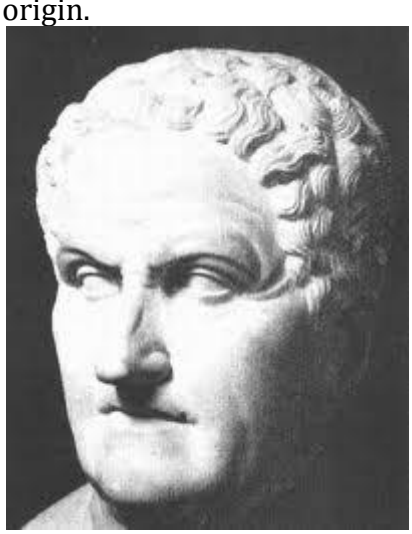
## Galenicals

Even if there have been spectacular advances in modern medicine including genetic engineering, biotechnology, organ transplant, designer drugs etc., a large population in the developing countries including India continue relying on herbal and other complementary medicines for primary health care. Herbal medicines formed the basis of health care throughout the world since the earliest days of mankind. They have considerable importance in international trade.

In earlier days the herbs were the main source of medicines. With development of sciences, the scientists have started identifying the constituents of herbs that are responsible for medicinal action. Such constituents (desirable or active constituents) were separated and used as such. Many of these are even the modern allopathic drugs and are synthesized commercially. The separation of active principles from crude drugs is achieved by a process called extraction and the products of extraction are called extracts. The crude extracts obtained from animal or vegetable crude drugs are called galenicals. 'Galenical' is a generic terminology and the term is derived from 'Galen' the famous Greek physician cum pharmacist of AD 129 to 217 who developed several medicinal preparations of vegetable origin.



At one time the crude extracts were extensively used in therapeutics and the pharmacist was involved preparing them extemporaneously. As the better forms of medications are available, their use is diminished over time. Though the crude extracts are not of much use, they are still a source of medicinal products in Indian System of Medicine. Some of the crude extracts which are still relevant clinically are discussed in the following section. This chapter deals with the principle, method of extraction and the types of extracts. The crude extracts are better form of medicine than the crude drugs. Crude drugs are vegetable or animal drugs which are just collected, cleaned and dried and not processed further.

The products of extractions currently in use are Tinctures and Extracts. The infusions are another category of extracts which are no longer in practice. Tinctures are alcoholic or

hydroalcoholic solutions of active principles of vegetable drugs or chemical substances. Extracts are concentrated form of preparations of vegetable or animal drugs prepared by extraction. The extracts are classified into three forms: liquid extracts, soft extracts and dry extracts.

**Principle:** Crude plant drugs contains several constituents and some of them are medicinally (therapeutically) active. The therapeutically active constituents are called active principles. Other constituents of the plant materials are considered inert or undesirable. The important plant constituents are alkaloids, glycosides, sugars, starches, mucilages, proteins, cellulose, gums, oils, resins, tannins, inorganic salts and many other substances. The principle of extraction is the leaching (withdrawal) of the desired constituents by use of solvent(s).

**Selection of Solvent(s):** The ideal solvent(s) for extraction should have the property of selectively dissolving the active principles only. Such solvents are not available. Thus the solvent(s) are selected based on their properties of dissolving the active constituents to maximum extent and undesired constituents to the minimum. The mixture of solvents is sometimes used. The solvent (or solvent mixture) used in extraction is called *menstruum*.

In addition to the preferential capacity to dissolve active principles, the solvents should have some other desirable properties: easy availability, safety, retaining potency and easy subsequent processing. The most commonly used solvent is alcohol – water mixture.

***Water:*** Cheap, non-toxic and readily available water is not a selective solvent and it dissolves almost all plant constituents: alkaloidal salts, anthraquinone derivatives, colouring matters, glycosides, gums, proteins, sugars, tannins etc. It has some other disadvantages too as menstruum:

- Many complex active principles are not soluble in water but more soluble in alcohol.
- Aqueous extracts are susceptible for microbial growth. Addition of alcohol is desirable as antimicrobial preservative. The chloroform water (water saturated with chloroform) is also alternative preservative menstruum.
- Enzyme degradation of active principles is possible in aqueous extracts. 25% alcohol in the water-alcohol mixture can prevent the enzymatic degradation.
- Some undesirable extracted constituents may get separated on standing leaving unsightly residue.
- Removal of excess solvent (water) requires more energy than other organic solvents.

***Alcohol:*** Alcohol (Ethyl alcohol) is a solvent for alkaloids, alkaloidal salts, anthraquinone derivatives, many organic acids and slats, some colouring matter like chlorophyll,

glycosides, resins, volatile oils. But it does not dissolve albuminous matter, gums, waxes, fats and many oils and sucrose. Though pure alcohol is not much used as solvent for drug extraction, hydro-alcoholic mixtures at various proportions are most frequently used menstruum due to preferential dissolving capacity and other advantages. The advantages of alcohol as solvent for drug extraction:

- Preferential dissolving capacity compared to water. With adjustment of alcoholic concentration the many substances which are dissolved in water can be made insoluble in hydro-alcoholic mixture.
- Hydro-alcoholic mixture at 20% or more alcohol concentration is a preservative menstruum. The microbes cannot grow in this solvent.
- The hydro-alcoholic mixtures require less energy for concentration compared to water alone as solvent.
- The chance of separation of certain substances on standing as occur with water as solvent is less.

However, alcohol as a solvent has some disadvantages: chances of abuse, cost and excise control. The excise control provides some relief of providing alcohol at a lesser cost for medicinal purpose.

***Glycerine:*** This is a good solvent for tannins. It is used in combination with water or alcohol to prevent the precipitation of inert materials on standing. The presence of glycerine in sufficient concentration in the extract provides preservative action and promotes stability of the extract.

The toxicity of the solvents is of no issue as they can be removed by evaporation or during concentration. The product can even be tested for presence of residual solvents.

**Method of Extraction:** Two main methods: *Maceration* and *Percolation* are used in drug extraction. Sometimes, the combination of methods is used. In the combination method, the crude drug is macerated first and then percolation procedure is followed. The following factors need to be considered for selecting the method of extraction: nature of crude drug (physical properties of the drug materials), its adaptability to the method, and the extent of extraction. Though in the laboratory scale the difference between the two methods is appreciable, on the industrial scale there is no significant difference between the two methods. Irrespective of the methods, the following steps are common:

- Size reduction of crude drugs: Size reduction exposes the cells and helps in penetration of menstruum. Moderately coarse powders are used for extraction. This can be achieved either by crushing or cutting the crude drugs. Fine powders are not used as the subsequent clarification would be difficult.

- Penetration of menstruum to the plant tissues: The powdered crude drugs are kept with the menstruum for sufficiently long time allowing penetration of menstruum to plant tissues to dissolve the soluble constituents.
- Diffusing out of the menstruum with dissolved constituents: The diffusion can be assisted by shaking or stirring. The agitation permits the repeated flow of fresh menstruum over the entire surface area of powdered crude drugs. The agitation disperses the concentrated solution which would otherwise accumulate round the particles of solid materials.
- Separation of the menstruum and the exhausted crude drug. The exhausted crude drug is called marc.

***Maceration***: The meaning of the word maceration is 'soaking'. The word's origin goes back to the Latin word *macerare* whose English equivalent is 'to soak'. The process of maceration involves soaking of the powdered crude drug with the menstruum in a closed vessel for enough time to for the menstruum to penetrate into the cellular structure of the crude drug and dissolve the soluble constituents.

The powdered crude drug (the drug to be extracted) is placed with the whole of the menstruum in a wide mouthed closed vessel. The closed vessel is required to prevent evaporation and batch to batch variation. The contents are agitated (shaking or stirring) repeatedly for a period ranging from 2 to 14 days. The mixture is then strained, the marc is pressed, and both liquids are combined. The combined liquid is then clarified by filtration or decantation after standing.

**Making tea is maceration**: A tea bag is suspended in required quantity of milk or water. As the soluble constituents from the tea bag dissolves, they tend to settle to the bottom of the cup because of increased density due to dissolved solids. Occasional dipping facilitates the extraction.

