LECTURE NOTES
ON
PHARMACEUTICAL TECHNOLOGY-II
(Subject Code:15R00503)

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KRISHNA TEJA PHARMACY COLLEGE(AF)
Chadalawada Nagar, Renigunta Road, Tirupati – 517 506

UNIT-I

TABLETS AND COATING OF TABLETS

General methods of tablet preparation:

- **Wet Granulation**

- The most widely used and most general method.

- **This due to the greater probability that the granulation will meet all the physical**

requirements for the compression of good tablets.

- **Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on a large scale.**

- **The steps in the wet method are:**

1-weighing, 2-mixing, 3-granulation, 4-screening the damp mass
5- drying, 6-dry screening, 7-lubrication and 8-compression.

Previously it was indicated that water-soluble colorants can migrate toward the surface of the granulation during the drying process, resulting in mottled tablets after compression.

- This is also true for water-soluble drug substances, resulting in tablets unsatisfactory as to content uniformity.

- Migration can be reduced by drying the granulation slowly at low temperatures or using a granulation in which the major diluent is present as granules of large particle size. The presence of microcrystalline cellulose in wet granulations also reduces migration tendencies.

- Dry Granulation

- When tablet ingredients are sensitive to moisture or are unable to withstand
elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form
granules.
- This method is referred to as dry granulation, pre compression or double-compression. It eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication and compression.

- The active ingredient, diluent (if one is required) and part of the lubricant are blended. One of the constituents, either the active ingredient or the diluent, must have cohesive properties. Powdered material contains a considerable amount of air; under pressure this air is expelled

and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug .

• For tablets in which the drug itself constitutes a major portion of the total tablet weight, it is necessary that the drug possess those physical characteristics required for the formulation to be compressed directly.

• Direct compression for tablets containing 25% or less of drug substances frequently can be used by formulating with a suitable diluent which acts as a carrier or vehicle for the drug.

• These properties are imparted to them by a preprocessing step such as wet granulation, slugging, spray drying, or crystallization.

• These vehicles include processed forms of most of the common diluents including dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, anhydrous lactose, spray-dried lactose, pregelatinized starch, compressible sugar, mannitol and microcrystalline cellulose.

• These commercially available direct- compression vehicles may contain small quantities of other ingredients (e.g, starch) as processing aids. Dicalcium phosphate dihydrate (Di-Tab,)

• The chemical is odorless, tasteless and non- hygroscopic. Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation.

• Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lubricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness.

* One commercial source is Di-Pac (Amstar) prepared by the cocrystallization of 97% sucrose and 3% dextrins.

* Some forms of lactose meet the requirements for a direct-compression vehicle. Hydrous lactose does not flow and its use is limited to tablet formulations prepared by the wet granulation method, Both anhydrous lactose and spray dried lactose have good flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present.

• microcrystalline cellulose (Avicel, FMC).
This non fibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in several grades which range in average particle size from 20 to 100 um. It is water insoluble but the material has the ability to draw fluid into a tablet by capillary action.

UNIT-II

CAPSULES

CAPSULE DOSAGE FORM

INTRODUCTION:

➢ Early 19th century, Mathes developed the first capsule dosage form from gelatin.

➢ Since then this technology has been continuously improved and refined, yielding range of capsule forms available today.

➢ Capsules are gelatin shells filled with the ingredients that make up an individual dose.

➢ Dry powders, semi-solids, and liquids that do not dissolve in gelatin may be encapsulated.

➢ Capsules account for about 20% of all prescriptions dispensed. 1. HARD GELATIN CAPSULE

2. SOFT GELATIN CAPSULE

MAINLY TWO TYPES

Capsules are used for filling different materials like Powders, Granules, Beads, Tablets, Capsules, Pastes etc..

Some of the disadvantages associated with conventional capsule:

They are easily tampered with (although techniques exist for preventing this). They are subject to the effects of relative humidity and to microbial contamination. **Some of the innovations are targeted to:**

Overcome the disadvantages associated with conventional capsules.

Achieve modified drug release.

Encapsulation of various kind of material.

Modified applications

INNOVATIONS IN CAPSULES:

1) **Innovations in Capsule Shells**: it includes modification of capsule shell to improve shell property.

2) **Innovations in Capsule System**: it includes modification of the system to achieve modified release.

1]INNOVATIONS IN CAPSULE SHELLS:

Targeted to :

Improvement in the shell property

DOSAGE FORM

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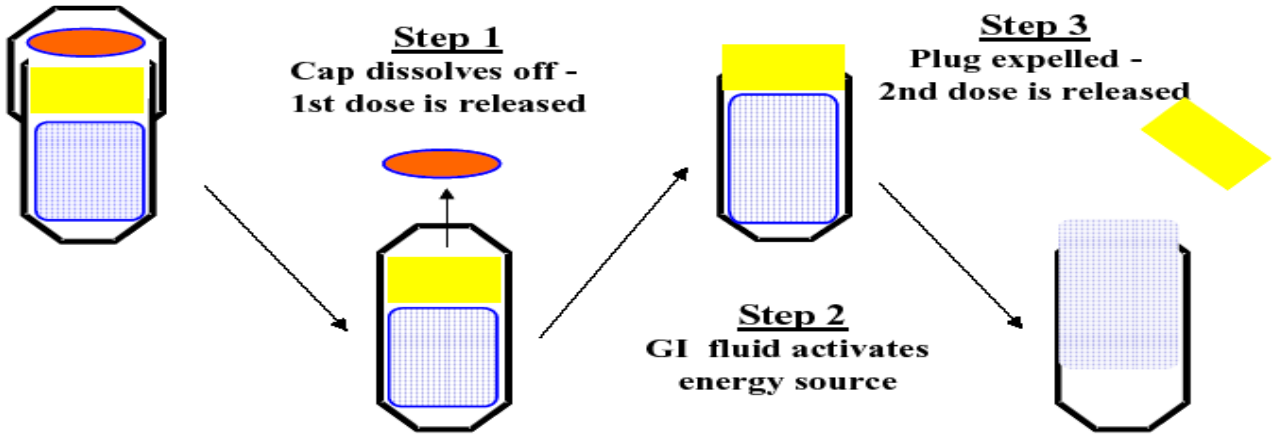

Figure 4. Drug release mechanism from the PORT Capsule.

