(Unit – 8)

Pharmaceutics – II

(Unit Operations I, including Engineering Drawing)

“ Material of Construction ”

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Material of Construction

Syllabus:

General study of composition, corrosion, resistance. Properties and applications of the materials of construction with special reference to stainless steel and glass.

A number of equipment are used in the manufacture of pharmaceuticals, bulk drugs, antibiotics, biological products etc. A wide variety of materials are used.

***Classification of material of construction*:**

Material of construction

- Metals
  - Ferrous
    - Cast Iron
    - Steel Carbon
    - Stainless Steel
  - Non-ferrous
    - Aluminium
    - Lead
- Non-metals
  - Inorganic
    - Glass
  - Organic
    - Rubber
    - Plastics

FACTORS INFLUENCING THE SELECTION OF MATERIALS OF CONSTRUCTION

The selection of a material for the construction of equipment depends on the following properties

1. Chemical factors

   a) Contamination of the product
   b) Corrosion of material of construction

2. Physical factors

   a) Strength
   b) Mass
   c) Wear properties
   d) Thermal conductivity
   e) Thermal expansion
   f) Ease of fabrication
   g) Cleaning
   h) Sterilization
   i) Transparency

3. Economic factors

1. Chemical factors

Whenever a chemical substance is placed in a container or equipment the chemical is exposed to the material of construction of the container or equipment. Therefore, the material of construction may contaminate the product (*contamination*) or the product may destroy the material of construction (*corrosion*).

***Contamination of product*:**

Iron contamination may change the color of the products (like gelatin capsule shells), catalyze some reactions that may enhance the rate of decomposition of the product.

Leeching of glass may make aqueous product alkaline. This alkaline medium may catalyze the decomposition of the product.

Heavy metals such as lead, inactivate penicillin.

***Corrosion of material of construction*:**

The products may be corrosive in nature. They may react with the material of construction and may destroy it. The life of the equipment is reduced.

Extreme pH, strong acids, strong alkalis, powerful oxidizing agents, tannins etc. reacts with the materials, hence some alloys having special chemical resistance are used.

2. Physical factors

a) Strength:

The material should have sufficient physical strength to withstand the required pressure and stresses.

- **Iron and steel** can satisfy these properties. Tablet punching machine, die, upper and lower punch sets are made of stainless steel to withstand the very high pressure.
- **Glass**, though has strength but are brittle.
  Aerosol container must withstand very high pressure, so **tin plate** container coated with some polymers (lacquered) are used.
- **Plastic** materials are weak so they are used in some packaging materials, like blister packs.

b) Mass:

For transportation light weight packaging materials are used. Plastic, aluminum and paper packaging materials are used for packing pharmaceutical products.

c) Wear properties:

When there is a possibility of friction between two surfaces the softer surface wears off and these materials contaminate the products. For example, during milling and grinding the grinding surfaces may wear off and contaminate the powder. When pharmaceutical products of very high purity is required ceramic and iron grinding surfaces are not used.

d) Thermal conductivity:

In evaporators, dryers, stills and heat exchangers the materials employed have very good thermal conductivity. In this case iron, copper or graphite tubes are used for effective heat transfer.

e) Thermal expansion:

If the material has very high thermal expansion coefficient then as temperature increases the shape of the equipment changes. This produces uneven stresses and may cause fractures. So, such materials should be used those are able to maintain the shape and dimension of the equipment at the working temperature.

f) Ease of fabrication:

During fabrication of an equipment, the materials undergo various processes such as casting, welding, forging and mechanization etc. For example, glass and plastic may be easily molded in to containers of different shape and sizes. Glass can be used as lining material for reaction vessels.

g) Cleaning:

Smooth and polished surfaces make cleaning easy. After an operation is complete, the equipment is cleaned thoroughly so the previous product cannot contaminate the next product. Glass and stainless-steel surfaces can be smooth and polished, hence are easy to clean.

h) Sterilization:

In the production of parental, ophthalmic and bulk drug products all the equipment is required to be sterilized. This is generally done by introducing steam under high pressure. The materials must withstand this high temperature (121^0C) and pressure (15 pounds per square inch). If rubber materials are there it should be vulcanized to withstand the high temperature.

i) Transparency:

In reactors and fomenters, a visual port is provided to observe the progress of the process going on inside the chamber. In this case borosilicate glass is often used.