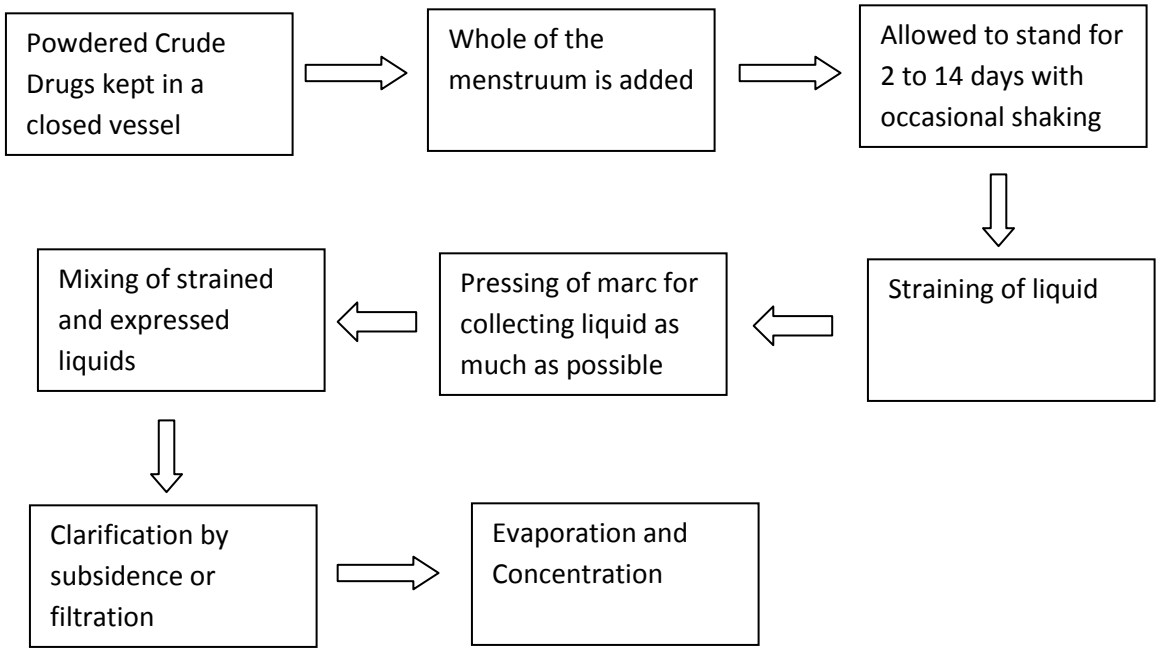



Fig: Schematic presentation of maceration process

There are two types of crude drugs: organized drugs and unorganized drugs. The organised drugs have definite cellular structure and the examples include barks, roots etc while unorganised drugs are without definite cellular structure and the examples include gums, resins, benzoin, tolu etc. The maceration process varies accordingly.

| **Parameter** | **Maceration Process for Organised Drugs** | **Maceration Process for Unorganised Drugs** |
|---|---|---|
| Quantity of menstruum | Drug and the *whole of the menstruum* are kept together. | Drug is kept with *4/5$^{th}$ of the menstruum*. |
| Period of maceration | Shaking occasionally *during 7 days* | Shaking occasionally *during 2 – 7 days* |
| Separation of liquid | *Straining of liquid and pressing the marc* | *Decanting the liquid. Marc is not pressed.* [Marc, a gummy substance is not pressable] |
| Mixing of liquids | The *two liquids* are mixed. | Only *decanted liquid* is available. |
| Clarification | By *subsidence or filtration* | By *filtration only* |
| Adjustment of volume | The filtrate is *not adjusted to volume.* [Pressing of marc may be different from situation to situation. The adjustment of volume may lead to different strength product which depend on | Sufficient menstruum is passed through the filter to *make the required volume*. |

| | | |
|---|---|---|
| | the volume obtained from pressing the marc] | |
| Example of a product | Orange Tincture | Compound Benzoin Tincture |

**Orange Tincture (Tincture from Organized Drugs)**:
*Fresh Orange Peel in thin slices – 250 g
Alcohol (90%) - 1000 ml.

The thinly sliced orange peels are placed with the whole of the menstruum in a closed vessel for seven days shaking occasionally. This is strained and the marc is pressed. Both the liquids are combined and clarified by filtration.
It is used as flavouring agent in pharmaceutical preparations.
* Fresh peels are used as they lose volatile oil content on drying.

**Compound Benzoin Tincture (Tincture from Unorganised Drugs):**
Benzoin Crushed – 100 g
Prepared Storax – 70 g
Balsam of Tolu – 25 g
Aloes – 20 g
Alcohol (90%) sufficiently quantity to make 1000 ml
The benzoin, prepared storax, balsam of tolu and aloes are macerated with 800 ml of the menstruum in a closed vessel for at least 2 days with occasional shaking. It is filtered and sufficient menstruum is added through the filter to make the required volume.
**Use**:

- It is used to protect and make the skin tough in the treatment of bedsores, ulcers, cracked nipples, fissures of lips and anal fissure.
- It is also used as inhalant (on dilution with boiling water) in bronchitis and other respiratory tract infections.

**Patient Counselling Points**: Add one teaspoonful of the tincture to about half a litre of boiling water and inhale.

**Modified Maceration:** A process described above for preparing tinctures made from organised drugs is known as maceration. The process described for preparing tinctures from unorganised drugs and the procedures involving repeated maceration are grouped under modified maceration.

Repeated or multiple macerations is more efficient than single maceration as there is chances of left out of significant amount of active principle in the pressed marc. The extraction process can be made more efficient in terms of complete extraction by following multiple maceration processes using a portion of total menstruum for successive macerations. The menstruum is divided in such a way that each maceration uses the same volume of the menstruum. This should take into account the solvent remains after pressing marc. The multiple maceration process is usually followed for preparing concentrated preparations. Examples: Concentrated Compound Gentian Infusion is prepared by double maceration.

In case of unorganized drugs, triple maceration process is followed. The second and third macerates are combined and concentrated by evaporation before mixing with first macerate. Example: Concentrated Compound Infusion of Gentian is prepared by double maceration with alcohol (25%) as menstruum. Concentrated infusion of Quassia is prepared by triple maceration using water as menstruum.

**Percolation:** The percolation is defined as a process in which the powdered drugs are extracted of soluble constituents by the slow passage of menstruum through a column of the drugs. The word percolation is derived from two Latin words: *per* (English meaning through) and *colare* (English meaning to strain). The extraction apparatus or equipment for percolation is called percolator and the extract obtained of percolation is called percolate.

Percolators for drug extraction are available in different size, shape, and utility. Glass percolators are used for small scale extraction (usually up to 1 kilogram drug) and are generally cylindrical shaped with or without tapering downward, or conical or funnel shaped. On the other hand, percolators used industrially are made of stainless steel or are glass lined metal vessels. The special percolators to percolate with hot menstruum are also available.

The cylindrical percolators are suited to the complete extraction of drugs with a minimal expenditure of menstruum. In this type of percolators each drug particle is more repeatedly exposed to passing menstruum. Funnel or conical shaped percolators are more suitable for the percolation of drugs that swell to a significant extent on maceration. In this type percolator, the large upper surface permits the expansion of the drug column with little risk of a too tightly packed column or breakage of a glass percolator. However, there is

a disadvantage that menstruum often fails to permeate through material near the sides at the bottom.

Process: The procedure usually involves the following steps: Imbibition, packing of percolator, maceration, percolation and collection of percolate.

I. Imbibition (also called preliminary moistening): The powdered drugs are mixed with sufficient menstruum and the moist mass is allowed to stand for four hours. During this period, the dried drugs swell on contact with the solvent as menstruum penetrates the cell wall. If this step is not done, the dry powder drugs are to be packed into the percolator. The subsequent swelling within the percolator may cause reduction in porosity of the material and choke the column. The preliminary moistening step has the following advantages:
    a. It prevents the swelling which would have occurred if percolator is packed with dry materials leading to choking;
    b. It assisted the packing of the percolator as the solvent displaces the occluded air and enables the materials to be more evenly distributed. In uneven packing, the menstruum will run mainly through the largest channels resulting in inefficient extraction; and
    c. It makes the fine particles less liable to be washed out of the column during percolation process.

II. Packing of the percolator: The preliminary moist mass is packed evenly into the percolator. Packing must be light and uniform as far as possible. The moistened crude drugs are supported in a loose plug of tow or other suitable substance which have been previously moistened with menstruum. The moist drugs are introduced layer by layer, each one being lightly tapped with a rod or other suitable device to give uniform compression. The extent of pressure to be applied is dependent on the nature of swollen materials and their permeability. A piece of filter paper may be placed on the top of the packed layer and weighted down with sand in order to prevent the disturbance of packed materials.

    In commercial scale large percolators, the moistened drugs are supported on a perforated metal plate covered with sacking or straw. Such percolators have portholes for inspection and running in of menstruum.

III. Maceration: On completion of packing, sufficient menstruum is poured over it to saturate it and when the liquid begins to drip from the bottom of the percolator the tap at its base is closed. The column should not be allowed to dry. The drying would cause cracks in the bed. Hence, enough menstruum is added to keep a layer of solvent above the bed.

The moistened crude drugs packed in the percolator are allowed to stand for 24 hours with enough menstruum. This maceration period allows time for complete penetration of tissues by the solvent. A significant amount of leaching of soluble material takes place. This maceration provides more efficient use of menstruum than direct percolation without this step.

IV. Percolation: This step involves downward displacement of saturated solution already formed during maceration and extraction of remaining soluble matter by the slow passage of the menstruum through the column of drugs. After the maceration period of 24 hours, the outlet of the percolator is opened sufficiently to produce a controlled rate of percolation.

