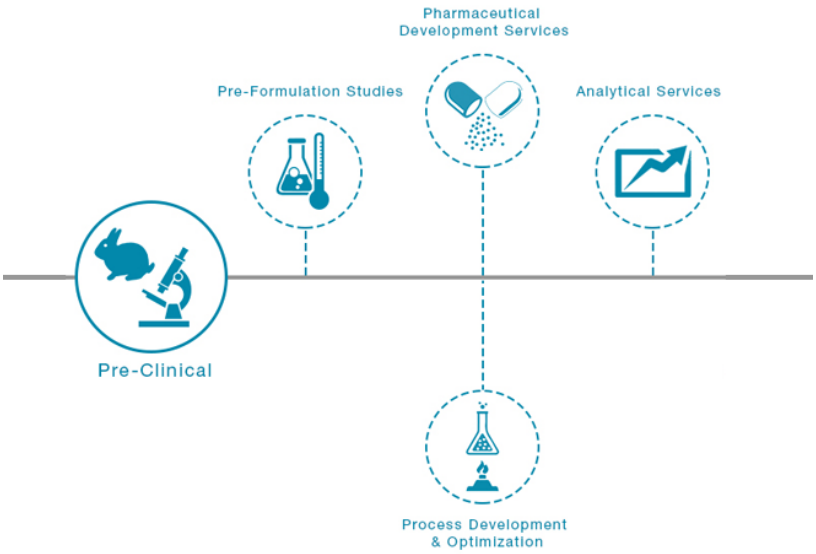
PH.D PHARMACEUTICS
PCEU-805: BIOPHARMACEUTICAL

DRUG MANUFACTURING PROCESS.

1. Drug Manufacturing process

Drug manufacturing is the process of industrial scale synthesis of pharmaceutical drugs by pharmaceutical companies.

The process of drug manufacturing can be broken down into a series of unit operations, such as dosage form design, pre-formulation, formulation, pilot scale manufacturing and Industrial scale.



The manufacturing to biopharmaceuticals is the most highly regulated and rigorously controlled processes.

1.1 Factors affecting the Manufacturing of drugs

- Design and layout of the manufacturing facility
- Raw materials utilized in the manufacturing process

- Manufacturing process itself
- Training and commitment of personnel involved in all aspects of the manufacturing operation
- Existence of a regulatory framework which assures the establishment and maintenance of the highest quality standards regarding all aspects of manufacturing.

1.2 Overview of Manufacturing process

1. Key elements - Clean room, Equipment, Personnel, Water, Documentation (Product standards, protocols, guidelines)
2. Infrastructure of a typical manufacturing facility and some relevant operational issues
3. Source of biopharmaceuticals
4. Up-stream and down-stream processing of biopharmaceutical products
5. Analysis of the final products: Quality control

2. Dosage form

Dosage forms (also called unit doses) are pharmaceutical drug products in the form in which they are marketed for use, with a specific mixture of active ingredients and inactive components (excipients), in a particular configuration (such as a capsule shell) and apportioned into a particular dose.

2.1 Types of Dosage Forms

1. Through Oral route

- Powder
- Tablet-buccal, sub lingual, orally disintegrating, modified release.
- Capsule-Hard gelatin and soft gels
- Liquids

2. Topical-applied over the skin surface and mucosa

- Cream, gel, liniment or emulsions, lotion, or ointment, etc.
- Ear drops (Otic), Eye drops (ophthalmic)
- Skin patch (transdermal)
- Vaginal rings

3. Parenteral

- IV, ID, IM, IT, SC etc.

4. Inhalational

- Instilled through the nasal and pulmonary route e.g. aerosol, inhale, nebulizer

5. Instilled in the body cavities

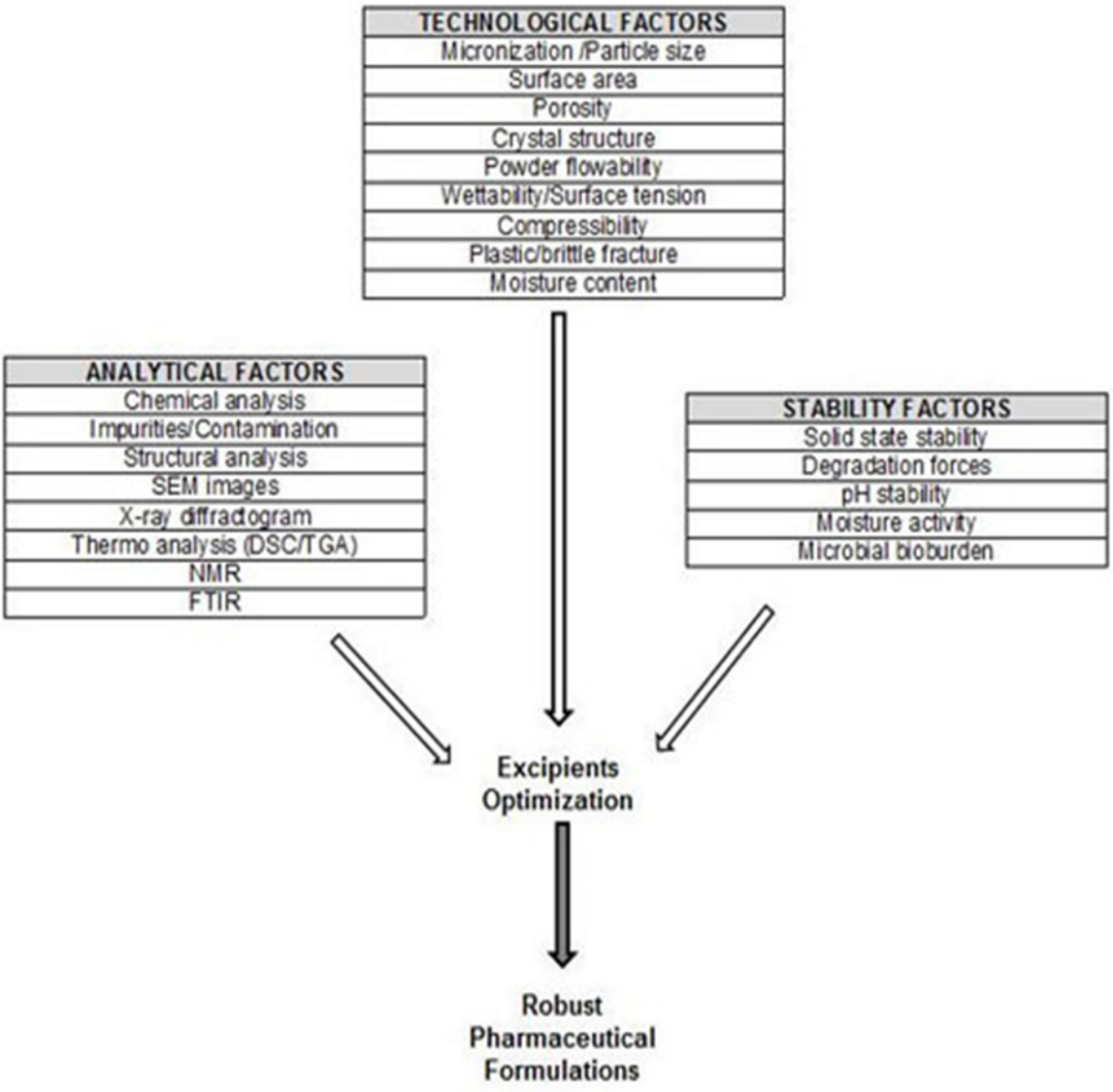
- Suppository, douche, pessary etc.

