

STERILE DOSAGE FORM

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STERILE DOSAGE FORMS

Definition:

A dosage form is said to be sterile when it is free from:

- Microorganisms
- Spores
- Pyrogens
- Pathogens

The sterile dosage form has to pass test for sterility.

These products are prepared and stored under aseptic conditions.

The dosage form is made sterile by using different methods of Sterilization:

1.Heat:

(a) **Wet heat in an autoclave:** The usual method is a time of 30 minutes at a pressure of 1.05 kg/cm² that will give a temperature of 121°C. This is the best method, if practicable.

(b) **Tyndallization:** This is a course of three periods of boiling at 100°C for 30 min. at daily intervals.

(c) **Dry heat:** This is done in a dry oven, where a temperature of 160° C for two hours is usually required.

2. **Filtration:** The liquid or gas to be sterilized is passed through a filter with porosity sufficient to remove any microorganism in suspension. The cotton wool is used for gases. For liquids, a variety of filters are available, made of materials such as cellulose nitrate (millipore filters). This method is very useful for sterilization of liquids containing heat-labile components.

3. **Radiation:** Ultraviolet light is very effective in sterilization of air. For solids, we generally use gamma rays or x-rays from a source such as radioactive cobalt. Ionizing radiation is often used to sterilize plastics and other heat labile materials.

4. **Chemicals:** Many chemicals are lethal to microbes. Hypochlorite solution and phenolic derivatives are used as general laboratory disinfectants. Similar chemical is gaseous ethylene oxide. However, these may not cause sterilization under some conditions.

Dosage forms that require to be sterile are:

- Ophthalmics
- Pulmonary drug delivery
- Parenterals:
 - Injectables
 - Infusions
 - Implants

OPHTHALMICS

Introduction:

- Ocular administration of the drug is primarily related with the treatment of ophthalmic diseases, not for gaining systemic action.
- This route is not used for systemic action because high concentration of drug damages eye.
- Goal: - "Increase Drug absorption in the eye and to decrease systemic absorption".
- Major classes of drugs used :-
 - Miotics
 - Mydriatics/Cycloplegics
 - Anti-inflammatories.
 - Anti-infectives
 - Surgical adjuvants
 - Diagnostics etc.

Conventional Ocular Formulation:

| Dosage form | Advantages | Disadvantages |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Solutions | <ul style="list-style-type: none"> ➤ Convenience | <ul style="list-style-type: none"> ➤ Loss of drug by drainage ➤ Nonsustained action |
| Suspensions | <ul style="list-style-type: none"> ➤ Patient compliance ➤ Best for drugs with slow dissolution | <ul style="list-style-type: none"> ➤ Drug properties decide performance |
| Emulsions | <ul style="list-style-type: none"> ➤ Prolonged release of drug from vehicle | <ul style="list-style-type: none"> ➤ Patient non compliance ➤ Blurred vision ➤ Possible oil entrapment |
| Ointment | <ul style="list-style-type: none"> ➤ Flexibility in drug choice ➤ Improved drug stability ➤ Increased tissue contact time ➤ Inhibition of dilution by tears ➤ Resistance to nasolacrimal drainage. | <ul style="list-style-type: none"> ➤ Sticking of eyelids ➤ Poor patient compliance ➤ Blurred vision ➤ No true sustained effect ➤ Drug choice limited by partition coefficient |
| Gels | <ul style="list-style-type: none"> ➤ Comfortable ➤ Less blurred vision than ointment | <ul style="list-style-type: none"> ➤ No rate control on diffusion ➤ Matted eyelids after use |
| Erodible inserts | <ul style="list-style-type: none"> ➤ Sophisticated and effective delivery system ➤ Flexibility in drug type and dissolution rate ➤ Need only be introduced into eye and not removed | <ul style="list-style-type: none"> ➤ Patient discomfort ➤ Requires patient insertion ➤ Movement of system around eye can cause abrasion |
| Non-erodible inserts | <ul style="list-style-type: none"> ➤ Controlled rate of release ➤ Prolonged delivery ➤ Flexibility for type of drug selected | <ul style="list-style-type: none"> ➤ Patient discomfort ➤ Irritation to eye ➤ Patient placement and removal ➤ Tissue fibrosis. |

Recent Controlled Release Ocular Formulations:

Two Major Approaches:

1. To prolong the contact time of drug with corneal surface.
2. To enhance corneal permeability either by mild as transient structural alteration of corneal epithelium or by modification of chemical structure of the drug molecules.

Formulations:

1. Polymeric solutions
2. Phase transition systems
3. Mucoadhesive/bioadhesive dosage form
4. Collagen shields
5. Pseudolatices
6. Micro emulsions.
7. Ion exchange resin suspension.
8. Iontophoresis

1. Polymeric Solution:

The addition of polymers to the eye drop solutions increases the contact time with cornea. The polymer used are:

- Methyl cellulose
- Poly vinyl alcohol,
- Hydroxy Propyl cellulose,
- Poly vinyl pyrrolidine etc.

TECHNOLOGIES:

DuraSite® DRUG DELIVERY TECHNOLOGY:

DuraSite® is a polymer that prolongs the residence time of the formulation in the eye.

The DuraSite delivery system, a patented eye drop formulation by Insite Vision, can be customized to deliver a wide variety of potential candidates. Importantly, whereas conventional eye drops typically last a few mins. and are unable to sustain therapeutic drug levels. DuraSite remains in the eye for several hrs., during that time the active ingredient is gradually released. This allows lower conc. of drug to be administered over a longer period of time.

This minimizes the inconvenience of frequent dosing reduces the potential related adverse effects.

AQUASITE®:

AquaSite was the first product developed utilizing DuraSit technology.

The product contains the DuraSite formulation and demulcents for the symptomatic treatment of dry eye.

AzaSite:

AzaSite (ISV- 401) is an ocular anti infective product candidate containing the drug azithromycin. AzaSite is formulated with DuraSite. DuraSite offers the benefit of prolonged release of the active drug azithromycin. Data from InSite Vision's Phase II trial, announced in Sept. 2002, indicated safe and effective treatment of bacterial conjunctivitis with seven drops of AzaSite over a five day period.

ISV-205:

ISV -205 product candidate contains the drug diclofenac, formulated in the DuraSite sustained release delivery vehicle. Diclofenac is a NSAID, currently used to treat ocular inflammation.

2. Phase transition system (In-situ gel):

- These are liquid dosage forms which shift to the gel or solid dosage form when instilled into the Cul-de-sac ".It is a Hydrogel.

Types of In- situ Gels:

I. Thermoreversible gel:-

This type of the hydrogel containing polymer which forms the gel when got to the physiological temperature. (37°C). e.g., Poloxamer F127.

II. pH induced gel:-

It contains polymer which forms the gel upon the physiological (native pH 4.5 to tear pH 7.4). e.g. Cellulose Acetate Phthalate Gerlite[®] : Cellulose acetate hydrogen phthalate latex, typically shows very low viscosity up to pH 5, and forms clear gel in few seconds when in contact with tear fluid pH 7.2 to 7.4 and hence, release contents over prolong period of time.

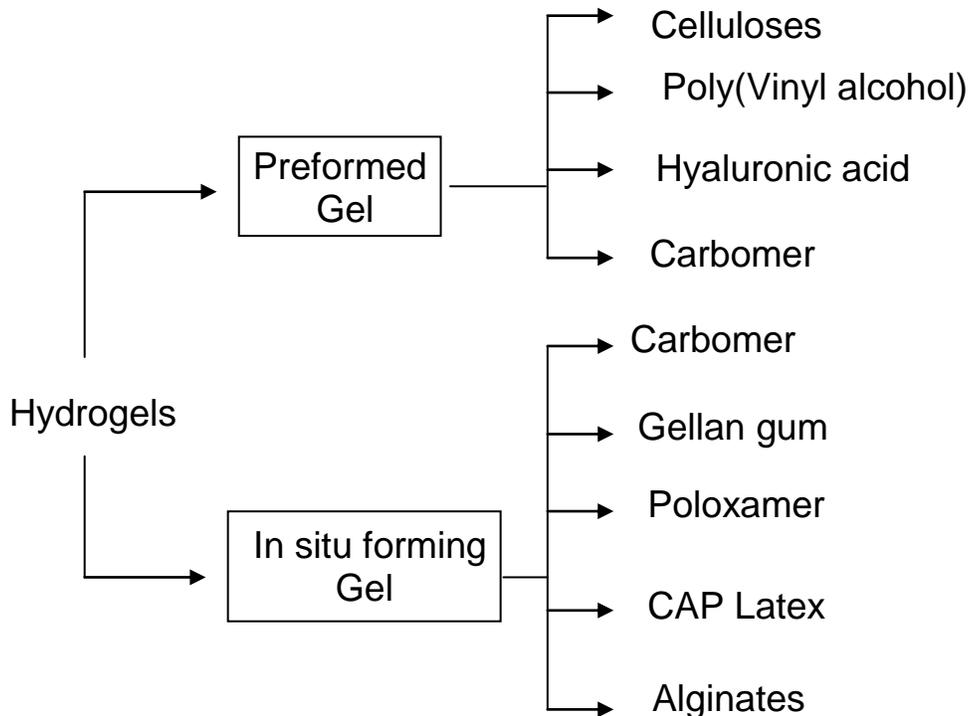
III. Ion induced gel:-

This produce gel of the polymer when it get sodium ion (2.6 g/L) in contact. e.g.,Low Acetyl Gellan Gum.

IV. Dilution induced gel:-

Gel is formed due to the dilution with aqueous phase(water). e.g., Lutrol.

