Clinical Pharmacology and Drug Development

Properties of drugs, Drug dosage forms, Formulation development and Manufacture of drugs

Module 2 Topic 2

Properties of drugs

Physical properties of Drugs

- **Solubility and permeability**
  - Solubility of a drug is the first requirement for drug absorption in (G-I) mucosa
  - Poor permeability means poor absorption of a drug in G-I tract and poor distribution across body tissues
- **Physical state**
  - Order of absorption of a drug based on its physical state from fast to slow is as follows – solution → emulsion → suspension → capsules → tablets → enteric coated tablets → modified release tablets/capsules

Properties of drugs

Physical properties of Drugs (contd)

- **Polarity**
  - 'polar' (hydrophilic) state to be soluble in water
  - to get across a cell membrane, a drug should be 'non Polar' (lipophilic)
- **Particle size**
  - Smaller particle size means higher dissolution and faster absorption in G-I tract

Properties of drugs

Chemical properties of Drugs

- **Partition coefficient**
  - Low lipid solubility in G-I mucous membrane leads to poor absorption of the drug
- **Isomerism**
  - Many drugs are optically active , different actions based on the spatial arrangement of the molecule
  - Diastereomers - Dextrorotatory isomer Dextorphan is an antitussive providing relief from cough while Laevorotatory isomer Levorphanol is an analgesic
  - Enantiomers - R Naproxen is inactive while S Naproxen is an NSAID

Properties of drugs

Chemical properties of Drugs (contd)

- **Ionization**
  - Ionized drug has higher water solubility - a requirement for administration or distribution of drug in the body but low lipid solubility
  - Non-ionized drug has low polarity, high lipid solubility and high permeability
- **pH**
  - Chemically, most drugs are weak acids or weak bases
  - An acidic drug dissolves in a basic medium and a basic drug dissolves in an acidic medium
  - pH of different body fluids is as follows: plasma - 7.35 to 7.45, stomach - 1 to 3, small intestine - 7.5 to 8

Drug Formulations

Drug Formulations

Form designed for the convenience of administration

- **Oral Preparations**
- **Injectable (Parenteral) Preparations**
- **Local preparations**

Drug Formulations

Oral Preparations

- **Tablet**
  - Drug compressed into a solid dosage form
  - Different sizes and shapes
  - In some tablets, the active ingredient is released slowly to produce a prolonged ('**sustained**') effect

Drug Formulations

Oral Preparations (contd)

- **Capsule**
  - Cylinder-shaped gelatin shell that breaks open in the stomach releasing the drug
  - Slow- or sustained-release capsules contain small pellets that dissolve in the small intestine releasing the drug gradually

Drug Formulations

Oral Preparations (contd)

- **Liquids**
  - active ingredient is combined in a solution, suspension, or an emulsion with other substances like solvents, preservatives, and flavouring and/or colouring agents

Drug Formulations

Injectable (Parenteral) Preparations

- Sterile (germ-free) preparations of a drug dissolved or suspended in a liquid
- Usually given intramuscularly or intravenously; less commonly subcutaneous (below the skin), intradermal (within skin layers), intrathecal (into the spine) etc.

Drug Formulations

Local preparations

- **Topical Skin Preparations** – Cream/ Ointment/ Lotion
- **Eye Drops**
- **Ear Drops**
- **Nasal Drops**

Miscellaneous Preparations

- Suppositories & Pessaries - bullet-shaped dosage forms specially designed for easy insertion into the rectum (rectal suppository) or vagina (pessary)

