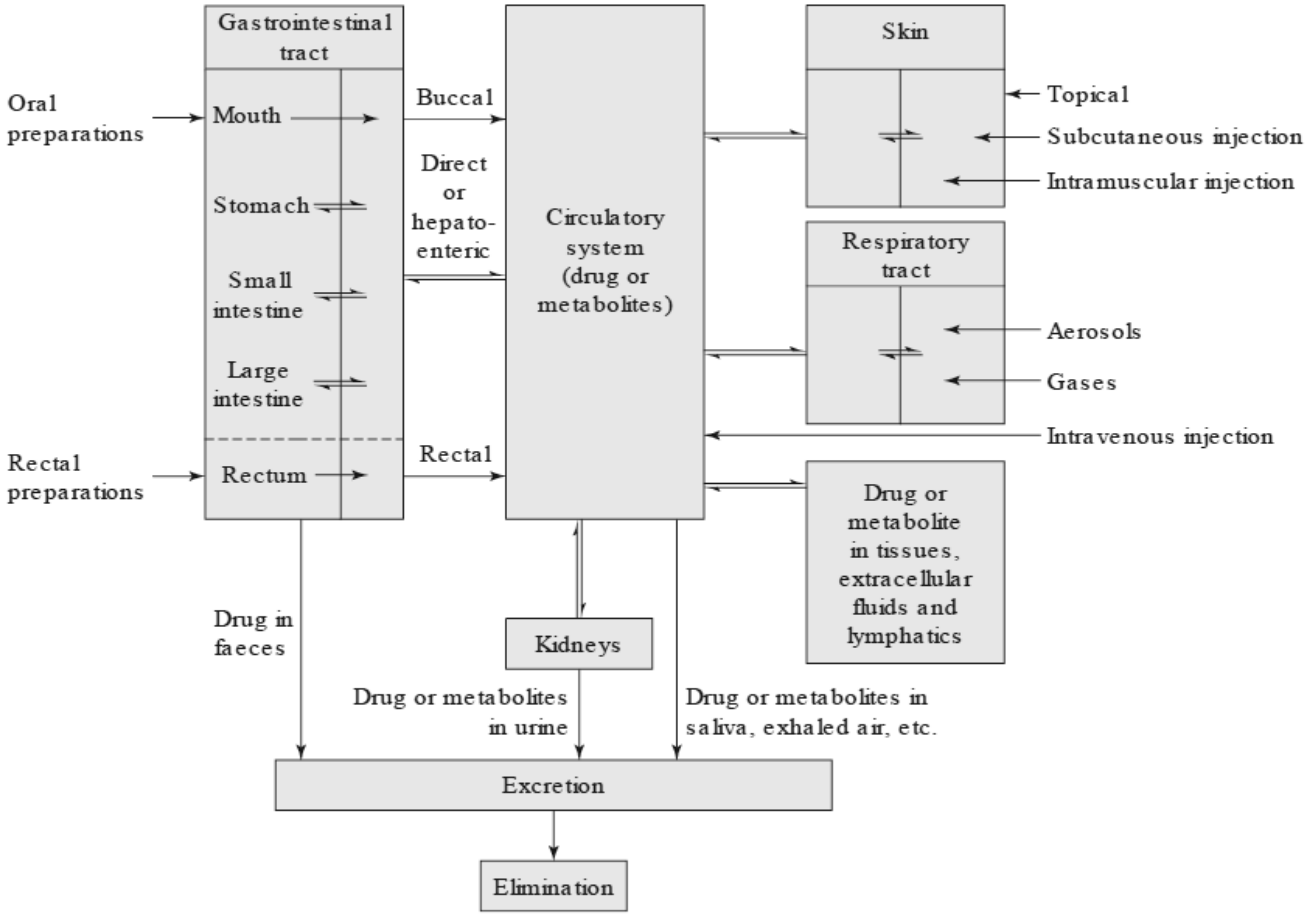


Table 1.2 Variation in time of onset of action for different dosage forms

Time of onset of action	Dosage forms
Seconds	Intravenous injections
Minutes	Intramuscular and subcutaneous injections, buccal tablets, aerosols, gases
Minutes to hours	Short-term depot injections, solutions, suspensions, powders, granules, capsules, tablets, modified-release tablets
Several hours	Enteric-coated formulations
Days to weeks	Depot injections, implants
Varies	Topical preparations

Therapeutic considerations in dosage form design

- Factors such as the need for systemic or local therapy, duration of action required, and whether the drug will be used in emergency situations, need to be considered.
- Chronic or acute condition.
- Patient age.