➢ **Less brittle** even in low humidity(≤1% moisture content)
➢ Fast dissolution (No change in dissolution profile under stress conditions) and soluble in water at room temperature.
➢ No cross linking.
➢ **Lower water vapor permeability** than Gelatin capsule.**(Gelatin>PEG- Gelatin>HPMC)**
➢ Low static electricity and light protected.
➢ No Millard reaction with fillings.
➢ Not substrate for protease.
➢ High tolerance to temperature
➢ Chemical inactivity and solubility at room temperature.
➢ In these type of capsules powder, tablet, granules, pellets, liquids and semisolids are filled.
➢ Suited to automatic capsule filling machines.

QUALI-V®-I:
A New Key for Dry Powder Inhalers
➢ Superior physical performance a moisture contents
➢ Content could easily arise in the usage of DPIs with capsules.
➢ Better cutting and puncturing performance in standard DPIs.
➢ Elimination of the generation of shell particles in use.
➢ Excellent microbiological quality.
➢ Higher weight specification available if required.
➢ Suitable for use in all types of DPIs ❖ Water-soluble polysaccharide
❖ Derived by bacterial fermentation from corn.
❖ Widely use in Japan
❖ They are odorless, tasteless, and completely biodegradable
❖ Used in production of foods, pharmaceuticals and cosmetics.
❖ The film formation properties of Pullulan are similar to gelatin.
❖ Dried capsules are comparatively weak in physical strength.
❖ Requires water to act as a film plasticizer, which may have a negative effect on active ingredients.
❖ Only one supplier of the raw material
❖ Does not show any meaningful advantages over hypromellose

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NP Caps™:

- ➢ Made up of pullalan.
- ➢ Pullulan is very stable and well-characterized, and has achieved wide regulatory acceptance with its proven safety record.
- ➢ Its generally use for those people who are vegetarians, diabetics and patients with restricted diets.
- ➢ It is 100% natural they are Vegetable origin, No chemical modification, Non-GMO, Starch-free, Preservative-free, Gluten-free.

PVA CAPSULES:

- PONDAC Capsule (name)
- Insoluble drugs can be dissolved in solvents such as macrogol 400, being filled in capsules.
- The bioavailability of insoluble drugs can be improved very much.
- The oxygen permeability of PVA copolymer capsule is significantly low.
- The gelatin capsule was developed in the 19th century.
- The HPMC capsule was developed in the 20th century.
- The PONDAC capsule is the hope for the 21st century

STARCH CAPSULES:

- Made from potato starch and represent a direct alternative to hard gelatin capsule.
- Manufactured by the injection moulding technique developed by Capsugel (Capill®).
- Offers advantages like.
    - pH independent dissolution
    - Suitable for enteric coating
    - Tamper evident

- Consists cap and body; which are sealed together at the time of filling to prevent separation.
- Sealing is achieved by applying a hydro alcoholic solution to inner section of the cap, immediately prior to its being placed on to the body.
- Different size capsules are manufactured (number 0, 1, 2, 3, 4) by changing the mold.
- Officially recognized in USP 23 and NF 18

ENTERIC STARCH CAPSULES:

- Overcome coating problems encounter during coating of HGC.
- Coating of starch capsules appear to be less problematic because of the smooth seal, coupled with the higher bulk density of capsules, which provide for a more uniform coating bed.
- Stability of coated starch capsule evaluated.
- Eg. TARGIT®

VCaps®:

- Two-piece capsules made from cellulosic raw materials that satisfy vegetarian and cultural needs
- easy to swallow
- effectively mask taste and odor
- allow product visibility
- Vcaps capsules are also starch-free, gluten-free and preservative-free, and meet the strict dietary needs of customers that choose a vegetarian lifestyle.
- They are also Kosher and Halal certified.
- Vcaps vegetable capsules are manufactured in a GMP facility that meets ISO 9000 certification criteria.

GELATIN/PEG CAPSULES:

- Reduce the brittleness of standard gelatin capsules when exposed to a low-moisture content thus making the capsules more compatible to hygroscopic formulations or moisture-sensitive ingredients

Gelatin/PEG Features

- Less brittle
- Good for hygroscopic and moisture-sensitive ingredients
- Odorless, tasteless,three-year shelf life

- At moisture contents between 8% - 12%, gelatin/PEG capsules have equivalent mechanical strength to standard gelatin capsules with moisture between 13% - 16%.

Gelatin/PEG capsules are available in commercial pharmaceutical products

- Cardiovascular (Tocopherol nicotinate)
- Vasodilators (Nifedipine)
- Antihypertensive (Captopril)
- Digestive Enzyme

Ocean CapsTM:

- ✓ OceanCapsTM is fish gelatin capsules
- ✓ It contain all-natural marine supplements
- ✓ Its over 40% of supplement users in France, Germany and the UK
- ✓ US consumers continue to move toward natural alternatives, and look for products like marine supplements in fish capsules
- ✓ Ideally suited for fish-eating vegetarians looking for fish capsules, and marine supplements such as fish oil, DHA, EPA, salmon liver oil, shark cartilage and glucosamine.
- ✓ Perfect for the supplement needs of fish-eating vegetarians, such as iron,zinc, calcium and vitamins B2 and B12
- ✓ Certified origin from high quality, farmed fish
- ✓ Preservative-free, starch-free, gluten-free

PRESS FIT® GELCAPS:

- a unique dosage form consisting of a high-gloss gelatin coating that encases a caplet core.
- Press-Fit gelcaps combine the best qualities of a gelatin capsule with the density of a tablet, creating an exciting new dosage form that can be custom engineered to meet specific product performance criteria.
- The elegant, geometric shape of Press-Fit gelcaps is distinct in the marketplace.
- The high gloss finish and extensive selection of color combinations provide additional opportunities for unique trade dress and enhanced consumer recognition.
- The outside gelatin shell is taste-free,
- Safe and effective utilization in oral dosage applications.

  Manufactured by exclusive cold- shrink process on a special filling and coating machine.