In parental and ophthalmic containers, the particles, if any, are observed from with polarized light. The walls of the containers must be transparent to see through it. Here also glass is the preferred material.

3. Economic factors

Initial cost of the equipment depends on the material used. Several materials may be suitable for construction from physical and chemical point of view, but from all the materials only the cheapest material is chosen for construction of the equipment.
Materials those require lower maintenance cost are used because in long run it is economical.

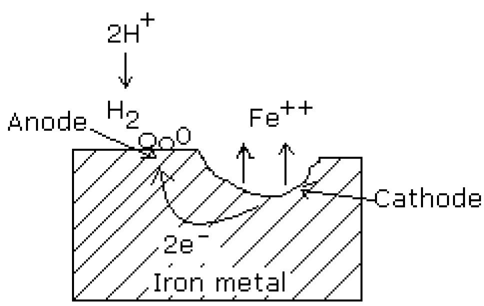
CORROSION

Definition: Corrosion is defined as the reaction of a metallic material with its environment, which causes a measurable change to the material and can result in a functional failure of the metallic component or of a complete system.

Classification of corrosion according to the environment

1. **Dry corrosion**: It involves the direct attack of gases and vapor on the metals through chemical reactions. As a result, an oxide layer is formed over the surface.

2. **Wet corrosion**: This corrosion involves purely electrochemical reaction, that occurs when the metal is exposed to an aqueous solution of acid and alkali.
   e.g. $Zn + 2HCl \rightarrow ZnCl_2 + H_2\uparrow$



THEORY OF CORROSION

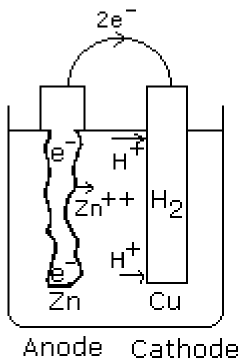
1. Corrosion reaction on single metal

A single piece of metal (e.g. Fe) when comes in contact with acid (e.g. HCl) small galvanic cells may be set up on the surface.
Each galvanic cell consists of (i) anode regions and (ii) cathode regions.

Reaction at anode: Fe on the iron leaves two electrons to the metal and itself becomes Fe^{++} ion. Fe^{++} ion is soluble in water, so it is released in the medium. Thus, the iron surface is corroded.

Reaction at cathode: The released electron is conducted through the metal piece into cathode region. Two electrons are supplied to two protons (H^+) to form two atoms of H. Hydrogen atoms are unstable, hence two H atoms will combine to form a molecule of stable H_2. In the absence of acid, water itself dissociates to generate H^+ ion.

$2H^+ + 2e^- \rightarrow H_2\uparrow$ Hydrogen (H_2) forms bubbles on the metal surface. If the rate of hydrogen formation is very slow then a film of H_2 bubbles will be formed that will slow down the cathode reaction, hence the rate of corrosion will slow down.
If the rate of hydrogen production is very high then hydrogen molecules cannot form the film on the surface. So, the corrosion proceeds rapidly.



2. Corrosion reactions between metals

If two metals come in contact with a common aqueous medium then one metal will form anode and the other will form cathode. Now if both the metals are connected with a wire the reaction will proceed. Anode metal will be corroded and hydrogen will form at the cathode.

For example, if a zinc and a copper plate is immersed in an acidic medium then zinc will form anode and will be corroded while hydrogen will be formed at copper plate.

Abode reaction: $Zn \rightarrow Zn^{++} + 2e^-$.

Cathode reaction: $2H^+ + 2e^- \rightarrow H^2\uparrow$

So, anode will be corroded and hydrogen will be evolved at cathode.

3. Corrosion involving oxygen

The oxygen dissolved in the electrolyte can react with accumulated hydrogen to form water. Depletion (reduction) of hydrogen layer allows corrosion to proceed.

At cathode: $O_2 + 2H_2 \rightarrow 2H_2O$

The above reaction takes place in acid medium. When the medium is alkaline or neutral oxygen is absorbed. The presence of moisture promotes corrosion.