3. Major Considerations in Dosage Form Design

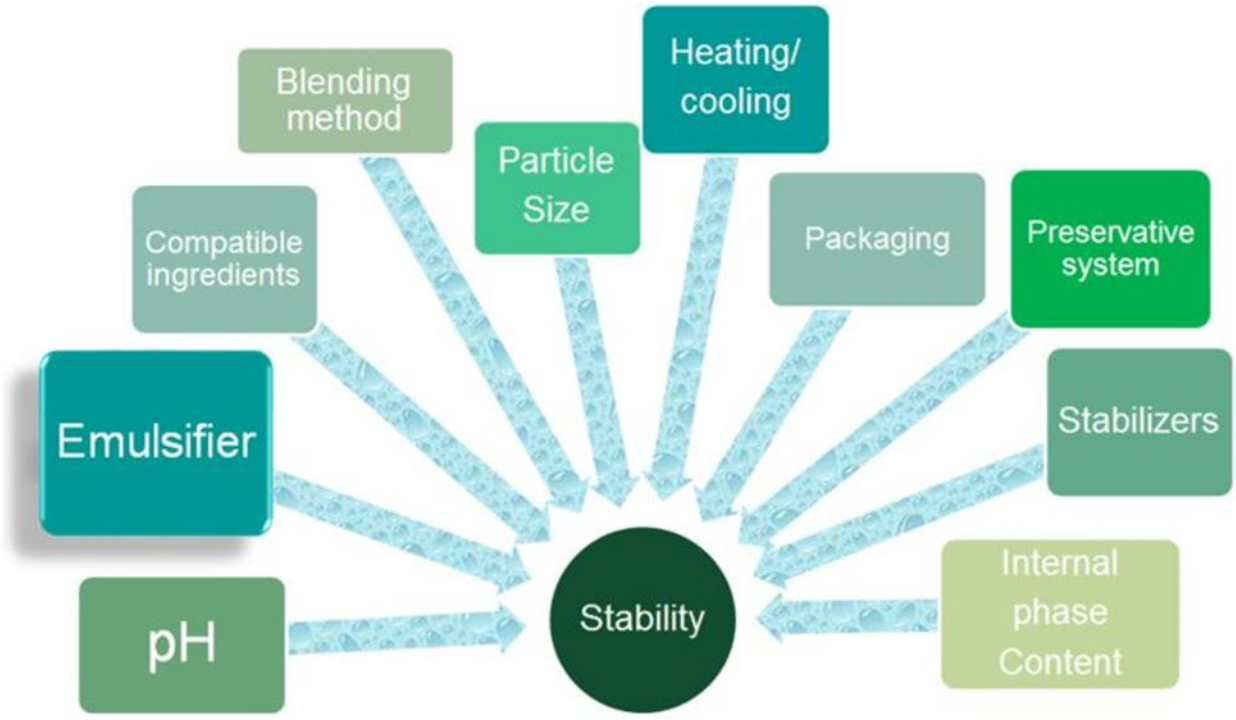
These should be considered before designing a dosage form:

- The physicochemical considerations
- The biochemical considerations
- Determination of the desired product type and establishment of a framework for product development
- Then, various initial formulations of the product are developed and examined for desired features (e.g., drug release profile, bioavailability, clinical effectiveness etc.)
- The formulation that best meets the goals for the product is selected as “Master formula”.

3.1 Considerations in Design of Tablets:



3.2 Considerations in Design of Emulsions

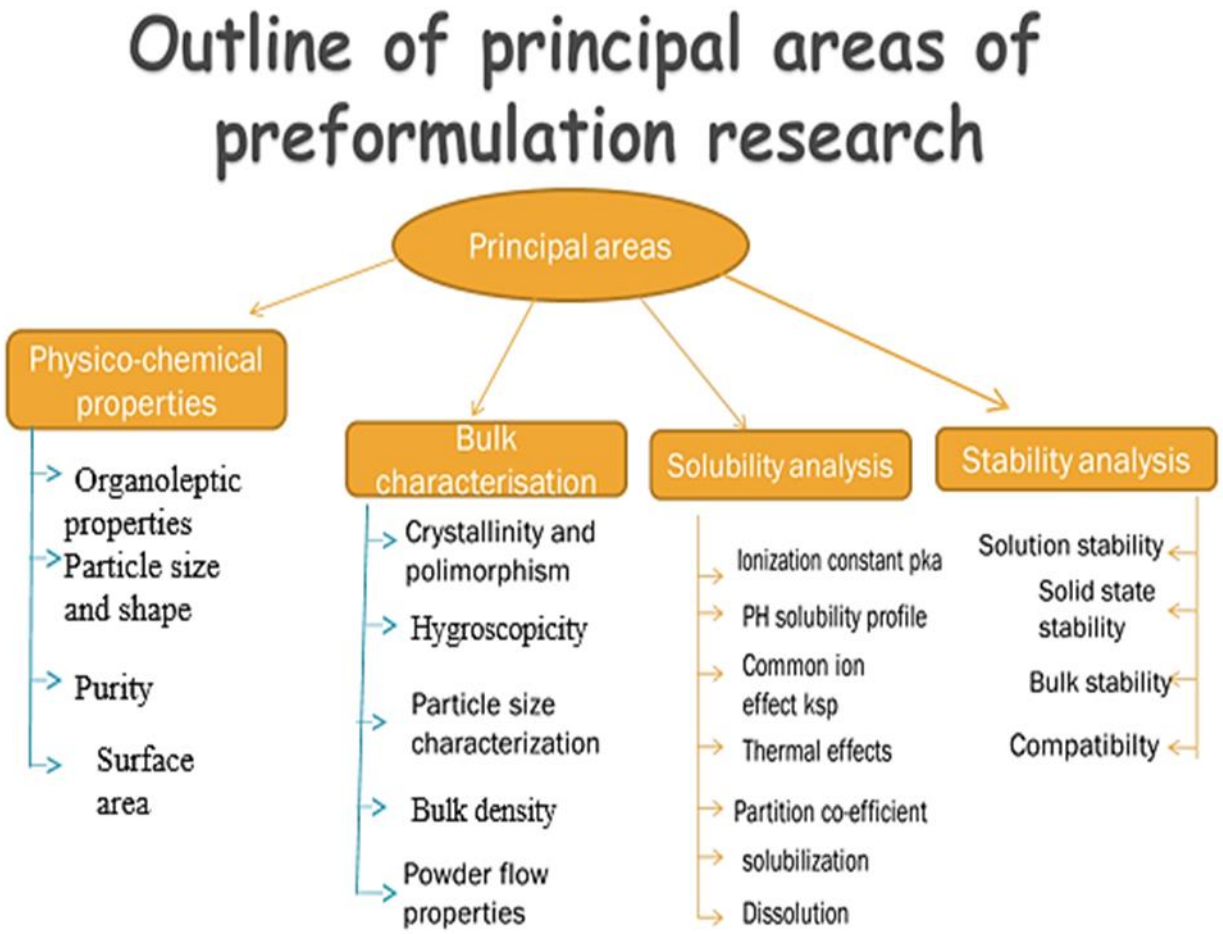


4. Pre-Formulation Studies

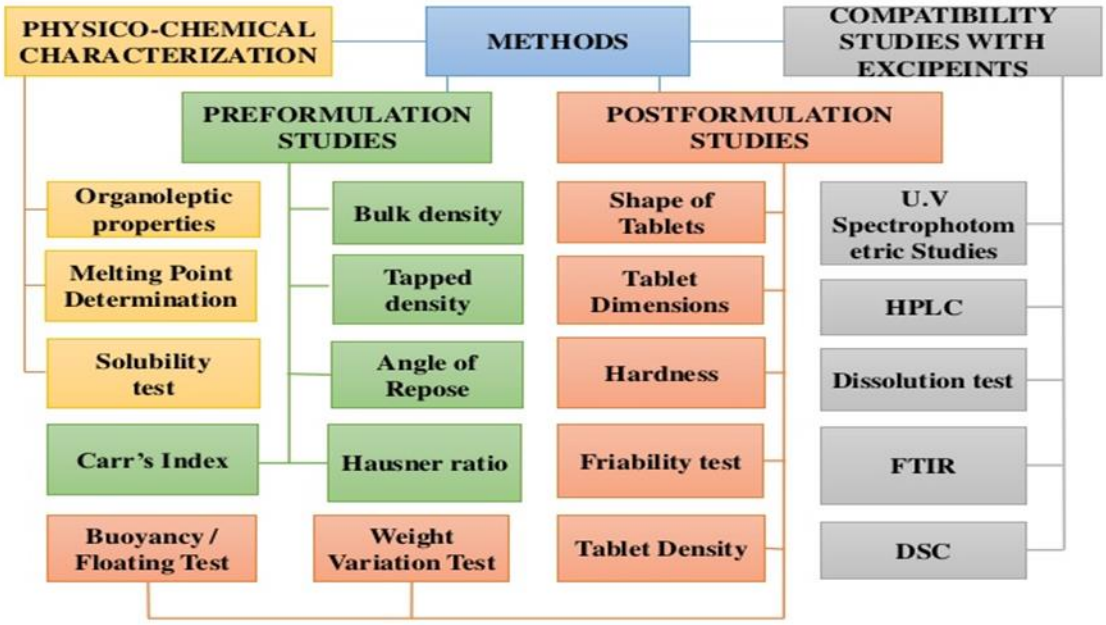
Pre-formulation studies are the investigation of physical and chemical properties of the API/ drug molecule alone or in combination with the excipients that are to be added to the final dosage form.

Goals

- To establish the physico-chemical parameters of new drug substance.
- To establish the physical characteristics
- To establish the kinetic rate profile.
- To establish the compatibility with the common excipient.
- To choose the correct form of a drug substance.