UNIT-III

MICROENCAPSULATION

MINICAPSULES:

The amount of material needed for testing is often very small(in mg)

Qualicap's Minicapsule(size9) provides a dependable method of delivering the material directly into animal's stomach with minimal waste & great flexibility in dosing & available in gelatin &HPMC option

CAPACITY	25 mm^3	
CAP LENGTH	4.3mm	+/-0.30mm
BODY LENGTH	7.3mm	+/-0.30mm
CAP DIAMETER	2.65mm	+/-0.10mm
BODY DIAMETER	2.40mm	+/-0.10mm
CLOSED JOINED LENGTH	8.40mm	+/-0.30mm
WEIGHT	9.5mg	+/-2mg

Some of the essential first pre-clinical tests that examine safety and pharmacokinetic factors are carried out on rodents or guinea pigs.

The amount of material needed for testing is often very small (milligram quantities).

Qualicap's Minicapsule (size 9) provides a dependable method of delivering material directly into the animal's stomach with minimal waste.

These small, size 9 capsules can be filled with small, yet precise doses.

Scientists have great flexibility in dosages because each capsule is filled individually and can be adjusted to the weight of the individual rodent.

Minicapsules are available in both gelatin and hypromellose (HPMC) options.

COATING METHOD FOR SOFT GELATIN CAPSULES WITH IMPROVED STABILITY .

Adding 10-90% ethanol into mixture of HPMC 20-150parts, Tween80 8.5-25vol parts, Titanium white powder 7.5-25wt parts, Talc powder 7.5-25wt parts, 2%chocolate brown solution, 7.5- 25wt parts, castor oil 15-40 vol parts to obtain coating solution, regulating flow rate of coating material at 25-40°C under relative moisture.

INNOVATIONS IN CAPSULE SYSTEM:

To provide modified release

- PORT CAPSULE TECHNOLOGY:
- HYDROPHILIC SANDWICH (HS) CAPSULE
- L-OROS®
- PULSINCAP
- CHEWABLE SOFT GELATIN CAPSULE ENCAPSULATING LIQUID FILL
- INNERCAP TECHNOLOGY
- GALACTICLES

PORT CAPSULE TECHNOLOGY:

eg.Pseudoephedrine delayed release

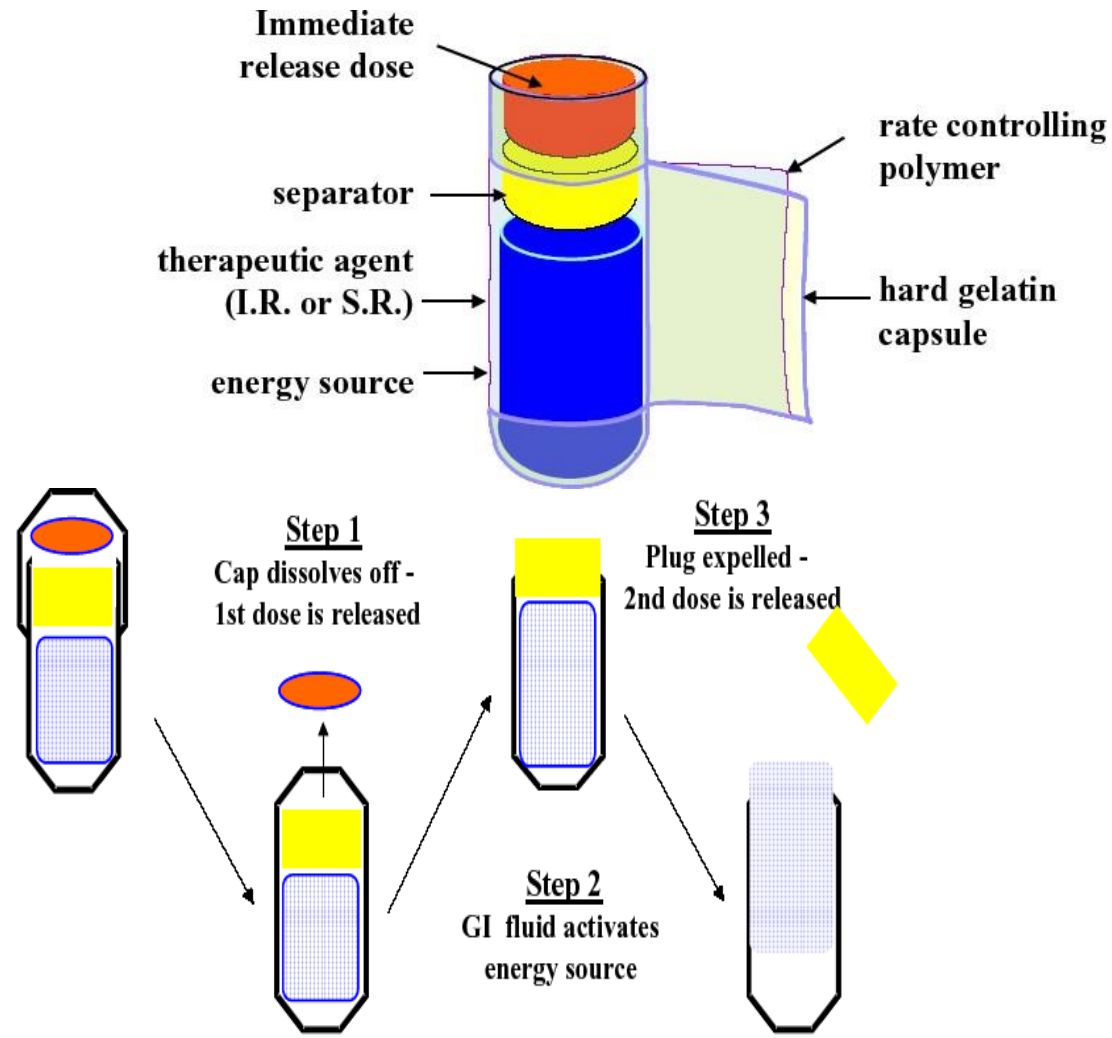
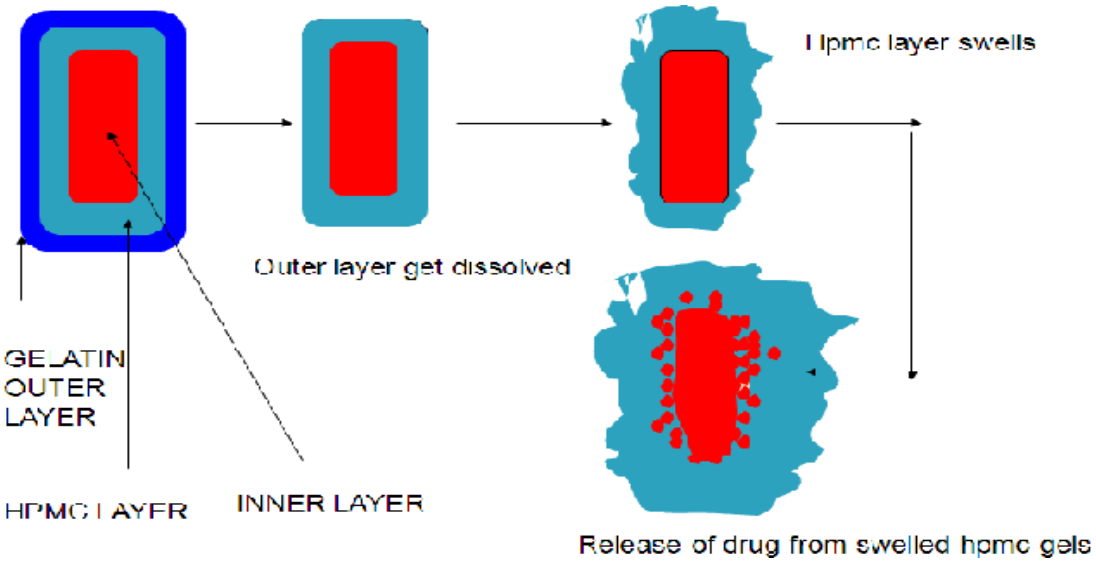