FACTORS INFLUENCING CORROSION

1. pH of the solution

- Iron dissolves rapidly in acidic pH.
- Aluminum and zinc dissolves both in acidic and alkaline pH.
- Noble metals are not affected by pH e.g. gold and platinum.

2. Oxidizing agents

Oxidizing agents may accelerate the corrosion of one class of materials whereas retard another class.

- e.g. O_2 reacts with H_2 to form water. H_2 is removed, corrosion is accelerated. Cu in NaCl solution follows this mechanism.
- e.g. Oxidizing agents forms a surface oxide (like Aluminum oxide) and makes the surface more resistant to chemical attack.

3. Velocity

When corrosive medium moves at a high velocity along the metallic surface, the rate of corrosion increases due to:

- Corrosion products are formed rapidly and washed away rapidly to expose new surface for corrosion reaction.
- Accumulation of insoluble films on the surface is prevented.
- The corrosion is rapid in the bends in the pipes, propellers, agitators and pumps.

4. Surface films

- Thin oxide films are formed on the surface of stainless (rusting). These films absorb moisture and increases the rate of corrosion.
- Zinc oxide forms porous films. Fluid medium can enter inside and thus corrosion continues. Nonporous films of chromium oxide or iron oxide prevent corrosion.
- Grease films protect the surface from direct contact with corrosive substances

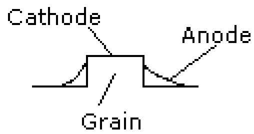
TYPE OF CORROSION

1. Fluid corrosion: General

When corrosion is generally confined to a metal surface as a whole, it is known as general corrosion. This corrosion occurs uniformly over the entire exposed surface area. E.g. Swelling, cracking, softening of plastic materials.

2. Fluid corrosion: Localized

(a) Inter-granular corrosion: During heat treatment or welding, some components get precipitated at the grain boundary of the metal. These boundaries acts as anodes and grains as cathodes. So, corrosion of anode region occurs.



(b) Pitting corrosion: On metal surface small holes or pits are created due to local corrosion and these pits increase in size rapidly. In the pits the metals dissolves rapidly especially by chlorine and chloride ions.

(c) Stress corrosion: Certain area of metal may be subjected to thermal, mechanical or chemical stresses. The surface area becomes anode and acts as corrosion area.

(d) Fretting corrosion: Equipment showing high vibrations destroys the surface of metal (e.g. steels balls in ball-bearing) by mechanical hitting.

(e) Corrosion fatigue: Cyclic stress breaks the protective film, so corrosion increases.

4. Fluid corrosion: Biological

Metabolic action of micro-organisms can either directly or indirectly cause deterioration of a metal by:

(i) Creating electrolyte concentration cells on the metal surface.
(ii) Influence the rate of anodic / catholic reactions.
(iii) Sulphates are reduced by reducing bacteria and produces hydrogen peroxide (H_2S) that reacts with iron to produce ferrous sulphide (FeS). Thus, the iron gets corroded.

PREVENTION OF CORROSION

Following methods may be adopted for preventing or reducing corrosion:

1. Material selection

(a) Pure materials have less tendency towards pitting, but they are expensive and soft. Therefore, only aluminum can be used in pure form.

(b) Improved corrosion resistance can be obtained by adding corrosion resistant elements. For example, inter-granular corrosion occurs in stainless steel. This tendency can be reduced by addition of small amount of *titanium*.
(c) Nickel, copper and their alloys are used in non-oxidizing environment, whereas chromium containing alloys are used in oxidizing environment.
(d) Materials those are close in electrochemical series should be used for fabrication.
(e) Corrosive materials are taken with suitable material of construction:

Corrosive material	Suitable material
Nitric acid	Stainless steel
Hydrofluoric acid	Monel metal
Distilled Water	Tin
Dilute Sulfuric acid	Lead
Caustic	Nickel

3. Proper design of equipment

Corrosion can be minimized in the following conditions:
(a) Design for complete drainage of liquids.
(b) Design for ease of cleaning.
(c) Design for ease of inspection and maintenance
(d) A direct contact between two metals should be avoided. They may be insulated from one another.

4. Coating or lining

Corrosion resistant coating may be applied on metal surface to improve corrosion resistance. It also separates the metal from corrosive environment.
(a) Organic coating is used as lining in equipment such as tanks, & piping.