4.1 Pre-formulation Studies of Tablets:



EXAMPLE: Pre-Formulation Study of Domperidone Tablets

S. No.	API Characterization	Results
1.	Physical Appearance	Domperidone is a white powder
2.	Melting point	242 °C
3.	Solubility	It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.
4.	Bulk density	1.11 gm/ml
5.	Tapped Density	1.42 gm/ml
6.	Carr's index/Compressibility Index	27.92
7.	Hausner's Ratio	1.27

- Bulk density the mass of many particles divided by the total volume they occupy
- Carrs Index is the indication of compressibility of powder
- Husner ratio is the flowability of powder or granular material if 1.25 or more then poor followability
- Tapped density is Mass by final volume of powder

4.2 Pre-Formulation Studies of Injectable

It is study about physical & chemical properties of drug substance prior to formulation is called as preformulation. They are

- pH
- Solubility
- pKa Dissociation constant
- Compatibility studies
- FTIR / DSC
- Oxidation & reduction
- Particle size

4.3 Pre-Formulation Studies of Emulsions

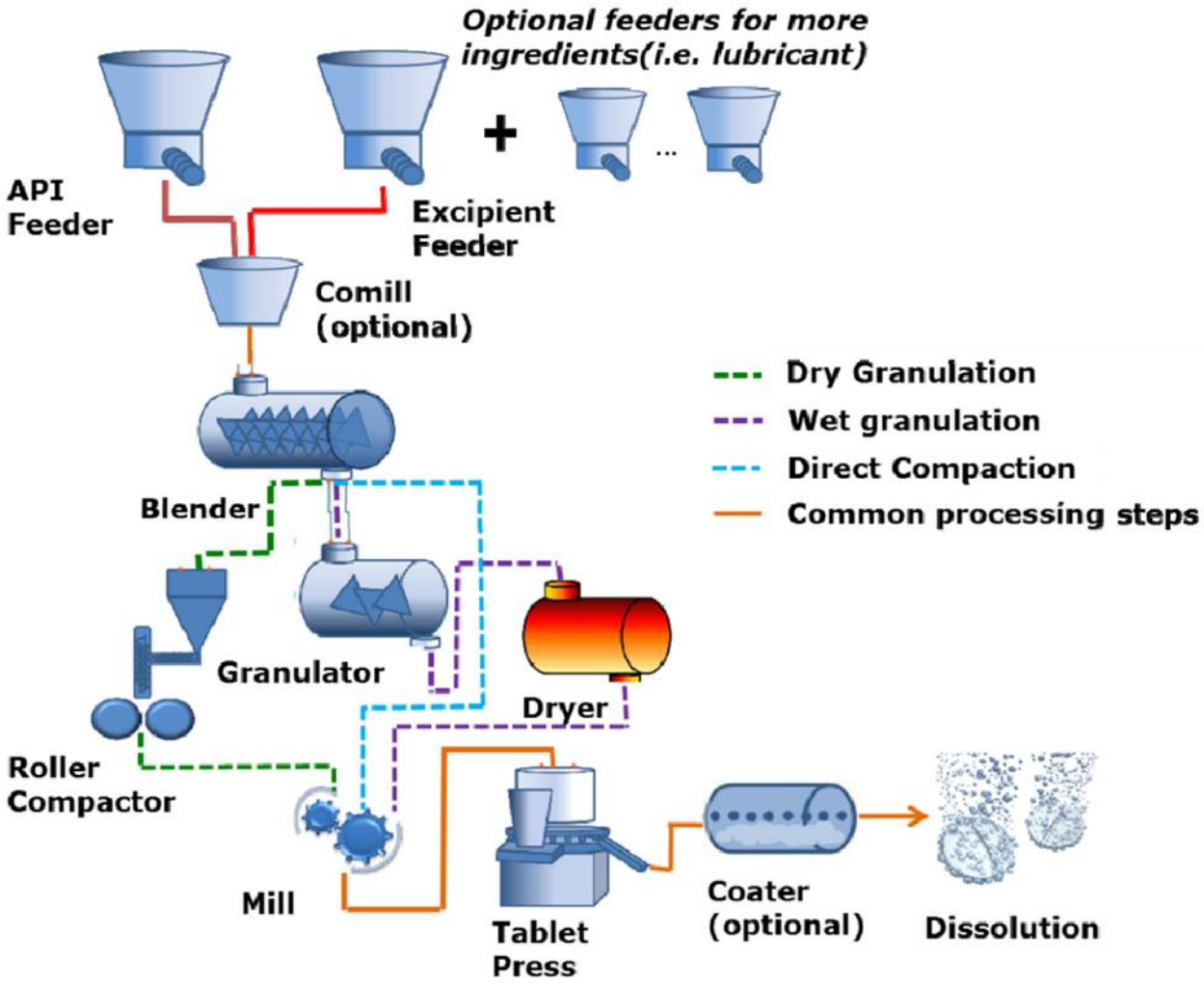
- Solubility
    - Aqueous Solubility
    - Intrinsic Solubility
- pKa from solubility data
- Solvents
- Partition Coefficient
- Stability Studies
    - Coalescence
    - Creaming

5. Manufacturing of Tablets

The design and manufacture of pharmaceutical tablets is a complex multi-stage process whereby formulation scientists ensure that the correct amount of drug substance in the right form is delivered at the appropriate time, at the proper rate and in the desired location with its chemical integrity protected to that point. Most drug substances do not possess the required properties which give satisfactory flow from the hopper to the die cavity of tablet presses. As a result, they are subjected to pre-treatment either alone or in combination with suitable excipients to form free-flowing granules that lend themselves to tableting.

Tablets are commonly manufactured by wet granulation, dry granulation or direct compression. These methods may be considered to consist of a series of steps (unit processes) – weighing, milling, mixing, granulation, drying, compaction, (frequently) coating and packaging. Regardless of the method used the unit processes – weighing, milling and mixing, are the same; subsequent steps differ.

Overview of drug manufacturing is shown in given figure;



5.1 Primary goals of tablet manufacturing process:

The primary goals include:

1. To formulate tablets that are strong and hard to withstand mechanical shock encountered during manufacturing, packing, shipping, dispensing and use.
2. To formulate tablets that are uniform in weight and in drug content.
3. To formulate tablets that are bioavailable according to indication requirements.
4. To formulate tablets that are chemically and physically stable over a long period of time.

5. To formulate tablets that have elegant product identity which is free from any tablet defects.

5.2 Requirements during tablet manufacturing process:

a) Choice of process:

In general, the choice of formulation process employed during tablet manufacture is dependent upon such factors as:

1. Compression properties of the Active Pharmaceutical Ingredient (API)/ drug substance.
2. Physical and chemical stability of the API during the manufacturing process.
3. Particle size of the formulation ingredients.
4. Availability of the necessary processing equipment.
5. Cost of the manufacturing/formulation process.

b) Personnel requirements during tablets manufacturing:

- Production pharmacists/ supervisors
- Manufacturing chemist
- Analytical chemist
- Quality assurance manager
- Machine operators
- Mechanics

In addition to the job-specific responsibilities of these personnel, all manufacturing employees must be versed and trained in Current Good Manufacturing Practices (CGMPs) and in the appropriate Standard Operating Procedures (SOPs) governing their area.

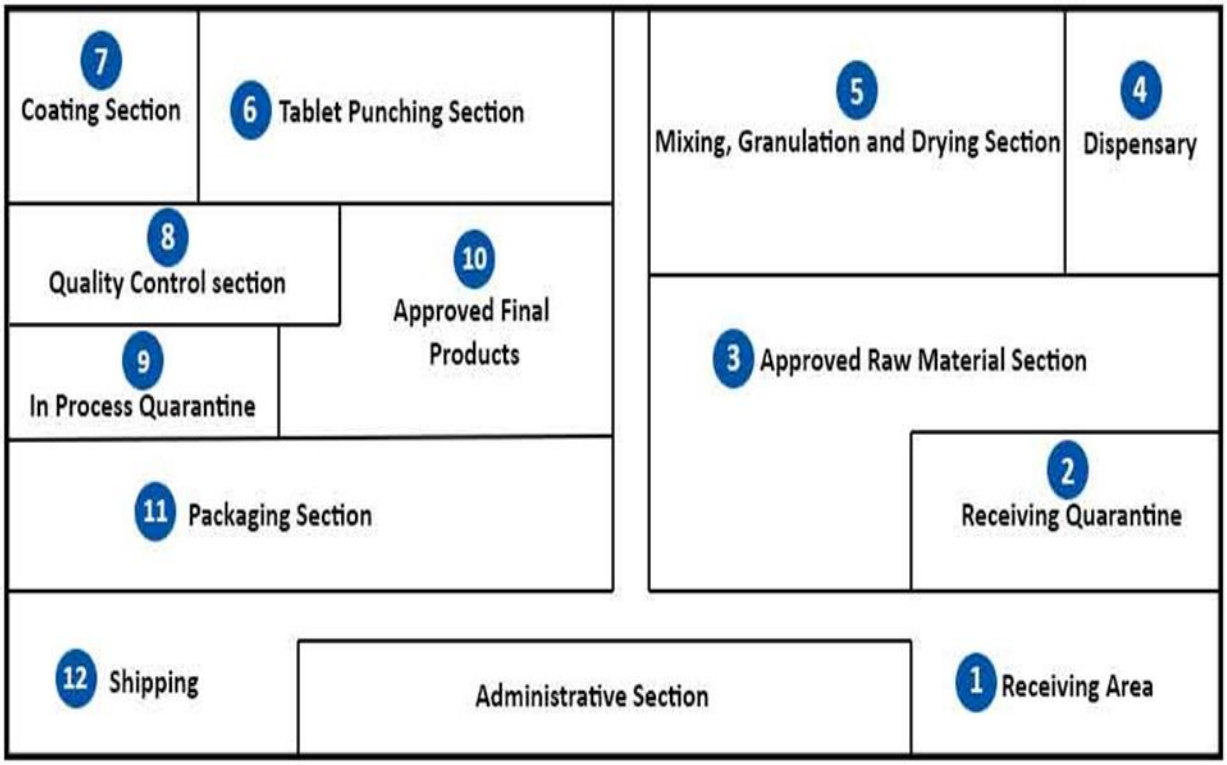
c) Area for manufacturing of tablets:

- Raw material warehouse
    - Receiving quarantine

- Approved raw material section

- Dispensary
- Production room
    - Mixing, Granulation and Drying Section
    - Tablet Punching Section
    - Coating Section
- Quality control section
- Packaging Section.