V. Collecting the percolate: The volume of percolate to be collected for a given quantity of crude drugs depends upon the nature of the intended product. Percolation is continued till the drug is exhausted of its active principles. In potent preparations, the percolate is assayed and based on assay result the calculated volume of menstruum is added to get a product of required strength.

In general, $3/4^{th}$ of the finished product is collected and the marc is pressed, making 80-90 percent of final volume. If no assay is available to determine the potency, the percolate and the expressed liquid are mixed and the final volume is made with the menstruum.

*In percolation it is assumed that the marc is completely exhausted of active principles and hence adjustment of volume is rational. The pressing of marc is just to avoid wastage of solvent. On the other hand, in maceration the menstruum left in the marc is of equal strength with that separated by straining. Hence, the volume is not adjusted in maceration where the marc is pressed. The adjustment of volume would give different strength as the expression volume varies as it depends on many factors including the pressure.*

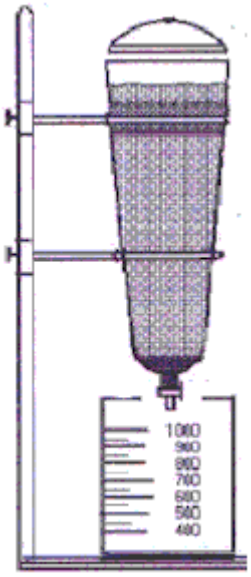
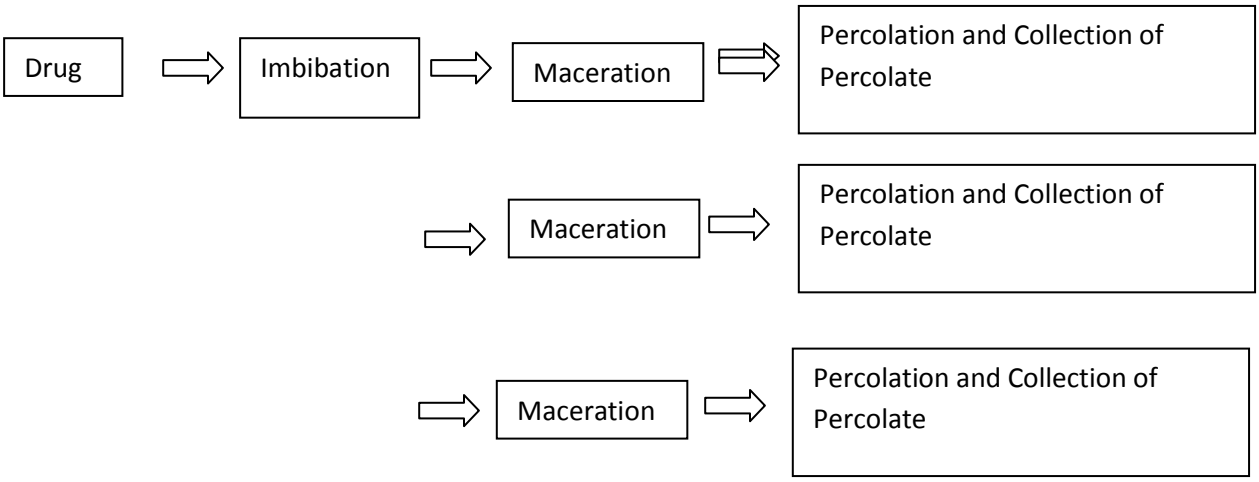


Fig: Percolation Process

Liquorice Liquid Extract:
Liquorice, unpeeled, in coarse powder
Chloroform water and Alcohol (90%) as in sufficient quantity
Procedure: Liquorice is exhausted with chloroform water by percolation. The percolate is boiled for 5 minutes and is kept aside for not less than 12 hours. The clear liquid is decanted and the remainder is filtered. The two liquids are mixed and evaporated until the weight per ml of the liquid at 20$^{o}$C is 1.198. To this liquid, when cold, one-fourth of its volume of alcohol (90%) is added. Then the mixture is kept as such for not less than four weeks and then filtered.
Category: Demulcent
Dose: 2 to 4 ml.
Use: The liquorice liquid extract is used in cough mixture and as a flavouring agent in mixture containing nauseous medicines like Ammonium Chloride.

**Modified Percolation:** With continuous percolation more menstruum is needed to effect exhaustion compared to percolation suitably interrupted by short maceration stages. The modified percolation stages can be systemically depicted as:




By modifying the percolation stage, the drug/percolate ratio is lowered. The smaller volume of percolate causes considerable savings in energy required for concentration, time and menstruum.

Percolation to exhaustion often produces dilute products and they require concentration by evaporation. In general, a ratio of 4 parts of menstruum to 1 part drug would affect exhaustion. Concentration of percolate is tricky. Thermolabile active materials cannot be concentrated by evaporation. The evaporation of hydro -alcoholic solution produces solution of less alcoholic strength. Alcohol evaporates faster than water and thus the solution would be largely aqueous which may be incapable to keep the extractive materials in solution.

The verification of exhaustion of the drug may be determined by either performing general or specific tests. The principles of these tests are:

General tests:

- Absence of appreciable residue in the dried percolate obtained by evaporation of last few millilitre of the percolate is an indication of exhaustion.
- The value of specific gravity of last few millilitre of the percolate is similar to that of menstruum is an indication of exhaustion.

Specific tests: These are based on the identifying tests of active principles of the drugs to be extracted.

- Absence of alkaloids – Slight or no reaction (opalescence) of last few millilitre of the percolate with dilute hydrochloric acid and Mayer's reagent is an indication of exhaustion.
- Absence of tannins – No precipitation or slight greenish black or bluish black colour of last few millilitre of the percolate with ferric chloride solution is an indication of exhaustion.
- Absence of bitter principles – No bitter taste of last few millilitre of the percolate is an indication of exhaustion.

**Concentration of Percolate:** Whether whole or part of the percolate is to be evaporated depends on the character of menstruum and the character of the required extract. The evaporation of the percolate is affected as follows:

- Heating at 90-130°C over a water bath or in a steam jacketed apparatus under pressure. When there is no need of recovery of menstruum, open vessel evaporation is acceptable. In the preparation of liquid extract of liquorice, open vessel evaporation is followed. In the preparation of liquid extract of hamamelis (used to stop bleeding), distillation is used in order to recover the menstruum (alcohol).
- Heating at a temperature not exceeding 60°C and is usually effected over a regulated water bath or distillation under reduced pressure. High temperature adversely affects the thermolabile active principles. Liquid extract of belladonna is prepared following this principle. Hyoscyamine, active principle of the preparation, gets converted to less effective atropine at high temperature.

**Continuous hot percolation:** Raising the temperature of the menstruum during drug extraction hastens the leaching process due to increased rate of diffusion, stronger convection current and better solubility of active principles. Sometimes, it is necessary to use hot menstruum for an extended period of time when the active principle is not readily soluble or penetration of cellular tissue is slow. A small volume of hot menstruum is made to percolate again and again through the drug. This hot continuous extraction is called Soxhletion and uses the apparatus, Soxhlet extractor.

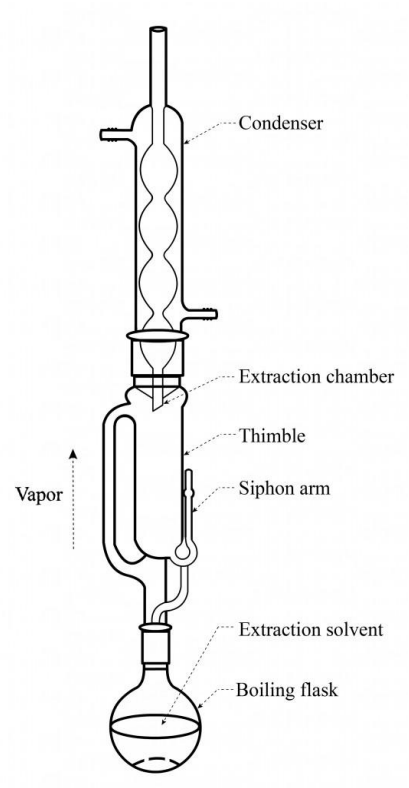



Fig: Soxhlet Extractor

The assembly for soxhletion consists of a flask, soxhlet extractor and a reflux condenser. The raw material is placed in the 'thimble' made of filter paper and inserted into the wide central tube of the extractor. Menstruum is placed in the flask and boiled. The vapour arising in the flask passes by the side tube into the condenser. The condensate then drops back on the drug, through which it percolates, leaching solutes in the process. A portion of the liquid passes into the siphon tube and symphonic takes place when sufficient liquid is collected reaching the top of the siphon tube. The whole of the collected percolate siphons over into the flask emptying the body of the extractor. The suction effect of siphoning assists permeation of the solvent through the drug.

The alternation of filling and emptying the body of the extractor goes on continuously. The dissolved materials remain in the flask and the solvent is volatilised and made to pass through the drug. A limited amount of hot solvent is thus made to percolate repeatedly through the raw materials.