FERROUS MATERIAL

Cast Iron, Steels, Stainless Steels

❖ Cast Iron

This iron consists of carbon more than 1.5%. Different proportions of carbon give different properties of the steel.

Properties:

1. Cast iron is resistant to concentrated sulfuric acid, nitric acid and dilute alkalis.
2. Cast iron is attacked by dilute sulfuric acid, dilute nitric acid and dilute and concentrated hydrochloric acid.
3. Cast iron has low thermal conductivity.
4. It is not corrosion resistance hence it is alloyed with Silicon, Nickel or Chromium to produce corrosion resistance.
5. It is brittle so it is tough to machine.

***Applications*:**

1. It is used as supports for plants.
2. Thermal conductivity is low hence used as the outer wall of steam jacket.
3. It is cheap hence used in place of more expensive materials by coating with enamel or plastic.

❖ Carbon Steel or Mild Steel

Mild steel (or carbon steel) is an iron alloy that contains a small percentage of carbon (less than 1.5%).

Properties

1. It has greater mechanical strength than cast iron.
2. It is easily weldable.
3. Has limited resistance to corrosion. This property can be increased by proper alloying.
4. It reacts with caustic soda, brine (concentrated NaCl solution).

Applications

1. Used for construction of bars, pipes and plates.
2. Used to fabricate large storage tanks for water, sulfuric acid, organic solvents etc.
3. Used as the supporting structures of grinders and bases of vessels.

❖ Stainless Steel

Stainless steel is an alloy of iron usually of nickel and chromium.

For pharmaceutical use stainless steel contains 18% chromium and 8% nickel. This steel is called 18/8 stainless steel.

In addition to corrosion resistance, the advantageous physical properties of stainless steel include:

1. It is heat resistant
2. Corrosion resistant
3. Ease of fabrication
4. Cleaning and sterilization is easy.
5. Has good tensile strength.
6. High and low temperature resistance.
7. Ease of fabrication.
8. High Strength.
9. Aesthetic appeal.
10. Hygiene and ease of cleaning.
11. Long life cycle.

12. Recyclable.
13. Low magnetic permeability.
14. During heat welding the corrosion resistant properties of stainless steel may be reduced due to deposition of carbide precipitate at the crystal grain boundaries. This steel is stabilized by addition of minor quantities of titanium, molybdenum or niobium.

Applications:

Stainless steel applications

1. **Automotive and transportation**

Stainless steel was introduced in automotive in the 1930s by Ford to manufacture their concept cars. Since then, it is used to produce a variety of automotive parts such as exhaust systems, grills, and trims. With advancing technology, stainless steel is being favored by manufacturers to make structural components.
It is also heavily featured in other fields of transportation like freighting to make shipping containers, road tankers and refuse vehicles. It's resistance to corrosion makes it ideal to transport chemicals, liquids and food products. The low maintenance of stainless steel also makes it an easy and cost-effective metal to clean and sustain.

2. **Medical technology**

Stainless steel is preferred in clean and sterile environments as it is simple to clean and does not easily corrode. Stainless is used in the production of a wide range of medical equipment, including surgical and dental instruments.
It is also used in building operation tables, kidney dishes, MRI scanners, cannulas, and steam sterilizers. Most surgical implants, such as replacement joints and artificial hips are made from stainless steel, as well as some joining equipment like stainless steel pins and plates to repair broken bones.

3. **Building trade**

Due to its strength, resistance, and flexibility, stainless steel application has become a vital element of the building trade. It is commonly featured in the interior on countertops, backsplashes, and handrails, and is also used externally in cladding for high impact buildings. It is a common feature in modern architecture due to its weldability, easy maintenance and attractive finish, which is used in the Eurostar Terminal in London and the Helix Bridge in Singapore. With the movement towards sustainable building, stainless steel, which is a highly recyclable metal, is becoming increasingly preferable to use in construction. With a polished or grain finish, it has aesthetically pleasing properties and can aid in improving natural lighting in the building.

4. **Aircraft Construction**

The aviation industry also has a preference for stainless steel. It is used in various applications including the frames of aero planes because of its strength and ability to withstand extreme temperatures. It can also be applied in jet engines as it can help prevent against its rushing Stainless steel is also an essential part of the landing gear. Its strength and rigidity can handle the weight of the landing aircraft.