Routes of drug administration

1. **ORAL:**

- The oral route is the most frequently used route for drug administration.
- Oral dosage forms are intended usually for systemic effects resulting from drug absorption through the various epithelia and mucosa of the gastrointestinal tract.

ADVANTAGES:

1. Simplest,
2. Most convenient
3. Safest means of drug administration.

DISADVANTAGES:

1. Relatively slow onset of action,
2. Possibilities of irregular absorption
3. Destruction by the enzymes and secretions of the GI. INSULIN??
4. Absorption variations (Solubility, Gastric emptying time, pH)

The most popular oral dosage forms are tablets, capsules, suspensions, solutions and emulsions.

First pass effect:

- The first-pass effect (also known as first-pass metabolism or pre-systemic metabolism) is a phenomenon of drug metabolism whereby the concentration of a drug is **greatly** reduced before it reaches the systemic circulation.
- After a drug is swallowed, it is absorbed by the digestive system and enters the **hepatic portal system**. It is carried through the *portal vein* into the liver before it reaches the rest of the body.
- The liver metabolizes many drugs, sometimes to such an extent that only a small amount of active drug emerges from the liver to the rest of the circulatory system. This first pass through the liver thus greatly reduces the bioavailability of the drug.

What is new

J Pharm Pharmacol. 2016 Sep;68(9):1093-108. doi: 10.1111/jphp.12607. Epub 2016 Jun 30.

Oral delivery of insulin for treatment of diabetes: status quo, challenges and opportunities.

Wong CY[1], Martinez J[1], Dass CR[1,2].

Author information

Abstract

OBJECTIVES: Diabetes mellitus is characterised by progressive β-cell destruction and loss of function, or loss of ability of tissues to respond to insulin. Daily subcutaneous insulin injection is standard management for people with diabetes, although patient compliance is hard to achieve due to the inconvenience of injections, so other forms of delivery are being tested, including oral administration. This review summarises the developments in oral insulin administration.

METHODS: The PubMed database was consulted to compile this review comparing conventional subcutaneous injection of insulin to the desired oral delivery.

KEY FINDINGS: Oral administration of insulin has potential benefits in reducing pain and chances of skin infection, improving the portal levels of insulin and avoiding side effects such as hyperinsulinemia, weight gain and hypoglycaemia. Although oral delivery of insulin is an ideal administration route for patients with diabetes, several physiological barriers have to be overcome. An expected low oral bioavailability can be attributed to its high molecular weight, susceptibility to enzymatic proteolysis and low diffusion rate across the mucin barrier.

CONCLUSIONS: Strategies for increasing the bioavailability of oral insulin include the use of enzyme inhibitors, absorption enhancers, mucoadhesive polymers and chemical modification for endogenous receptor-mediated absorption. These may help significantly increase patient compliance and disease management.

KEYWORDS: diabetes; formulation; insulin; oral; tablet

2. Buccal Routes

- Drugs are absorbed from the buccal cavity.
- Can be used for a local action.
- Highly effective because:

1. The highly vascular nature of the tongue and buccal cavity.
2. The presence of saliva which can facilitate the dissolution of drug.

Two sites of absorption from the buccal cavity:

(i) **Sublingual** absorption:

- The area under the tongue is used.
- Fast onset of action.
- **Short duration** of action.

(ii) **Buccal** absorption

- Buccal (region between the upper lip and gum).
- Quick onset of action.
- **Longer duration** of action than sublingual route.
- Employed for drugs with a longer half-life for an extended duration of action

- **Advantages**

- Quick onset of action
- Drugs absorbed into systemic circulation *avoiding first pass metabolism.*
- Administered for unconscious patients.
- Suitable for antiemetic drugs because tablet is not swallowed.