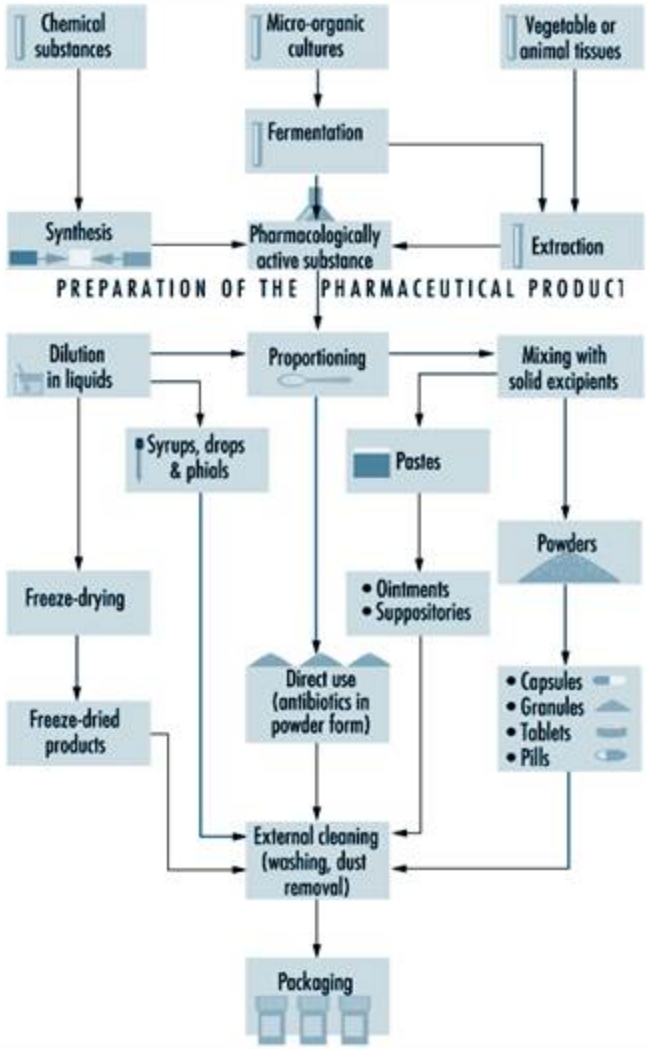
Manufacture of Drugs

Pharmaceutical ingredients e.g.

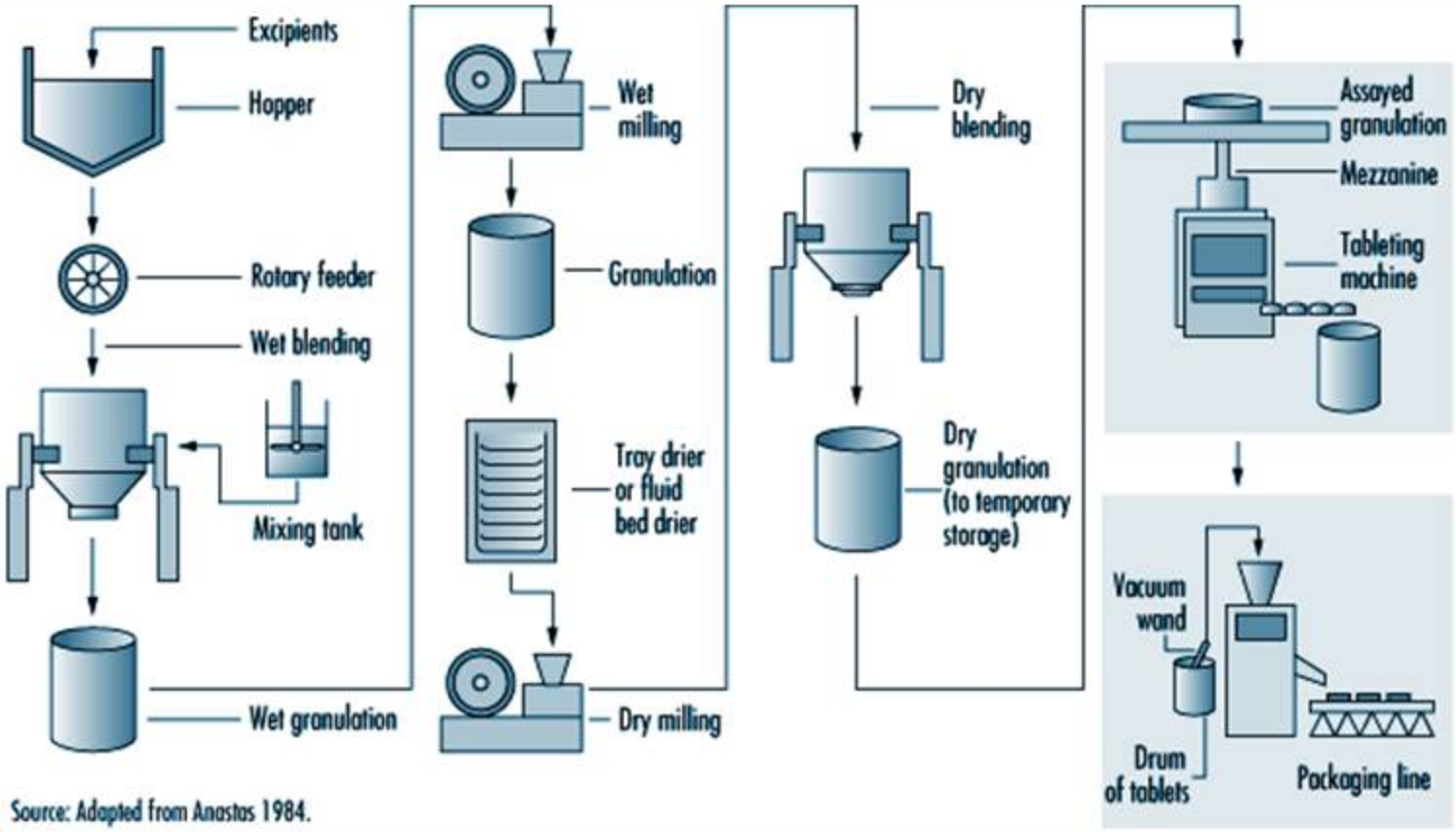
- Binders
- Fillers
- Flavouring and bulking agents
- Preservatives and antioxidants
- Colouring
- Diluting agents
- Emulsifiers and suspending agents
- Ointment bases
- Pharmaceutical solvents and excipients etc.