The crude drugs must be in powder form for hot continuous extraction. They are kept in a cylindrical column (thimble) made of filter paper. If the drugs are not kept inside or kept free, they may block the siphon tube or be drawn over the flask.

Application of continuous hot extraction:

- Useful for extraction active principles from crude drugs.
- Useful for drug extraction in phytochemical research.
- Useful in drug assay.

**Maceration Vs Percolation – Selection of Methods:**

| For Preparation of Tinctures | For Preparation of Concentrated Products |
|---|---|
| 1. Physical Characteristics of the drug: For percolation the drugs must be of definite cellular structure (organised drugs) and they should be in powder form. Hence, the unorganized drugs and the drugs which are difficult to powder are not suitable for percolation.<br>Examples: Compound Benzoin Tincture is prepared by maceration (described in box). Tincture of orange is prepared by maceration as fresh peels cannot be powdered.<br>2. Processing Cost: Percolation process requires more time and skill than the simple maceration. Relatively less potent or unimportant drugs can be processed by maceration. Gentian or Quassia (bitter principles as appetite stimulant) is processed by maceration.<br>3. Value of the product: The product is yield is higher in percolation compared to maceration products. If the product is expensive, percolation is preferred. For Ginger tincture, percolation is followed while for Quassia maceration is followed. | Percolation method is preferred for concentrated products because:<br>• multiple maceration* (double or triple ones) is expensive due to increased labour cost;<br>• menstruum loss is high in multiple maceration;<br>• yield is less in maceration as solvent cannot be completely separated from marc.<br>*Multiple maceration is followed for concentrated preparations. |

**Galenical Products:** The products may be infusions, tinctures and extracts.

*Infusions:* There are two types of infusions: fresh infusions and concentrated infusions. The fresh infusions used to be prepared by pouring water (usually boiling water) over the drug and allowing standing for 15 minutes. The marc is not pressed. The products are very unstable and they are to be used within 12 hours of preparation. Infusion of Quassia is an example of fresh infusion.

Concentrated infusions are eight times stronger than fresh infusions and also more stable than fresh infusions. Concentrated infusions can be prepared either by multiple maceration or percolation. Though infusions were popular earlier, they are no longer in use.

*Tincture:* The tinctures are alcoholic or hydro-alcoholic solutions prepared from vegetable materials or from chemical substances. Tinctures from plant materials are prepared by extraction (Compound Benzoin Tincture, Orange Tincture) as described above while tinctures from chemical substances are prepared by dissolving the chemical substances (Weak solution of Iodine also known as Tincture Iodine).

The alcoholic content in tincture usually varies from 15 to 80%. The alcohol content helps protecting the preparation against microbial growth and keeps the alcohol soluble materials in solution. As the alcohol may evaporate the preparations must be kept in tightly closed containers.

Because availability of better dosage forms, tinctures have almost lost their usefulness.

*Extracts:* The extracts are preparations of vegetable or animal drugs obtained by extraction using suitable menstruum. Depending upon the consistency they can be grouped as liquid extracts, soft extracts and dry extracts. The liquid extracts are no longer used and even when used, they are suitably modified to improve palatability or as a drug source for preparing pharmaceutical dosage forms. Liquorice liquid extract is an example of liquid extract. The soft extracts have syrupy consistency prepared without removing complete menstruum. In dry extracts, the product is in the form of dry powder. The dry extracts are prepared by complete removal of the menstruum. Such products are susceptible to moisture absorption and they should be protected from moisture by keeping in air tight container. The extracts as such are not used in modern medical practice, but the dry extracts can be used as source of drugs for making powders, capsules or tablet dosage forms.

References:

1. Howard C. Ansel, Nicholas G. Popovich and Loyd V. Allen, Jr, Pharmaceutical Dosage Forms and Drug Delivery Systems, Sixth Edition, 1995, BI Waverly Pvt Ltd, New Delhi.
2. EA Rawlins, Bentley's Textbook of Pharmaceutics, 1975, ELBS, Churchill Livingstone.
3. JW Cooper and Colin Gunn, Register of General Pharmacy,

**Surgical dressings:**
**Absirbable Gelatin Sponge**

**Absorbable Hemostatic Agents**

Several agents are used to control bleeding by promoting the formation of an artificial clot or by providing a matrix framework for a clot to form. They are designed to control oozing in instances of hemorrhage from multiple tiny vessels. Hemorrhaging from solid organs with enveloping capsule damage (e.g., small spleen or liver tears) can be controlled in this manner. Occasionally, such agents can be applied to a vascular anastomosis to control needle-hole bleeding.

**Thrombin.**

Thrombin applied topically as a powder or solution is particularly useful for capillary oozing. In its liquid form, it can be used in conjunction with an absorbable gelatin sponge to form a bulky hemostatic plug for highly vascular regions such as the liver or spleen.

**Absorbable Gelatin Sponge (Gelfoam).**

Gelfoam helps form a bulky artificial clot in vascular areas, as mentioned previously. It is usually wetted with thrombin or isotonic saline to allow pliability (saline) or greater clot formation (thrombin). It can be left in the surgical site and will be absorbed in 4 to 6 weeks. The diffuse but copious bleeding frequently encountered in liver surgery, including biopsies, can often be controlled with this agent.

An **absorbable gelatin sponge** is a sterile hemostatic agent composed of purified porcine-derived gelatin. In regional chemotherapy, absorbable gelatin sponge may be used to embolize arteries in the region of a tumor in order to block or retard blood flow; this blockage results in a locally increased concentration of chemotherapeutic agents delivered to the tumor when chemotherapeutic agents are infused into the embolized arterial circulation upstream of the blockage.[1] It is sometimes soaked with buprenorphine.[2]

# Absorbable Gelatin Sponges


These small, sterile, surgical sponges are prepared from specially treated, purified gelatin solution. Each sponge is a hemostatic device that is capable of absorbing and holding within its meshes many times its weight in whole blood.

- Highly absorbent
- Holds many times its weight in blood
- Completely absorbed within four to six weeks

**Oxidized Cellulose (Surgicel).**

A treated surgical gauze, oxidized cellulose acts as a physical matrix for clot formation and does not actively cause any alteration of the clotting cascade. It is produced in several forms, including strips, gauze pads, and pledgets. Pledgets can be sewn into place with sutures to seal needle punctures created during vascular or cardiac procedures. Oxidized cellulose can be left in the surgical site, but it is commonly removed after coagulation has taken place.

Microfibrillar Collagen Hemostat.

(Avitene, Angiostat) This agent is packaged as a friable, flat pad that works through adhesion to the bleeding site by platelet aggregation. This agent is very efficacious for spleen or liver tears and for diffuse bleeding from multiple small vessels.

Vascular Anastomoses

Vascular anastomoses are searched for in monochorionic twin placentas. These are usually superficial arterial-to-arterial and venous-to-venous connections which are inconsequential, but there may be a deep A-V anastomosis which has implications for possible twin-twin transfusion syndrome. A membrane roll from between the placentas is taken first (to document chorionicity). To assess the presence of anastomoses, the entire amnion is peeled away from the chorionic surface. This allows optimal visualization of the fetal vessels. Arteries and veins can then be readily traced, and A-A, V-V, and A-V anastomoses can be visualized. The arteries run *over* the veins in the chorionic plate.

Monochorionic placentas without twin-twin transfusion syndrome tend to have multiple anastomoses, whereas monochorionic placentas with twin-twin transfusion syndrome almost always have a single deep anastomosis.[3]

# Surgical Ligatures and Sutures

**Outline:**

Surgical Ligatures and Sutures – threads or strings – prepared and sterilized – for use in surgery.

Ligatures for tying blood vessels and Sutures – sewing tissues together

E.g of materials incl. intestines, tissues, tendons of large animals or birds.

Threads spun from vegetable fibers, hairs of human, camel, horse

Synthetic threads and metallic wire.
Some sutures - absorbed/ digested in body tissue – required prop – non-irritant & sterile.
Some insoluble – but disintegrate after long time/ encysted- cause no trouble.
Surface stitches – non-absorbable - bind to edges of wound – removed after healing.
Essential properties of Ligatures and Sutures:

1. Should be Sterile,
2. Strength –be adequate – for stitching & withstand body wt and stress.
3. Little/ no irritation.
4. Gauge as fine as possible.
5. Absorbable – time of absorption to be known.

**Catgut**
Widely used absorbable Ligatures and Sutures material.
Catgut – violin gut -obtained from intestine of sheep.
Kit – small violin, gut – intestine
Ref: Tutorial Pharmacy by Cooper & Gunn

**Catgut – manufacture consist of following steps:**

1. Raw materials
2. Selection and washing.
3. Splitting and casting.
4. Removal of unwanted layers.
5. Orientation of fibers.
6. Hardening
7. Spinning.
8. Drying.
9. Finishing
10. Gauging
11. Sterilization
12. Difficulties
13. Heat process.
14. Irradiation Process.

