# Targeted Drug Delivery System


**By**

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# INTRODUCTION

- A special form of drug delivery system where the pharmacologically active drug is selectively targeted or delivered only to its site of action or absorption and not to the non target organs or cells or tissues.

- Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at preselected target in therapeutic concentration, while restricting its assess to non target cellular linings, thus minimizing toxic effects and maximizing therapeutic index.

**ADVANTAGES:-**

- Reduced toxicity
- Bypass first pass metabolism
- Reduce dose and dosing interval
- Enhancement of absorption of targeted molecules

**DISADVANTAGES:-**

- Rapid clearance of targeted system
- Immune reactions against IV administered carrier system
- Redistribution release drug
- Difficult to maintain stability of dosage form

# APPROACHES:-

- Controlling the absorption of drug by incorporating it in a carrier
- Altering the structure of drug at molecular level

# Pharmaceutical Carrier:-

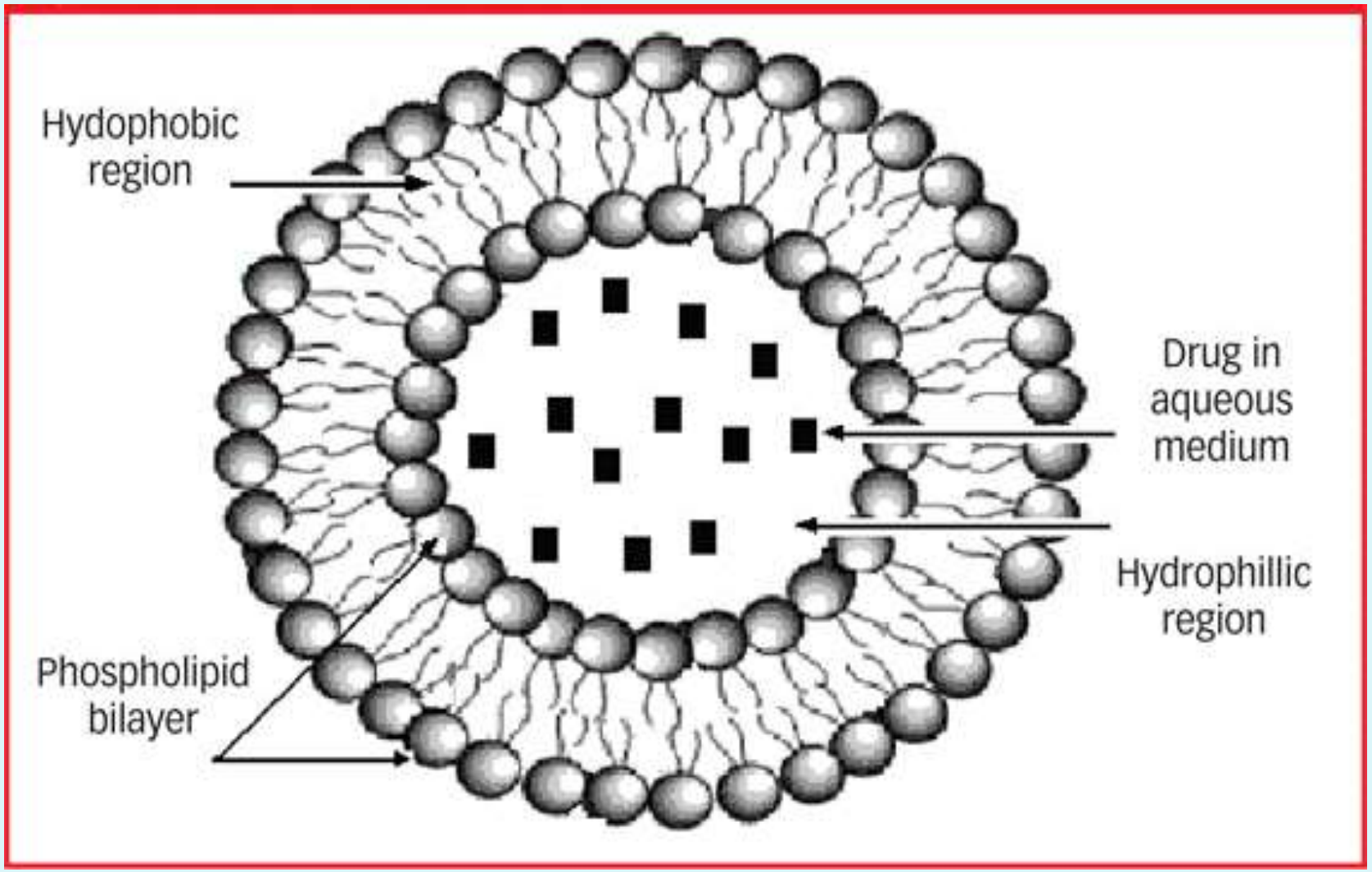
- Liposomes
- Niosomes
- Nanoparticles
- Monoclonal antibodies

# LIPOSOMES

# Liposomes:-

- Liposomes are simple microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecule
- Structurally, liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayers mainly composed of natural or synthetic phospholipids
- Liposomes is a Greek word means **Lipo** mean Fat and **Somes** means Body
- Liposomes were first produced in England in 1961 by Alec D. Bangham