are mixed with active drug substances, providing the desired physical and pharmacological properties in the dosage form

Manufacture of Drugs



Manufacture of Drugs



Source: Adapted from Anastas 1984.

Typical oral tablet manufacturing process flow

Manufacture of Drugs

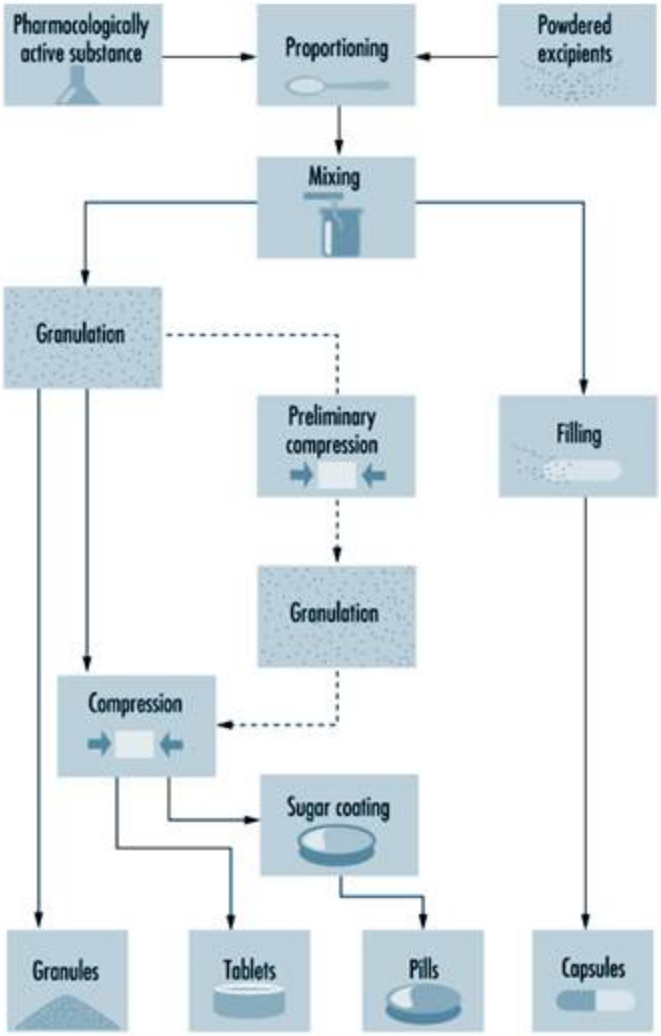
Tablets

Pharmaceutical blends may be compressed by

- Wet granulation,
- Direct compression or
- Slugging

to obtain the desired physical properties, before their formulation as a finished drug product