Classification of Hydrogels



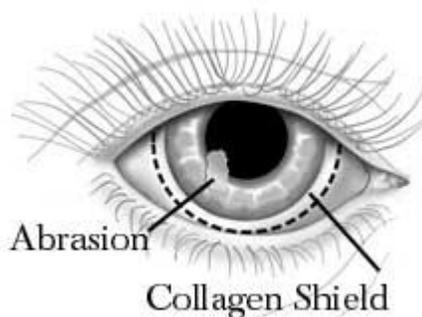
3. Mucoadhesive / bioadhesive Dosage form:

- BODI – Bioadhesive Ocular Drug Inserts

- Any polymer solution / suspension placed in the eye first encounters mucin at the cornea and conjunctival surface . If the polymer adhere to the mucin the interaction referred to as mucoadhesion.”
- Mucoadhesive adjuvants are generally macromolecular hydrocolloids with numerous hydrophilic functional groups like carboxyl, hydroxyl, amide, sulphate show electrostatic or hydrophobic interaction and H-bonding with surface.
- Ideal properties:
 - Exhibit a nearly zero contact angle to allow maximum contact time with mucin.
 - Chain flexibility to diffuse and penetrate through mucin.
 - Higher molecular weight.

4. Collagen Shields:

- Collagen corneal bandages in the shape of contact lens as an alternative to soft contact lenses to protect the healing corneal epithelium after surgery.
- For drug delivery, The shields are rehydrated in a water solution of the drug , where by the drug is absorbed by the protein matrix and is released once the shield dissolves in the eye .
- Application of shield requires to anaesthetize the cornea and they often produce some discomfort and interfere with vision.
- Bausch & Lomb Pharmaceuticals acquired the rights to develop and market these collagen contact lenses, now known as BioCora collagen shields. After much research, Bausch & Lomb has been able to produce the shields in a reproducible manner and in a variety of shapes and thickness. Additionally, of great significance, Bausch & Lomb has been able to slightly alter the biochemical composition of the shields and thereby vary their dissolution rate. Shields have now been produced to dissolve in 6, 12, 24, 48, and 72 hours and even one week.
- One of the most exciting areas that has stemmed from these investigations is drug delivery. The collagen shield, it has been found, can serve as a "sponge" to collect medications that are placed in drop form on the surface of the eye and then slowly release them over a period of time as the shield dissolves.



- A new preparation referred to as collasomes consists of small pieces (1mm× 2mm × 0.1mm) of collagen suspended in a 1% methyl cellulose vehicle. Collasomes provide same therapeutic advantages of shields while shields disadvantages are circumvented.

5. Pseudolatices:

- Organic solution of polymer is dispersed in an aqueous phase to form o/w type emulsion.
- Water is removed partially to an extent that residual water is sufficient enough to keep polymeric phase discrete and dispersed, such dispersions are referred to a pseudolatices.
- Which on application leave an intact non invasive continuous polymer film which reserves drug.
- The drug from such systems is released slowly over a prolonged period of time ensuring better ocular availability and patient compliance by avoiding frequent instillation of preparation.

6. Micro Emulsion:

- They are polymeric colloidal systems, ranging in size from 10 nm to micrometers, in which the drug is dissolved, entrapped, encapsulated or adsorbed.
- Some of these systems appear promising for vitreoretinal drug delivery.
- The attention of some researchers has also been focused on the potentiality of microemulsions as carriers for ophthalmic drugs. These consist of large, or «swollen» micelles containing the internal phase, and, unlike emulsions, appear as clear transparent dispersions.
- Ocular delivery of various drugs (antibiotics, antivirals, antiinflammatories, etc.) by all of these formulations is being successfully explored in a number of laboratories. E.g., Microemulsion-Based Dexamethasone Eye Drop.

7. Ion exchange resin suspension:

- The new delivery system involved both the binding and release of drug from ion exchange resin particles.
- The ocular comfort of drug can be greatly enhanced by reducing the availability of free drug molecules in the precorneal tear film.
- The amount of resin concentration was selected to obtain optimum binding of the drug. The zeta potential of suspended particles was adjusted to produce flocculated suspension.
- Drug resin particles were then incorporated into the structured vehicle, containing Carbomer as a polymer, to enhance the physical stability and ease of resuspendability of the product.

8. Iontophoresis:

Iontophoresis is an active method of drug delivery, which uses a small electrical current to transport ionized drugs into and through body tissues. Iontophoresis offers a noninvasive and reproducible means of delivering a model anionic drug to eye tissues, specifically to the retina/choroid. Studies on ocular iontophoresis of 6-hydroxy dopamine and methyl para tyrosine carried by number of investigators⁵⁹⁻⁶². Iontophoresis application of antibiotics may enhance bactericidal activity of the antibiotics and reduce the severity of the disease.

Ocular Drug Delivery Devices:

- These ocular inserts are capable to diminish the systemic absorption of ocularly applied drugs, as a result of a decreased drainage into the nasal cavity, which is one of the major systemic absorption sites of topical ocular medications.
 - Another potential advantage of insert therapy is the possibility of promoting non-corneal drug penetration, thus increasing the efficacy of some hydrophilic drugs which are poorly absorbed through the cornea.
- 1) Matrix type
 - A. Hydrophilic soft contact lenses.
 - B. Soluble ocular inserts.
 - C. Scleral bulking materials
 - 2) Capsule type
 - A. ocusert & related devices
 - B. Implantable silicone rubber devices.
 - 3) Particulate System
 - A. Microspheres and Nanospheres

- 4) Vesicular system
 - A. Liposomes
 - B. Niosomes
 - C. Pharmacosomes
 - D. Discosomes
- 5) Other delivery devices
 - A. Ocufit[®] and lacrisert[®]
 - B. Minidisc ocular Therapeutic systems.
 - C. The New ophthalmic delivery systems (NODS[®])

1) **Matrix type:**

A. Hydrophilic Soft Contact Lenses:

- Hard contact lenses, soft contact lenses, and intraocular lenses are popular for correction of refractive errors.
- Because of easy to fit & rapid tolerance hydrophilic soft contact lenses are more popular.
- Because of hydro gelling property, they absorb aqueous solutions and useful for drug delivery to anterior segment of the eye.
- Two Hydrophilic contact lenses Bionite[®](Griffin lab) and softlens[®] (Baush & lomb) was developed as device for maintaining high concentration in anterior chamber of the eye.
- Disposable contact lenses could provide an acceptable means of drug delivery for some situations and overcome drawbacks associated with the use of nondisposable hydro gel lenses.

B. Soluble Ocular Inserts:

- Poly(vinyl alcohol)insert(PVAI):
Thin, elastic & oval shaped plates impregnated with antibiotics, sulfonamides , pilocarpine, atropine, or other drugs used in ophthalmology.
Limitations:- Poor patient compliance and difficulty of self –insertion.
- Soluble ophthalmic drug insert (SODI)
Thin, elastic, oval plates made of polymers & copolymers of polyacrylamide, ethyl acrylate & poly vinyl pyrrolidine impregnated with drug.
When SODI inserted in to the conjunctival sac, it absorbs tears rapidly, swells and dissolves in about 30 to 90 min.
- Polypeptide device:-
Insert composed of cross-linked polypeptide matrix.
The insert gradually erodes in the eye and dissolves out completely after about three weeks of wear.

C. Scleral Bulking Material:

- Scleral bulking materials cause post operative infection as they are used in retinal detachment surgery. To prevent this complication it can be made to absorb an antibiotic.
- Two common scleral bulking materials (1) Gelatin film &(2) Solid silicone rubber impregnated with antibiotics.
- Antibiotic impregnated gelatin disc & silicone rubber were prepared by immersing in to an aqueous antibiotic solution and then dried & they found sustained release from this device.

2) **Capsular Type of Drug Delivery System:**

A. Ocusert:

- A truly continuous controlled release and Zero order kinetic fashion was achieved using ocusert.

- For hydrophilic Drugs.
- Pilocarpine ocuserts (by Alza corporation of California.)
- The system consists of a Pilocarpine – alginate core (drug) in gel form sandwiched between two transparent, rate controlling ethylene-vinyl-acetate copolymer membranes. Titanium dioxide encloses the drug reservoir circumferentially.
- The micro porous membrane permit the tear fluid to penetrate into the drug reservoir compartment to dissolve drug from the complex.
- When this is placed under the upper or lower eyelid, the pilocarpine molecules dissolved in the lacrimal fluid are released through the rate-controlling membranes at predefined rates for a week.
- Two types of Ocuserts® are available
 - (1) Ocusert® pilo- 20
 - (2) Ocusert® pilo- 40
- This device is more popular among younger patients as compared to elder population who have difficulties in insertion, do not retain device well and often do not notice if it falls out.
- Clinical studies with the pilocarpine Ocusert® demonstrated that slow release of the drug can effectively control the increased intraocular pressure in glaucoma, with a minor incidence of side-effects, such as miosis, myopia, browache, etc.
- The major drawback for using this therapy is high cost of the device and as this system is non biodegradable, required to be removed and replaced with a fresh one adds to the cost of already expensive therapy.