# Basic liposomes structure



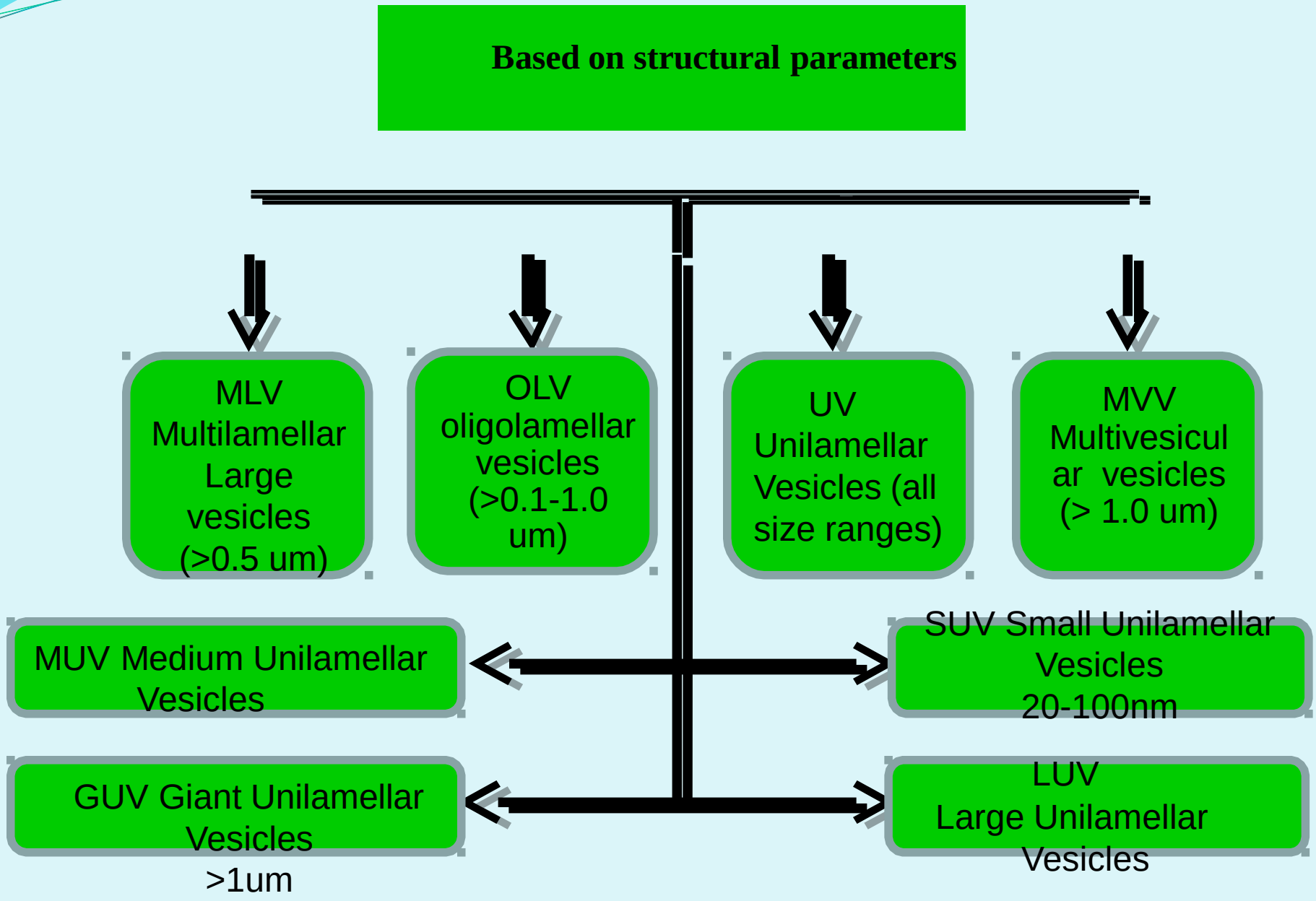
# Advantages of liposomes

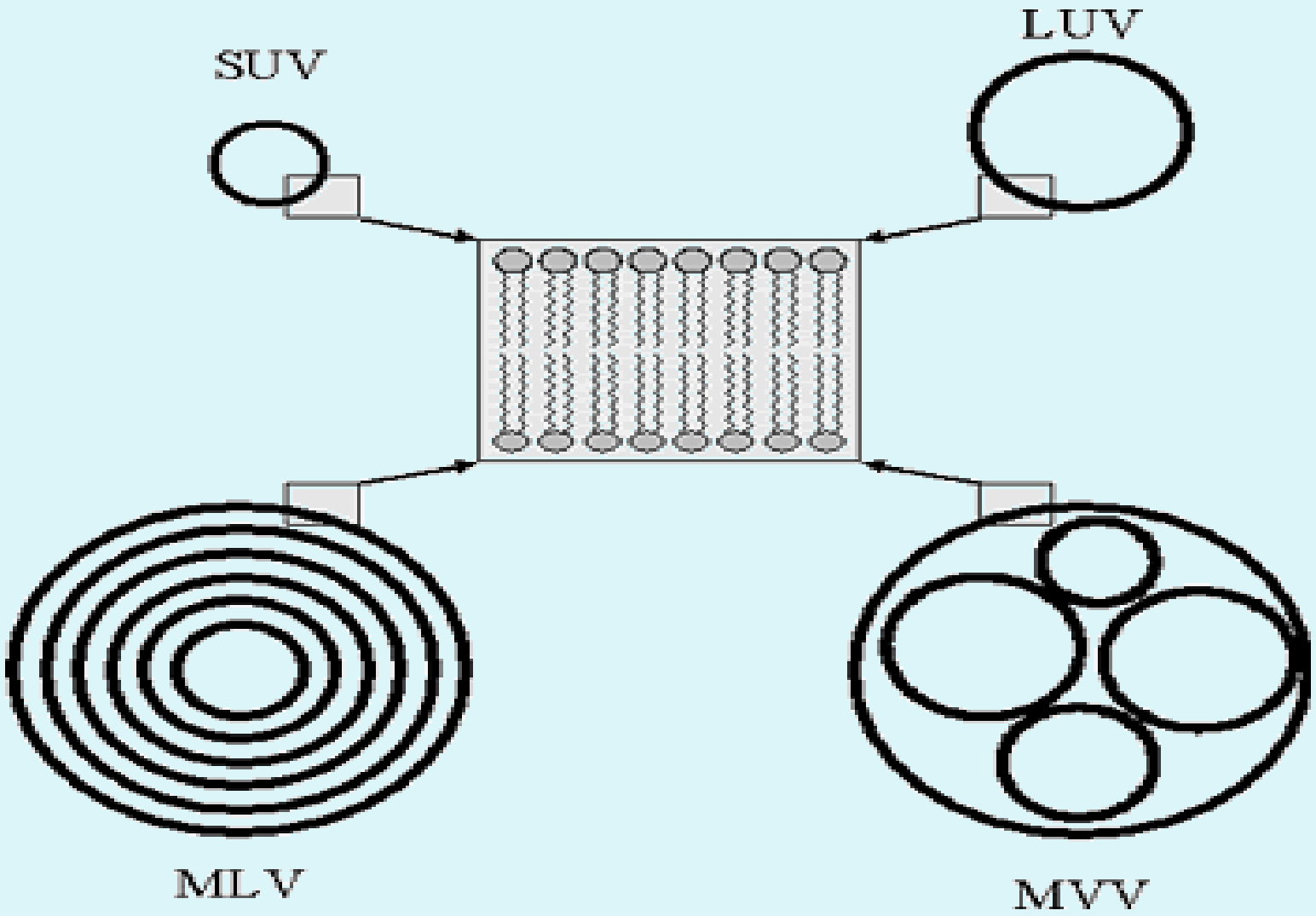
- Provides selective passive targeting to tumor tissues.
- Increased efficacy and therapeutic index.
- Increased stability of encapsulated drug.
- Reduction in toxicity of the encapsulated agent.
- Site avoidance effect (avoids non-target tissues).
- Improved pharmacokinetic effects (reduced elimination increased circulation life times).

# Disadvantages of liposomes

- Physical/ chemical stability
- Very high production cost
- Drug leakage/ entrapment
- Sterilization
- Short biological activity / $t_{½}$