Boilable and Non boilable catgut

**Standards:**

1. Sterility test. –
2. Gauge – thickness –
3. Tensile strength –

**Other Materials**

1. Kangaro tendons
2. Bracofil

**Non- Absorbable materials:**

1. Silk, linen, cotton.
2. Synthetic threads: nylon and polyester sutures.
3. Silkworm guts
4. Horse hairs
5. Metal and Alloys

**Key points:** (Refer original material for more details)

**Catgut – manufacture consist of following steps:**

1. Raw materials – sheep slaughtered – content removed – placed in cold storage – brine (NaCl soln), first 7.5 m used for gut.
2. Selection and washing. – Alternately drawn – soaking in water, cleaned, inspect abnormalities, and reject poor samples.
3. Splitting and casting.- spilted (divided) into rough and smooth ribbon – corresponding to mesenteric and antimesentric parts of intestine
4. Removal of unwanted layers.- gut contains 4 layers – outer mesenteric, muscular, subcutaneous and mucous layers. subcutaneous and mucous layers by using blunt knifes and soaking in alkaline soln
5. Orientation of fibers. – Arranged in more parallel way – to improve tensile strength.
6. Hardening: Ribbons tanned or hardened by soaking in chromic salts – cause delay in absorption - depending on strength of soln. Prev they were called 10 day, 20, 40 day. Days of absorption depend on tissues where implanted and body conditions. Hence now referred as plain, chromic and extra chromic.
7. Spinning. – Ribbons tied at end in groups of 2, 3, or more, pulled to even tension. No. of twists in spinning is carefully controlled to give good tensile strength. Hardening or chromicing can be done (at this stage instead of earlier) –produce case hardening effect –centre of string is unaffected.
8. Drying. Under controlled temp and humidity.
9. Finishing: polished by mech means – strings are rubbed against an abrasive surface – to produce smooth, uniform string of circular section. . gives good quality surgical gut.
10. Gauging: carefully checked to ensure uniformity between strings of same batch & along length of each string.
11. Sterilization: can be sterilized by heat, chemicals ($I_2$), radiation (α - gamma rays) . Heat sterilization – have dis adv - produce satisfactory product gamma radiation adv – can be used even on finally sealed containers.
12. Difficulties: Sheep intestine – infected with bacteria – may contain pathogenic organisms like sporing anaerobic bacteria responsible for tetanus, gas gangrene. Hence - rigorous check for sterility. Catgut consist of

collagen – if heated with moisture - convert to gelatin – spoil suture material.

13. Heat process.
    (a) Tubing: Suitable lengths of guts - coiled on heat resistant fiber card – placed in glass tubes along with label of heat resisting materials.
    (b) Drying: Tubes placed in baskets – dried in drying oven – temp raised slowly – to avoid gut damage. After drying gut ready for sterilization in 2 ways.
        (i) Baskets of tubes – paced in autoclave – cont anhydrous fluid like toluene or xylol. Temp of $160^0$C - for several hrs.
        (ii) or heating in non-pressure vessel using anhydrous liquid of high boiling point - temp of $160^0$C is maintained
    (c) Then tubes are filled with sterile tubing fluid – process under strict aseptic conditions.
14. Irradiation Process. Prepared gut packed in alum foil cont 90% IPA – passed through irradiation area. 40% greater than reqd to destroy most resistant bacteria to ensure complete sterilization. Min dose of 2.5 megarads.

**Boilable and Non boilable catgut:**

Non boilable catgut: If tubing fluid cont water – it is non-boilable. Warning - to avoid heat sterilization. But adv- because water keeps it more pliable and ready to use. Here outside tube sterilized by soapy water and soak in germicidal soln.

Non boilable catgut are filled with alc cont small amt of water. Ooficail catgut is non-boilable variety

Boilable: If tubing fluid is anhydrous –tubes can be boiled. Gut from boilable – conditioned by soaking few min in IMS (industrial methylated spirit) or in sterile saline soln.

**Standards:**

Catgut for surgical use in UK are subjected to Sterility test under Therapeutic Substance Act. Following test are described in BPC.

1. Sterility test. – free from pathogens, presence of bactericides
2. Gauge – thickness – dial reading micrometer at several points.
3. Tensile strength – load reqd to rupture gut is measured at straight and knotted samples.

**Incompatibilities**

The dictionary defines 'Incompatibility' as unable to exist together in harmony. Similarly in pharmacy, the incompatibility may be defined as the adverse effects that may result in due to mixing of two or more medicaments (including the additives) while making medicines or at the time of administration. In an expanded definition, the dosing error involving only one medicament is also included within the purview of incompatibility. Mixing of two or more medicaments (drugs), if not compatible with each other, may result in a physical problem like insolubility, immiscibility; or chemical problem like a chemical interaction. The incompatibility may cause no action from the medication to harming the patients. The pharmaceutical incompatibility may be classified into three broad groups, though the classification is arbitrary: Physical Incompatibility, Chemical Incompatibility and Therapeutic Incompatibility. Often, they are classified as pharmaceutical incompatibility and therapeutic incompatibility and physical and chemical incompatibilities are grouped with pharmaceutical incompatibility. Though classically the incompatibility of any of these types may be grouped into intentional or unintentional, such grouping is of no significance at present day pharmacy practice.

The physical incompatibility is manifested by immiscibility, insolubility or liquefaction. These physical changes occur when the materials are mixed together and there is no chemical reaction takes place among the materials mixed. The chemical incompatibility results from the chemical reaction among the materials mixed. It produces a new compound. The therapeutic incompatibility may result when the medicine contains two or more drugs (drug substances) and one affects the action of the other.

The incompatibility continues to be an important area in pharmacy practice in spite of little scope of compounding. As the medicines are available as readymade package, there is limited scope of compounding and making medicines. The industries have taken up the responsibility of providing the medicines in appropriate form. But sometimes the appropriate form is not available and the pharmacists are called upon to do compounding to make the required medicines. For example, the adult dosage form is available commercially and no child form is available, in such situation the physician may require a paediatric preparation. The pharmacist may have to prepare a suspension using the tablets. In addition, the mixing of several medicines is common while preparing intravenous admixtures. The intravenous admixture helps to administer several medicines with one injection. The knowledge of incompatibility would help the pharmacists to over them while preparing the required dosage form. As the medicines are commercially manufactured by the pharmaceutical industries, incompatibility becomes the important consideration while selecting other components (including another drug substance) during development of dosage form or formulation. The compatibility study is a primary component of pre-formulation studies. However, currently many of the components

of therapeutic incompatibility are known by different terminologies like medication error, contraindication etc. The knowledge of therapeutic incompatibility is essential during formulation to avoid irrational combination and promote rational combinations only. The pharmaceutical companies are also concerned with the effect of co-administration of other preparation along with theirs.

In short, the incompatibility leads to change in physical, chemical and therapeutic changes in the pharmaceutical dosage forms. The pharmaceutical incompatibility may affect the safety, efficacy or appearance of a pharmaceutical preparation (medicine). Physical and chemical incompatibilities occur *in vitro* while therapeutic incompatibility occurs *in vivo*. Avoidance of physical and chemical incompatibilities is the direct professional responsibility of the pharmacist while the avoidance of therapeutic type is the shared responsibility of the physician and the pharmacist.

**Physical Incompatibilities**: In the physical incompatibility, the physical properties of mixed ingredients produce an unacceptable appeared product or inaccuracy of dosage. Immiscibility, insolubility and liquefaction are common physical incompatibilities.

*Immiscibility:*

1. Oil and water: Oils are immiscible with water. Mixing of oil with water requires when oil (or oil soluble substance) is a medicament. Oil is unpalatable and it is necessary to mix with water. The immiscibility problem of oil and water can be solved by emulsifying the oil in water or by solubilisation. Example: liquid paraffin (laxative) is emulsified in water using acacia or methyl cellulose to make liquid paraffin emulsion which is more palatable than the liquid paraffin alone. Cresol (a disinfectant) is solubilised in water to make cresol with soap solution for easy mixing with water before use.
2. Dilution of hydro-alcoholic solution with water: Spirits are concentrated hydro-alcoholic solution of volatile oils and they are used as flavouring agents for aqueous preparations. The dilution of the spirit with water may cause separation of volatile oils as large globules. In order to prevent this separation, the spirits should be gradually diluted with the aqueous vehicle before mixing with remaining ingredients or added slowly into the aqueous vehicle with constant stirring.
3. Addition of high concentration of electrolytes to saturated solution of volatile oils: When high concentration of electrolytes is added to a saturated aqueous vehicle of volatile oil, oil gets separated as an unsightly top layer. Example: The potassium citrate mixture contains potassium citrate, citric acid, lemon spirit, quillaia tincture, syrup, chloroform water and water. Here the lemon spirit is a flavouring agent. If the lemon spirit is added to an aqueous solution of potassium citrate and citric acid, lemon oil will be thrown out of the solution due to salting out effect of high concentration of dissolved

salts and due to change of solvent (alcohol to aqueous). In order to prevent the separation of lemon oil as top layer, quillaia tincture is used in the formula as emulsifying agent. It is important to add the lemon spirit in small quantity at a time to the mixture of all other ingredients, shaking after each addition.