3. Rectal Routes

- Drugs are formulated as liquids, solid or semisolid dosage forms.
- Effect could be either systemic or local.
- Rectum is supplied by three veins
- Rate of dissolution and drug release is low due to the small amount of fluid in the rectum (3 ml of mucus).

- **Advantages**

- When oral route is not suitable.
- Useful when the drug causes GI irritation
- Can be used for local action

- **Disadvantages**

- Irregular and unpredictable absorption implying a variable effect.
- Less convenient than oral route
- Low patient acceptability of this route

4. Vaginal Route

- Drugs are formulated as pessaries, tablets, capsules, solutions, sprays, creams ointments and foams.
- Used for local effect.
- Drugs won't be degraded by first pass effect thus a better bioavailability is expected than oral.

5. Inhalation Route

- Inhalation through nose or mouth.
- Effect is systemic or local.
- Used in the Rx. of respiratory conditions such as asthma.
- Drugs are delivered directly to the site of action (lungs).
- Drug dose required to produce a desired effect in inhalation is smaller than oral route thus minimising side effect.
- **Advantages**
- High blood flow to the lungs.
- Large surface area.
- Drug absorption is extremely rapid.

6. Nasal Route

- Drugs are formulated as solution (drops and sprays).
- Produce local effects.
- Used for systemic action because of its good vascular supply which avoids 1st pass metabolism.

7. Topical Route

- Skin is used as the site of administration.
- Used for local effects using liquids, powders, ointments, creams and pastes dosage forms.
- Avoid 1st pass effects.
- Produce zero-order kinetics over prolong time interval.

8. Parenteral Route

- Drugs are administered by injection.
- Intravenous route:
  - Drugs are injected directly into the systemic circulation.
  - Very fast onset of action.
- Subcutaneous route:
  - Drugs are injected into the subcutaneous layer of the skin
  - Easiest and least painful type of injection.
- Intramuscular route:
  - Drugs are injected into muscle layers.
  - When drug is formulated as an aqueous solution, it produces a fast onset of action.
  - When drug is formulated as a suspension or in an oily vehicle, it produces a slower and more prolonged action.

Respiratory route

- The lungs provide an excellent surface for absorption when the drug is delivered in gaseous, aerosol, mist or ultrafine solid particle form.
- For drug particles presented to the lungs as an aerosol, particle size largely determines the extent to which they penetrate the alveolar region.
- This delivery route is particularly useful for the direct treatment of asthmatic problems, using both powder aerosols and pressurized metered.
- Importantly, this delivery route is being increasingly recognized as a useful means of administering the therapeutic agents for systemic distribution and targeted delivery, such as peptides and proteins.

Dosage Forms

1. Aerosols
2. Capsule
3. Colloids
4. Creams
5. Dusting Powders
6. Ear drops
7. Elixirs
8. Emulsions
9. Enemas
10. Eye drops
11. Gargles
12. Gels
13. Granules
14. Implants
15. Inhalations
16. Injections
17. Insufflations
18. Irrigations
19. Linctuses
20. Liniments
21. Lotions
22. Lozenges
23. Mixtures
24. Mouthwash
25. Nasal drops and Sprays
26. Ointments
27. Paints
28. Pastes
29. Pastilles
30. Pessaries
31. Pills
32. Powders (oral)
33. Suppositories
34. Suspensions
35. Syrups
36. Tablets
37. Transdermal delivery systems

1. Aerosoles

- Pressurised packs that contain the drug in solution or suspension and a suitable propellant.
- Used for the local effect in the treatment of asthma.
- Metered valve with known dose of drug.
- Used for topical use in the treatment of muscle injuries.
- May contain agents such as non-steroidal anti-inflammatory drugs.