TECHNOLOGIES:

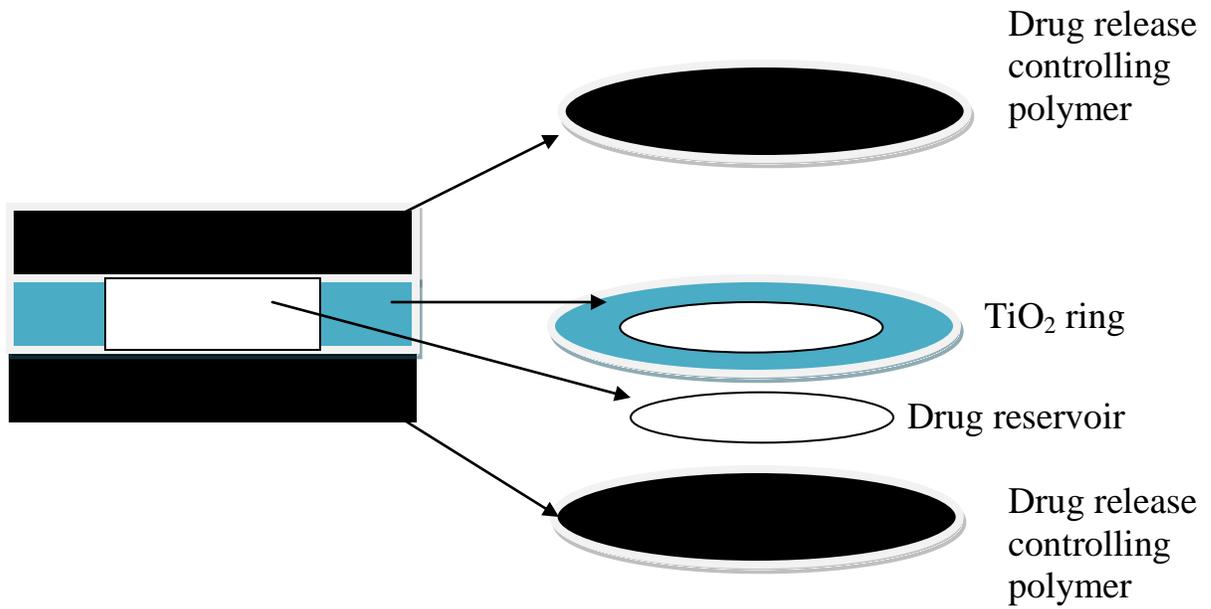
PROSERT: It is an ophthalmic placebo insert which is insoluble, sterile, and biocompatible. This system can contain one or several active components and allow its releasing in a programmed or controlled way. It is constituted of a matrix able to contain one or several active components, surrounded by a dialysant membrane of a changeable thickness which allows the releasing controlled by the tears. The entity has the shape of a small oblong cylinder (reservoir) with rounded forms.

Advantages of PROSERT:

- An excellent bioavailability by permanent contact of the active component with the ocular tissues and the absence of therapeutic window.
- Consequently the use of a smaller of active component in comparison with liquid treatment.
- No preservatives so no risk of allergy.
- A better adhesion to the treatment as only one PROSERT can cover a long period.
- As PROSERT is a dry device without solvent it is possible to associate several active components with different solubility or physico-chemical properties to obtain complementary or synergistic effect.
- PROSERT doesnot either dissolve in water or fragment, unlike other inserts, and allows a controlled releasing of the active component without blurred vision.
- Changing the features of the dialysant membrane, we can master the release of the active component that can be very fast for certain applications. (For e.g. for diagnostic purpose).
- PROSERT can be removed at any time.
- With PROSERT, we can interrupt instantaneously the spreading of active component.

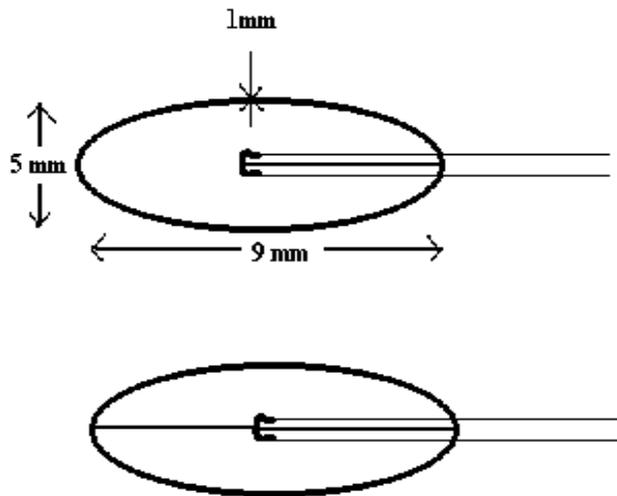
MYDRIASERT:

The first application of PROSERT technology is a mydriatic called MYDRIASERT that received its Marketing Authorisation Application. It is an insoluble ophthalmic insert, gradually releasing two well known active ingredients: phenylephrine & tropicamide. It is indicated in pre surgical mydriasis.



B. Implantable Silicon Rubber Device:

- Implantable silicone rubber device for hydrophobic drug.
- This device consists of two sheets of silicone rubber glued together only at the edges with silicone adhesive. A tube of the same material extends from device.



Schematic Representation of Implantable silicone Rubber Device.

3) Particulate System:

A. **Microspheres and Nanospheres:**

- The drug absorption in the eye is enhanced significantly in comparison to eye drop solutions.
- Smaller particles are better tolerated by the patients than larger particles therefore nanoparticles may represent very comfortable ophthalmic prolonged action delivery systems.
- This approach shows promise only for delivering lipophilic drugs.
- They may cause to the corneal epithelium cell membrane disruption.

4) Vesicular system:

A. **Liposomes:**

- The nature and extent of altered ocular uptake of liposomes associated agents appear to depend on no of factors.
 - Physicochemical properties of the entrapped agent
 - Chemical composition
 - Physical characteristics of liposomes.
- It was determined that liposomes taken up by the cornea in the order of positively charged MLV>positively charged SUVs> Negatively charged MLV> Negatively charged SUVs>MLV=SUV.
- The combination of liposomes with collagen shields may be useful mainly with respect to the encapsulation of drugs and strongly helps ocular penetration of drug and provides prolonged contact and retention of the liposomes.
- Limitation:-
 - Chemical instability
 - Oxidative degradation of phospholipids.
 - Cost & Variable purity of natural phospholipids.

B. **Niosomes:**

- Developed to overcome the limitations of liposomes.
- Vesicular system were formed when a mixture of cholesterol and single alkyl chain &,Non-ionic surfactants was hydrated. The resultant vesicles, termed as niosomes.
- Osmotically active & relative stable .
- It behaves in vivo like liposomes prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability.
- Advantages of Niosomes:
 - Chemically stable
 - Entrap both hydrophilic & hydrophobic drug.
 - Flexible in their characterization (composition, fluidity & size)
 - Improve the performance of drug molecule via delayed clearance from circulation, better bioavailability & controlled drug delivery at desired site.

C. **Pharmacosomes:**

- Vesicle formation takes place by the association of phospholipids amphiphilic molecule.
- Most topically applied drugs gain access to their receptor site within eye by transcellular diffusion across the corneal epithelium being lipoidal in nature.
- The barrier may present a high resistance to ionic or relatively hydrophilic drug . These resistance can be overcome by pharmacosomes.

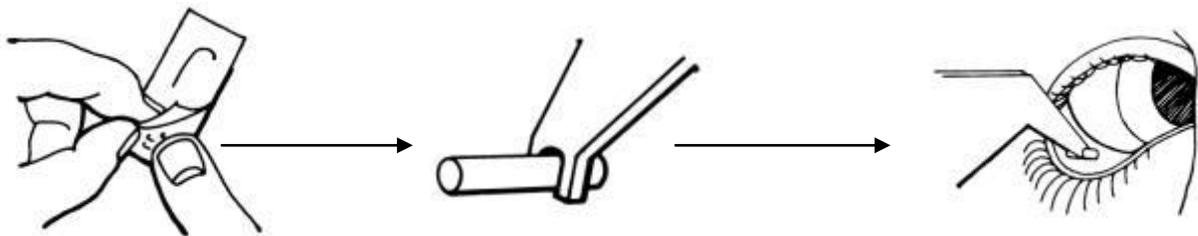
D. **Discosomes:**

- Soluble surface active agents when added in critical amount to vesicular dispersion leads to solubilization or break down of vesicles and translates them in to mixed micellar systems. As a result, large, flattened disc like structure is formed.
- Advantages of discomes :
 - Housing of drug in cul-de-sac becomes easier.
 - Large size (12-60 um) prevent their drainage in to systemic pool;
 - Increased patient compliance .
 - Malleability / Flexibility makes the system approvable.
 - Minimal opacity imposes no hindrance to vision .
 - Drug can itself be incorporated in the system.
 - Cornea contact time is more so better bioavailability can be anticipated.
 - Zero-order release can easily be attained.

5) Other delivery devices:

A. Ocufit[®] and Lacrisert[®] :

- Ocufit[®] ocular insert is a flexible, rod-shaped formulation made of medical-grade silicone rubber that can be loaded with a variety of drugs.
- Lacrisert[®] is indicated in patients with moderate to severe dry eye syndromes, including keratoconjunctivitis sicca. Lacrisert is indicated especially in patients who remain symptomatic after an adequate trial of therapy with artificial tear solutions.
- The device is inserted into a patient's upper or lower fornix, which is the space between the eyeball and the upper or lower eye lids.

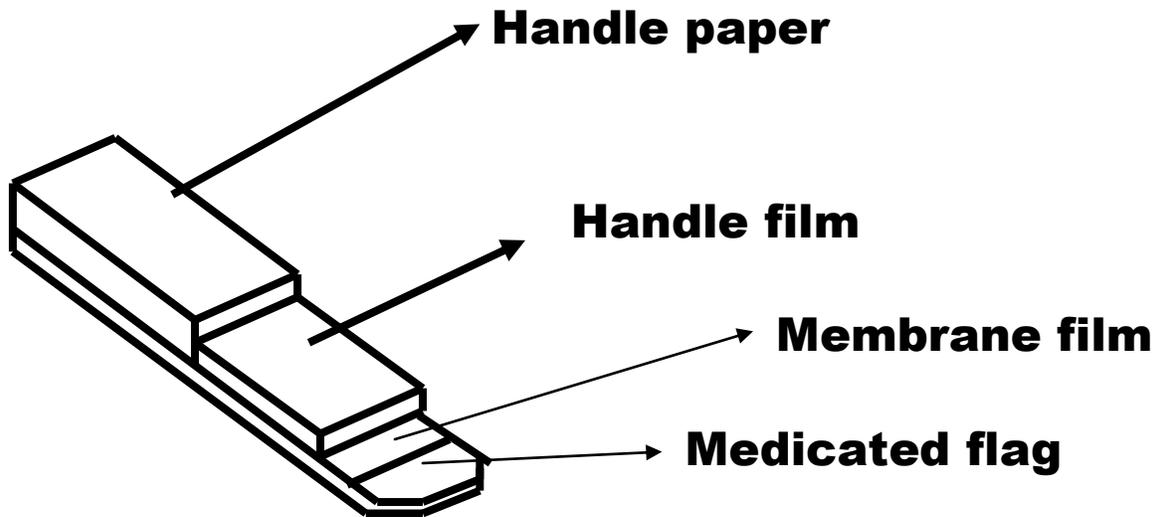


B. Mini disc ocular Therapeutic System:

- It is a monolithic polymeric device, shaped like miniature contact lens, with a convex front and a concave back surface in contact with eyeball.
- Different versions of the device have been evaluated such as non erodible hydrophilic non erodible hydrophobic & erodible. Gelfoam[®]

C. The New Ophthalmic Delivery system[®] :

- ❖ Three compartment strip:
 - Water soluble “Medicated film”
 - A thin water soluble “Membrane film”
 - A thicker water soluble “Handle flag”



- For use the flag is touched on to the surface of lower conjunctival sac.
- The membrane proceeds to dissolve in the lacrimal fluid, delivering the drug.
- An 8 fold increase in bioavailability for pilocarpine with respect to standard eye drop formulations was seen using this patch.