# Classification of liposomes




SUV
LUV
MLV
MVV

# Preparation of liposomes

Methods of liposome preparation

**Passive loading:**
Involves loading of the entrapped agents before or during the manufacturing procedure.

**Active or remote loading:**
Involves loading of the entrapped agents after formation of liposomes.

# On the basis of lipid dispersion

**A] Physical dispersion method**

1] Film hydration

2] Sonication

3] Extrusion

4] Microremulsification

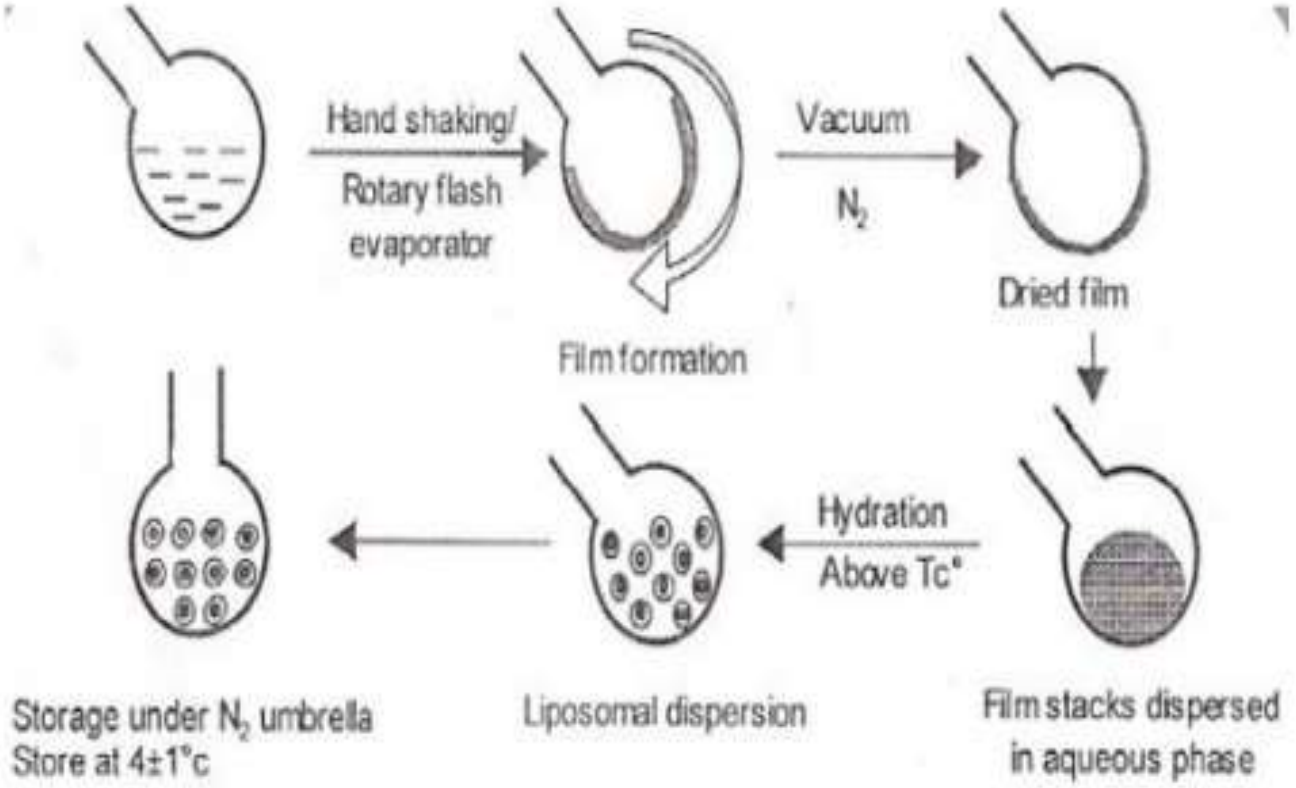
5] French pressure cell liposomes

6] Dried reconstituted vesicles

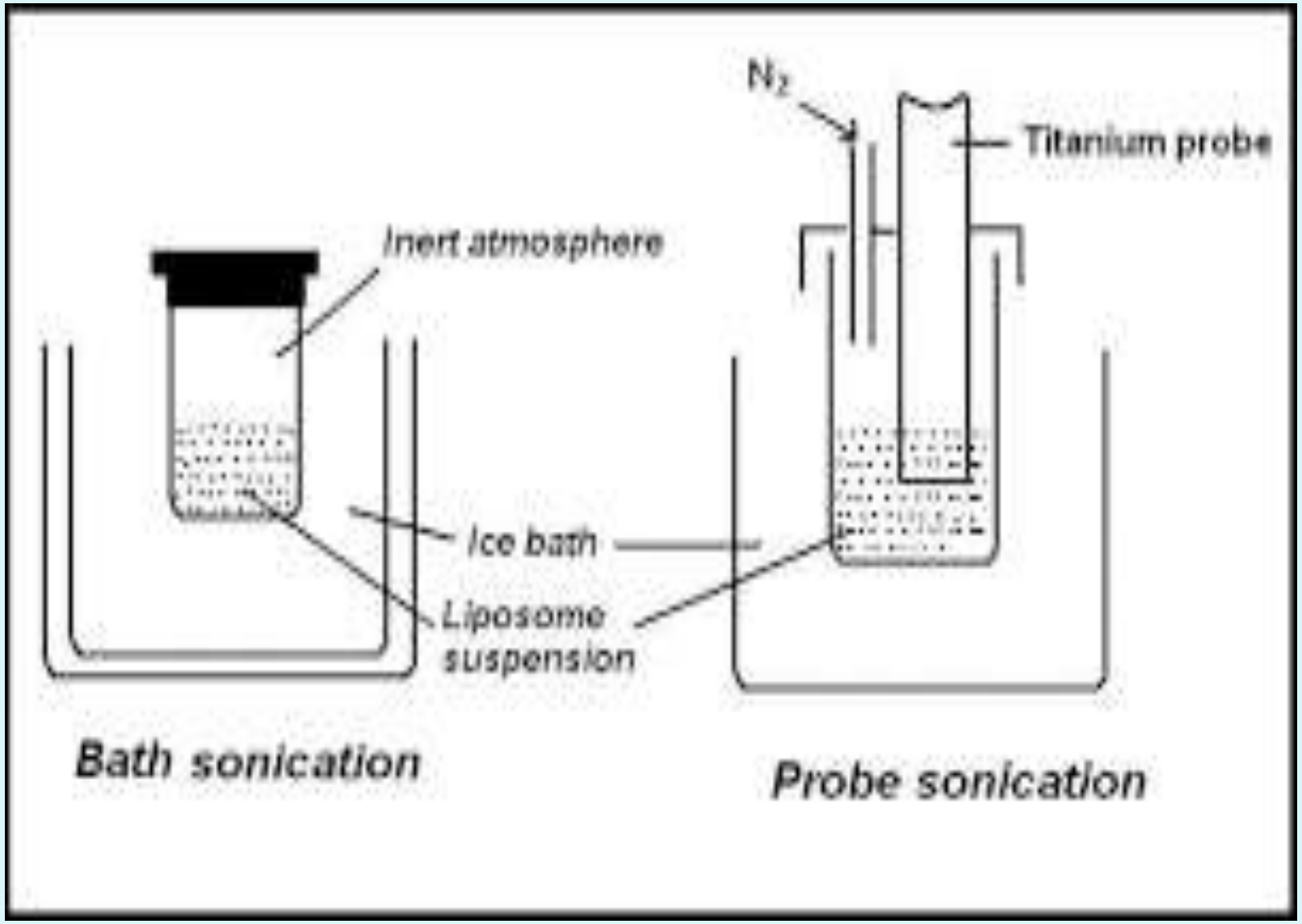
7] Fusion method

# 1] Film hydration

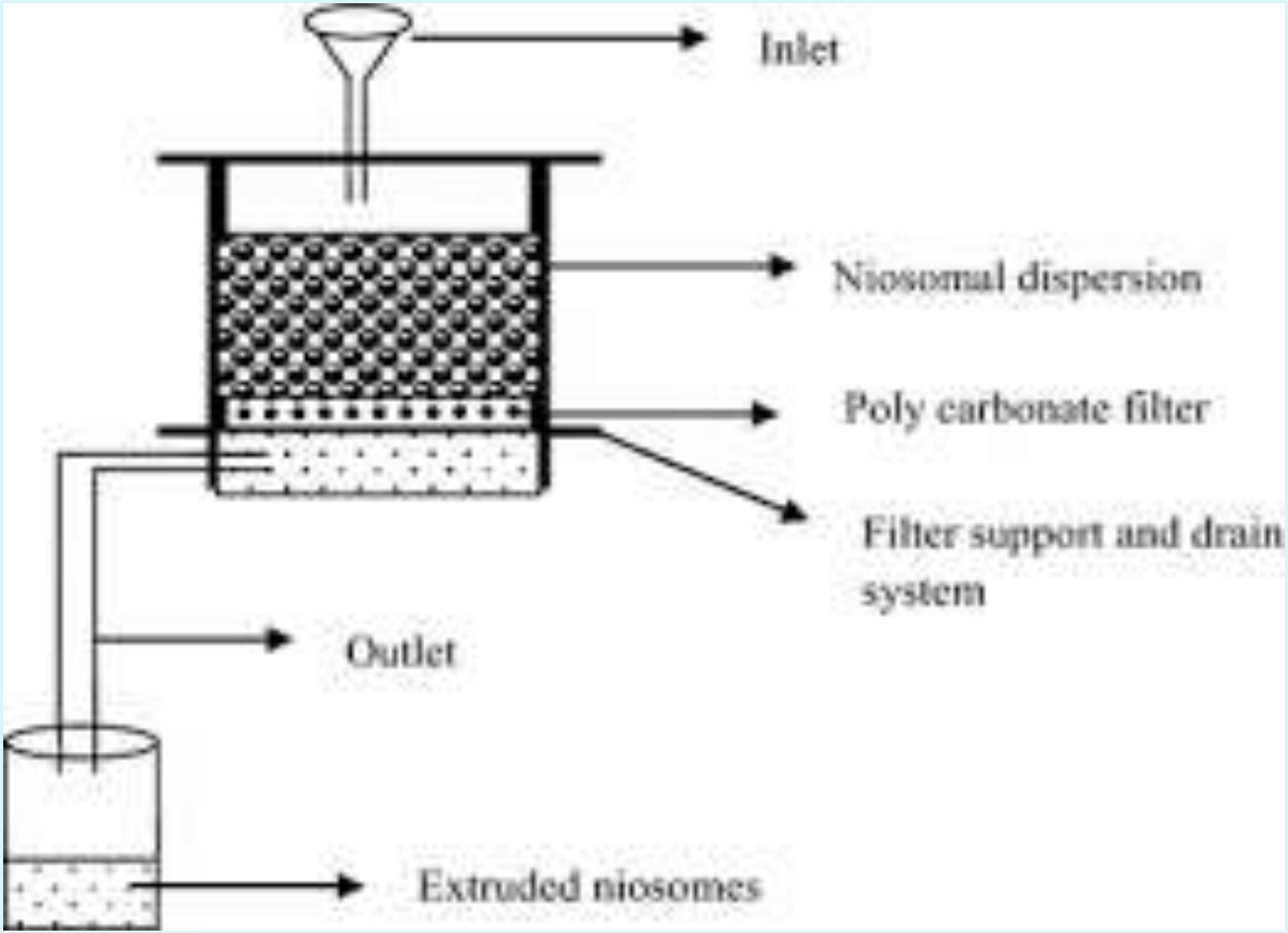
## Lipid film hydration by hand shaking/non hand shaking:



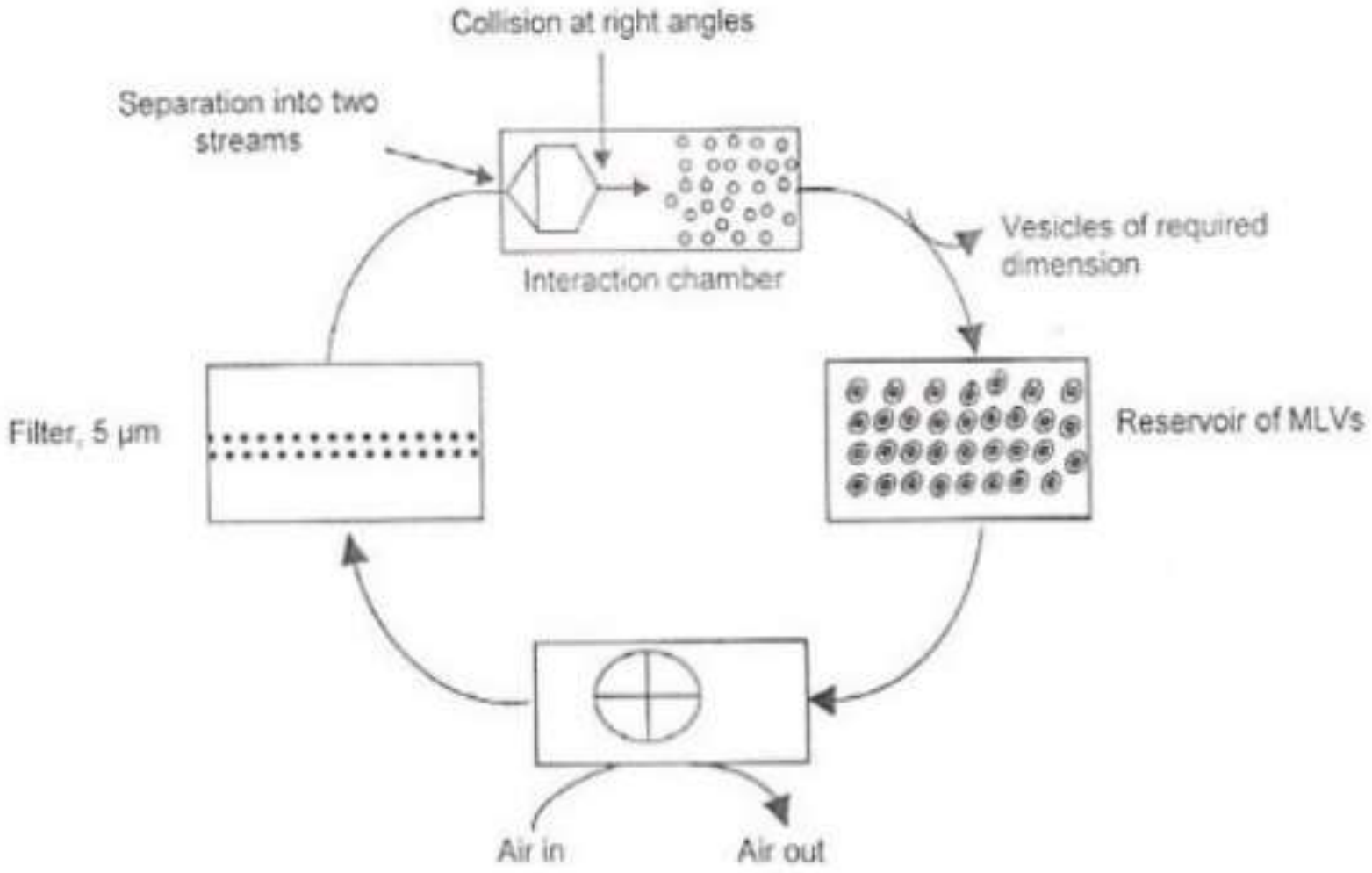
# 2] Sonication



# 3] Extrusion


Inlet
Niosomal dispersion
Poly carbonate filter
Filter support and drain system
Outlet
Extruded niosomes