Figure 4. Drug release mechanism from the PORT Capsule.

HYDROPHILIC SANDWHICH(HS) CAPSULES:

- Simple and time delayed probe capsule
- Based on a capsule within a capsule, in which the inter capsular space was filled with a layer of hydrophilic polymer (HPMC).
- This effectively created a " Hydrophilic Sandwich " between two gelatin capsule



- When the outer capsule dissolved, the sandwich of HPMC formed a gel barrier layer that provided a time delay before fluid could enter the inner capsule and cause drug release
- The time delay was controlled by
    - Molecular weight of polymer
    - Inclusion of a soluble filler eg. Lactose

- **Advantages:**

- Enhanced bioavailability of class II drugs
- Uniform blood levels over specific period of time

- A delivery orifice in drilled through semi-permeable membrane,osmotic engine and barrier layer.
- When the osmotic engine expands it compresses the soft capsule and the drug drug formulation is pushed out through the delivery orifice.

3.DELAYED LIQUID BOLUS SYSTEM:

- Delivers the pulse of the liquid drug.
- The system consists of the placebo delay layer, a liquid drug layer, an osmotic engine all encased by a subcoat and then surrounded by semi-permeable membrane.
- The delivery orifice is drilled on the placebo layer of the system.
- When the osmotic engine expands, the placebo is released first delaying the drug release.
- Delay in drug release can be srom 1-10 hours depending on the permeability of the rate controlling membrane and the size of the placebo layer.

PULSIN CAP:

Used for pulsatile drug delivery.

In general consists of insoluble capsule body and a soluble capsule cap.

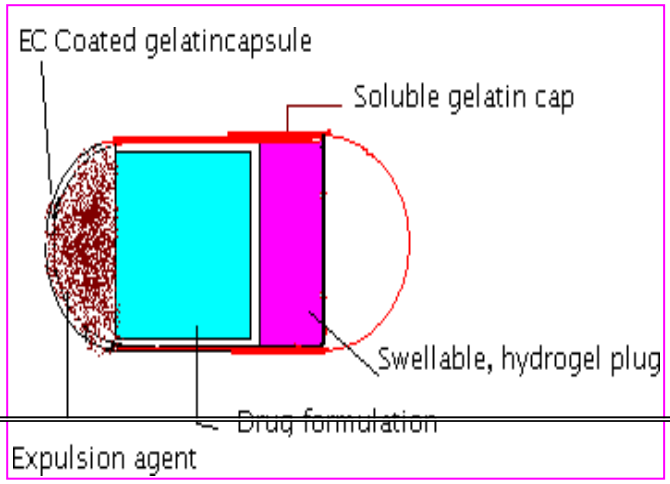
- **First concept** : separation of a plug form an insoluble capsule body.
- It comprised of a water permeable body prepared from a water-swellable hydrogel cross linked PEG polymer
- A swelling agent mixed with the drug, was filled into the internal cavity of capsule body and a plug was used to seal the contents into the internal cavity.
- Upon oral administration by the patient, cap dissolves. Water diffuses through capsule body. Swelling causes plug to move in upward direction causing drug release.

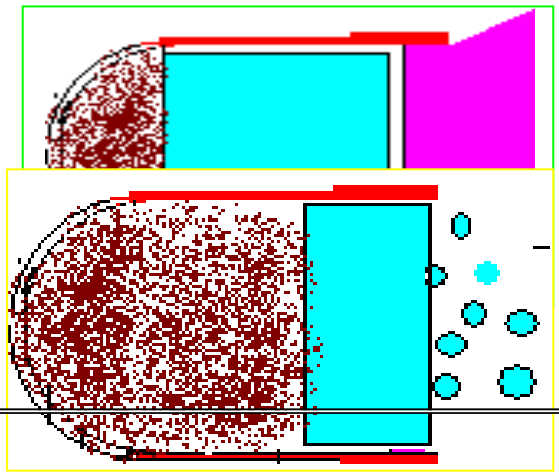
SECOND CONCEPT:

- capsule body is made of gelatin coated with ethyl cellulose.
- In the presence of fluid, the plug swelled at a controlled rate that was independent of the nature of pH of the medium.
- As the plug swells it attains frustroconical shape and it gets slowly pulled out of the capsule.
- Pulse time is controlled by:

  The length of the plug and insertion distance of plug into the capsule.