D. The Ophthalmic Rod:

The ophthalmic rod (OR) is a new ophthalmic drug-delivery system. The rod is made of nontoxic plastic. The active substance is deposited as a thin film on the end of the rod.

To deliver the drug, the tip of the rod is introduced into the conjunctival sac and rubbed against the palpebral conjunctiva of the lower lid.

The OR is a single-dose sterile applicator. By using the OR the problems of preservation and sterility of eyedrops are eliminated, and the risk of cross-infection is avoided.

PULMONARY DRUG DELIVERY

INTRODUCTION:

The first nasal/pulmonary administration of drugs was primarily employed for local drug effects. The potential nasal route for systemic delivery was discovered after the observation that nasally administered sympathomimetic and antihistaminic drug for local action has significant systemic effects. Nasally administered small dose display a rapid absorption that is comparable to intravenously administered drugs.

ADVANTAGES OF NASAL/PULMONARY ROUTE AS SYSTEMIC DELIVERY ARE:

- ✓ A non-invasive route
- ✓ Convenience of administration and amenable to chronic self administration
- ✓ Avoids first pass metabolism or gastro intestinal tract destruction
- ✓ A large permeable surface area and rich vasculature availability
- ✓ Plasma concentration time profile is comparable to intravenous administration
- ✓ Macromolecules like proteins and peptides can be successfully administered.

LIMITATIONS:

- ✓ Rapid mucociliary clearance
- ✓ Chances of immunogenic reaction
- ✓ Inadequate availability of toxicity data for penetration enhancement
- ✓ Nasal pathology may adversely affect product effectiveness.

FORMULATIONS:

- The drugs can be administered by pulmonary route utilizing two techniques: aerosol inhalation (also used in intranasal applications) and intratracheal instillation.
- By applying aerosol technique, we could achieve more uniform distribution with greater extent of penetration into the peripheral or the alveolar region of the lung, but this costs more and also faced with difficulty in measuring the exact dose inside the lungs.
- In contrary to this, instillation process is much simple, not expensive and has non-uniform distribution of drugs.

1) AEROSOLS:

Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs, delivery by aerosols are deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion. Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion.

There are three commonly used clinical aerosols: jet or ultrasonic nebulizers, metered-dose inhaler (MDI), and dry-powder inhaler (DPI). The metered-dose inhalers are most frequently used aerosol delivery system.

The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs.

Almost all aerosols were using a CFC (chlorofluorocarbon) propellant but in mid-nineties efforts were made to consider an alternative to ozone depleting CFC by other classes of environmental friendly propellants such as hydrofluoroalkanes (HFAs: HFA –134a and HFA-227). These HFA compounds contain no chlorine, which infact causing the ozone depletion effect.

2) INTRATRACHEAL INHALATION:

This technique delivers a small amount of solution into the lungs by syringe. This route provides a rapid and quantifiable method of drug delivery to the lungs. The drug deposition is localized and uneven and only small absorptive area is used for the absorption from deposition.

3) INSUFFLATION:

This method administers drug's powder formulation by syringe or any other similar device into the lungs.

NOVEL EXCIPIENTS FOR INHALATION DRUG DELIVERY:

➤ **Goals :**

- To expand the range of compound
- To increase the clinical benefits obtained from MDI by providing new capabilities like sustained release or greater respirability.

➤ **Three primary Applications :**

- (1) Suspension aids – to increase the number of compounds that can be prepared as high quality suspensions.
- (2) Solubilizers – to enable solution formation at high doses.
- (3) Sustained release agents – to enhance lung residence time of the compound.

Liposome & Lipid based Formulation:

Promising in sustaining the drug residence time within lung, improving therapeutic index and delaying systemic dilution and thereby, reducing side effects and to control the extent of release.

Delivery of corticosteroids for asthma, ribonucleotides for respiratory influenza, aminoglycosides (Tobramycin sulphate, Amikacin sulphate) and other antibiotics (Ciprofloxacin) for local pulmonary infections and cystic fibrosis has been reported using Liposome technology.

In Liposomal DPI formulations, drug encapsulated liposomes are homogenized, dispersed into carrier and converted into DPI by spray or freeze drying. On Inhalation, drug encapsulated liposomes get rehydrated in lung and release drug over a period of time.

Fatty acid esters were incorporated in the lipid in the portion of liposomes for prolonged retention in the respiratory tract.

Lactose carrier systems:

When drug particles are in the size range required for lung deposition, the surface electric forces associated with the particles exceed the gravitational force acting upon them, resulting in the development of cohesive powders with poor flow. To overcome this problem, the drug is blended with a coarse carrier system (30–100 μm), such as lactose. At present, marketed dry powder inhalers contain either the drug alone or mixed with a bulk carrier, usually lactose (α -lactose monohydrate). Lactose is one of three sugars (the others being glucose and mannitol) allowed as carriers by the Food and Drug Administration.

Lactose has an established safety profile and improves the flow properties of the formulation necessary for reproducible filling and promoting dosing accuracy. The drug particles become bound by physical forces to active sites on the surface of the carrier particles. The mixture provides a degree of resistance to segregation caused by the interaction between lactose and drug molecules, but also allows for deaggregation of the drug from the carrier during drug delivery. Any drug still adhering to the lactose after the aerosol has been generated will be deposited in the oropharyngeal region, which has the potential to cause local side-effects, as in the case of inhaled corticosteroids.

Large porous particles:

A new type of aerosol formulation is the large porous hollow particles, called Pulmospheres™. They have low particle densities, excellent dispersibility and can be used in both MDI and DPI delivery systems. These particles can be prepared using polymeric or nonpolymeric excipients, by solvent evaporation and spray-drying techniques.

Pulmospheres™ are made of phosphatidylcholine, the primary component of human lung surfactant. They are prepared in a two-step process. In the first step, an oil-in-water emulsion is prepared using oils, such as perflubron or perfluorooctyl ethane. The oil phase serves as a 'blowing agent' during the spray drying step, retarding shrinkage of droplets while simultaneously creating pores in the particle surface. The second step in the preparation is the spray-drying of the emulsion.

Pulmospheres™ are lighter and larger than the typical dry powder particles with a mass density of approximately 0.4 g cm^{-3} and geometric diameter of $>5 \mu\text{m}$. By virtue of their hollow and porous characteristics, Pulmospheres™ give rise to smaller aerodynamic diameters than their geometric diameter. Because of their large size and low mass density, the particles can aerosolize more efficiently (less aggregation) than smaller nonporous particles, resulting in higher respirable fractions of the formulation.

Biodegradable polymers:

In addition to liposomes, biodegradable polymer microspheres are currently being studied as sustained-release pulmonary drug carriers

e.g. Oligolactic acid, an oligomer of lactic acid, has a shorter biological half-life and therefore may be better suited for pulmonary drug delivery.

RECENT INNOVATIONS IN MDI TECHNOLOGY:

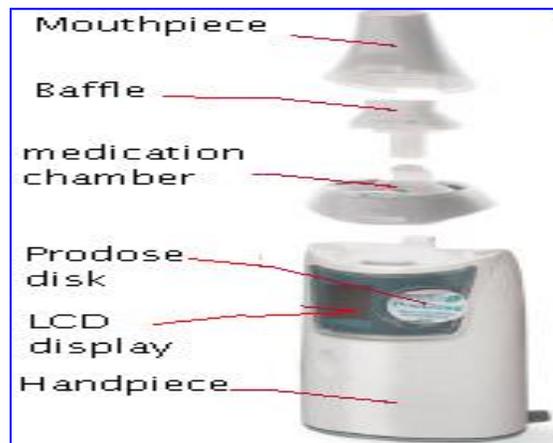
- Research on area of formulations, valves, canisters, elastomers, mouthpieces, etc.
- Other Improvements includes,
 - Breathe-actuation technology
 - Ability to deliver therapeutic proteins and peptides
 - sustained drug delivery
 - Improved shelf life

AERx® SYSTEM :

- Sophisticated technology in order to provide precise dosing which includes,
 - Controlled dose expression
 - Control of aerosol particle size
 - Management of the inhalation and delivery
- Inhalation and delivery coordination is optimized through a microprocessor-controlled flow sensing system that actuates delivery only at the beginning of the inspiration and within the correct inspiratory flow rate.

ADAPTIVE AEROSOL DELIVERY TECHNOLOGY :

- Adapts to the patient's breathing and ensures accurate drug delivery. Detects pressure changes during breathing and constantly adapt to the inspiratory and expiratory flow pattern of the patient.
- AAD systems deliver drug until all the preprogrammed dose has been received and gives audible feedback at the completion of treatment, irrespective of the time taken.



SPIROS INHALER TECHNOLOGY: (DURA PHARMA)

- Small handheld, breath-actuated, battery operated system.
- The high speed rotating impeller provides mechanical energy for dispensing.
- The Spiros DPI blister disk powder storage system designed for potentially moisture sensitive substance, (protein, peptides)
- Clinical trials through phase-3 have been completed for Albuterol sulfate and Beclomethasone dipropionate.
- Next generation model of this system is Spiros S2 which is motor less, cost effective, easy to use and for both unit dose and multidose system.