5.3 Layout of tablet manufacturing section:



5.4 Excipients used in tablet formulation:

Tablets in addition to the therapeutic agent(s) also contain excipients that are required to ensure satisfactory production process. These materials which are inert may be added to the drug substance to increase its bulk and give those desirable properties lacking in the drug substance alone. Depending on the intended use, tablet excipients may be subcategorized into:

- Those that help to impart satisfactory processing and compression properties to the formulation and
- Those that help to give additional desirable physical characteristics to the compressed tablet.

Excipient/concentration in formula	Use
Ethylcellulose	
1–3%	Wet or dry binder
1–3%	Controlled-release coating
Glyceryl palmitostearate	
0–5%	Lubricant
10–50%	Controlled-release excipient
Hydroxypropylmethyl cellulose (HPMC), low viscosity	
2–5%	Wet or dry binder
2–10%	Film former
5–25%	Controlled-release excipient
Magnesium aluminum silicate	
2–10%	Binder
2–10%	Disintegrant
Microcrystalline cellulose (MCC)	
0–8%	Improve adhesion of film coat to core
0.2–0.5%	Glidant
5–20%	Antiadherant
5–20%	Disintegrant
5–95%	Binder/filler
Polyethylene glycol	
0–10%	Lubricant
0–15%	Thermoplastic filler/binder
5–40%	Controlled-release excipient
Poly(methacrylates)	
2–10%	Film former
5–20%	Controlled-release excipient
10–50%	Filler
5–10%	Coating excipient
Poly(vinyl pyrrolidone) (Povidone, PVP)	
5–15%	Wet binder
5–10%	Coating excipient
5–30%	Disintegrant
10–35%	Controlled-release excipient
Starch	
3–15%	Intragranular binder/disintegrant
5–25%	Wet binder
5–20%	Disintegrant

Adapted from Modern Pharmaceutics 4th ed. (p. 499), by M. Kottke and E. Rudnic, 2002, New York: Marcel Dekker Inc.

5.5 Tablet manufacturing equipment/ Machines:

Common equipment used in pharmaceutical tablet manufacturing include:

1. **Size reduction equipment/ communition equipment** e.g., hammer mill, vibration mill, roller mill, pin mill, fluidized energy mill, end-runner mill, edge-runner mill, cutter mill and ball mill.
2. **Weighing balance/ balances** e.g., bulk weighing balance (weighs in kilogram), electronic weighing balance (weighs in grams and milligrams).
3. **Mixing equipment** e.g., pneumatic mixers (air-mix mixer or air-driven mixer), diffusion/ tumbling mixers (e.g., V-blender, double cone blender, cubic mixer, drum blender),

convective mixers (e.g., ribbon blenders, orbiting screw mixers, horizontal high-intensity blenders, planetary blenders, diffusion mixer with intensifier bar/agitator, Forberg blenders, horizontal double arm mixers, vertical high-intensity mixer).

4. **Granulators** e.g., rotating shape granulators, mechanical agitator granulators (e.g., ribbon or paddle blender, sigma blade mixer, planetary mixer, orbiting screw mixers), high-shear granulator, fluidized bed granulator, dry granulator etc.
5. **Dying equipment** e.g., spray dryer, rotary dryer, fluidized bed dryer etc.
6. **Tableting machine** – single punch tablet press and multi-station/ rotary tablet press (e.g., High-speed rotary tablet machines and multi-layer rotary tablet machines).
7. **Quality control equipment** e.g., disintegration equipment (Manesty single unit disintegrating apparatus or Erweka multiple unit disintegrating apparatus), USP Dissolution Tester, Tablet Hardness Tester, Tablet Thickness Tester, Tablet Friability Testers etc.
8. **Coating and polishing machines for coated tablets** e.g., standard coating pan, perforated pan, fluidized bed/ Air suspension coating system etc.
9. **Packaging machines** e.g., blister packaging machines, strip packing machine, aluminium foil packaging machine, etc.

Tablet Manufacturing Equipment continues to improve in both production speed and uniformity of the tablets compressed.

5.6 Steps involved in Tablet formulation:

1. **Dispensing:** Each ingredient in the tablet formula is weighed and accurately dispensed as per dose. This is one of the critical steps in any type of formulation process and should be done under technical supervision.

2. **Sizing:** Formulation ingredients must be in finely divided form, otherwise, size reduction should be carried out for better flow property and easy mixing.

3. **Powder blending:** Powders are mixed using a suitable blender to obtain a uniform and homogeneous powder mix. The drug substance and excipients are mixed in geometric dilution.

4. **Granulation:** Here small powder particles are gathered together into layers, and permanent aggregates to render them into free-flowing states.

5. **Drying and dry screening:** Screened wet granules need to be dried for a particular time period in tray dry or fluid bed dryer at controlled temperature not exceeding 55^0C. Dried granules are screened through the appropriate mesh screen.

6. **Tablet compression:** This step involves the compression of granules into a flat or convex, round, oblong, or unique shaped, scored or unscored tablets; engraved with an identifying symbol and/ or code number using tablet press.

7. **Coating:** Tablets and granules are coated if there is need to mask the unpleasant taste/odor of some drug substance or to increase the aesthetic appeal of uncoated tablets as well as to modify the release or control the release of drug substance from tablets. This is achieved by enclosing or covering the core tablet or granules with coating solutions.

5.7 Techniques/ Methods used in Tablet formulation:

Tablets are commonly manufactured by

a) Wet granulation
b) Dry granulation or
c) Direct compression.

One important requirement is that the drug mixture flows freely from the hopper of the tableting machine into the dies to enable high-speed compression of the powder mix into tablets.

a) Manufacture of Tablets by Wet granulation method:

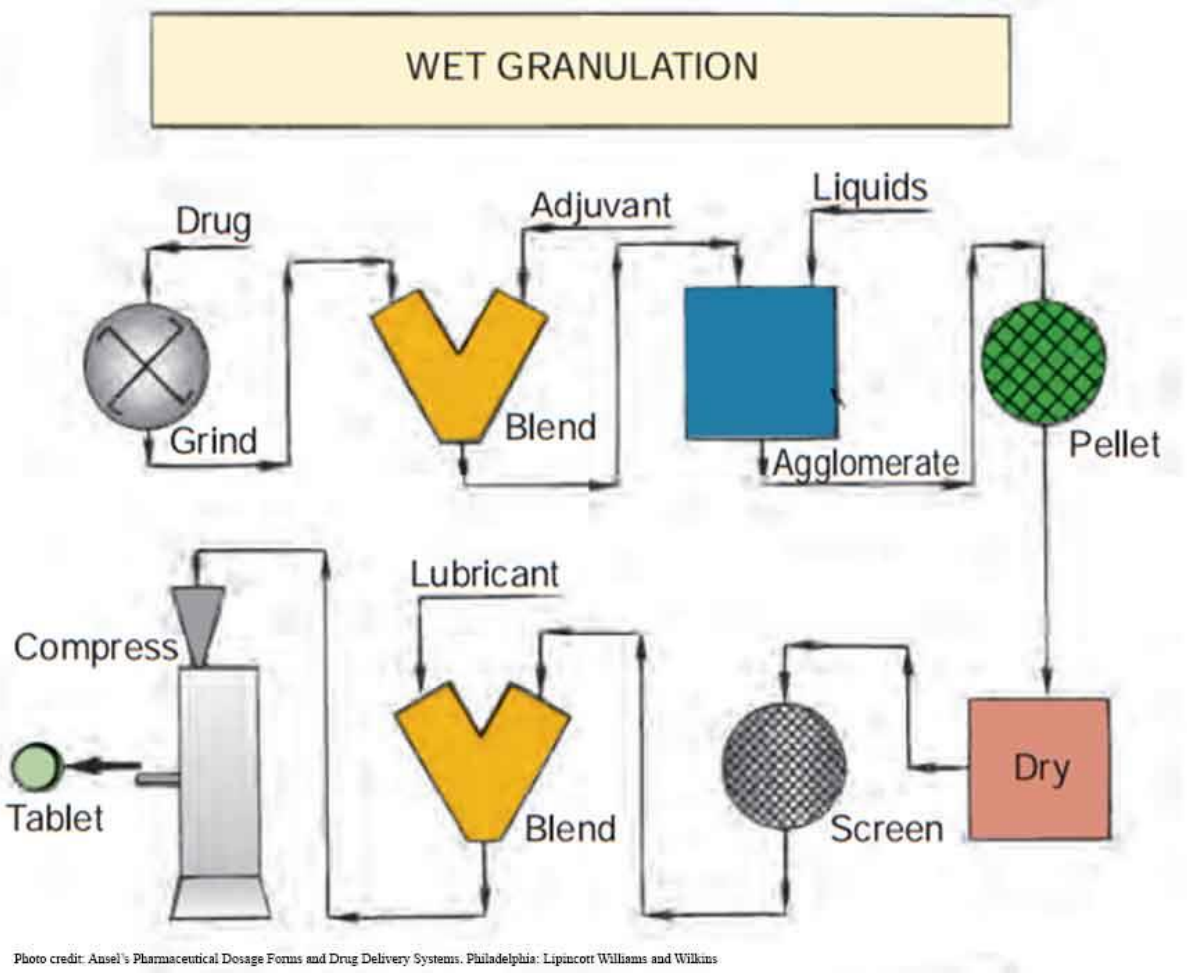


Photo credit: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lipincott Williams and Wilkins

Wet granulation is a widely used method for the production of compressed tablet. It is essentially a process of size enlargement involving several steps and the use of an adhesive substance known as binder. The granules produced using this method of granulation has a greater probability of meeting all the physical requirements for tablet formation.

A stepwise summary of the manufacturing steps used in the manufacture of tablets by the wet granulation method are listed below.

1. Weighing, milling and mixing of the APIs with powdered excipients (excluding the lubricant)
2. Preparation of binder solution
3. Mixing of binder solution with powders to form a damp mass

4. Screening the dampened powder into pellets or granules (wet screening) using 6- to 12-mesh screen
5. Drying of moist granules
6. Sizing the granulation by dry screening using 14- to 20-mesh screen
7. Mixing of the dried granules with lubricant and disintegrants
8. Compression of granules into tablets.

Tablets manufactured by wet granulation exhibit sufficient mechanical properties to be subsequently exposed to other unit operations, e.g. film coating.

b) Manufacture of Tablets by Dry granulation method:

The formation of granules by compacting powder mixtures into large pieces or compacts which are subsequently broken down or sized into granules (often referred to as dry granulation, double compression or pre-compression) is a possible granulation method which, however, is not widely used in the manufacture of tablets. This method is used when tablet excipients have sufficient inherent binding properties. The procedure can also be used as a means to avoid exposure of drug substances to elevated temperatures (during drying) or moisture. Double compression method eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication, and compression of granules into tablets. Compaction for the dry granulation process is generally achieved either by slugging or roller compaction.

Slugging:

In this method, the powder mix is compressed into a soft large flat tablet (about 1 inch in diameter) using a tablet press that is capable of applying high stress. Following this, the slugs are broken by hand or milled using conventional milling equipment to produce granules of the required size. Lubricant is added in the usual manner, and the granules then compressed into tablets. Aspirin is a good example of where slugging is satisfactory. Other materials, such as aspirin combinations, acetaminophen, thiamine hydrochloride, ascorbic acid, magnesium hydroxide, and other antacid compounds, may be treated similarly.

Roller compaction:

Results similar to those accomplished by the slugging process are also obtained with powder compactors. In roller compaction method, the formulation ingredients are mixed and are passed between high-pressure (oppositely) rotating rollers that compress the powder at 1 to 6 tons of pressure. The compacted material is then milled to a uniform granule size and compressed into tablets after the addition of a lubricant. The roller compaction method is often preferred to slugging. Excessive pressures that may be required to obtain cohesion of certain materials may result in a prolonged dissolution rate.