*Insolubility:*

1. Insoluble solids and water: The insoluble solids if left as just mixture with water, they quickly settle at the bottom. The simple mixing (shaking the bottle) may not disperse the solids for sufficient time to allow the measurement of uniform dose. This type of problems can be solved by the following methods:
    a. Solubilisation: The use of a mixture of solvents in place of just water is often helpful in preparing solution of insoluble substances. A classic example is paracetamol. Paracetamol is not soluble in water but a solution product can be prepared using a mixture of propylene glycol, alcohol and water. The paracetamol syrup can be prepared using the following ingredients: paracetamol, Benzoic acid, Disodium calcium EDTA, Propylene glycol, Alcohol, Saccharin sodium, Water, and Sorbitol solution.

    The solubilisation can also be achieved by use of solubilising agents (suspending agents). In case of Lysol (Cresol with soap solution) preparation, the solubilising agent (soap) is prepared *in situ* to dissolve cresol in water.

    b. Changing the order of mixing: Dissolving the ingredients separately in maximum amount of available solvent before mixing them together often reduce the possibility of precipitation and makes solution. Even if precipitate forms, it would be in a form of fine particles which are easily dispersible.

    In the preparation of elixir, alcohol soluble and water soluble ingredients are dissolved separately in the respective solvents. The aqueous solution is then added to the alcoholic solution in order to maintain the highest possible alcoholic strength and minimise the separation of alcoholic soluble components. If the order of mixing changed, then the oils/drug may separate from the solution as soon as alcohol solution comes in contact with water. Example: the formula for Phenobarbital elixir contains Phenobarbital, Alcohol, Orange oil, Glycerin, Amaranth solution, Syrup and Water. In the preparation of this elixir, first Phenobarbital and orange oil are dissolved in alcohol. The remaining ingredients are then added and the solution is adjusted to the required volume with water. On the other hand, if all ingredients are mixed first and then Phenobarbital is added last, it would be difficult to dissolve Phenobarbital to make solution.

The formula of a liquid preparation contains Magnesium carbonate, Sodium bicarbonate, Citric acid and Water. In this preparation, if the citric acid is mixed first with sodium bicarbonate, some magnesium carbonate may be insoluble and that would result in a suspension. But if magnesium carbonate is first mixed with citric acid in water, it gets easily solubilised. The addition of sodium bicarbonate to this solution of magnesium carbonate would give a clear solution.

c. Addition of suspending agent: The insoluble solids especially which are indiffusible like chalk, sulpha drugs, calamine, zinc oxide when present in water do not get dispersed sufficiently long time on shaking to take out uniform dose or amount for use. In order to make them uniformly dispersed for sufficiently long time on shaking, suspending agents are added to the formulation. These suspending agents increase the viscosity of the preparation and reduce the rate of settling of insoluble solids. The use of tragacanth in paediatric chalk mixture and the use of bentonite in calamine lotion are few examples.

*Precipitation*: The salting out or change of solvent may cause precipitation. Example: Combination of high concentration of electrolytes and soap emulsions – the electrolytes causes the salting out of the soap (emulgent) and causes cracking.

A substance precipitates from solution when a solvent in which it is insoluble is added to it. Example: Alcohol and hydrophilic colloids – Alcohol causes the precipitation of polysaccharides from mucilage (aqueous solution). Colloidal solutions frequently show precipitation on addition of electrolytes. The addition of tincture or fluid extract to aqueous solution causes precipitation. Compound benzoin tincture, Myrrh tincture etc. contain resinous matters which get precipitated when added to water. To prevent these precipitates, a protective colloid (compound tragacanth powder) is first dispersed in aqueous solvent before adding tincture. A shake well before use label is necessary.

The precipitation issues can also be grouped under insolubility.

*Liquefaction:* The powdering of certain solids together results in a liquid or soft mass. This phenomenon is called liquefaction and occurs either due to eutaxia (of being easily melted) or release of water of hydration.

Aspirin, Benzocaine, Camphor, Menthol, Phenol, Salicylic acid, Thymol etc are common drugs that get soften or liquefy when mixed. The two methods are suggested to overcome this problem and make dry powders. First method: Addition of adsorbent powder to each component before mixing – The individual ingredients are mixed separately with adsorbent powder like light magnesium oxide or magnesium carbonate and the mixed powders are triturated lightly preferably in tile not in mixing with mortar and pestle. The pestle and mortar

may cause compression and cause liquefaction. Second method: Allowing the eutectic to occur and then adsorbing with adsorbent – This approach requires that the individual ingredients are mixed to get the liquid mass and then liquid mass is mixed with the adsorbent like magnesium oxide or magnesium carbonate to develop the dry powder mixture.

The efflorescent powders like atropine sulphate, citric acid, codeine, ferrous sulphate, sodium acetate, sodium phosphate, terpin hydrate are crystalline substances which contain water of hydration or water of crystallisation. This water gets liberated either during manipulation or upon exposure to high humidity environment. On liberation of water, the powder becomes sticky and pasty or even liquid. In order to avoid this problem, the anhydrous form of the drug is used. Care is necessary to calculate the proportionate quantity of anhydrous form.

**Total Parenteral Nutrition Solutions:** The total parenteral nutrition is provided to patient when the patient cannot be given nutrition orally especially during pre and post surgery period, malignancy, inflammatory bowel disease, pancreatitis, severe trauma, burns, sepsis, hepatic failure, renal failure. They are mixtures of amino acids, dextrose, fat emulsions, multiple electrolytes salts, trace minerals and vitamins. There are ample possibilities of insoluble salts. With this, they cannot be administered. They need to be checked visually to find out whether there is any precipitation. The concomitant administration of calcium and phosphate may cause precipitation of calcium phosphate. Dibasic calcium phosphate is nearly insoluble while monobasic calcium phosphate has better soulublity. Many factors influence this including pH and temperature. The occurrence of calcium phosphate precipitation in the central venous catheter was reported.

While preparing the admixture proper order of the mixing can avoid the solubility issue. Lipids should never be added directly to dextrose before amino acids are added. Administration of lipids results from instability of lipid emulsions can give rise to fatty deposits in the lung and other tissues.

The addition of other drugs to Total Parenteral Nutrition is required to be considered carefully. This is practiced only when the patient's vein access is limited. Visual compatibility is observed when heparin is added in high concentration; Insulin binds to intravenous administration sets are some examples of incompatibility in admixture.

The physical incompatibilities should be prevented before they occur.

**Chemical Incompatibilities:** When two or more ingredients of a formulation react to give a new compound, then the chemical incompatibility is said to have occurred. Thus the chemical incompatibilities occur due to chemical interaction among the ingredients of a formulation. They need to be corrected before preparing the product. Earlier the chemical incompatibility in compounding practice was divided into two types based on the rapidity of these reactions:

immediate incompatibility and delayed incompatibility. The immediate incompatibility occurs readily while preparing the product or immediately after that and is manifested by effervescence, precipitation or colour change. On the other hand the delayed incompatibility does not occur immediately but does occur late due to slow reaction rate. However, such terminologies like immediate and delayed incompatibility have no significance in present day pharmacy practice.

While it is difficult to predict the chemical incompatibility, the literature search provides a good deal of information which can be used to make a stable formulation or product. The common chemical reactions encountered in pharmaceutical product preparation are: oxidation, hydrolysis, photodegradation etc.

a. *Oxidation*: Oxidation is one of the most common causes of drug and formulation additive degradation. The oxidation reaction either involves reaction with oxygen or reversible loss of electrons. The former type is called autoxidation and occurs only in presence of atmospheric oxygen. The oxidation with loss of electrons can occur in anaerobic condition and in absence of atmospheric oxygen.
   Autoxidation is a chain reaction and is self limiting too. The primary products of this type of oxidation are the colourless and tasteless hydroperoxides and they may further break down to aldehydes, ketones and short chain fatty acids. Oils, fats, volatile oils undergo this autoxidation which are manifested with change in colour, consistency and odour. Example: The oily injection vehicles like ethyl oleate and arachis oils on autoxidation develop unpleasant odour and taste. Such injection vehicles should not be used. The factors that affect the autoxidation includes: the degree of unsaturation of the compound ( linoleic acid with two unsaturated bonds oxidizes rapidly compared to oleic acid with only one unsaturated bond), the presence of fatty acids (Linoleic acid with free carboxylic acid group is more susceptible to oxidation compared to its ester methyl linoleate), temperature (higher the temperature, more is the rate of oxidation), the presence of catalysts (heavy metals like copper and iron catalyse the oxidative reaction) and physical state of the susceptible compound ( solid fats oxidises slowly compared to their liquid form).