RESPIMAT: A NEW SOFT MIST INHALER

- Patented mechanism of generating a soft fine mist from dosed volume of drug solution
- It uses simply mechanical energy
- Delivers multiple doses without propellants

ELECTRONIC DPI FOR INSULIN:

- 1st completely electronic DPI
- Pulmonary insulin delivery requires a particle diameter of 3.3 μm or less. This is achieved by spray drying process.
- Here in first step, the drug is aggregated in aluminum blister and then in 2nd step, high frequency piezo vibrator deaggregates the powder in primary particles but still in blister and then in 3rd step, deaggregated particles circulates the top of blister which is then forced through pierced hole to air stream.

®
e.g. Exubera



RAD (RAGIME ASSURANCE DEVICE):

- pMDI are robust delivery mechanism in treatment of asthma.
- The use is increased day by day for pain relief and other systemic therapies. e.g., Opioids.
- The consequence of over dosing on these more powerful drugs are more severe and risk is grater too, as the patient may be disoriented through the use of other medication or suffering such severe pain that they will take too much of potentially lethal therapy.
- There is also the risk of accidental misuse or deliberate abuse.to mitigate such risks, pMDI design concepts have been developed to improve their safety and security.
- A Regime Assurance Device (RAD) has ability to prevent access at non-administration times, which not only helps patient comply with the prescribed regimen but also enables to monitor usage and of course prevent easy access by unauthorized users.
- Audible or visual reminders have been incorporated to provide patient with information on when last and next dose should be administered.
- The RAD design also incorporates a dose counter and is breath-actuated, removing the need for a patient experiencing discomfort or suffering disability to then have to co-ordinate the actuation with inhalation.

Electrospray technology (Battelle Pharma):

- Produces fine mists of several different solution formulations.
- This technique produces a small aerosol with the potential for efficient lung delivery by adding a high voltage to sprayed aerosol droplets. As the droplets evaporate in entrained air, the surface charges on each droplet repel each other and cause the droplets to shatter, thereby producing a smaller aerosol cloud.
- The technique has limitations: it is unlikely that all solvents and solutes are suitable and electric charge is known to affect aerosol deposition.

Breath-actuation technology:

- An established product in this area is 3M's "Autohaler," which removes the need for press-and-breathe coordination. More recently, 3M has developed a dose-by-dose counter for inclusion

within the pMDI delivery system to meet new guidelines by the **US Food and Drug Administration** on dose-counting mechanisms in MDI products and to help patients manage their therapies.

- Contains integrated features to enable patients to track the remaining number of doses. This would prevent the patient from either discarding an inhaler unnecessarily or, more importantly, using the product beyond the number of doses specified in its labeling.

Capillary aerosol generator:

- The device enables thermally stable drugs and vehicles to be evaporated and subsequently condensed in entrained air in a controlled fashion.
- Different formulations require different heating profiles, and manipulation of the entrained air at the capillary exit appears to enable control of particle nucleation and ultimately, the final aerosol size (0.25–2 μm has been reported; 29, 30). It is unlikely that all drugs can be aerosolized in this way without degradation.
- Nevertheless, this is the only technique that appears to offer the possibility of truly high delivery efficiencies for solutions metered in fractions of a milliliter.

RECENT ADVANCES IN DPI (DRY POWDER INHALERS):

Volumetric Metering of Small Quantity of Ultra Fine Powder From Fluidized Bed : A novel fluidization bed design that can precisely meter amounts as small as 0.02 mg of ultra fine powder (including small molecule and peptide formulations) without the need for excipients, and that can be filled into pure-drug blisters for dispensing.

Micro Fine, No Excipient, Dry Powder Inhaler:

A novel DPI design that can precisely dispense amounts as small as 0.02 mg of dry powder (including small molecule and peptide formulations) with an accuracy of +5%, without requiring the use of excipients.

PARENTERALS

INTRODUCTION:

Parenteral preparations are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body.

Parenteral preparations may require the use of excipients, for example:

- To make the preparation isotonic with respect to blood,
- To adjust the pH, to increase solubility,
- To prevent deterioration of the active substances or
- To provide adequate antimicrobial properties, but not to adversely affect the intended medicinal action of the preparation or, at the concentrations used, to cause toxicity or undue local irritation.

Several categories of parenteral preparations may be distinguished:

- ❖ Injections
- ❖ Infusions
- ❖ Implants
- ❖ Concentrates for injections or infusions
- ❖ Powders for injections or infusions
- ❖ **Gels for injections:** Gels for injections are sterile gels with a viscosity suitable to guarantee a modified release of the active substance(s) at the site of injection.

Continuous IV infusion has been recognized as a superior mode of systemic drug delivery, that can be tailored to maintain a constant and sustained drug levels within a therapeutic concentration range as long as required for effective treatment. But it requires continuous hospitalization during treatment and requires close medical supervision it entails certain health hazards .

To duplicate the benefits of IV drug infusion without its potential hazards effort has been invested in the **development of depot type parental controlled release.**

Examples of injectable depot formulation are:

- 1) Penicillin G procaine suspension
- 2) Cyanocobalamin Zn tannate suspension
- 3) Insulin Zinc suspension.

INJECTABLE DRUG DELIVERY:

Injections are sterile solutions, emulsions or suspensions. They are prepared by dissolving, emulsifying or suspending the active substance(s) and any added excipients in water, in a suitable non-aqueous liquid, that may be non-sterile where justified, or in a mixture of these vehicles.

Approaches:

Several pharmaceutical formulation approaches may be applied to the development of parental controlled release or sustained release formulations.

The most commonly used techniques are as follows.

- 1) Use of viscous, water miscible vehicles such as an aqueous solution of gelatin or poly vinyl pyrrolidone.
- 2) Use of water immiscible vehicles such as vegetable oil plus water repelling agent such as aluminium mono stearate.
- 3) Formation of thixotropic suspensions
- 4) Preparation of water insoluble drug derivatives such as salts, complexes and esters
- 5) Dispersion in polymeric micro spheres or microcapsules such as lactide glycolide homopolymer or copolymers.
- 6) Coadministration of vaso constrictors.
- 7) These techniques may be used alone for example formation of aqueous insulin zinc suspension or in combination for example penicillin G procaine suspension in vegetable oil gelled with aluminium monostearate.

INJECTABLE CONTROLLED RELEASE FORMULATION:

The injectable depot formulation was developed with the primary objective of simulating the continuous drug administration of IV infusion.

It often results in reduced drug dose, decreased side effects, enhanced patient compliance and improved drug utilization.

Reasons for development of PDS (Parenteral Depot System):

1. No surgical removal of depleted system is required as it is metabolized in non toxicological by product.

2. The drug release from this system can be controlled by following : Diffusion of drug through the polymer, Erosion of the polymer surface with concomitant release of physically entrapped drug, Cleavage of covalent bond between the polymer bulks or at the surface followed by diffusional drug loss, Diffusion controlled release at the physically entrapped drug with bio adsorption of the polymer until drug depletion.

Depot formulation may be classified on the basis of the process used for controlled drug release as follows:

1) DISSOLUTION CONTROLLED DEPOT FORMULATION:

In this depot formulation the rate of absorption is controlled by the slow dissolution of drug particles in the tissue fluid surrounding the formulation or in the formulation

The rate of dissolution (Q/t) d under sink condition is defined by :

$$(Q/t) d = \frac{sa d_s c_s}{hd}$$

Where sa = surface area of the drug particles in contact with the medium

ds= is the diffusion coefficient of drug molecules in the medium

Cs= is the saturation solubility of the drug in the medium.

Hd = thickness of the hydrodynamic diffusion layer surrounding each drug particle.

Basically two approaches can be utilized to control the dissolution of drug particle to prolong the absorption and hence the therapeutic activity of the drug.

A) Formation of salt or complexes with low aqueous solubility:

Examples of dissolution controlled depot formulation using salt formation technique are:

- Penicillin G procaine (cs = 4 mg / ml) and penicillin G benzathine (cs=0.2 mg /ml)
- Naloxone pamoate and naltrexone Zn tannate from water soluble hydrochloride salts of naloxone and naltrexone respectively

Both aqueous suspension as well as oleaginous suspension of penicillin G procaine and penicillin G benzathine produces prolonged therapeutic activities.

Penicillin benzathine and penicillin G procaine combination as well as oleaginous suspension of naloxone pamoate and naltrexone Zn tannate in vegetable oil all produce prolonged therapeutic activities.

B) Aqueous Suspension:

Suspension of macro crystals large crystals are known to dissolve more slowly than small crystals this is called macro crystal principle and can be applied to control the rate of drug dissolution e.g.: aqueous suspension of testosterone isobutyrate for I.M injection in contrast with the suspension in plain peanut oil i.e. without gelation with aluminium monostearate or with aqueous suspension this macrocrystal principle was followed fairly well.

Several years following the development of depot penicillin oleaginous suspension, it was discovered that the therapeutic serum concentration of penicillin can be substantially prolonged by formulating penicillin G procaine in an aqueous thixotropic suspension.

This was accomplished by maintaining a high solid vehicle ratio (40% to 70% of milled and micronized penicillin G procaine particles)

Its prolonged action is partly because these thixotropic suspensions tend to form compact and cohesive depots at the site of intramuscular injection. Leading to the slow release of penicillin G procaine and partly because of the low aqueous solubility of the procaine salt of penicillin G that renders the intramuscular absorption of penicillin under the control dissolution of penicillin G procaine in the tissue fluid.

2) ADSORPTION TYPE DEPOT FORMULATION:

This type of depot preparation is formed by the binding of drug molecule to adsorbents in this only the unbound, free species of the drug is available for absorption as soon as the unbound drug molecules are absorbed a fraction of the bound drug molecule is released to maintain equilibrium.

E.g. vaccine preparations in which the antigens are bound to highly dispersed aluminium hydroxide gel to sustain their release and hence prolong the duration of stimulation of antibody formation.

Prolongation of insulin activity was made by complexing insulin with protamine.