# 4] Microemulsification



# 5] French pressure cell liposomes

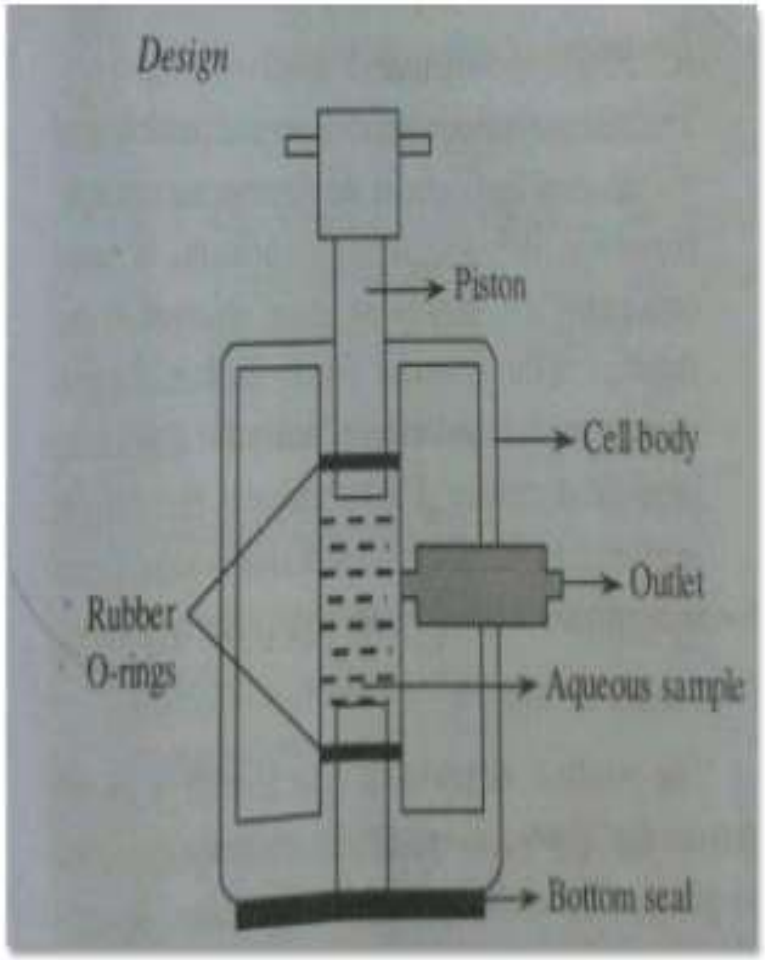
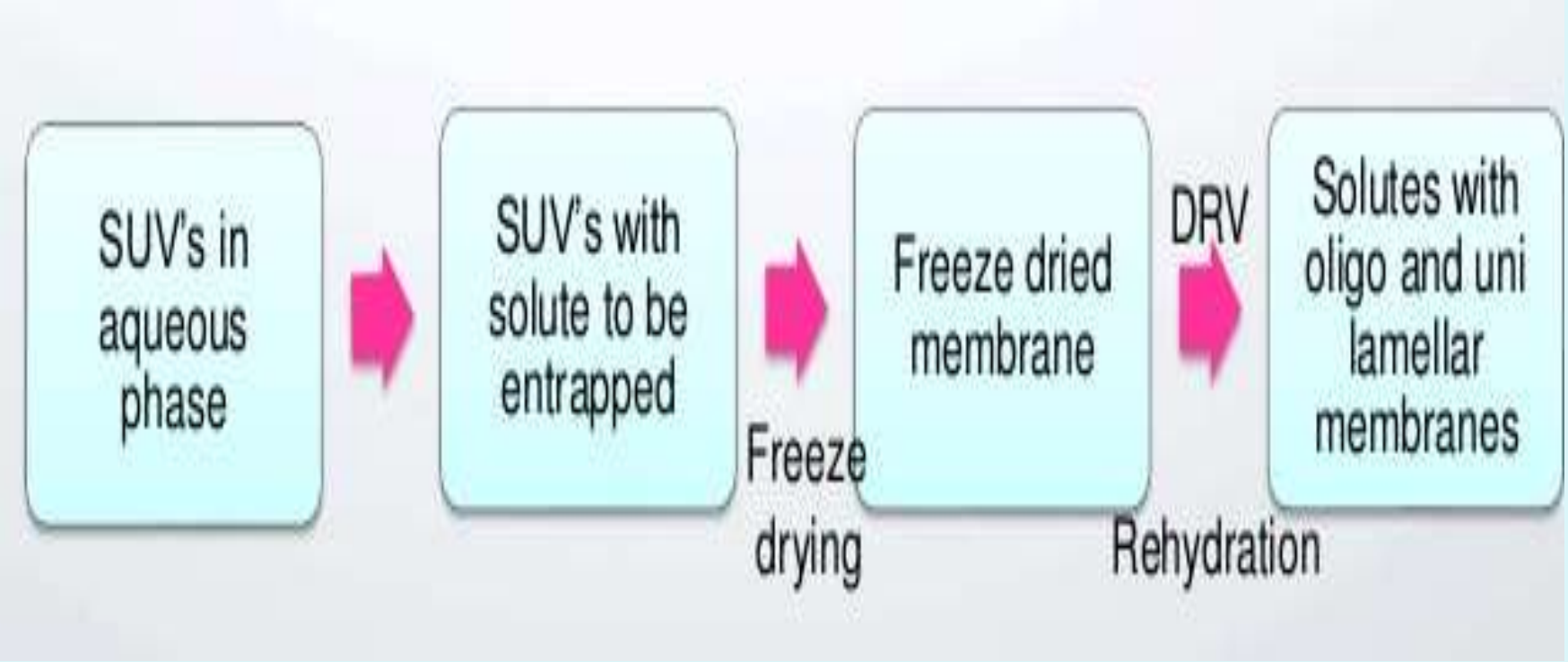



Fig.4- French pressure cell.

- The french pressure cell is constructed from stainless steel and is capable of withstanding very high pressures, even up to 20,000 - 40,000 psi.
- The body of the cell contains a pressure chamber, an outlet, a piston, bottom seal, etc. both the piston and the bottom seal contain an O-ring each, which enables in tight sealing the pressure cell.

# 6] Dried reconstituted vesicles



# On the basis of lipid dispersion

**B] Solvent dispersion method**

1] Ethanol injection

2] Ether injection

3] De-emulsification method

4] Rapid solvent exchange method

5] Double emulsion method

6] Reverse phase evaporation

# 1] Ethanol injection

Lipids + ethanol

↓

Rapidly inject through a fine needle

↓

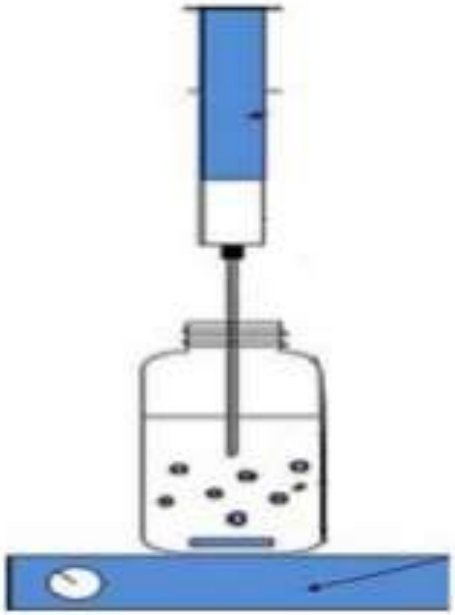
Saline buffer containing materials to be entrapped

↓

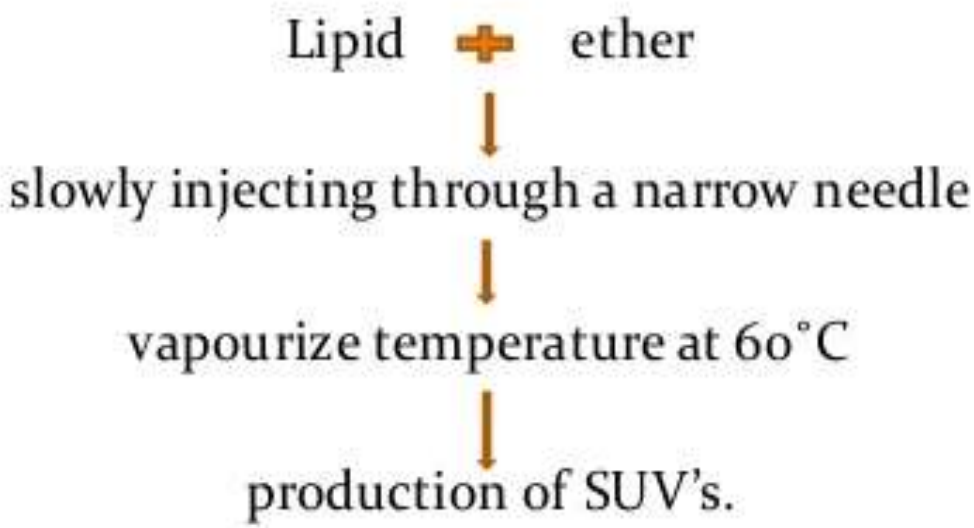
dissolution of ethanol

↓

Formation of SUV's.