In oxidation involving loss of electrons from an atom or molecule, each electron lost is accepted by another atom or molecule. Thus oxidation and reduction reaction take place together. Adrenaline, ferrous sulphate, riboflavin and ascorbic acid are the examples of drugs undergo this type of oxidation. The oxidation may result in alteration in colour of the preparation, result in precipitation or a change in colour besides change in therapeutic activity. Example: Adrenaline is susceptible to oxidation and it reduces activity on oxidation. The colour of the

solution too gets changed to red (due to formation of adrenochrome). The coloured solution of adrenaline should not be used.

The oxidation reactions during the preparation of a pharmaceutical product can be prevented by the following methods:

1. Using antioxidants (including reducing agents): They are more susceptible to oxidation than the drug. These agents react with the other components of the formula and spare the drug from undergoing reaction. They provide electrons and easily available hydrogen atoms which are more readily accepted compared to the electrons of the drug. The common antioxidants for aqueous solution are: sodium sulphite, sodium bisulphite, sodium bisulphite, hypophosphorous acid, ascorbic acid; for oily solutions are: alpha-tocopherol, butyl hydroxyl anisole, and ascorbyl palmitate. As the sulphites are often allergic to certain persons especially with asthma, they should be carefully considered. If the preparation has sulphite and it should not be given to such persons.
   Example: Sodium metabisulphite is used to protect adrenaline from undergoing oxidation.

   Paediatric Ferrous Sulphate Oral Solution BP (1988): It has ferrous sulphate, ascorbic acid, orange syrup, double strength chloroform water and water. In this preparation ascorbic acid is used to prevent the oxidation of ferrous sulphate. The oxidation of ferrous to ferric leads to a product that would have less bioavailability (absorption). It is necessary first to develop a reducing environment before dissolving ferrous sulphate.
   The sequence of steps in preparation should be:
   - First dissolve ascorbic acid in double strength chloroform water;
   - Then dissolve ferrous sulphate in the above solution;
   - Add orange syrup and adjust to volume with vehicle.

   Patient Guidance:
   - Guide the mother on dose.
   - Tell her to dilute with drinking water before giving to the child.
   - Tell her to give the medicine after feeding.

2. Avoiding contact with oxygen: The oxygen (air) present in the airspace of the container may cause autoxidation of the medicament. Such oxygen needs to be removed from the containers and replaced with inert gas such as nitrogen. Example: In the preparation of chorphenirmine maleate injection, nitrogen gas is used to replace air to prevent oxidation of the drug. Supplying the product in well filled and air tight container is also helpful protecting against oxidation.

3. Using chelating agents: They are useful when the heavy metals catalyse reactions. They act by complexing or chelating the heavy metals present in the solution. Example: Sodium edetate and 2,3 – dimercaptopropane sodium in vitamin c injection.

*b.* *Hydrolysis:* Hydrolysis is reaction with water and it yields breakdown productions. Hydrolytic reactions are the single most reaction issues in drug instability. The following categories of chemical groups are susceptible to hydrolysis: esters (acetyl salicylic acid, cocaine, procaine, and methyl dopa), amides (sulphonamides), lactones (spironolactone) and lactam (penicillin and cephalosporin).

Example: Acetylsalicylic acid (Aspirin) on hydrolysis gets converted to salicylic acid and acetic acid. Hence, aspirin liquid preparation is not available. Even for tablets, it requires moisture free environment for processing. Aspirin tablets with acetic acid (vinegar) smell should not be used. Hydrolysis is often dependent of pH and temperature. The following approaches may be useful overcoming the hydrolytic reactions during preparation of the pharmaceutical products:

1. Elimination or reduction of water component in the formula: The use of non – aqueous solvents like alcohol and propylene glycol to replace complete or part of water is beneficial in reducing the hydrolytic reactions. Example: Phenobarbital elixir formula has these ingredients – phenobarbitone, orange oil, propylene glycol, alcohol, sorbitol solution and water. Alcohol and propylene glycol are included to improve the stability of Phenobarbital against hydrolysis. [Barbiturates are more stable at room temperature in propylene glycol – water system than water alone].
2. Supplying as dry powders for reconstitution before use: The drugs that are susceptible to hydrolysis can be supplied as dry powders. These dry powders are to be reconstituted with required quantity of drinking water. After reconstitution, they are to be used within 7-14 days based on the drug stability. Amoxycillin powders for oral suspension and cloxacillin for oral solution are two examples.

**Incompatibility involving Oxidation** [For illustration only as no compounding takes place in present day pharmacy practice]

The formula of an oral liquid preparation contains sodium salicylate, sodium bicarbonate and vehicle peppermint water. In this formula, sodium salicylate is the medicament but when comes in contact with gastric acid gets converted into salicylic acid. Salicylic is needle shaped crystal and cause gastric irritation. In order to prevent or at least to reduce this conversion, sodium bicarbonate is included in the formula.

The salicylate undergoes alkali catalysed oxidation with change of colour to reddish brown but there is no therapeutic loss. However, the colour change may be a cause of concern in patients' mind. Three methods are suggested for dealing with this problem: addition of sodium metabisulphate; darkening the preparation to mask the colour change; or informing the patient about this harmless change in colour.

Keeping in refrigerator after reconstitution may also reduce the rate of hydrolytic reaction.

**Amoxicillin dry syrup**: Amoxicillin is not stable in liquid preparation. Hence, it is available as dry syrup (dry power for liquid). This needs to be reconstituted prior to use. It is available in two strengths: 125 mg per 5 ml and 250 mg per 5 ml. Often the packages look similar and the pharmacist should be careful dispensing the correct strength product. The counselling points:

- Guidance on reconstitution with boiled and cooled drinking water.
- Shaking the bottle before measuring each dose.
- Measuring the dose using the supplied measuring spoon only.
- Keeping the medicine in a cool place. Reading the label.
- Not using the remaining portion after 7 days or so of reconstitution. Reading the label.
- Completion of the course even if one feels better.

3. Adjusting the pH of the preparation: As the hydrolytic reactions are often pH dependent, the pH of the product may be adjusted to the pH of optimum stability using buffers. However, the pH must be biologically acceptable too. Often a compromised pH between stability and biologically is the choice. Example: pilocarpine (ophthalmic drug) has maximum stability at pH 4.0 but most active form of the drug is available at pH 9.0. The pilocarpine eye drop is prepared with pH of 5.0 considering both stability and therapeutic activity.

c. *Photo-degradation:* The room light or sun light cause degradation of susceptible drugs. These drugs are called photolabile or light sensitive drugs. Shorter wave length light causes more damaging effect than the larger wavelength ones. Thus UV light is more damaging than visible. Light not only causes direct degradation of photolabile drugs, it also catalyses oxidation reaction. Chloroquine, Primaquine, nifedipine, reserpine, nitropruside, riboflavin, and chlorpromazine are few examples of photosensitive drugs.

The light sensitive drugs must be supplied in light resistant containers. The amber coloured glass or plastic bottles are good light resistant containers and provide good protection against the photo degradation. However, it is difficult to detect the signs of precipitation or discolouration in the colour containers. Hence, it may be preferable to supply the injections in clear glass containers and placing them in light proof enclosures. The plastic containers too have the issues of leaching out of toxic chemicals.
The patients should also be advised not to expose the medicines to light.

The detection of incompatibilities is extremely difficult. But the good understanding of chemistry of drug molecules and science of making different dosage forms help the pharmacists to solve the incompatibility issues. Even the pharmacists need to look into the incompatibility of the product with the containers. Ointment containing methyl salicylate is supplied only in glass containers not in plastics as it dissolves the latter.

**Intravenous Admixtures**: Addition of ampicillin to low pH infusion fluids is an example of chemical incompatibility. Ampicillin is stable in normal saline up to 24 hours while it is stable only for one hour in dextrose injection. The pH of 5% dextrose injection is 4.0 – 4.5. Similarly erythromycin is stable for one day in saline while stable only for four hours in dextrose injection.

**Therapeutic Incompatibilities**: The therapeutic incompatibility is said to occur when the response to one or more medicines is of different nature or intensity than the desired. The physical and chemical incompatibilities may also lead to therapeutic incompatibility. However, currently the therapeutic incompatibility term is not in practice and perhaps more appropriately called as 'medication error'. Therapeutic incompatibility may occur either of wrong use of single medicine or due to medicine – medicine interaction when more than one medicine is advised to the patient. Though it is not intended to describe all types of therapeutic issues or complete review of drug –drug interactions in this text, a brief description is made to give the preliminary idea and how to prevent such occurrences. The readers are also advised to refer the chapter on prescription.