Protamine-insulin complex releases upto 24 hrs on subcutaneous injection. Protamine-Zn-insulin complex when given subcutaneous releases upto 36 hrs but it has slow onset of action 4 to 8 hrs.

Others: **Insulin-Zn-Protein complexes like:**

- a) Isophane insulin suspension (USP) has rapid onset of action (1-1.5 hrs) and moderate duration of activity (24 hrs).
- b) Gliobin-Zn-insulin injection USP, onset of action and release pattern similar to Isophane.

3) ENCAPSULATION TYPE DEPOT FORMULATIONS:

This type of depot formulation is prepared by encapsulating drug solids within a permeation barrier or dispersing drug particles in a diffusion matrix.

Both permeation barrier and diffusion matrix are fabricated from biodegradable or bioabsorbable macromolecules such as gelatin, dextran, polylactate, lactide glycolide co polymers phospholipids and long chain fatty acids and glycerides.

E.g: Naltrexone palmoate releasing biodegradable micro capsules, the release of drug molecules is controlled by the rate of permeation across the permeation barrier and the rate of biodegradation of the barrier macromolecules.

4) ESTERIFICATION TYPE DEPOT FORMULATION:

This depot preparation is produced by esterifying a drug to form bioconvertible pro drug type ester and then formulating it in an injectable formulation this formulation forms a drug reservoir at the site of injection. Eg. fluphenazine enanthate testosterone 17 β cypionate in oleaginous solution.

IMPLANTS:

Implants are sterile, solid preparations of a size and shape suitable for parenteral implantation and release of the active substance(s) over an extended period of time. These are made by compression, melting or sintering. They generally consist of the drug and the rate controlling excipients.

APPROACHES TO THE DEVELOPMENT OF IMPLANTABLE DRUG DELIVERY SYSTEM:

A number of approaches have been developed to achieve the controlled administration of biologically active agents via implantation (or insertion) in tissue these approaches are outlined as follows

- 1) **CONTROLLED DRUG DELIVERY BY DIFFUSION PROCESS.**
- 2) **CONTROLLED DRUG DELIVERY BY ACTIVATION PROCESS.**
- 3) **CONTROLLED DRUG DELIVERY BY FEEDBACK REGULATED PROCESS.**

1) CONTROLLED DRUG DELIVERY BY DIFFUSION PROCESS IS FURTHER CLASSIFIED AS:

- a) Polymembrane permeation controlled drug delivery system.
 - 1) Nonporous membranes.
 - 2) Micro porous membrane.

- 3) Semi permeable membranes.
- b) Matrix diffusion controlled drug delivery system.
 - 1) Lipophilic polymers
 - 2) Hydrophilic polymers
 - 3) Porous polymers.
- c) Micro reservoir partition controlled drug delivery system.
 - 1) Lipophilic membrane with hydrophilic matrix.
 - 2) Hydrophilic membrane with lipophilic matrix.

2) CONTROLLED DRUG DELIVERY BY ACTIVATION PROCESS :

- 1) Osmotic pressure activated drug delivery.
- 2) Vapour pressure activated drug delivery.
- 3) Magnetically activated drug delivery.
- 4) Hydration activated drug delivery
- 5) Hydrolysis activated drug delivery.

3) CONTROLLED DRUG DELIVERY BY FEEDBACK REGULATED PROCESS.

- 1) Bioerosion regulated drug delivery.
- 2) Bioresponsive drug delivery.

1) CONTROLLED DRUG DELIVERY BY DIFFUSION PROCESS:

A) **POLYMER MEMBRANE PERMEATION CONTROLLED DRUG DELIVERY SYSTEM:**

In this implantable controlled release drug delivery system, the drug reservoir is encapsulated by a rate controlling polymeric membrane having a specific permeability the drug reservoir may exist in solid, suspension or solution form.

The polymeric membrane can be fabricated from a nonporous (homogenous or heterogeneous) polymeric material or a micro porous or semipermeable membrane.

The encapsulation of drug formulation inside the reservoir compartment is accomplished by:

- a) Injection moulding
- b) Spray coating
- c) Capsulation
- d) Micro encapsulation
- e) Extrusion molding or other techniques.

Different shapes and size of drug delivery systems can be fabricated:

- a) Sphere.
- b) Cylinder.
- c) Sheet.

MECHANISM OF RATE CONTROL:

The release of drug molecule from this type of rate controlled drug delivery system is controlled at a pre-programmed rate by controlling the partition coefficient and diffusivity of the drug molecule and the thickness of the rate controlling membrane.

Example: Norplant subdermal implant:

It is fabricated from nonporous silicone medical grade tubing (with both ends sealed with silicone medical grade adhesive) to encapsulate either levo norgestrel crystal alone (generation I) or a solid dispersion of (levonorgestrel) in silicone elastomer matrix (generation II) it is designed for the continuous subcutaneous release of levonorgestrel at a daily dosage rate of 30µgm to each subject for up to 7 years.

B) POLYMER MATRIX DIFFUSION CONTROLLED DRUG DELIVERY SYSTEMS:

In this type the drug delivery system the drug reservoir is prepared by homogeneously dispersing drug particle in a rate controlling polymer matrix fabricated from either a lipophilic or hydrophilic polymer

The drug dispersion in the polymer matrix is accomplished by either:

- 1) Blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross-linking of the polymer chains.

Or

Mixing drug solids with a rubbery polymer at an elevated temperature the resultant drug polymer dispersion are then molded or extruded to form a drug delivery device of various shapes and sizes

- 2) It can be fabricated by dissolving the drug and the polymer in a common solvent followed by solvent evaporation
- 3) The rate of drug release from this polymer matrix diffusion controlled drug delivery system is time dependent.

Example: Compudose subdermal implant:

Fabricated by dispersing micronized estradiol crystals in a viscous silicone elastomer and then coating the estradiol dispersing in a viscous silicone elastomer and then coating the estradiol dispersing polymer around a rigid (drug free) silicone rod by extrusion.

C) MICRO RESERVOIR PARTITION CONTROLLED DRUG DELIVERY SYSTEM:

In this type of drug delivery systems the drug reservoir is fabricated by micro dispersion of aqueous suspension of drug using a high-energy dispersion technique in a biocompatible polymer, such as silicone elastomer to form a homogenous of many discrete, unreachable microscopic drug reservoirs.

Different shapes and size of drug delivery devices can be fabricated from this micro reservoir drug delivery system by molding or extrusion.

Depending upon the physicochemical properties of drugs and the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and the rate of drug release.

Example: Subdermal syncro –mate –c implant:

Fabricated by dispersing suspension of norgestoment in an aqueous solution of PEG in a viscous mixture of silicone elastomer by high-energy dispersion.

After adding catalyst, the suspension will be delivered in to the silicone medical grade tubing which serves as mold as well as coating membrane and then polymerized in situ.

The polymerized drug polymer composition is then cut in to a cylindrical drug delivery device with open ends.

Note: When inserted in to the sc tissue of the live stock ear flap release norgestoment for up to 20 days for control and synchronization of estrus and ovulation as well as up to 160 days for growth promotion.

2) CONTROLLED DRUG DELIVERY BY ACTIVATION PROCESS:

- 1) Osmotic pressure activated drug delivery.
- 2) Vapor pressure activated drug delivery
- 3) Magnetically activated drug delivery
- 4) Hydration activated drug delivery

5) Hydrolysis activated drug delivery.

1) OSMOTIC PRESSURE ACTIVATED DRUG DELIVERY SYSTEM:

In this implantable controlled release drug delivery device osmotic pressure is used as the energy source to activate and modulate the delivery of drugs.

The drug reservoir is either a solution or a semisolid formulation with in a semipermeable housing with controlled water permeability.

Example of this type of implantable drug delivery device is the alzet osmotic pump:

Ionized drugs macromolecule steroids and peptides (insulin) can be delivered by such a device.

Example: Implantable osmotic pump of bleomycin (used for Lewis lung carcinoma).

2) VAPOR PRESSURE ACTIVATED DRUG DELIVERY DEVICE:

In this implantable controlled release drug delivery device vapor pressure is used as the power source to activate the controlled delivery of drugs.

The implant system is a disc shaped device which consists of two chambers:

- An infusate chamber containing drug solution, it is physically separated from the [pumping compartment by a freely movable partition.
- Pumping compartment contains inexhaustible vaporizable fluid such as fluorocarbons.

After implantation the volatile liquid vaporizes at the body temperature and creates a vapor pressure that compress the movable partition this forces the drug solution in the infusion compartment to be derived through a series of flow regulator and delivery cannula in to the blood circulation at a constant flow rate.

Eg: Insulin for the diabetics and the morphine for terminally ill cancer patients have been successfully delivered by such a device.

3) MAGNETICALLY ACTIVATED DRUG DELIVERY DEVICES:

In this implant able controlled release drug delivery device electromagnetic energy is used as the power source to activate the delivery of the drugs and to control the release of drug delivery.

This subdermally implantable magnetically modulated device is hemispherical in shape.

Fabricated by positioning a tiny donut shaped magnet at the center of medicated polymer matrix.

The external surface of the hemispherical pellet is further coated with a pure polymer such as ethylene vinyl acetate copolymer or silicon elastomer on all sides except one cavity at he center of the flat surface, which is left uncoated to permit the drug molecule to be delivered through the cavity.

Under nontriggering condition this implantable hemispherical magnetic pellet releases drugs at a controlled rate by diffusion alone.

By applying an external magnetic field drugs are activated by the electronic energy to release from the pellet at a much higher rate of delivery.

Eg: Bovine serum albumin release rate profile was checked under triggering and nontriggering conditions.

4) HYDRATION ACTIVATED DRUG DELIVERY SYSTEM:

Drug is released upon activation by hydration of the drug delivery device by tissue fluid at the implantation site.

Drug delivery system is fabricated from a hydrophilic polymer that becomes swollen upon hydration.

Drug molecules are released by diffusing through the microscopic water saturated pore channels in the swollen polymer matrix.