# 2] Ether injection

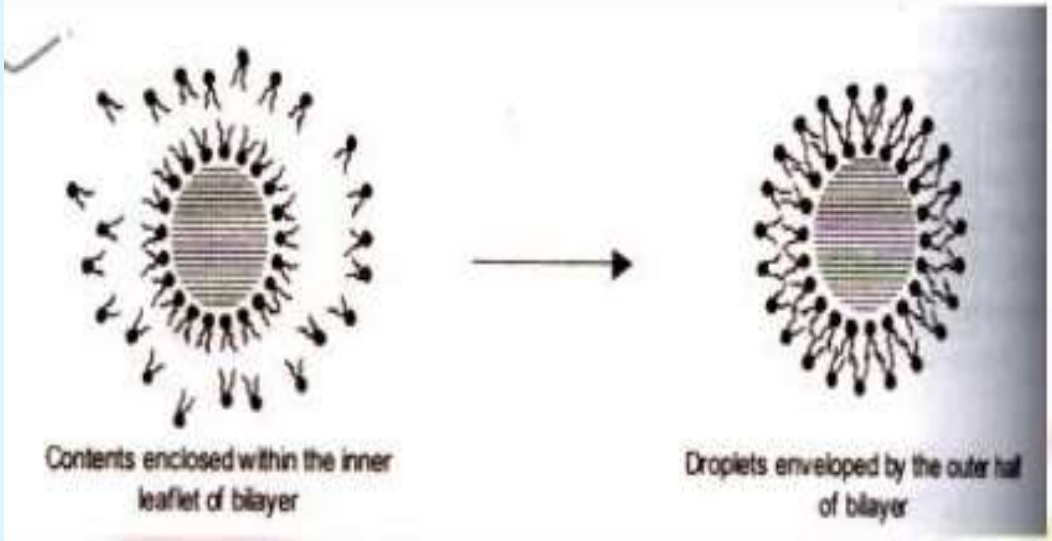



- Less risk of oxidation as ether is free of peroxides.
- Low efficiency.
- Long time needed for production.

# 3] De-emulsification method

Generally the liposome is made up in 2 steps:

- I st the inner leaflet of the bilayer .
- Then the outer half.




Aqueous medium containing material to be entrapped

Add to immiscible organic solution of lipid

Mechanical agitation

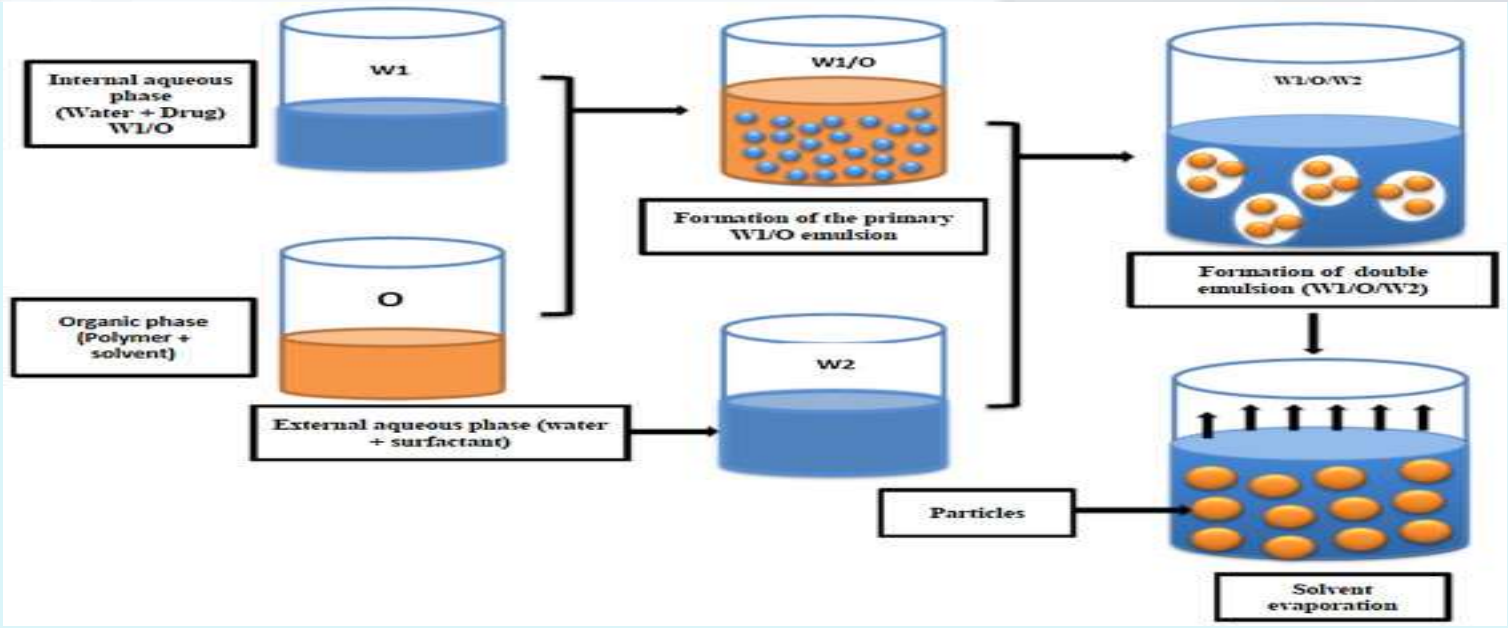
Microscopic water droplets

# 4] Rapid solvent exchange method

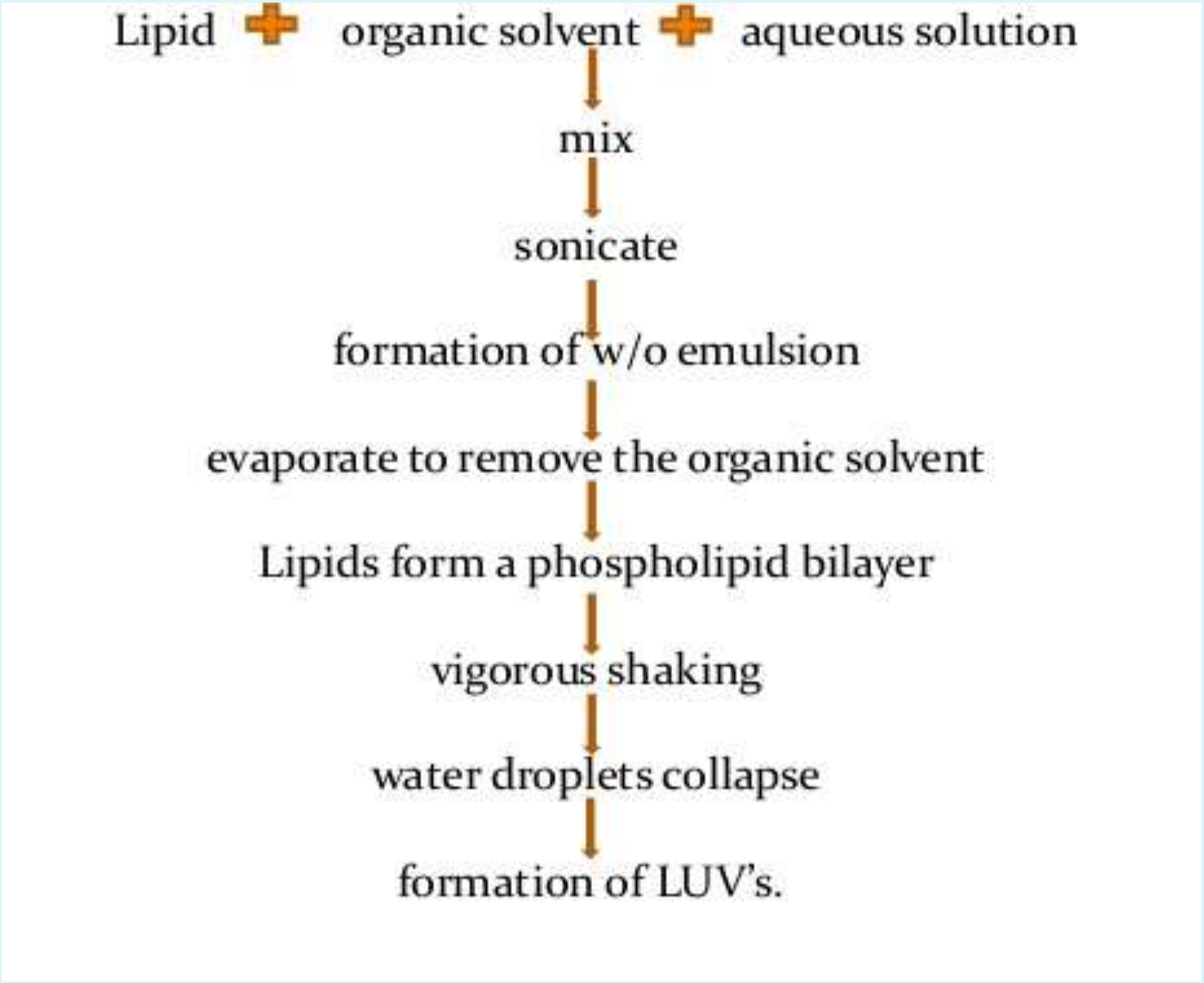
This method involves passing the organic solution of the lipids through the orifice of blue tipped syringe under the vacuum into a tube containing aqueous buffer. The tube is mounted on the vortexes. Bulk solvent vaporizes & is removed within seconds before coming in contact with aqueous environment, while the lipid mixture rapidly precipitates in an aqueous buffer.

# 5] Double emulsion method

- In this process, an active ingredient is first dissolved in an aqueous phase (w1) which is then emulsified in an organic solvent of a polymer to make a primary w1/o emulsion.
- This primary emulsion is further mixed in an emulsifier-containing aqueous solution (w2) to make a w1/o/w2 double emulsion.
- The removal of the solvent leaves microspheres in the aqueous continuous phase, making it possible to collect them by filtering or centrifuging.