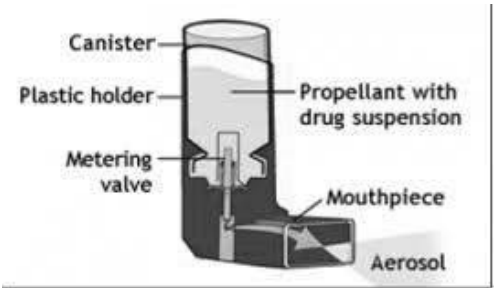


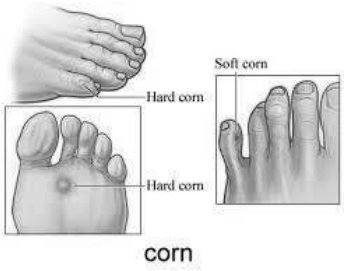
Fig. 7. General Formulation and Manufacturing components of Aerosols for metering valvesa [12]

2. Capsules

- Solid dosage forms for oral use.
- Drug is contained in a gelatin shell as a powder or a liquid.
- Modified-release preparations: drug is presented in the gelatin container as small pellets with different coatings.

3. Collodions

- Liquid preparations for external use.
- Liquid is painted on the skin forming a flexible film (nitrocellulose, ether, alcohol..).
- Contains substances such as salicylic acid used for the treatment of corns.



4. Creams

- Semi-solid emulsions for external use.
- Susceptible to microbial growth because of the water content.
- Contain a preservative or have short shelf life.
- Creams are easier to apply and less greasy than ointments.

5. Dusting Powders

- Finely divided powders for external use.
- Used as lubricant, disinfection and antisepsis.

6. Ear Drops

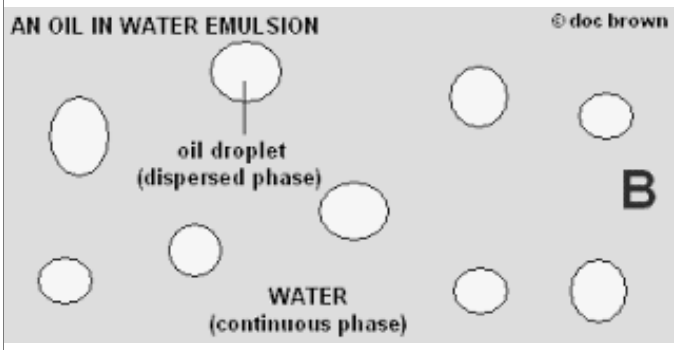
- Used topically to treat a variety of ear problems.
- Drugs are formulated in solutions and suspensions.
- Drops are inserted into the ear, using a dropper.

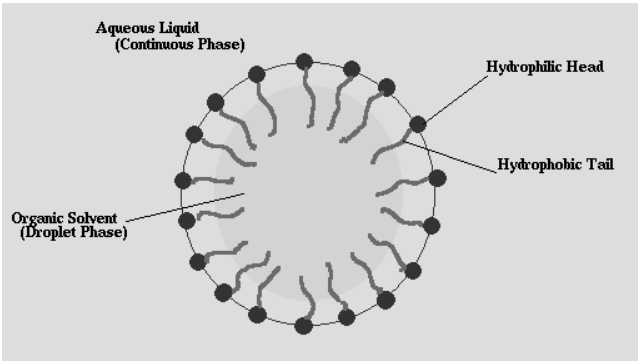
7. Elixirs

- Solution of one or more drugs for oral use.
- Contains high proportions of sucrose or sorbitol (for sugar-free preparation).
- The therapeutic actions: antihistamines, antibiotics, and decongestants.

8. Emulsions

- Mixtures of two immiscible liquids (oil in water).





9. Enemas

- An oily or aqueous solution administered rectally.
- Used to treat constipation or ulcerative colitis.
- Used in X-ray examination of the lower bowl and for systemic effects.

11. Gargles

- Aqueous solutions used to treat infections of throat.
- Present in concentrated form, with instructions to the patient for dilution.
- Should not be swallowed but held in the throat while exhaling through the liquid.
- It is recommended that patient spit out the gargle after a suitable time period (one minute).

12. Gels

- Semisolid dosage forms for topical or other local use.
- Usually transparent or translucent.
- Used as lubricants and for treatment or psoriasis and eczema.
- Non-greasy preparations.

13. Granules

- Describe a drug which is presented in smaller irregularly shaped particles.
- Packed in individual sachets containing a unit dose of medicament.
- May be provided in bulk where the dose is measured using a 5 ml spoon.
- Example: laxatives.