While the major responsibility of avoiding or preventing therapeutic incompatibility (medication error) lies with the physician, the pharmacist is also professionally responsible not to dispense prescription with medication error. The pharmacist needs to use his or her training to avoid medication error. Here are some types or examples of therapeutic incompatibilities:

a. *Dosing Errors:* The dispensing of an overdose is the most serious type of medication error. The excessive dose may harm the patient. The ineligible prescription leads to confusion. The prescription should mention the strength of the product. In absence of clear instruction, there is possibility of dispensing different strength of the product which would lead to dosing error. The pharmacist needs to confirm this before dispensing. Example: Amoxycillin Dry Syrup is available commercially in two strengths: 125 mg/5ml and 250 mg/5ml. Dispensing of wrong strength product would either lead to overdosing or sub-therapeutic dosing.

b. *Contraindicated Drugs*: The use of certain drugs may be contraindicated in some individuals or disease conditions. Examples: Aspirin is not recommended for children below 12 years [It causes Reye's syndrome, a fatal condition, with detrimental effects to many organs including brain and liver.]. Ibuprofen (anti-inflammatory drug) is not recommended for asthma patients as it is known to precipitate bronchospasm. Corticosteroids used in the treatment of asthma, arthritis are contraindicated in peptic ulcer. The steroids may not only delay the healing, may even cause bleeding.

   The patient may be pregnant. The doctors other than gynaecologists may miss this observation. The medicines may affect pregnancy or the foetus. The pharmacist needs to ensure that the person is not pregnant before dispensing certain medicines. Examples: Vitamin A may cause threat of abortion. Phenytoin (anti-epilepsy drug) may cause bleeding problem in new born or may cause birth defects.

c. *Antagonistic drugs:* Example: The cough liquid preparation containing both expectorant and suppressant. The patient requires either expectorant (mucolytics) in productive cough or cough suppressant (codeine) in dry cough.

d. *Drug – Drug Interaction*: An interaction occurs when the effects of one drug are altered by the co-administration of another drug. The combination may result in additive or enhanced effect or antagonism of the effect or any other alteration in the effect. Though drug – drug interaction may occur at any stage of drug's life from formulation to absorption to elimination, the present chapter deals with those interactions which influence clinical effects. The *in vivo* interactions are only considered. The extent of discussion is also restricted looking into the need and understanding of the students in their earlier years of study.

   - *Interaction affecting gastrointestinal absorption:* Drug – Drug interaction may affect the absorption of drugs because of their affect on gastrointestinal motility or pH of gut contents or due to direct interaction. Examples – Metoclopramide (anti-vomiting drug) accelerates gastric emptying and thus increases the absorption rate of paracetamol. Purgatives decrease the absorption of other drugs by speeding their passage. Gastric antacids increase the pH of stomach fluid and thus influence the ionization of the weakly acidic drugs. Acidic drugs like nitrofurantoin ionized and absorbed slowly. Unionized portion is preferably distributed to lipid phase and thus better absorbed than the ionized portion which is more aqueous soluble. Antacids, Histamin $H_2$ antagonist (Omeprazole) significantly decrease the bioavailability of ketoconazole and itraconazole. But the absorption of fluconazole and voriconazole is not significantly influenced.

     Iron or gastric antacids containing calcium, aluminium, magnesium complexes with tetracycline and reduce the absorption of the latter. In the treatment of osteoporosis bisphosphonates are prescribed along with calcium supplements. If

both are taken simultaneously, the bioavailability of the both is reduced significantly leading to therapeutic failure.

Keep an interval of 2 – 3 hours between the interacting drugs to avoid such interaction.

- *Interaction affecting metabolism:* The drugs are metabolized in the body and the metabolism helps in easy removal or excretion. Liver is the main organ responsible for drug metabolism. Some drugs inhibit the hepatic metabolism of other drugs and some drugs can induce the metabolism of others. The inhibition of metabolism increases the drug's stay in the body while induction of metabolism accelerates their removal. Though most of the time the metabolytes are not therapeutically effective, some metabolytes are therapeutically effective.

  The drugs that inhibit the metabolising enzymes potentiate the effect of other drugs whose intensity and duration of action are dependent on these enzyme systems. The concurrent use of Metronidazole (Antiamoebic and antibacterial) and warfarin (anticoagulant) – Metronidazole inhibits the metabolising enzymes of warfarin leading to haemorrhage (due to excess warfarin). The simultaneous administration of coumarin (Anticoagulant) and phenytoin (anti-epilepsy) may result in phenytoin toxicity due to inhibition of phenytoin metabolism. Ciprofloxacin, clarithromycin , erythromycin inhibit the Theophylline metabolism leading to serious Theophylline toxicity.

  The drugs which induce metabolising enzymes may reduce the therapeutic efficacy of the drugs whose metabolism is dependent on these enzymes. Barbiturates, phenytoin, carbamazepine, Rifampicin, and griseofulvin are the potential inducers of hepatic P-450 microsomal enzymes. When the patient is prescribed warfarin and barbiturate together, the latter induces the enzyme responsible for warfarin metabolism. This means more warfarin is necessary to maintain therapeutic action. But when the barbiturate (hypnotic) is discontinued, if the dose of warfarin is not adjusted back (reduced) may lead to bleeding due to overdosing.
- *Interaction involving excretion:* Body eliminates all the drugs that are introduced. Renal excretion is the major excretion pathway. Though theoretically there are possibilities of one drug affecting the elimination of other concurrently available drug in the body, the clinically significant examples are not much. Here are few clinically significant examples: Quinidine (treatment for abnormal heart rhythms) decreases the elimination of digoxin (treatment in heart failure) from the body. There is possibility of much increased level of digoxin if combined with quinidine resulting digoxin toxicity like nausea, vomiting and even death.

  The intake of sodium bicarbonate increases the pH of urine while Vitamin C and ammonium chloride causes a decrease in pH of the urine. pH influences the ionization of drugs and thus their passive diffusion (re-absorption). Acidification of urine decreases the elimination of sulpha drugs and causes the formation of crystals. This can lead to the formation kidney stone. Separation of sulpha drugs and the urine acidifying drugs by at

least three years would avoid this problem. Alkalization of urine increases the excretion of barbiturates (hypnotics). Co-administration of indomethacin (anti-inflammatory) and lithium (treatment of mania) can lead to elevated lithium concentration in plasma with symptoms like restlessness, difficulty in controlling fine hand movement, loss of appetite etc.

Interventions recommended preventing the risk of drug-drug interactions:

- Changing one of the potential interacting drug;
- Allowing an interval of 2 to 3 hours between the administration of interacting drugs;
- Altering the dose of the affected drug;
- Advising the patients to tell the medicines they have been taking including the herbals to doctor or pharmacist.

e. *Medicine and Food Interaction*: The foods including drinks profoundly influence the affect of medicines. The impacts of the influence are often significant and may occur at any stages of medicines' journey in the body. The effects of foods in medicines' action are described under broad headings: Concept of taking medicines before food and taking medicines after food.

The food influences the entry of drugs into the systemic circulation from oral administration. The entry into the systemic circulation is called absorption and the absorption is affected by many factors but our discussion is restricted to influence of food which would be discussed under concept of before food and after food. Some drugs are advised to be taken before food while some are advised to be taken with or after food.

a. *Concept of taking medicines before food:* When the food interfere the absorption of drugs, such drugs are advised to be taken before food. Calcium rich foods like milk, diary products, cabbage, lettuce, spinach etc. form complexes with tetracycline, oxytetracycline, ciprofloxacin, Norfloxacin causing a decrease in their absorption. These medicines are required to be taken one hour before or two hour after meals. Anti-vomiting medicines like domperidone, promethazine should be given at least half an hour before giving other medicines or before starting journey.
b. *Concept of taking medicines after food:* The foods may increase the absorption. Taking medicines after food reduces the gastric irritation. Griseofulvin (anti-fungal antibiotic), Fluconazole (treatment for fungal infection) and fat soluble vitamins like A, D and K are better absorbed after food (especially with fatty food). Non-steroidal anti-inflammatory agents, corticosteroids, Doxycyline, Allupurinol (treatment of high level of uric acid or kidney stone or preventing gout) etc. may cause stomach irritation, acidity, nausea, vomiting etc. They should be taken on full stomach. The iron preparations are also advised to be taken after food to reduce gastric irritation.

When advised to be taken after food, it means the medicine is to be taken while one is eating or just after that preferably within 30 minutes of the meal.

It is not that the food alone has influence on the action of medicines. The drinks especially alcoholic ones have profound influence on medicines' action. Alcohol potentiates the liver toxicity of paracetamol. Alcohol is central nervous depressant and can cause increase in sedative action of medicines like diazepam, lorazepam (sedatives), chlorphenarmine, promethazine, cyproheptadine (anti-histamines). The combined use can be dangerous. Alcohol may increase the side effects of Metronidazole. The patient may be advised to stop taking alcohol while on Metronidazole and wait for at least 24 hours before drinking again. Grape fruit juice may inhibit the enzyme system responsible for metabolism of nifedipine, felodipine (treatment for hypertension). The level of nifedipinee, felodipine is increased in blood and may cause pronounced decreased blood pressure, facial flushing, and headache.