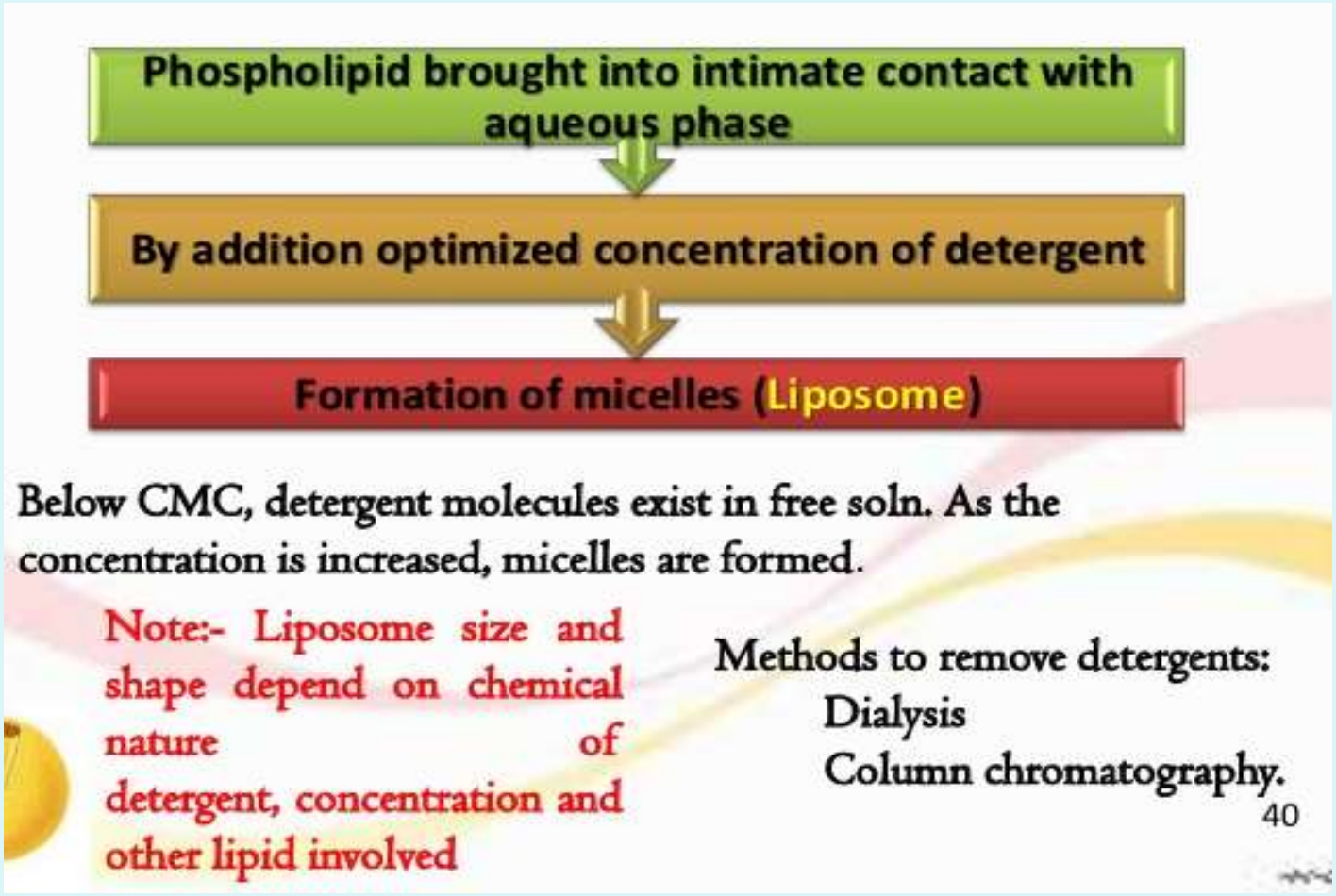


# 6] Reverse phase evaporation



# On the basis of lipid dispersion

## C] Detergent solubilization method



# Characterization

**1] Physical characterization**

- Entrapment efficiency
- Vesicle shape and lamellarity
- Particle size and size distribution
- Surface charge
- Phase transition behaviour

**2] Chemical characterization**

**3] Biological characterization**

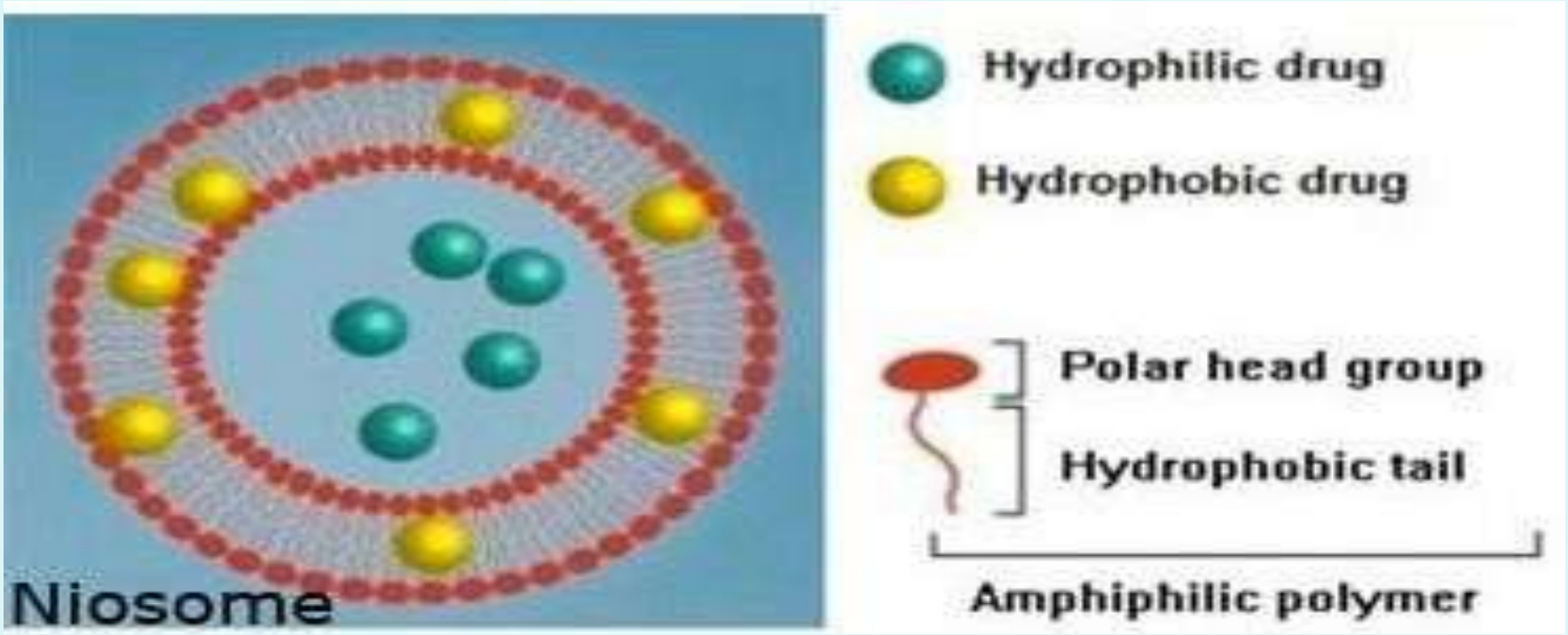
**4] Stability of liposomes**

# Applications

- Drug delivery vehicle
- Tumour therapy
- As vaccine carriers
- In  gene delivery
- As artificial blood surrogates
- As radiopharmaceutical & radiodiagnostic agents
- Cosmetics & dermatology
- Enzyme immobilization

# NIOSOMES

Niosomes are non-ionic surfactant based multi lamellar or uni lamellar vesicles in which an aqueous solution of solute is entirely enclosed by a membrane resulted from the organization of surfactant macromolecules as bilayers.



# Structure of Niosomes

- Niosomes are microscopic lamellar structures
- Basic structural components are
  - ✓ ***Non ionic surfactant***
  - ✓ ***Cholesterol***
  - ✓ ***Charge inducing molecule***
- A number of non-ionic surfactants used are:

*polyglycerol alkyl ether, glucosyl dialkyl ethers, crown ethers, ester linked surfactants, polyoxyethylene alkyl ether and a series of spans and tweens*

# Methods of preparation

## Ether injection Method:

Surfactant : cholesterol (150µmole) solution is dissloved in ether

↓

Slowly injected into preheated 4.0ml aqueous phase maintained at 60 c through a 14 gauge needle

↓

Vaporization of ether leads to formation of single layered vesicles.

↓

formation of a bilayer sheet, which eventually folds on itself to form sealed unilamellar vesicles.

# Hand shaking method:

Surfactant & cholesterol (150µmole) solution is dissloved in 10ml ether in round bottom flask

↓ Rotary evaporator

Ether is evaporated under vacuum at room temperature

↓ hydration

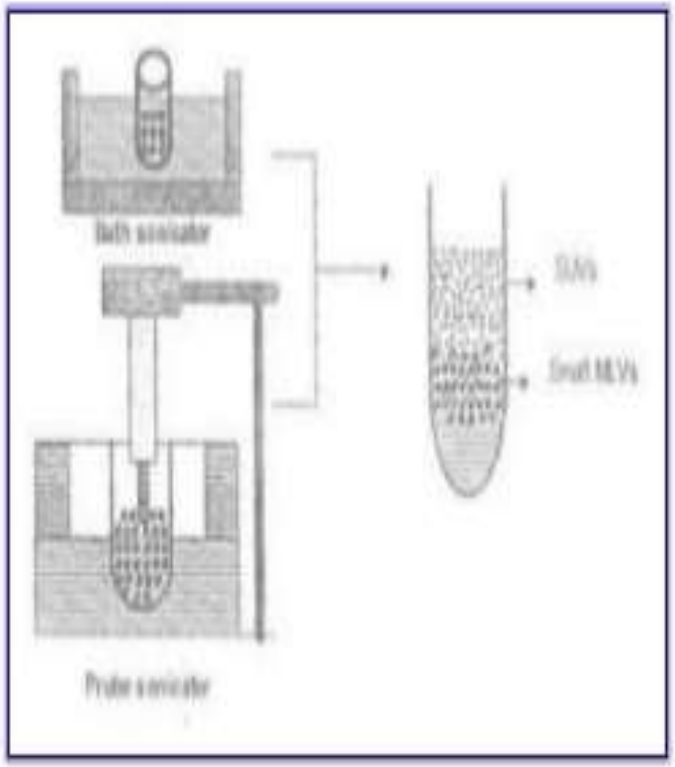
Surfactant swells and peeled off into a film like lipids

↓

swollen amphiphiles fold to form vesicles.