5. **Food and the catering industry**

In the food and catering industry, stainless steel is used to manufacture kitchen accessories, cookware, and cutlery. Utensils such as knives are made using less ductile grades of stainless steel. The more ductile grades are used to make grills, cookers, saucepans, and sinks. Stainless steel can also be used to finish freezers, dishwashers, refrigerators, and countertops. In food production, stainless steel is ideal because it doesn't affect the flavor of the food. It is also corrosion resistant, and hence able to hold acidic drinks including orange juice. The ease of cleaning stainless steel makes it difficult to harbor bacteria, adding to its usefulness in food storage.

6. **Tanker manufacture**
7. **Vessel manufacture**

❖ **Aluminum**

Properties:

1. Pure aluminum is soft and more corrosion resistant than its alloys. Small percentages of manganese, magnesium or silicon produces strong, corrosion resistant aluminum alloys (e.g. Duralumin)
2. It is attacked by mineral acids, alkali, mercury and its salts.
3. It is resistant to strong nitric acid.
4. It is resistant to acetic acid due to the formation of a gelatinous surface film of aluminum sub acetate.
5. Low density hence lighter.

Applications:

1. The salts of aluminum is colorless and non-toxic to microorganisms, hence used for fermenting vessels for biosynthetic production of citric acid, gluconic acids and streptomycin.
2. Used for making extraction and absorption vessels in preparation of antibiotics.
3. Storage vessels of acetic acid and ammonia.
4. Plants for nitric acid is used.

5. Because of its lightness large containers such as drums, barrels, road and rail tankers are made with aluminum.

GLASS

Preparation of glass:

Glass is composed principally of sand (silica - SiO_2), soda-ash (Na_2CO_3 - sodium carbonate) and lime-stone (Ca CO_3-calcium carbonate).

Glass made from pure silica consists of a three-dimensional network of silicon atoms each of which is surrounded by four oxygen atoms an in this way the tetrahedral are linked together to produce the network.

Glass prepared from pure silica require very high temperature to fuse, hence soda-ash and lime is used to reduce the melting point.

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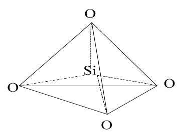

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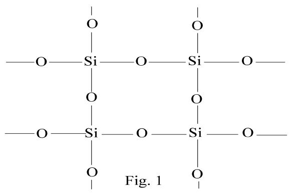


Fig. 1

(i) glass made of pure silica has network (Fig-1)

<u>Properties</u>:

(a) It is very hard and

(b) chemically resistant but

(c) melting point very high so it is very difficult to mould.

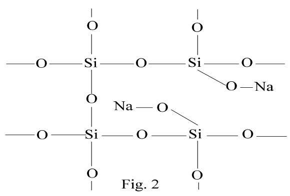
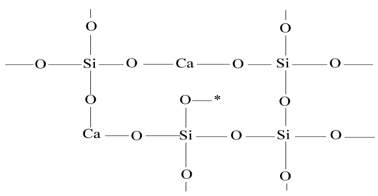


Fig. 2

(ii) Glass made of pure silica + Na_2O (Fig.-2)

(valency of Na = 1)



* Connected to another Ca ion or tetrahedron

Fig. 3

<u>Properties</u>:

(a)Structure is less rigid so low

m.p. and easier to mould

(b) the glass is too rapidly attacked

by water and NaOH is leached out of the glass.

(iii) Pure silica + CaO (or BaO, MgO, PbO and ZnO) (Fig.-3)

(valency of Ca, Ba, Mg, Pb, Zn = 2)

Properties:

(a) divalent oxides do not break the network of pure silica, but only push the tetrahedron

apart. It is more rigid than soda-silica network.

(b) Since the bond is more stronger, hence chemical reactivity is lowered.

(iv) Pure silica + Boric(B_2O_3) or aluminum oxide (Al_2O_3)

(valency of B and Al = 3, i.e. trivalent)

Properties:

(a) Since boric oxide, like silica, is acidic. it does not disrupt the network of silica but forms tetrahedron itself; however, these are not the same size as the silicon tetrahedral; as a result, the lattice become distorted, and this produces flexibility.

(b) It is chemically resistant.