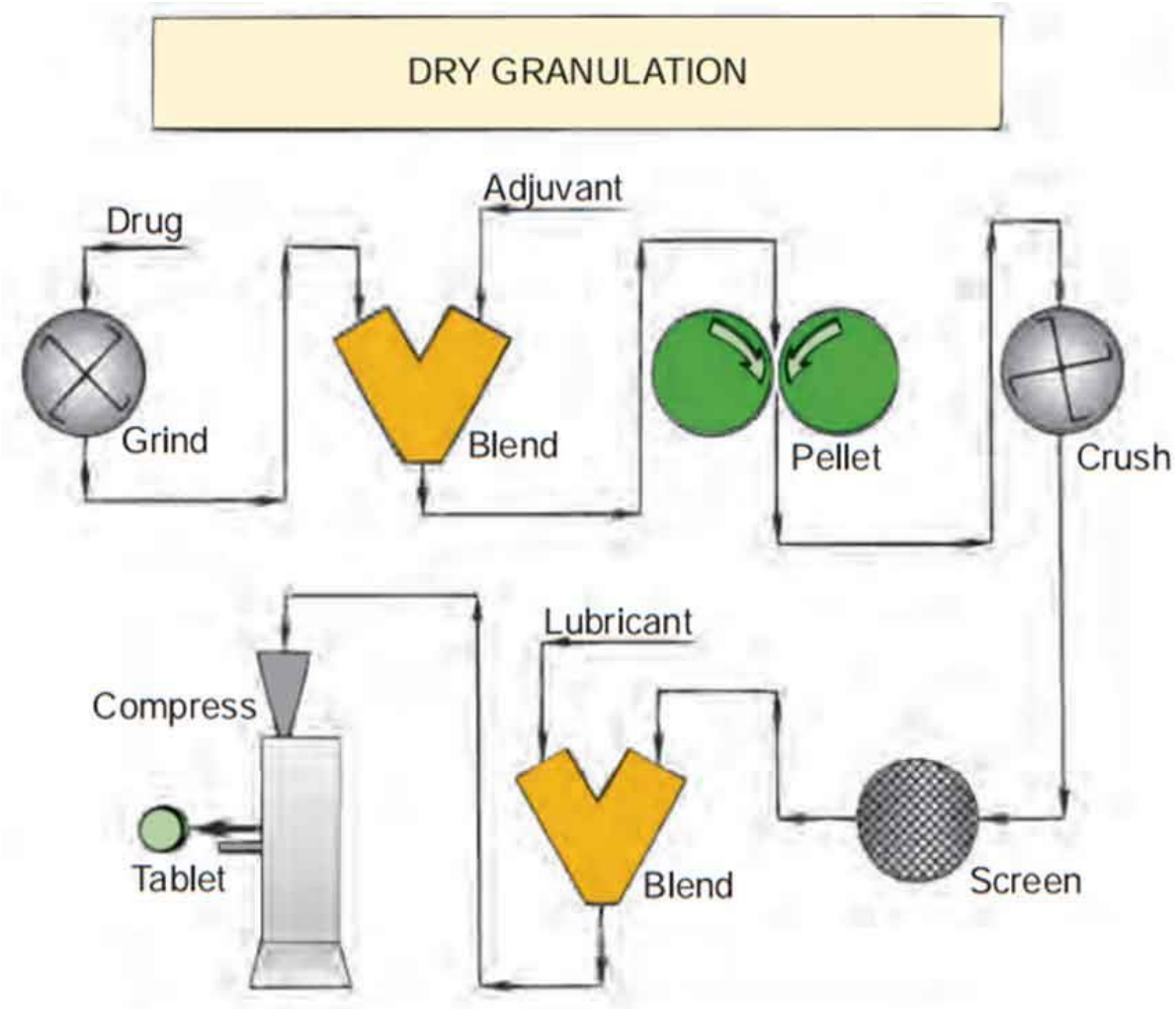


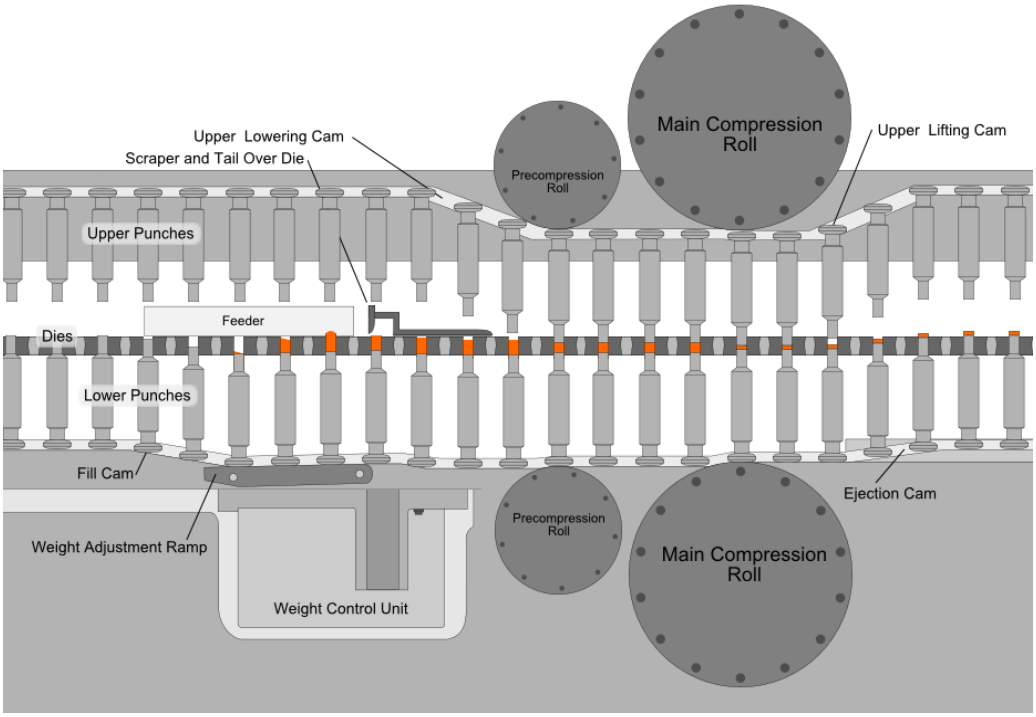
Photo credit: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lipincott Williams and Wilkins.

A stepwise summary of the manufacturing steps used in the manufacture of tablets by the dry granulation method are listed below.

1. Weighing and Milling of formulation ingredients (drug substance and excipients)

2. Mixing of milled powders.
3. Compression of mixed powders into slugs.
4. Milling and sieving of slugs.
5. Mixing with disintegrant and lubricant.
6. Compression into tablets.

c) Manufacture of Tablets by Direct compression method:



As its name implies, direct compression involves direct compression of powdered materials into tablets without modifying the physical nature of the materials itself. The technology involved in this method assumes great importance in the tablet formulations, because it is often the cheapest means, particularly in the production of generics that the active substance permits. Direct compression avoids many of the problems associated with wet and dry granulations. Its successful application in tablet formulation rests on two fundamental issues:

1. The availability of suitable excipients
2. The availability of suitable machinery.

A stepwise summary of the manufacturing steps used in the manufacture of tablets by the dry granulation method are listed below.

1. Milling of therapeutic agent and excipients
2. Mixing of milled powders, disintegrants and lubricants
3. Compression into tablets.

5.8 Quality control of Tablets:

Tablets should be subjected to a number of tests before they are deemed fit for marketing and consumption. These tests can be divided into two broad categories namely;

a) Pharmacopeial or official tests:

1. Content of active ingredient/ absolute drug content test/ assay of active ingredient.
2. Weight uniformity test/ weight variation test
3. Content uniformity test
4. Disintegration time test
5. Dissolution test

b) Non-pharmacopeial or non-official tests:

1. Crushing strength test/ hardness test
2. Friability test.
3. Tensile strength determination

5.9 Packaging and storing of Tablets:

Before tablets are sent out for distribution, they are usually packaged using appropriate packaging materials. The type of packaging material used is a matter of choice and is dependent on several factors including:

1. The degree of protection required
2. Compatibility of the packaging material with the formulation.
3. Presentation, particularly for those products which may be the subject of impulse buying
4. Customer convenience in terms of size, weight, method of opening or reclosing legibility of printing, etc.
5. Filling method and

6. Cost

Tablets are commonly packaged using blister and strip packs and are kept in places of low humidity and protected from extremes temperature. The packaging provides excellent environmental protection for each unit of tablet, coupled with an aesthetically pleasing and efficacious appearance. Blister and strip packaging also provide some degree of tamper resistance to the dosage form.

For larger quantities delivered to the pharmacist, glass or plastic bottles, metal containers, cartons, or paperboard drums may be used along with polyethylene liners, where necessary, to give added protection from moisture. If cotton wool stuffing is used under these circumstances it is an advantage for it to be external to the liners so that any moisture that it contains does not gain access to the tablets. Tablets that are decomposed when exposed to moisture can also be packaged with a desiccant packet. Light sensitive tablets are packaged in light-resistant containers. With a few exceptions, tablets that are properly stored will remain stable for many years.

6. Pharmaceutical Liquid Dosage Forms:

Liquid dosage forms are pourable pharmaceutical formulations which contain a mixture of active drug components and nondrug components (excipients) dissolved or suspended in a suitable solvent or mixtures of solvents. They are pharmaceutical preparations designed to provide the maximum therapeutic response in a target population with difficulty swallowing solid dosage forms and/or to produce rapid therapeutic effects.

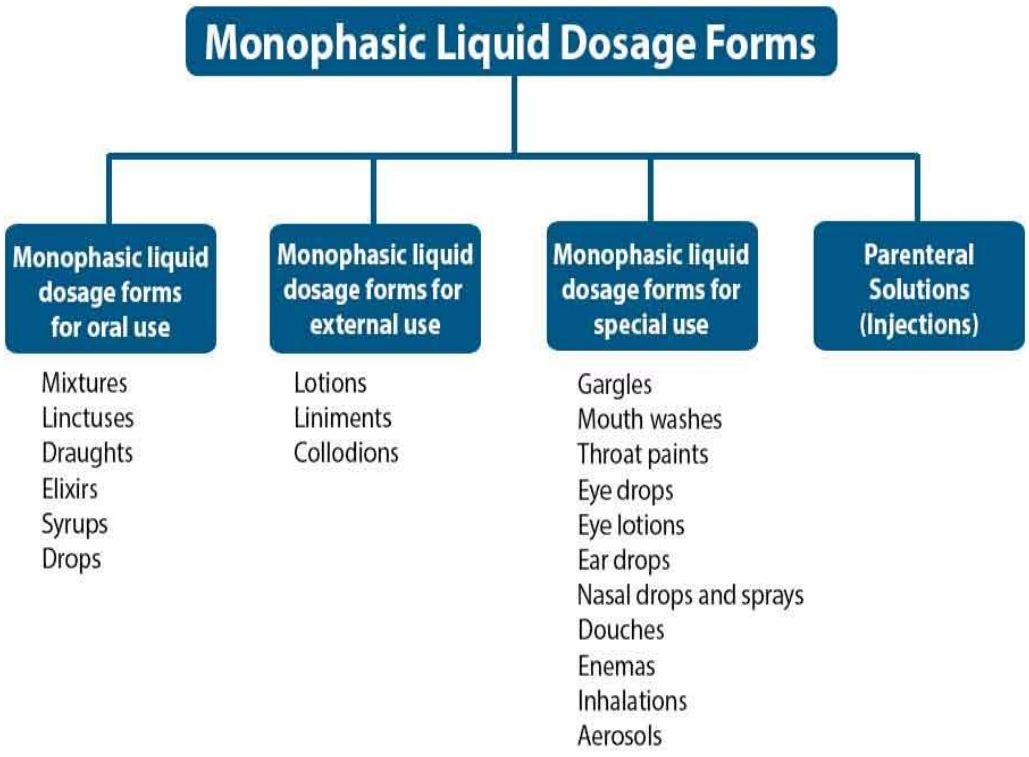
Liquid dosage forms can be supplied as ready-to-use liquids or powders for reconstitution. They are administered by oral and parenteral (injectable, inhalation, ophthalmic, otic, nasal, and topical) routes. Oral liquids are nonsterile, whereas liquids administered by the parenteral route are available as sterile and nonsterile formulations.