# Sonication Method

- A typical method of production of the vesicles is by Sonication of solution.
- In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial.
- The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield Niosomes.



# Reverse phase evaporation technique :

Surfactant is dissolved in chloroform ond 0.25 volume of PBS buffer is emulsified to get a W/O emulsion.

↓ sonicated

chloroform is evaporated under reduced pressure.

↓

The lipid or surfactant forms a gel first and hydrates to form vesicles.

↓

Free drug (unentrapped) is generally removed by dialysis.

# Microfluidization method

In this method two fluidized streams (one containing drug and the other surfactant) interact at ultra high velocity, in precisely defined micro channels within the interaction chamber in such a way that the energy supplied to the system remains in the area of niosomes formations. This is called submerged jet principle. It results in better uniformity, smaller size and reproducibility in the formulation of niosomes

# Applications Of Niosomes

- It is used as Drug Targeting.
- It is used as Anti- Neoplastic Treatment i.e. Cancer Disease.eg.Methotrexate
- It is used as Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
- It is used act as Delivery of Peptide Drugs.
- It is used in Studying Immune Response.
- Niosomes as Carriers for Hemoglobin.
- Transdermal Drug Delivery Systems Utilizing Niosomes. eg.Erythromycine
- It is used in Ophthalmic drug delivery. eg.Cyclopentolate

# NANOPARTICLES

# INTRODUCTION

» DEFINITION:

» Nanoparticles are subnanosized colloidal drug delivery systems

» particle size ranges from 10-1000 nm in diameter.

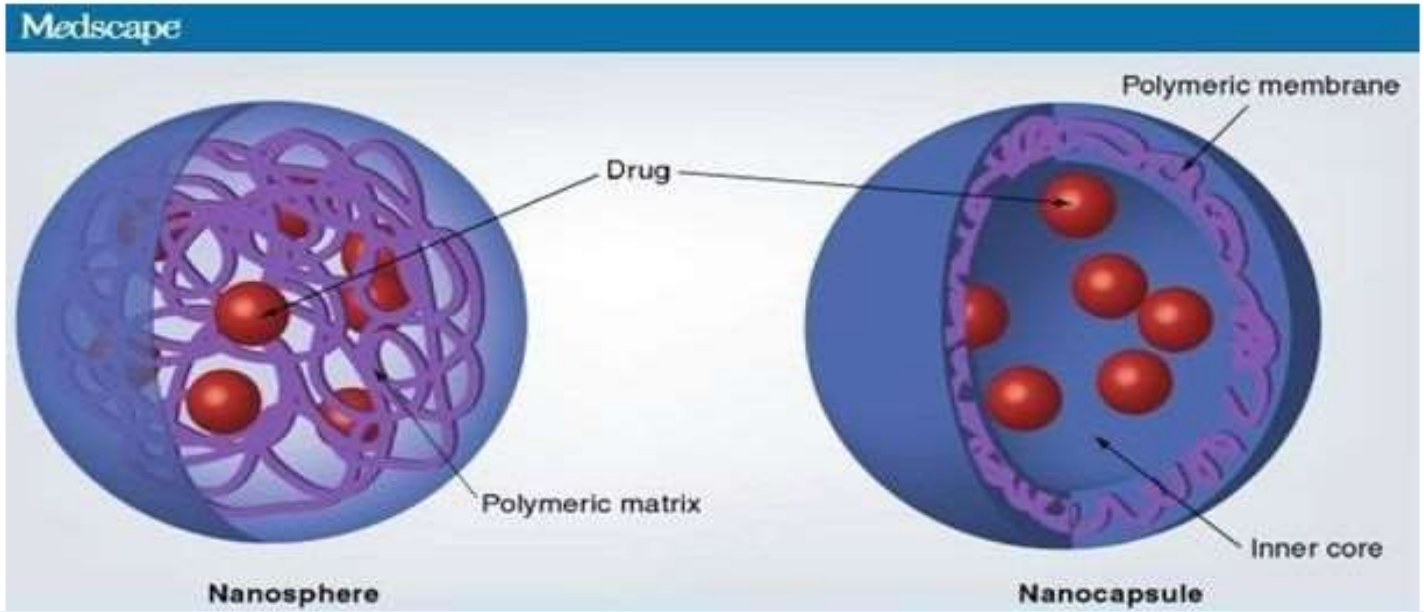
» They are composed of synthetic or semi synthetic polymers carrying drugs or proteinaceous substances, i.e. antigen(s).

» Drugs are entrapped in the polymer matrix particulates or solid solutions or may be bound to particle surface by physical adsorption or in chemical form.

Nanoparticle

Nanospheres

Nanocapsule



# Advantages:-

- Suitable for different routes of administration
- High drug carrying capacity
- Suitable for combination therapy
- Increases bioavailability of drug
- Both hydrophilic and hydrophobic drugs can be incorporated

# Disadvantages:-

- High production cost
- Difficult to handle
- Extensive use of poly vinyl alcohol as a stabilizer may have toxic issues
- Can start allergic reactions in body

# Polymers for Nanoparticles

**A]Natural Hydrophilic Polymers:-**

**1] Proteins:-** Gelatin, Albumin, Lectins, Legumins

**2] Polysaccharides:-** Alginates, Dextran, Chitosan, Agarose

**B] Semisynthetic Polymers:-** Pseudolatex of ethylcellulose

**C] Synthetic Polymers:-**

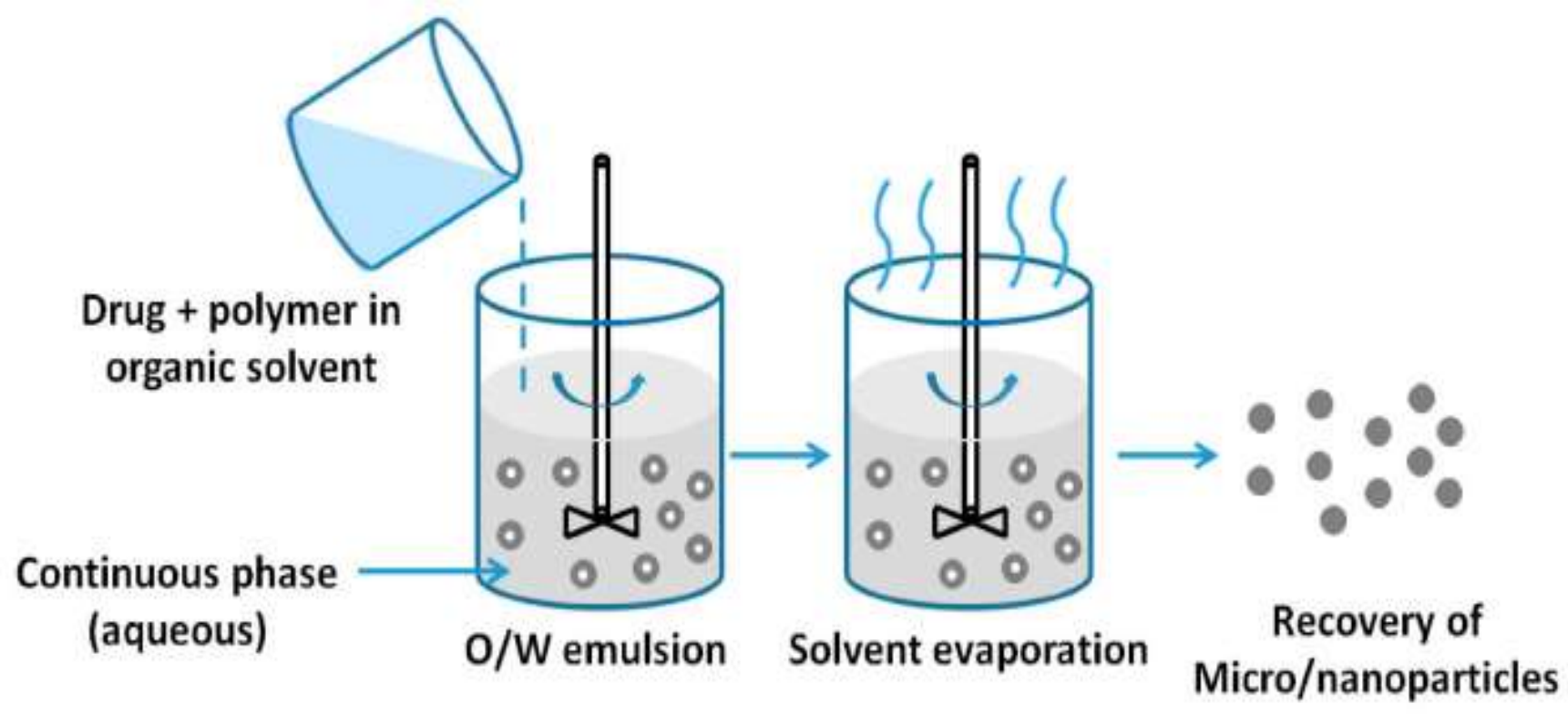
**1] Prepolymerized polymers:-** PLA, PLGA