Eg: Norgestomet releasing Hydron Implant (2x21 mm in size)

Formulation:

This was fabricated by polymerizing ethylene glycol methacrylate in an alcoholic solution that contains Norgestomet & a cross linking agent (such as ethylene dimethacrylate) and an oxidizing catalyst to form cylindrical water swellable (but insoluble hydron implant).

5) HYDROLYSIS ACTIVATED DRUG DELIVERY DEVICE:

Drug is released upon the hydrolysis of the polymer base by tissue fluid at the implantation site. It is fabricated by dispersing a loading dose of solid drug in micronized form. Homogeneously dispersed throughout a polymer matrix made from bioerodible or biodegradable polymer which is then molded into a pellet or a bead shaped implant.

The controlled release of embedded is made possible by the combination of polymer erosion by hydrolysis and diffusion through the polymer matrix.

Eg: Naltrrexone pellets fabricated from poly (lactide –glycolide) copolymer for the antinarcotic treatment of opiod dependent addicts.

In addition to poly (lactide –glycolide) copolymer, several other biodegradable polymers such as Polysaccharide, polypeptide and homopolymer of polylactide or Polyglycolide, Polyanhydride and polycaprolactone can also be used.

NOVEL TECHNOLOGIES IN IMPLANTS:

1) ZOLADEX (gosereline acetate implant) :

Zoladex is a sterile, biodegradable product containing goserelin acetate designed for sub cutaneous injection, continuous release for 28 days.

Zoladex is also available as zoladex-3 months. The base consists of a matrix of D,L- lactic & glycolic acid copolymer.

It is indicated for no. of disorders, including palliative treatment of advanced carcinoma of prostate. It is also used in the treatment of advanced breast cancer.

It should be stored at room temp. & should not exceed 25°C.

Zoladex safe system syringe:

The advanced design of the Zoladex safe system syringe makes it safer & convenient for the health care professional:

- ❖ Built in protective needle sleeve.
 - Reduces potential for needle stick injury.
 - Automatically activates upon complete plunger depression.
 - No safety clip and no added steps.
- ❖ Preloaded to ensure precise and accurate dosing.
- ❖ Ready to use at your convenience- no mixing, reconstitution or refrigeration necessary.

2) GLIADEL[®] Wafer IMPLANT:

GLIADEL[®] Wafers are small, dime-sized, half-inch white discs biodegradable polymer wafers that are designed to deliver BCNU or carmustine directly into the surgical cavity created when a brain tumor is surgically removed.

Immediately after a neurosurgeon operates to remove the high-grade malignant glioma, up to eight wafers are implanted along the walls and floor of the cavity that the tumor once occupied. Each wafer contains a precise amount of carmustine that dissolves slowly, delivering carmustine to the surrounding cells.

GLIADEL[®] Wafer therapy is used in conjunction with **surgery** and **adjuvant radiation** to treat certain kinds of **brain tumors** called high-grade malignant gliomas.

3) DURIN™ Biodegradable IMPLANTS:

The DURIN biodegradable implant technology is based on the use of biodegradable polyesters as excipients for implantable drug formulations. This family of materials, which is used extensively in medical devices and drug delivery applications, includes the polymers and copolymers prepared from glycolide, DL-lactide, L-lactide, and ϵ -caprolactone.

The overall form of the implant is typically a small rod or pellet that can be placed by means of a needle or trochar. The composition of the rod or pellet can be monolithic, where the drug is uniformly dispersed throughout the excipient. Alternatively, reservoir-type designs are also possible in which the rod or pellet is composed of a drug-rich core surrounded by a rate-controlling membrane.

e.g. Naltrexone, a narcotic antagonist, from a reservoir type DURIN implant.

4) DUROS® TECHNOLOGY:

The DUROS technology (Figure 1) is a miniature drug-dispensing system that operates like a miniature syringe and releases minute quantities of concentrated drug formulations in a continuous, consistent flow over months or years. The system is implanted under the skin and can be as small as 4 mm OD X 44 mm L or smaller.

The system consists of an outer cylindrical titanium alloy reservoir. This reservoir has high-impact strength and protects the drug molecules from enzymes, body moisture, and cellular components that might deactivate the drug prior to delivery. To address the needs of chronic pain sufferers, DUROS technology has been applied to the delivery of the opioid drug sufentanil. The resulting DUROS system, the CHRONOGESIC[™] (sufentanil) Pain Therapy System, is designed to deliver the drug at physician-specified doses for 3 months, and is targeted to patients with opioid-responsive chronic pain that results from a variety of causes.

5) ATRIGEL® IN SITU IMPLANT SYSTEM:

The ATRIGEL system is a proprietary delivery system that can be used for both Parenteral and site-specific drug delivery. It contains a biodegradable polymer dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using conventional needles and syringes, it solidifies upon contact with aqueous body fluids to form a solid implant. If a drug is incorporated into the polymer solution, it becomes entrapped within the polymer matrix as it solidifies, and is slowly released as the polymer biodegrades.

The solvents employed in the ATRIGEL system to dissolve the polymers range from the more hydrophilic solvents, such as N-methyl-2-pyrrolidone (NMP), polyethylene glycol, tetraglycol, and glycol furol, to the more hydrophobic solvents, such as triacetin, ethyl acetate, and benzyl benzoate. NMP is most frequently used because of its solvating ability and its safety/toxicology profile.

ADVANCED PARENTERAL DRUG DELIVERY SYSTEM:

1) Liposomes:

Liposomes are formed by the self-assembly of phospholipid molecules in an aqueous environment, the amphiphilic phospholipid molecules form a closed bilayer sphere in an attempt to shield their hydrophobic

groups from the aqueous environment while still maintaining contact with the aqueous phase via the hydrophilic head group. The resulting closed sphere may encapsulate aqueous soluble drugs within the central aqueous compartment or lipid soluble drugs within the bilayer membrane. Alternatively, lipid soluble drugs may be complexed with cyclodextrins and subsequently encapsulated within the liposome aqueous compartment.

The encapsulation of drugs with liposomes alters drug pharmacokinetics and this may be exploited to achieve targeted therapies. Alteration of the liposome surface is necessary in order to optimize liposomal drug targeting and to achieve prolonged circulation times

liposome size between 70-200nm is necessary. Liposomes are the most widely studied modern drug delivery system because of its amazing application for the management of following diseases:

i) Liposomal anticancer agent -

The use of liposomes as anticancer drug delivery systems was originally hampered by the realization that liposomes are rapidly cleared from the circulation and largely taken up by the liver macrophage.

It was observed that doxorubicin loaded stealth liposomes circulate for prolonged periods, accumulate and extravagate within tumours & also improve tumoricidal activity.

In one study it has been reported that in patients, liposomal doxorubicin accumulates within Kaposi's sarcoma lesions and produces a good therapeutic response. Liposomal doxorubicin is now licensed as Caelyx, for the treatment of Kaposi's sarcoma.

This formulation is currently in clinical trials for ovarian cancer and could be approved shortly for use in ovarian cancer patients who have failed to respond to paclitaxel and cisplatin.

ii) Liposomes as vaccine adjuvants -

Liposomal vaccines can be made by associating microbes, soluble antigens, cytokines or deoxyribonucleic acid (DNA) with liposomes, the latter stimulating an immune response on expression of the antigenic protein. Liposomes encapsulating antigens, which are subsequently, encapsulated within alginate lysine microcapsules to control the antigen release and to improve the antibody response.

Liposomal vaccines may also be stored dried at refrigeration temperatures for up to 12 months and still retain their adjuvanticity.

iii) Liposomal anti-infective agents -

Liposomal amphotericin B (Ambisome), used for the treatment of systemic fungal infection. This is the first licensed liposomal preparation. It was observed in one study that liposomal amphotericin B, by passively targeting the liver and spleen, reduces the renal and general toxicity of the drug at normal doses.

2) Niosomes:

Niosomes are unilamellar or multilamellar vesicles, where in an aqueous solution is enclosed in highly ordered bilayer made up of nonionic surfactants with or without cholesterol (chol) and dicetyl phosphate

and exhibit a behavior similar to liposomes *in-vivo*. They can be used in the treatment of cancer and also used as vaccine adjuvant. Some of its applications are:

i) Anticancer niosomes -

Anticancer niosomes, if suitably designed will be expected to accumulate within tumours. For example niosomal encapsulation of methotrexate and doxorubicin increases drug delivery to the tumour and tumoricidal activity. It was reported that doxorubicin Niosomes having size 200nm with a polyoxyethylene (molecular weight 1,000) surface are rapidly taken up by the liver and accumulate to a lesser extent in tumour, this technology may prove advantageous for the treatment of hepatic neoplasms. It was also observed that the activity of other anticancer drugs, such as vincristine, bleomycin, plumbagin and a plant derived anticancer agent are improved on niosomal encapsulation.

ii) Niosomes at targeted site-

Uptake by the liver and spleen make niosomes ideal for targeting diseases manifesting in these organs. One such condition is leishmaniasis and a number of other studies has shown that niosomal formulations of sodium stibogluconate improve parasite suppression in the liver spleen and bone marrow. Niosomes may also be used as depot systems for short acting peptide drugs on intramuscular administration.

iii) Niosomes as vaccine adjuvants-

It was studied that niosomal antigens are potent stimulators of the cellular and humoral immune response. The formulation of antigens as a niosome in water-in-oil emulsion further increases the activity of antigens and hence enhanced the immunological response.

3) Nanoparticles and Microparticles:

Nanoparticles and microparticles are usually prepared by the controlled precipitation of polymers solubilised in one of the phases of an emulsion. Precipitation of the polymer out of the solvent takes place on solvent evaporation, leaving particles of the polymer suspended in the residual solvent. For particulate dispersions, the required particle size of nanoparticles lies between the range of 30-500nm while for microparticles in excess of 0.5micron. Their applications in management of diseases are:

i) Tumor targeting nanoparticles and microparticles-

The accumulation of non-stealth doxorubicin nanoparticles within the Kupffer cells of the liver may be used to target hepatic neoplasms indirectly, this is achieved by providing a depot of drug for killing nearby neoplastic tissue.