Type of glass	**Main Constituents**	**Properties**	**Uses**
Type-1 Borosilicate glass e.g. Pyrex, Borosil	SiO_2 – 80% B_2O_3 – 12 Al_2O_3 - 2% Na_2O+CaO - 6%	• Has high melting point so can withstand high temperature • Resistant to chemical substances • Reduced leaching action	• Laboratory glass apparatus • For injections and • for water for injection.
Type-II Treated soda-lime glass	Made of soda lime glass. The surface of which is treated with acidic gas like SO_2 (i.e. dealkalised) at elevated temperature (500^0C) and moisture.	• The surface of the glass is fairly resistant to attack by water for a period of time. • Sulfur treatment neutralizes the alkaline oxides on the surface, thereby rendering the glass more chemically resistant.	• Used for alkali sensitive products • Infusion fluids, blood & plasma. • large volume container

Type-III Regular soda-lime glass	SiO_2 Na_2O CaO	• It contains high concentration of alkaline oxides and imparts alkalinity to aqueous substances • Flakes separate easily. • May crack due to sudden change of temperature.	• For all solid dosage forms (e.g. tablets, powders) • For oily injections • Not to be used for aqueous injection • Not to be used for alkali-sensitive drugs.
Type NP Non-parenteral glass or General-purpose soda-lime glass.			• For oral and • Topical purpose • Not for ampoules.
Neutral Glass	SiO_2 – 72-75% B_2O_3 – 7-10% Al_2O_3 – 6% Na_2O – 6-8% K_2O – 0.5 – 2% BaO – 2-4%	• They are softer and can easily be moulded • Good resistance to autoclaving • Resistant to alkali-preparations (with pH up to 8) • Lower cost than borosilicate	• Small vials (<25 ml) • Large transfusion bottles
Neutral Tubing for Ampoules	SiO_2 – 67% B_2O_3 – 7.5% Al_2O_3 – 8.5% Na_2O – 8.7% K_2O – 4% CaO – 4% MgO – 0.3%	• In comparison to neutral glass its melting point is less. After filling the glass ampoules are sealed by fusion and therefore the glass must be easy to melt.	• Ampoules for injection.
Colored glass	Glass + iron oxide	• Produce amber color glass • Can resist radiation from 290 $\longleftrightarrow$ 400 $\longleftrightarrow$ 450nm UV -Visible	• For photosensitive products.

Advantages of glass container

Physical aspect

1. They are quite strong and rigid.
2. They are transparent which allows the visual inspection of the contents; especially in ampoules and vials.
3. They are available in various shapes and sizes. Visually elegant containers attract the patients.
4. Borosilicate (Type-I) and Neutral glasses are resistant to heat so they can be readily sterilized by heat.
5. Glass containers can be easily cleaned without any damage to its surface e.g. scratching or bruising.

Chemical aspect

1. Borosilicate type of glass is chemically inert. Treated soda lime glass has a chemically inert surface.
2. As the composition of glass may be varied by changing the ratio of various glass constituents the proper container according to desired qualities can be produced.
3. They do not deteriorate with age, if provided with proper closures
4. Photosensitive drugs may be saved from UV-rays by using amber color glass.

Economical aspect

1. They are cheaper than other packaging materials.

Disadvantages:

Physical aspect

1. They are brittle and break easily.
2. They may crack when subject to sudden changes of temperatures.
3. They are heavier in comparison to plastic containers.
4. Transparent glasses give passage to UV-light which may damage the photosensitive drugs inside the container.

Chemical aspect

1. *Flaking:* From simple soda-lime glass the alkali is extracted from the surface of the container and a silicate rich layer is formed which sometimes gets detached from the surface and can be seen in the contents in the form of shining plates – known as ‘flakes’ and in the form of needles – they are known as ‘spicules’. this is a serious problem, especially in parenteral preparations.

2. *Weathering*: Sometimes moisture is condensed on the surface of glass container which can extract some weakly bound alkali leaving behind a white deposit of alkali carbonate to remain over there, further condensation of moisture will lead to the formation of an alkaline solution which will dissolve some silica resulting in loss of brilliance from the surface of glass – called weathering.

   To prevent weathering, the deposited white layer of alkali carbonates should be removed as early as possible by washing the containers with dilute solution of acid and then washing thoroughly with water.