Disadvantage: not adopted for large scale manufacturing because of high cost

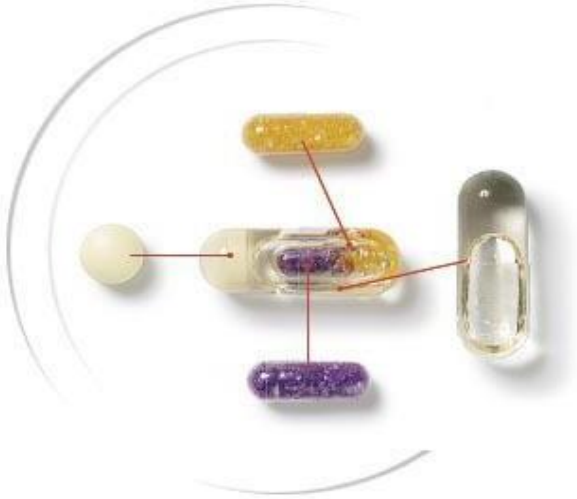




HIRD CONCEPT:

- Here in this approach in place of hydrogel plug, simple erodible compressed tablet is placed.
- This overcomes the need for the precise dimensional tolerance between capsule and plug for sliding mechanism of the plug.

ENCAPSULATING LIQUID FILL

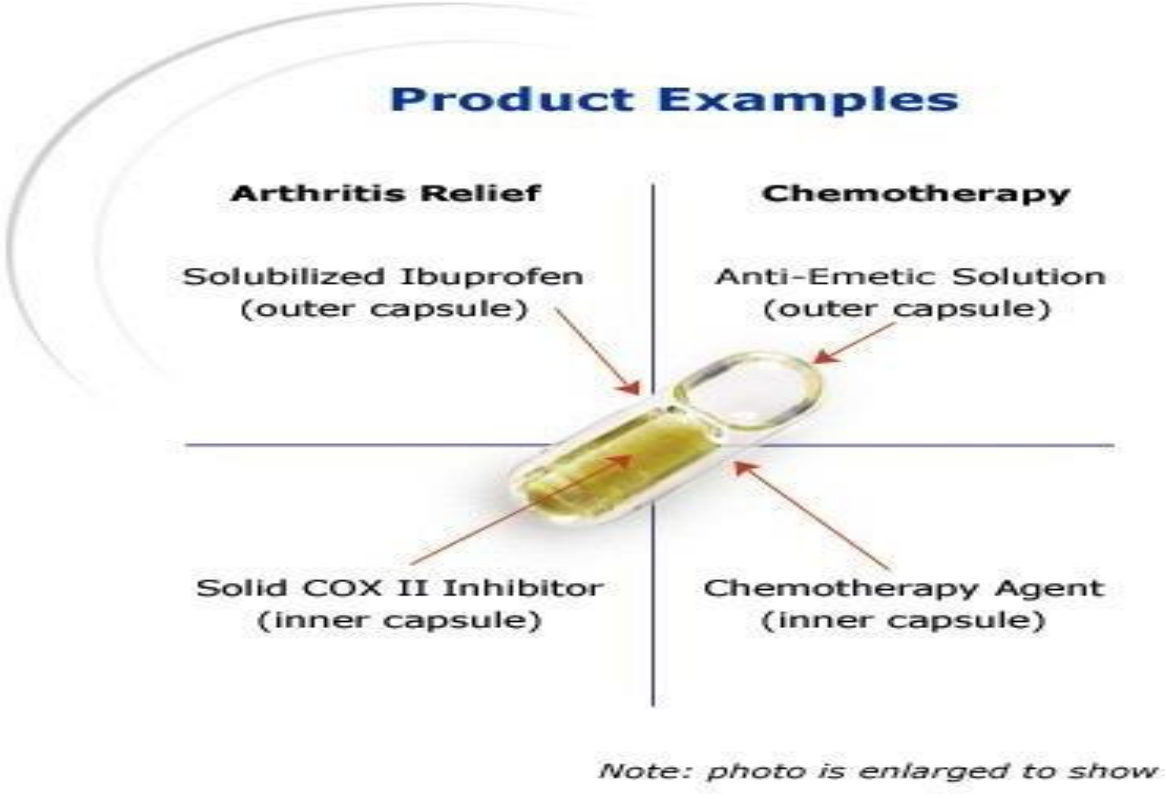


Chewable SGC require mixture of gelatin having different bloom values.

- Most preferable combination ration : 3:1 to 5:1
- It contains ingredients like,
  - Low bloom gelatin
  - Medium bloom gelatin
  - Plasticizers
  - Water
  - Moisture retaining agent
  - Other

INNER CAP TECHNOLOGY:

- The combination example consists of a high potency insoluble active in a lipid emulsion, sustained release tablet and a cocktail of two crystalline active materials.
- A combination of release profiles can be incorporated in the system.
- Can deliver incompatible and compatible drugs using different physical phases.
- The combination dosage form consists of a primary HPMC capsule containing an emulsion, pH coated tablet, crystalline filled HPMC capsule



Delivery System Examples

Capsular system delivering a liquid, enrobed tablet and crystalline filled capsule.

Capsular system delivering a lipophilic matrix and two synergistic compounds separated by two separate capsules.

HPMC capsular system administering a solubilized compound, two coated tablets and crystalline filled capsule.

components of delivery system.

Opportunities offered by Multi – Phase Multi-compartment Capsules

- Multi -Phased Materials
- Incompatible Drugs in Single Dosage
- Capsule Shell Materials
- Multiple Release Profiles
- Single Therapies
- Multiple Therapies
- Ease of Scale-Up
- Less Excipient
- Increased Bioavailability Through Absorption
- Increased Stability

UNIT –IV

PARENTERAL PREPARATIONS

Parenteral (Gk, *para enteron*, beside the intestine) dosage forms differ from all other drug dosage forms, because they are injected directly into body tissue through the primary protective systems of the human body, the skin, and mucous membranes. They must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice current good manufacturing practices (cGMPs) in the manufacture of parenteral dosage forms and on pharmacists and other health care professionals to practice good aseptic practices (GAPs) in dispensing parenteral dosage forms for administration to patients.