Manufacture of Drugs



Manufacture of Drugs

- **Wet granulation**
  - Active ingredients and excipients are wetted with aqueous or solvent solutions producing coarse granules that dried, mixed with lubricants (e.g., magnesium stearate), disintegrants or binders and then compressed into tablets

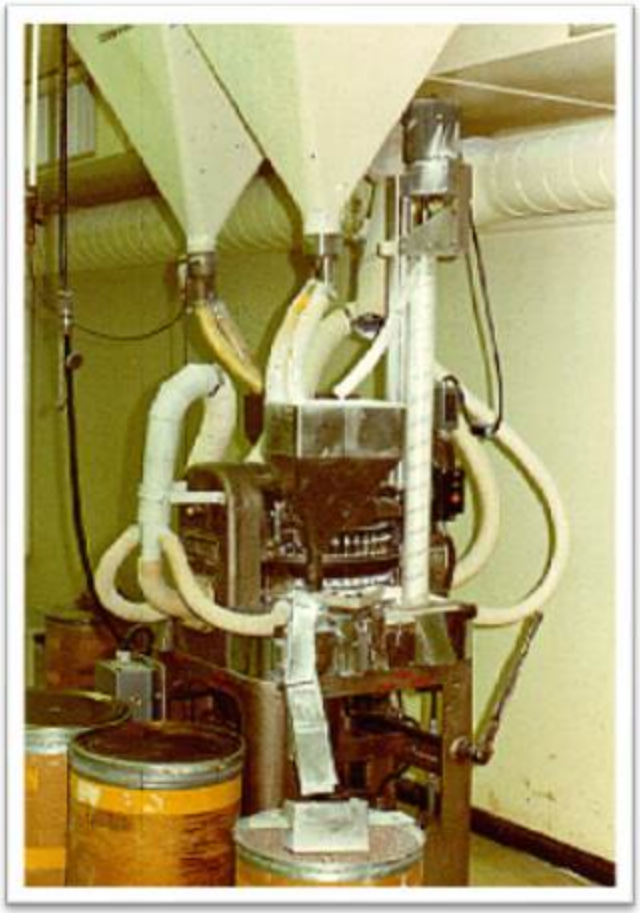
- **Direct compression**
  - A metal die holds a measured amount of the drug blend while a punch compresses the tablet.

Manufacture of Drugs

- **Slugging**
  - Drugs that are not sufficiently stable for wet granulation or cannot be directly compressed are slugged
  - Dry granulation blends and compresses relatively large tablets which are ground and screened to a desired mesh size, then recompressed into the final tablet

Tablets are packaged by sealing them between layers of aluminium foil and plastic film (blister-packaging) or they are bottled

Manufacture of Drugs



Tablet press with load hopper

Manufacture of Drugs

Capsules

- Blended and granulated materials may also be produced in capsule form
- Hard gelatin capsules are dried, trimmed, filled and joined on capsule-filling machines.

Liquids

- May be produced as
  - sterile solutions for injection into the body or
  - administration to the eyes;
  - liquids, suspensions and syrups for oral ingestion;
  - tinctures for application on the skin

Manufacture of Drugs

Parenteral liquids to be injected by intradermal, intramuscular or intravenous administration into the body and solutions to be administered to the eyes (ophthalmic) are sterilized by dry or moist heat under high pressure with bacteria-retaining filters

Manufacture of Drugs

Oral liquids are prepared by mixing the active drug substances with a solvent or preservative to inhibit fungal and bacterial growth.

- Liquid suspensions and emulsions are produced by colloid mills and homogenizers, respectively.

Manufacture of Drugs

Creams and ointments are prepared by blending or compounding active ingredients with petrolatum, heavy greases or emollients before packaging in metal or plastic tubes.