6.1 Classification of Liquid Dosage Forms:

Liquid dosage forms are broadly classified into two groups:

1. Monophasic liquid dosage forms
2. Biphasic liquid dosage forms

1. Monophasic liquid dosage forms:



The monophasic liquid dosage forms are further classified into

i. Liquids for oral use e.g., mixtures, linctuses, draughts, elixirs, syrups, and drops

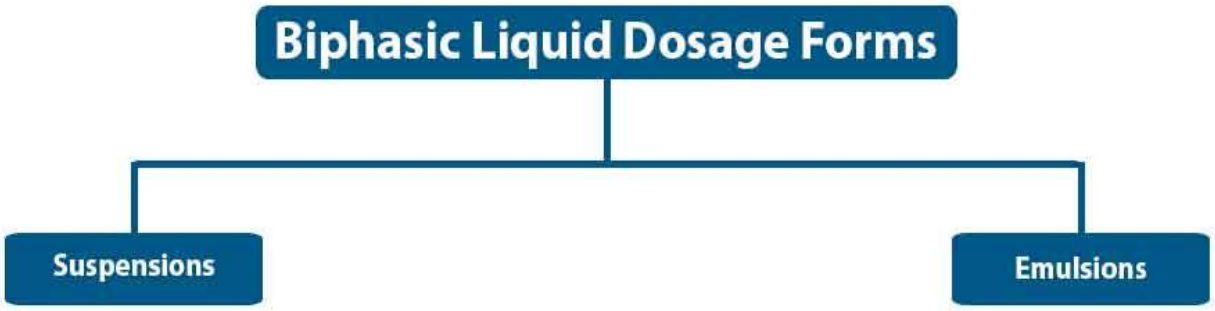
ii. Liquids for external use e.g., lotions, liniments and collodions

iii. Liquids for special use e.g. gargles, mouthwashes, throat paints, eye drops, eye lotions, ear drops, nasal drops and sprays, douches, enemas, inhalations and aerosols.

iv. Parenteral solutions (injections)

2. Biphasic liquid dosage forms:

Biphasic liquid dosage form is one which contains two phases. A good example of such liquid dosage form is suspensions and emulsions.



Suspensions are biphasic liquid dosage forms containing essentially insoluble finely divided solid particles or drug(s) suspended with the help of a suspending agent(s) in a liquid medium. The solid particles act as disperse phase whereas liquid acts as a continuous phase.

An emulsion is a biphasic liquid preparation containing two immiscible liquids (usually oil and water) one of which is dispersed as minute globules into the other and rendered homogeneous by the addition of an emulsifying agent. The liquid which is converted into minute globules is called the disperse phase and the liquid in which the globules are dispersed is called the continuous phase.

Emulsions are of two types

a. **Oil in water type (O/W):** Emulsion in which oil is in the dispersed phase whereas water is in the continuous phase.
b. **Water in oil type (W/O):** Emulsion in which water is in the dispersed phase whereas oil is in continuous phase.

6.2 Advantages of liquid dosage forms:

i. Liquid dosage forms (for oral use) are the most suitable dosage form for patients who have difficulty taking tablets or capsules, as might be the case with paediatric or geriatric patients.

ii. They are attractive in appearance and gives beneficial psychological effects.

iii. Drugs with bitter and unpleasant taste can be given in sweetened, coloured and flavoured vehicles.

iv. There is higher flexibility in dosing when compared to solid dosage forms like tablet and capsules. The dose of the drug substance can be easily and conveniently adjusted by measuring a different volume.

v. If given orally, liquid dosage forms are rapidly available for absorption than tablets and capsules.

vi. Hygroscopic and deliquescent medicaments which are not suitably dispensed in solid dosage forms can easily be given in liquid dosage form.

vii. The products like adsorbents and antacids are more effective in liquid dosage form.

viii. The liquid dosage form is expected for certain types of products like cough medicaments

6.3 Disadvantages of liquid dosage forms:

i. Liquid dosage forms are usually more susceptible to chemical degradation when compared to solid dosage forms.

ii. They are bulky and therefore inconvenient to transport and store.

iii. Accidental breakage of the container results in loss of whole dosage form.

iv. The shelf-life of a liquid dosage form is often much shorter than that of the corresponding solid preparation due to low stability.

v. Solution often provides suitable media for microbial growth and may, therefore, require the incorporation of a preservative.

Excipients	Role	Example(s)

vi. Liquid dosage forms e.g., vaccines may require special storage conditions

vii. The taste of a drug which is usually unpleasant is always more prominent when in solution than in a solid form.

viii. There is a higher chance of dose variability since the delivery of the dose depends upon the patient measuring the proper volume. This can be significant issue for vision-impaired patients, patients with arthritis, or patients unable to read the numbers on an oral dosing syringe or medicine

6.4 Manufacture of liquid dosage forms:

Most liquid dosage forms are prepared;

1. by simply dissolving the solutes (active pharmaceutical ingredient and excipients) in an aqueous or nonaqueous solvent or solvent mixture.
2. by suspending the solutes in appropriate medium.
3. by incorporating the solutes into an oil or water phase.

On an industrial scale, they are prepared in large mixing vessels with ports for mechanical stirrers. The vessels are generally thermostatically controlled to maintain a certain temperature if desired. The order of addition of components is fixed through product development and scale-up exercises.

6.4.1 Excipients used in the formulation of liquid dosage forms:

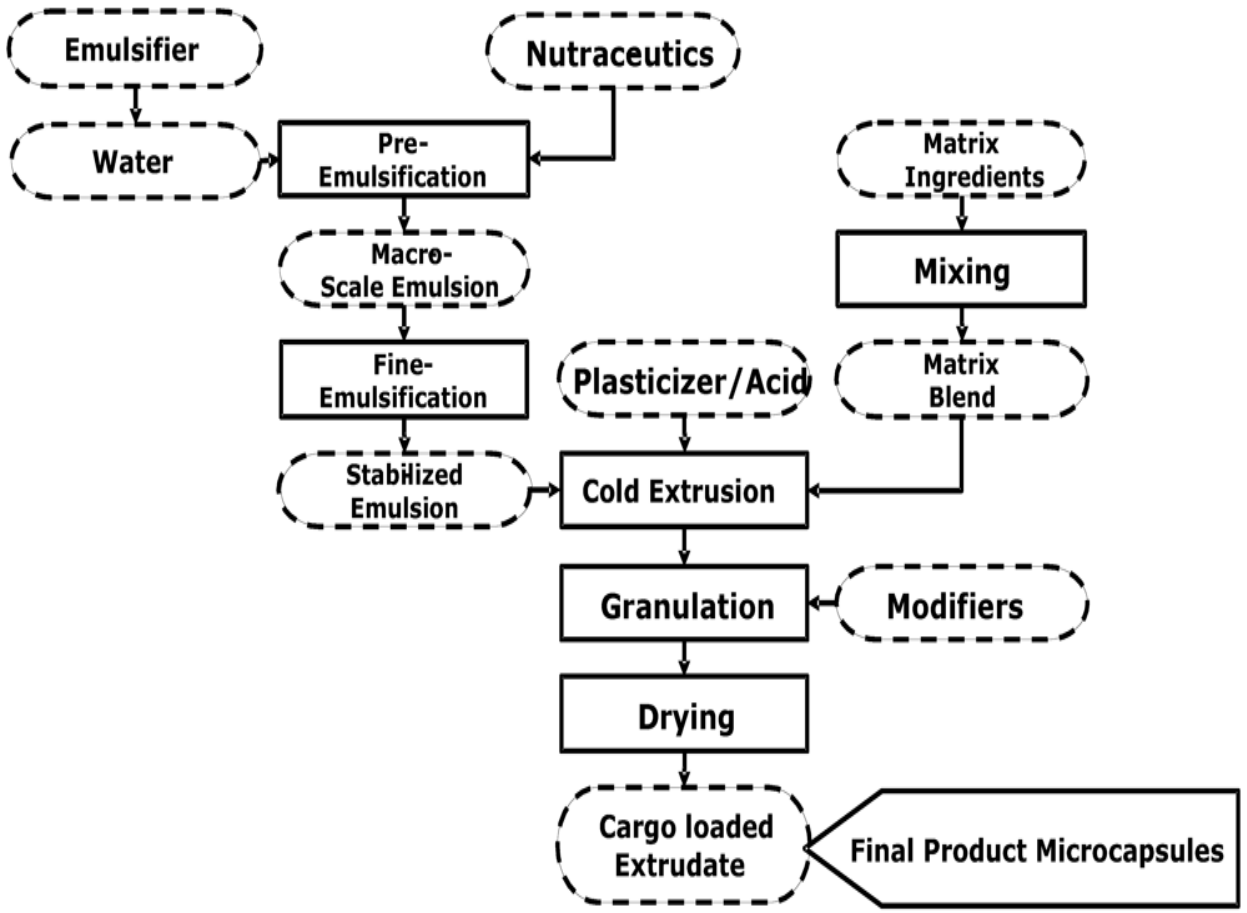
Liquid dosage forms are prepared by combining drug substance(s) with different excipients. These excipients serve a variety of function in the liquid formulation; however, several excipients behave differently at different concentration and one excipient can be used for multiple purposes depending upon the need of the dosage form.

When formulating liquid medicines, it is essential to ensure that all the different excipient used is physically and chemically compatible with the drug substance and every other component of the formulation. Below is a list of common excipients generally used in the formulation of liquid dosage forms.