Characteristics of parenteral dosage forms

- Parenteral products are unique from any other type of pharmaceutical dosage form for the following reasons:

- All products must be sterile.

- All products must be free from pyrogenic (endotoxin) contamination.

- Injectable solutions must be free from visible particulate matter. This includes reconstituted sterile powders.

- Products should be isotonic, although strictness of isotonicity depends on the route of administration.

- Products administered into the cerebrospinal fluid must be isotonic.

- Ophthalmic products, although not parenteral, must also be isotonic. Products to be administered by bolus injection by routes other than intravenous (IV) should be isotonic, or at least very close to isotonicity.

CLASSIFICATION

Injections may be classified in six general categories:

- 1. Solutions ready for injection

- 2. Dry, soluble products ready to be combined with a solvent just prior to use

- 3. Suspensions ready for injection

- 4. Dry, insoluble products ready to be combined with a vehicle just prior to use

- 5. Emulsions

- 6. Liquid concentrates ready for dilution prior to administration

Components

- Components of parenteral products include the active ingredient, formulation additives, vehicle(s), and primary container and closure. Establishing specifications to ensure the quality of each of these components of an injection is essential. Secondary packaging is relevant more to marketing considerations, although some drug products might rely on secondary packaging for stability considerations.

Quality control shall be concerned with sampling, Specifications, Testing, documentation, Release procedure which ensure that necessary and relevant tests are actually carried out and materials are not release for its use or For sale, until its quality has been judged to satisfactory. The 3 General areas of parenteral quality control are incoming stocks, manufacturing and Finished products. The Basic quality control tests which are performed on sterile parenteral products include :-

1) Sterility tests:- Sterility is the most important and Absolutely Essential characteristics of Parenteral products. Sterility means complete absence of all viable Micro-organism. It is an absolute term. The methods which are used to perform sterility tests are a) Direct transfer method. B) membrane filtration method.

A) Direct Transfer method:- it is an traditional sterility test method which involves a direct inoculation of required volume of a sample in two tests tube containing a culture medium that is FTM, SCDM. This method is simple in theory but difficult in practice when the demand for repetition in opening container, sampling Transferring, and mixing increases causes potential fatigue to the operator and detoriation in operator technique. So chances of Accidental contamination is there.

B) Membrane Filtration method:- It is official in U.S.P. 1970. It is more popular and widely used method over direct transfer method. Successful Employment Requires a more skill and knowledge than Direct transfer method. This method basically involves filtration of Sample through membrane filters of porosity 0.22 micron and Diameter 47mm with hydrophobic characteristics. The filtration is assisted under Vaccum, After filtration completion the membrane is cut into 2 halves and one halve is placed in two test tubes containing FTM, SCDM medium.

*Interpretation: - If no visible evidence of microbial growth in culture medium in test tube then it is interpreted that the sample representing lot is without intrinsic contamination. If visible microbial growth is seen or if the test is judged to be invalid because of inadequate environmental conditions the sterility test is repeated such interpretation must be made by those personnel who have adequate knowledge of aseptic processing, industrial sterilization methods, and environmental control procedures used in test facility.

2) Pyrogen Test: - Pyrogens are products of metabolism in microorganisms Gm-ve bacteria produces most potent pyrogens. These are lipopolysacchrides chemically and heat stable and are capable of passing through bacteria retentive filter. When these pyrogens are introduced into a body they produce a mark response of fever with body ache and vasoconstriction within an onset of 1 hour. Basically there are test performed to detect the presence of pyrogens in sterile parenteral products they are C) Rabbit Test D) LAL Test.

C) Rabbit test:- This test basically involves the injection Sample solution which is to be tested into a Rabbits Which are use as test animals through ear vein. The Temperature sensing probe (Clinical Thermometer, Thermosistor or similar probe) into a rectum cavity of Rabbit at the depth of 7.5 cm the test solution must be warmed at 37 degrees prior to injection. Then Rectal temperature is recorded at 1,2,3 hr subsequent to injection. This test is performed in separate area designed solely for this purpose under environmental conditions similar to animal house should be free from disturbances that likely to excite them. Initially this test is performed on 3 Rabbits but if required results are not obtained this test is repeated on 5 additional Rabbits with same sample solution administer to initial 3 rabbits. Prior to 1hr of injecting sample solutions the control temperatures of rabbits are determined. Use only those rabbits whose control temperature is no vary by more than 1 degree Celsius.

*Interpretation:- The solution is judged to be non pyrogenic if no single rabbit show rise in temperature of 0.5 degree Celsius but if this condition is not met then the test if repeated on 5 additional rabbits with same preparation administer to initial first 3 rabbits the solution is judged to be non pyrogenic if NMT 3 of 8 rabbits show individual temperature rise of 0.5 degree Celsius.

D) LAL test:- It is an recently developed in vitro test method for pyrogen utilizing gelling property of lysates of amebocytes of limulus polyphemus which is found only at specific locations along the east coast of North America and along southeast Asia. It is derived from horse shoe crab, The basic procedure is the combination of 0.1 ml of test sample with LAL Reagent after incubation for 1 hr at 37 degree Celsius the mixture is analyzed for the presence of Gel clot. The LAL Test is positive indicating that the presence of endotoxin. Its applications are mainly to Pharmaceutics, Biological, devices, disease states, food, and validation of heat cycles. This method has several advantages of Rabbit test they are Greater sensitivity and reliability specificity, less variation, wider application, less expensive and simplicity.

Properties of Parenteral Preparations

Parenteral preparations are intended to be administrated through the human or animal body, either by direct injections (for example, bolus intravenous (IV), intramuscular (IM) or subcutaneous (SC)) or by infusion with a controlled infusion rate or by direct implantation through IM or SC. They must meet the following minimum com-pendia criteria:

- To be sterile and pyrogen-free.
- To be clear or practically exempt of visible particle and to be free from sub-visible particles as required by pharmacopeias EP, USP and JP
- No evidence of phase separation for the emulsions, or aggregates formation for aqueous dispersions such as injectables Mab (monoclonal antibody) preparations
- In case of suspensions, the use of appropriate particle size and any sediment should be readily dispersed upon shaking to give stable formulations and ensure the correct dose to be withdrawn and injected.