Microparticles may also be injected directly into tumours. It was observed that the direct injection of

microparticles into solid tumours increases the tumoricidal activity of the drugs 5-fluorouracil and doxorubicin.

ii) Vaccine adjuvants-

Nanoparticles have also been used as vaccine adjuvants. It was reported that antigens, which adsorbed onto the surface or entrapped in the matrix of polymethylmethacrylate nanoparticles induces an enhanced immunological response. For example polymethylmethacrylate nanoparticles containing the influenza antigen may protect people against disease to a greater extent than the antigen alone.

iii) Other applications-

Restenosis, defined as the re-obstruction of an artery following procedures such as angioplasty or artherectomy may be treated by the local application of dexamethasone-loaded polylactic acid co-glycolic acid nanoparticles.

Cyclosporin A, an immunosuppressant drug used to prevent graft rejection after transplantation by the inhibition of T-lymphocytes, may be targeted to regional lymph nodes by the intramuscular administration of cyclosporin A polylactic acid nanoparticles.

In short it can be said that, by virtue of their small size solid nanoparticles provide opportunities for targeted parenteral therapies and may also be used as immunoadjuvants.

4) Prodrugs -

A prodrug is a pharmacological substance, which is administered in an inactive form. Once administered, it is metabolized in the body *in vivo* into the active compound. The use of prodrugs in cancer chemotherapy as a means of targeting relatively toxic compounds to specific areas of pathology is enjoying renewed activity.

Two of the technologies being evaluated at present are antibody directed enzyme prodrug therapy (ADEPT) and the use of polymeric prodrugs.

i) ADEPT-

Basically, an antibody-enzyme conjugate is administered intravenously, localizes in tumour tissue and subsequently activates an administered prodrug predominantly within such tumours.

Prodrug activating enzyme is carboxypeptidase G2.

ii) Polymeric prodrugs -

This involves the use of an active substance and possibly a targeting moiety, both linked via spacers to a water-soluble polymeric backbone. From this basic blueprint a number of polymer drug conjugates used for cancer chemotherapy and have been synthesized with cleavable drug polymer linkers. These include soluble polymeric prodrugs of daunorubicin, doxorubicin, cisplatin and 5-fluorouracil. Passive tumour targeting with polymer drug conjugates improves the tumoricidal activity of anticancer agents.

Distribution to potential sites of toxicity, such as the distribution of doxorubicin to heart tissue, is also

decreased with polymer drug conjugates. In short, polymer drug conjugates have progressed from an elegant scientific concept to the clinic and may result in a new form of therapeutics for routine use.

RECENT INNOVATIONS IN STERILE DRUG DELIVERY DEVICES:

❖ Needle free Injection Devices:

Crossject has developed a range of needles-free injection devices for sub-cutaneous, intramuscular or intradermal routes.

The device reconciles all 'needle phobics' with injections. It eliminates the risk of needle-stick injury and needle contamination, and thanks to its ease of use, it improves patient quality of life.

Characteristics:

- **Safe and user friendly Injection systems:**
To perform an injection, simply pick up the device, open the cap, and the device is ready to use. Place the device on the injection site; press on the skin surface until the device starts automatically. The device is fast & silent.
- **Innovative Gas generating system:**
This device uses a totally original gas generating system. Unlike other devices, which encase compressed gas, here the gas propelling the device is generated at the same time as the injection starts.
- **Reliable Injection system:**
Two reactions take place to ensure that the needle-free injection is completely reliable. An initial, fast reaction generates gas in an appropriate pressure profile, allowing medicine to be propelled through and penetrate into the skin. The reaction can be preset with regard to tissue type, depth of injection & viscosity of the liquid.
Total penetration of the drug into the tissue is completed by the second slower reaction. This generates the end part of the pressure profile, so that the product is continuously distributed to the desired depth. This counter balances the natural release of gas from the first reaction.
- **Optimal Safety & Precision**

❖ Inter-Vial Plus - A reconstitution device:

Duoject's **INTER-VIAL PLUS™** system is a technologically advanced, simple to operate, closed system designed to safely, precisely and intuitively dissolve or suspend and deliver a solid dose drug such as a protein or peptide compound.

An important variation in the design of Duoject's **INTER-VIAL PLUS™** system has been to reverse the traditional position of the wet and dry chambers of our Inter-Vial system.

Since the drug admixture is not transferred between the chambers, transfer losses are nil. The drug reconstitution is performed in its original container (a syringe) and delivered to the patient from this same container. The wet chamber consists of a prefilled vial which can contain Sterile Water for Injection conforming strictly to USP, EP or JP.

Other than the added benefits with the reversed chambers, the **INTER-VIAL PLUS™** and the **INTER-VIAL™** systems function similarly with a unique prefillable syringe attached to a vial connector for use with a standard pharmaceutical vial (13mm or 20mm).

❖ **Vari-Vial - A unique prefillable syringe:**

VARI-VIAL™ is a prefillable syringe and novel bottomless vial capable of being processed on standard "in-house or outsourced" vial production machinery.

VARI-VIAL™ is an effective prefillable syringe system used for either Subcutaneous, Intramuscular or syringe pump based Intravenous applications.

❖ **UltraSafe® Needle Guards:**

UltraSafe® Needle Guards are activated manually and designed to attach easily to most prefilled glass syringes commonly used with vaccines, low molecular weight heparins, and other medicines, including many of the newer biotechnology drugs.

Features:

- Color-coded guards to assist in identification of correct size.
- High-strength, transparent plastic facilitates visualization of syringe markings, labels, and contents, and maximizes protection.
- "Click" lock provides tactile and audible confirmation of guard activation.
- Patented locking mechanism ensures maximum security and locking force.
- Familiar sliding guard activation and ease of assembly assist with compliance and user education.
- Square body design offers improved grip on narrow syringe barrels and enlarges finger flanges for a more secure grip.

SSI's UltraSafe® anti-needle stick devices prevent sharp injuries and provide the highest level of safety.

❖ **UltraSafe® PASSIVE™ Delivery System:**

This system offers a complete pharmaceutical delivery system as well as an effective solution for protecting workers from the horror of needle stick.

❖ **Tamper Evident UltraSafe® PASSIVE™ Delivery System:**

This system helps prevent or make evident, attempts to counterfeit and adulterate unit dose pharmaceutical presentations. It is first and only solution to combine a tamper evident feature with passive needle stick prevention for prefilled glass syringes.

❖ **Insulin Pen Injectors - typical dosing range: 0.01–0.6ml (1–60 I.U):**

Insulin pens are reusable or disposable multi-dose injectors for frequent injections designed for dedicated 3ml cartridges and pen needles.

All Ypsomed's insulin pens include easy dose-setting and clear last-dose indication for when the cartridge is nearly empty. For reusable devices simple cartridge exchange is essential. Above all the dose display must be large and easy to read, while the device itself needs to suit the target patient group. With most current devices the injection process (needle insertion and injection) is performed manually. Spring aided injection can provide benefits to patients.

❖ **Pen Injectors for Other Indications Typical dosing range: 0.05–0.5ml**

Ypsomed has a range of pen devices to cover frequent injection therapies such as hGH, FSH, GLP-1 and PTH. Some of these therapies require a fixed dose whereby the device must clearly communicate that the dose has been set and injected. Other therapies benefit from dose-memory functions which simplify handling so that the patient only needs to set the required dose once for each new cartridge. All pen platforms are designed to accommodate a single-chamber (liquid-stable) or a dual-chamber cartridge.

❖ **Monodose Pens for Dual-Chamber Cartridges**

Many new Injectable therapeutics are available only as lyophilized formulations where a dual-chamber cartridge is required and the device is disposed of after a single injection. The use of dual-chamber cartridges puts special demands on the pen system in terms of intuitive reconstitution, priming and dose-setting steps. It is very important for the patient that these steps are easy to learn and always performed in the correct order.

❖ **Disposable Auto-Injectors Typical dosing range: up to 1ml**

Disposable auto-injectors are typically single-dose delivery devices used for the infrequent injection of larger doses of drugs of different viscosities. The standard device is designed for 1ml long pre-filled syringes. The complete injection process (needle insertion, injection and subsequent needle shielding) is performed automatically. Ease of use, full needle safety and clear injection feedback are standard features of Ypsomed's auto-injectors.

❖ **Standard Pen Needles Penfine® and Clickfine®:**

Ypsomed's patented "click-on" pen needles have been accepted for their quick and easy handling. They are distributed in more than 30 countries under the brand names of Penfine® universal click™, Clickfine® universal and Optifine® and under private label. The broad range of universal "click-on" pen needles is compatible with all major cartridge-based pen systems and can be supplied through pharmacy distribution or as a package directly with the pen injector.

❖ **Safety Pen Needle Clickfine® AutoProtect™:**

Ypsomed's safety pen needle reduces the risk of accidental needle stick injuries and has been developed for frequent injections performed in care-giving situations for insulin and for treatments with a risk of infections such as aids and hepatitis C. The needle also reduces patient anxiety by hiding the needle before and after injection. The locking mechanism is indicated by a red safety bolt which extends over the needle after use.

❖ **Pens With Replaceable Cartridges:**

Insulin cartridges for pens come in 3.0 ml and 1.5 ml sizes, with 3.0 being the predominant size.

❖ **Prefilled Pens:**

Pens that come with a prefilled insulin cartridge are thrown away when the insulin is used up. Prefilled pens using pre-mixed insulin are usually marketed for use by people with type 2 diabetes.

❖ **A Pen with a memory:**

"HumaPen MEMOIR is the first and only insulin pen with a memory. HumaPen MEMOIR records the date, time, and amount of your last 16 doses (including priming doses). You can see exactly when and how much insulin you last took. With HumaPen MEMOIR, you simply "dial" your dose by turning the dose knob in one-unit increments (up to 60 units) after initial set-up. If you dial too many units, you can correct the dose without wasting any insulin. HumaPen MEMOIR is a reusable pen for use only with Humalog (insulin lispro injection [rDNA origin]) 3 mL insulin cartridges.