Solvents/ vehicles	Liquid in which drugs and other excipients are dissolved or dispersed.	Purified water, alcohol, acetic acid, acetone, vegetable or mineral oils, organic oily bases, emulsified bases etc.
Co-solvents	Enhance solubility of drug substance in the vehicle	Ethanol. glycerol, propylene glycol etc
Surfactant	Enhance solubility of drug substance in the vehicle	Cetrimide, sodium lauryl sulphate, triethanolamine
Preservatives	Prevents microbial growth in the formulation	Parabens, phenylmercuric nitrate, sodium benzoate, benzalkonium chloride
Viscosity modifiers	Control the viscosity of the formulation	Cellulose polymers, polyvinyl pyrrolidone, alginic acid, xanthan gum
Buffers	Regulate the pH of the formulation	Phosphate buffers, Acetate buffers, Citric acid Phosphate buffers etc
Antioxidants	Control oxidation	Sodium bisulphite, ascorbic acid, butylated hydroxytoluene etc
Thickening agents.	Prevent settling/sedimentation, modify viscosity.	Methylcellulose, Hydroxyethylcellulose, Microcrystalline cellulose etc.
Chelating agents	Enhance stability of drug substance	Disodium edetate, phosphoric acid
Sweeteners	Enhance the palatability of oral liquid formulations	Sucrose, saccharin, aspartame, sorbitol
Flavouring agents	Enhance the palatability of oral liquid formulations	Lemon oil, orange oil, peppermint, menthol
Colourants	Enhance the aesthetic appearance of the formulation	Amaranth, Erythrosin, Eosin, Tartarazine etc.
Antifoaming	Discourage formation of stable foam	Simethicone, Organic

agents		phosphates, Alcohols, Paraffin oils, Sterates and glycols.
Humectants	Retard evaporation of aqueous vehicles from dosage forms	Propylene glycols, Glycerol, Polyethylene glycol etc.
Emulsifying agents	Prevent coalescence of the dispersed globules	Sodium Lauryl Sulphate, Cetrimide, Macrogol esters, Sorbitan esters etc.

6.4.2 Manufacturing process of Emulsions:



6.5 Packaging of liquid dosage forms:

Liquid dosage forms vary widely both physically and chemically, and in the ways they are distributed and used. Consequently, the materials from which the containers and packaging components are made also vary considerably and these containers are usually in direct contact with the formulation. For stability concerns, the container must not physically or chemically interact with the product so as to alter the strength, quality, or purity of the product beyond the official requirements.

Liquid dosage forms that contain light-sensitive active ingredients should be supplied in containers that are light resistant. If the preparation contains volatile ingredients, the liquid preparation should be kept in a tightly closed container. Except where indicated in the individual monograph, containers used in packaging liquid preparations for parenteral and oral use should be made from material that is sufficiently transparent to permit the visual inspection of the contents.

6.6 Labelling of liquid dosage forms:

Every pharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice. The label should include:

i. The name of the pharmaceutical product
ii. The name(s) of the active ingredients; International Nonproprietary Names (INNs) should be used wherever possible
iii. The amount of active ingredient in a suitable dose-volume
iv. The name and concentration of any antimicrobial preservative and the name of any other excipient
v. The batch (lot) number assigned by the manufacturer.
vi. The expiry date and, when required, the date of manufacture.
vii. Any special storage conditions or handling precautions that may be necessary
viii. Directions for use, warnings, and precautions that may be necessary
ix. The name and address of the manufacturer or the person responsible for placing the product on the market.

If the Liquid preparation is supplied as granules or powder to be constituted just before issue for use, the label should include:

i. That the contents of the container are granules or powder for reconstitution
ii. The strength as the amount of the active ingredient in a suitable dose-volume of the constituted preparation
iii. The directions for preparing the liquid including the nature and quantity of liquid to be used

The storage conditions and shelf-life of the constituted preparation.

6.7 Quality control tests for liquid dosage forms:

a) Quality Control requirements for semi-solid dosage forms (Ointments, Creams, Jellies and Suppositories)

Tests include:

1. Evaluation for visual appearance, colour, odour, labelling, and homogeneity
2. Loss of water
3. Consistency
4. Softening range (for suppositories)
5. Viscosity
6. Particle size distribution
7. PH
8. Assay of active ingredients and of degradation products
9. Identification test for active ingredient and possible contaminants
10. Stability of the active ingredient in the dosage form
11. Release of the active ingredient from the dosage form and
12. Storage conditions.

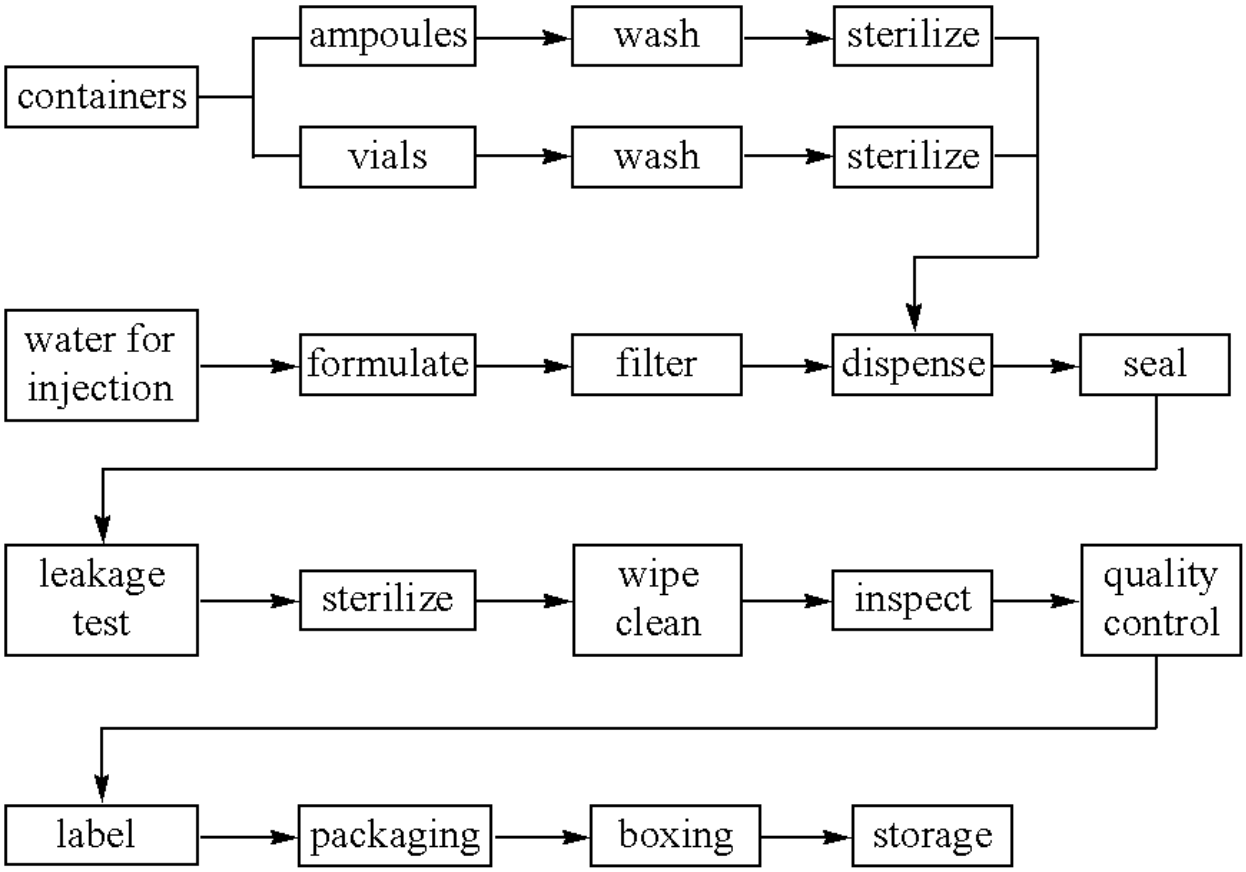
b) Quality control requirements for liquid preparations

Tests include:

1. Evaluation for visual appearance, colour, taste, odour, labelling, and homogeneity,
2. Assay of active ingredients and of degradation products.
3. Pourability
4. Viscosity
5. Isotonicity
6. Particle size agglomeration and particle size distribution
7. Clarity
8. Crystallization and precipitation
9. Gas evolution
10. Relative density
11. pH
12. Surface tension
13. Microbial limit tests
14. Stability of the active ingredient(s), and identification tests
15. Light stability
16. Container and closure compatibility
17. Re-dispersibility
18. Suspenibility
19. Storage condition

For liquid products to be used as injections, eye drops or vaccines sterility, apyrogenicity test and particulate matter testing are necessary as additional tests.

7. Overview of Manufacturing process of injectables:



7.1 Equipment's Involved in Parenteral Manufacturing:

- Steam sterilizers
- Dry heat sterilizers
- Membrane filter assemblies
- Manufacturing vessels
- Blenders
- Liquid filling machines
- Powder filling machines
- Sealing and labelling machines
- Vacuum testing chambers

7.2 Quality control tests for Parenteral formulations:

The finished parenteral products are subjected to the following test in order to maintain the quality control

- Sterility test
- Clarity test
- Leakage test
- Pyrogen test

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