Parenteral preparations may require the use of excipients that should be biocompatible, be selected for the appropriate use and to be included at the minimum efficient concentration.[3] The functionality of these excipients is as follows:

- To make the preparations isotonic with respect to blood (glucose/dextrose, mannitol, sodium chloride…)
- To adjust the pH to the physiological one (mineral or organic acids or salts)
- To prevent the degradation of the drug substances (stabilizer…)
- To ensure or increase the drug substance's solubility
- To provide adequate antimicrobial preservative property (only applicable to multidose preparations)

It should be stressed that excipients should not adversely affect the intended medicinal action of the drug products, nor at the concentration used to cause toxicity or undue local irritation.

Challenges in Formulations

The main challenge of all the different parenteral dosage forms is to achieve a good compatibility of the drug substances with the excipients (no formation of new impurities either by degradation of the drug substance or formation of new chemical entity between the drug substance and the excipients) as well as the compatibility of the preparations with the primary container (no leachable or adsorption to container).[3]

With regards to solutions and emulsions, the drug substances should be soluble and remain soluble during the entire shelf-life of the drug products. When drug substances are not soluble, dissolution can be achieved by the use of co-solvents, surfactants, or a soluble pro-drug, or eventually the use of solubility enhancers such as cyclodextrins thanks to the formation of inclusion complex.

The pH is one of the critical aspects of parenteral preparations which should have a pH close to the physiological one. However in certain cases, a compromise should be found between the pH ensuring stability of the drug substance (such for peptides requiring alkaline pH or proteins at pH close to the isoelectric point) and the physiological one. In all cases, large volume preparations (LVP, i.e. more than 100 ml as defined in pharmacopeia) should not contain a pH buffer as the blood has already a buffer effect property that could enter into competition with the injected drug product.

The stability of the drug substance is another critical point that a formulator can face during the development of the formulation. Unstable drug substances will lead to the formation of new impurities jeopardizing the safety of use of the preparations. When the use of a stabilizer is justified (for instance the use of mannitol as free-radical scavenger or cysteine in paracetamol solution for injection), it should be included at the minimum concentration demonstrated to be efficient at release and during the entire shelf-life.[3]

In the cases of powders for injection or infusion obtained through a freeze-drying process, the use of bulking agent (such mannitol) and/or a cryoprotector will be needed when the dose of drug substance(s) cannot ensure solely the formation of acceptable "cake".

Finally the process of the sterilization should be selected according to the characteristics of the parenteral preparations (for instance, heat steam sterilization for aqueous solutions and dry heat for non-aqueous solutions), but in any case it can be justified by the nature of the primary containers.[4] Figures 1 and 2 display the decision trees for the selection of the sterilization process for aqueous products or non-aqueous solutions including semi-solid and dry powder products.

Different Types Of Parenteral Preparations

Parenteral preparations are sterile pharmaceutical products administered to the human body by injection. Only liquids can be injected which means that the pharmaceutical parenteral preparation must either be a liquid which can itself be injected safely, or it may be a material that can be diluted with sterile water (commonly referred to as 'water for injection') or other sterile solvent before it is administered. Liquids other than water must not interfere with the stability and efficacy of the preparation. Some substances may be added to increase the stability and efficacy of the preparation, but it is important that such additives do not cause adverse effects or toxicity. Coloring agents are not permitted in parenteral preparations.

If parenteral preparations are to be stored in multiple dose containers, antimicrobial preservatives may be added to the formulations, which prevents and inhibits the growth of microbes in the container. It is necessary to validate the effectiveness of such preservatives before the start of the parenteral production process. Also, if the active ingredient(s) have the potential to oxidize and degrade, manufacturers can add anti-oxidants to the parenteral preparation, or the air in the container in which it is to be stored may be eliminated by evacuation, or displaced with nitrogen or other inert gas.

Containers

Parenteral preparations may be supplied and stored in a variety of containers, including vials, bottles ampoules and, for large quantities of liquids, bags. All of these containers must be transparent to allow for visual inspection of the content. The container must not contain any materials that may adversely affect the quality of the product during the handling, storage and use. Traditionally glass has been preferred for containers that store parenteral products, especially borosilicate glass

which is more resistant to chemical attack than low cost soda lime glass. Plastics are now becoming more common, however, and several types are in common use. The choice of material is governed by the composition of the parenteral product and standards governing the choice of materials are set by the National pharmacopeias, for example the U.S. Pharmacopeial Convention (USP), The Japanese Pharmacopoeia (JP), and The European Pharmacopoeia of the Council of Europe (EP). These institutions set quality standards for active pharmaceutical ingredients, drug products, excipients, packaging materials, labelling and storage conditions,

Closure/Sealing

In the case of bottles from which injectable samples are to be withdrawn, a special type of closure is required. These must prevent any microorganism or bacteria from entering, The closure material must be made of compatible material that will allow a hypodermic needle to pass through with minimal disruption or shedding of material and at also has the ability to reseal itself once the needle is removed. Elastomers are widely used as closure materials for bottles. They are also used in other primary parenteral packaging as stoppers for vials, plungers and tip caps for pre-fillable syringes, plungers and seals for cartridges and ports for plastic bags.

Inspection/Quality Control

To ensure the high quality, according to the Good Manufacturing Process, is maintained for parenteral product containers, each final container must be individually inspected for any contaminants. Contaminated containers must be rejected and removed.

Labelling

Parenteral products labels must include the name of the preparation, active ingredient amount, storage condition and the diluent or solvent required to achieve the desired concentration for the product to be administered. The label should not cover the whole bottle so that the product can easily be inspected.

Parenteral Preparation Types

- **Injection.** Injections contain sterile solutions and are prepared by dissolving the active ingredient and other substances in Water for Injection or other suitable non-aqueous base or a mixture of both. The solution to be injected may show sediments which can be dispersed easily by shaking the container. The suspension should remain stable in order to deliver a homogenous dose whenever withdrawal is made from the container.
- **Infusions.** These parenteral preparations are composed of sterile aqueous solution with water as its continuous phase. The preparations are free from bacterial endotoxins or pyrogens and are turned isotonic with blood. They do not contain any antimicrobial preservatives.
- **Powder for Injection.** These are sterile solid compounds that are distributed in their final volume when the vial or container is shaken to form a clear particle-free solution.