14. Implants

- Solid dosage forms which are inserted under the skin by a small surgical incision.
- |Used for hormone replacement therapy or as a contraceptives.
- Release of drug from implants is slow.
- Has a long-term therapy (three years in contraceptives).
- Must be sterile.

15. Inhalations

- Contain volatile medicaments which have a beneficial effect in upper respiratory tract disorders such as nasal congestions.
- Inhalations can be added to hot water and steam is then inhaled.
- Steam can damage the delicate mucus membranes of the upper respiratory tract.

17. Insufflations

- Drugs presented in a dry powder form inside a capsule.
- A capsule inserted into a specially designed device, where the capsule is broken, the contents released and inhaled by the patient.
- Used in the treatment of asthma.

18. Irrigation

- Sterile solutions used in the treatment of infected bladder.
- Examples:
  - Sterile solutions of 0.9% NaCl (physiological saline)
  - Antifungal drugs.

19. Linctuses

- A viscous liquid for oral use.
- The viscous nature of the preparation coats the throats and helps to alleviate the irritation.
- Linctuses should not be diluted prior to administration because the viscous nature is beneficial.

20. Liniments

- Liquids for external use.
- Used to alleviate (reduce or remove) the discomfort of muscle strains and injuries.
- Examples of active ingredients: turpentine oil and methyl salicylate.

21. Lotions

- Solutions, suspensions or emulsions for external use.
- Used as antiseptics, soothing and parasiticidal.

22. Lozenges

- Large tablets designed to be sucked and remain in the mouth for up to 15 minutes.
- Do not contain a disintegrant.
- Active ingredient is incorporated into a sugar base such sucrose and glucose.
- Used in the treatment of mouth and throat infections.

24. Mouthwashes

- Similar to gargles.
- Used specifically to treat conditions of the mouth.
- Active ingredients are antiseptics or bactericidal agents.

25. Nasal Drops and Sprays

- Isotonic solutions used to treat conditions of the nose.
- Nose drops: locally acting decongestants.
- Dropper device is used to deliver the appropriate dose into the affected nostril(s).
- Preparations for local and systemic use are presented as sprays (metered or pumps).

26. Ointments

- Seim-solids for topical use.

27. Paints

- Solutions for application to the skin or mucus membranes.
- Paints for skin use are formulated with a volatile vehicle (evaporates on application and leaves a film of active ingredient on the skin).
- Paints on the throat and mucus surfaces are viscous vehicles such as glycerol (remain in contact with the affected area).
- Used for antiseptic, analgesic, caustic or astringent.
- Supplied with a brush to assist application.

28. Pastes

- Semi-solids for external use.
- Contain a high proportion of fine powder such as starch.
- This makes pastes very stiff and not spread readily over the skin’s surface.

30. Pessaries

- Solid dosage forms for insertion into the vagina.
- Used for either local and systemic actions.

32. Powders (oral)

- Occur as both bulk and divided powders
- Bulk powders contain non-potent active ingredients such as antacids. |The dose is measured using a 5 ml spoon.
- Individual powders are used for more potent drugs, where accuracy of dosage is important.
- Individual dose is packed separately, either in a sheet of paper or in a sachet.

33. Suppositories

- Solid dosage forms for insertion into the rectum.
- Used for local and systemic actions.

34. Suspensions

- Liquid dose forms where the active ingredients is insoluble.
- Available for oral and external use.

35. Syrups

- Concentrated aqueous solutions of sugars such as sucrose.
- The term “syrup” is frequently-however-incorrectly. Applied to sweetened liquids intended for oral use.
- The term “syrup” should only be used to refer to flavoring vehicles.
- In order to reduce dental care; sucrose is being replaced by sorbitol.

36. Tablets

- Compressed solid dosage form for oral use.
- Different types of tablets: dispersible, enteric-coated, modified-release.
- Produce systemic effect.

37. Transdermal Delivery Systems

- Adhesive patches applied to the skin.
- Deliver a controlled dose of drug over a specified time period.
- Produce systemic effect.