- **Concentrated Solutions for Injections.** The concentrated solutions are diluted with water for injection before they are administered through injection or through intravenous infusion.
- Implants. These solid sterile preparations are implanted in the tissue in order to release the active ingredient for long periods. They are stored in sterile containers individually.

STERILE DOSAGE FORMS

Sterile dosage forms are those which are free from any microorganisms, dust, fibres, and foreign particles, and should be isotonic. Parenteral preparations as name suggests (*par+enteral)* are those which are administered other than enteral routes. Enteral route involves esophagus, stomach, intestines but parenteral route bypasses all these. Sterile dosage forms include parenteral preparations and ophthalmic preparations. Parenteral preparations include Injections, transfusions fluids, sterile suspensions, sterile solids, sterile solutions or emulsions. Ophthalmic preparations include eye drops, eye lotions, eye ointments, eye gels, eye suspensions, contact lens solutions.

Parenteral preparations can be divided into small volume parenterals and large volume parenterals.

Small volume (SVPs) according to U.S.P "an injection that is packaged in containers labelled as containing 100ml or less".

Large volume parenterals (LVPs) according to FDA are aqueous solutions which are supplied in volumes of at least 100ml with sizes of 250ml, 500ml, 1000ml and more. Examples are sodium chloride infusion, ringers, dextrose, plasma expanders etc.

IDEAL PROPERTIES OF STERILE DOSAGE FORMS

Preparations of parenteral products and ophthalmic products involve various considerations:

1. **STERILITY:** Sterile preparations should be free from all types of microorganisms. Ophthalmic formulations must be especially free from *Pseudomonas aeruginosa,* gram negative bacteria which is commonly found in ophthalmic formulations and can cause serious infections to cornea.

2. **ISOTONICITY:** Parenteral preparations should be isotonic with blood plasma and body fluids. Ophthalmic formulations must be isotonic with lachrymal secretions.

3. **FREE FROM PYROGENS:** Sterile formulations must be free from pyrogens and toxins. These products must pass pyrogen test as pyrogens are responsible for rise in body temperature.

4. **FREE FROM FOREIGN PARTICLES:** These products must be free from foreign particles, dust, fibres and must pass clarity test.

5. **pH OF OPHTALMIC FORMULATIONS:** pH of tears is about 7.4. pH plays crucial role in therapeutic activity, solubility, stability and comfort to the patient.

6. **STABILITY:** Physical and chemical stability of sterile formulations should be maintained during storage.

TYPES OF PARENTERAL PREPARATIONS

1. **TRANSFUSION FLUIDS:** Parenteral solutions which are administered by intravenous route for example. Sodium chloride, ringers, dextrose.

2. **SOLUTIONS/EMULSIONS OF MEDICAMENTS FOR INJECTIONS:** commonly used as injections and available in single dose containers or multiple dose containers. For example, diclofenac sodium, dexamethasone.

3. **STERILE SOLIDS:** These drugs are supplied as dry sterile solids which are dissolved in a suitable solvent for administration into the body. These are available in dry solids because drugs are not stable in solution form. For example benzyl penicillin G sodium injection.

4. **STERILE SUSPENSIONS:** sterile suspension of drugs in a suitable solvent and are administered by intramuscular route for example hydrocortisone suspension, methylprednisolone.

FORMULATION OF PARENTERAL PREPARATIONS

Following substances are added in the formulation of stable product.

2. Adjuvants

- Stabilizers
- Solubilising agents
- Antibacterial agents
- Buffering agents
- Chelating agents
- Emulsifying, suspending and wetting agents
- Tonicity factors

In aqueous vehicle water is used which is well tolerated by body. It is used as

- Water for injection
- Water for injection free from carbon dioxide
- Water for injection free from dissolved air.

Water for injection should be free from pyrogens, volatile and non-volatile impurities.

Commonly used non-aqueous vehicles are alcohols and oils. In oils fixed oils such as almond oil, arachis oil, sesame oil are use as vehicle. These are used when depot effect of drug is needed or when drug is insoluble in water.

UNIT-V

PACKING OF PHARMACEUTICALS

INTRODUCTION

DEFINITION:

Packing: Packing consists of enclosing an individual item, or several items, in a container, usually for shipment or delivery. This operation is mostly done by hand and machine.

Pharmaceutical Packaging: Pharmaceutical packaging means the combination of components necessary to contain, preserve, protect & deliver a safe, efficacious drug product, such that at any time point before expiration date of the drug product, a safe & efficacious dosage form is available.

Types of Packaging Systems:

- Primary package system: Made up of those package components & subcomponents that come into direct contact with the product, or those that may have a direct effect on the product shelf life.

- Secondary or tertiary package system: Includes cartons, corrugated shippers & pallets.

Packaging must meet the following Requirements: [ideal requirements]

- Protect the preparation from environmental conditions.
- Non-reactive with the product and so does not alter the identity of the product
- Does not impart tastes or odors to the product
- Nontoxic
- FDA approved
- Protect the dosage form from damage or breakage
- Meet tamper-resistance requirements, wherever applicable.
- Adaptable to commonly employed high-speed packaging equipments.

Criteria for the Selection of package type and package material:

Stability

- Compatibility with the contents
- Strength of container and the degree of protection required
- Moisture-proofness
- Resistance to corrosion by Acids or Alkalis
- Resistance to grease
- Protection against salt
- Resistance to microorganisms
- Resistance to insects and rodents
- Resistance to differences in temperature
- Protection against light, fire and pilferage
- Odor retention and transmission
- Aesthetic effect
- Cost
- Machine suitability of packaging and the filling method

TYPES OF GLASS

Type I – Borosilicate Glass

Type II – Treated Soda-Lime Glass

Type III – Regular Soda-Lime Glass

Type NP – General Purpose Soda-Lime Glass

Type I: Borosilicate Glass

- Highly resistant glass
- A substantial part of the alkali & earth cations are replaced by boron and/or aluminum & zinc.
- It is more chemically inert than the soda-lime glass (which contains either none or an insignificant amount of these cations).
- It is used to contain strong acids & alkalies as well as all types of solvents.