**2] Polymerized in process polymers:-** PICA, PBCA

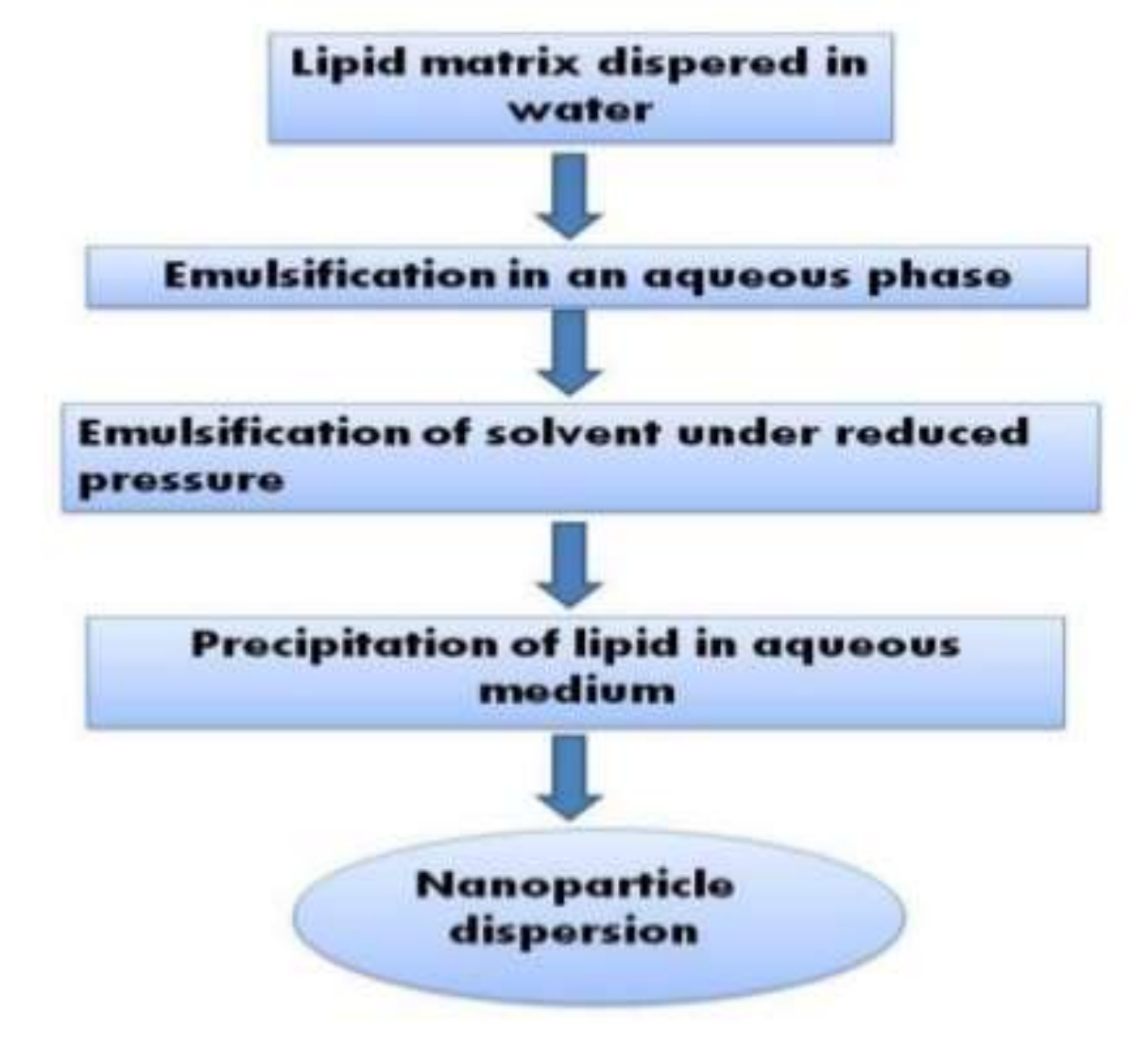
# Formulation of Nanoparticles

**A] Dispersion of preformed polymers:-**

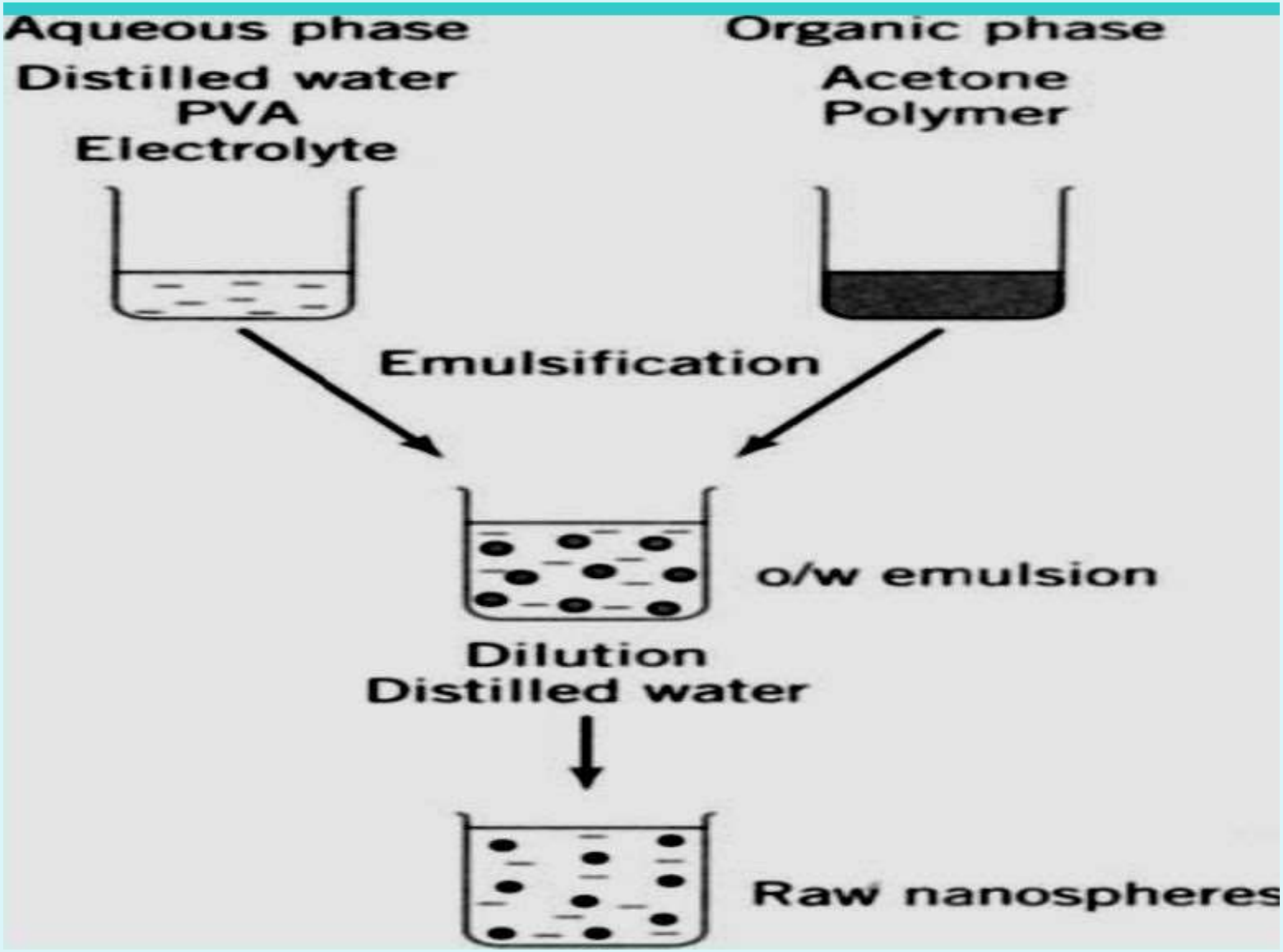
**1] Solvent Evaporation Method**



# 2] Solvent Diffusion Method



# 3] Salting Out



**B] Polymerization method**

**1]** Emulsion Polymerization

**2]** Dispersion Polymerization

# C] Coacervation or Ionic Gelation Method

- Polymeric nanoparticles are prepared by using **biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate.**

- The method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a poly anion sodium tripolyphosphate (TPP).

# D] Supercritical Fluid Technology

**Supercritical Fluid Technology:**

Supercritical Fluid Technology has been investigated as an alternative to prepare biodegradable micro and nanoparticles because supercritical fluids are environmentally safe.

A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure.

Supercritical $CO_2$ is the most widely used supercritical fluid because of its mild critical conditions, non-toxicity, non-flammability and low price.

# Evaluation

1] Size and morphology

2] Surface hydrophobicity

3] Surface charge

4] Density

5] Chemical analysis

6] Biodegradation

7] Molecular weight

8] In vitro drug release

# Applications

1] In chemotherapy

2] Administration of proteins and peptides

3] Intra-arterial administration

4] Ocular delivery

5] Brain delivery

6] Lymph targeting

7] Transdermal delivery

8] Radioactive agent

# Monoclonal Antibodies

- ✓ **Monoclonal Antibodies** are antibodies that are identical because they were produced by one type of immune cell (B cell), all clones of a single parent cell
- ✓ **Polyclonal Antibodies** represent the antibodies from multiple clones of B lymphocytes, and therefore bind to a number of different epitopes

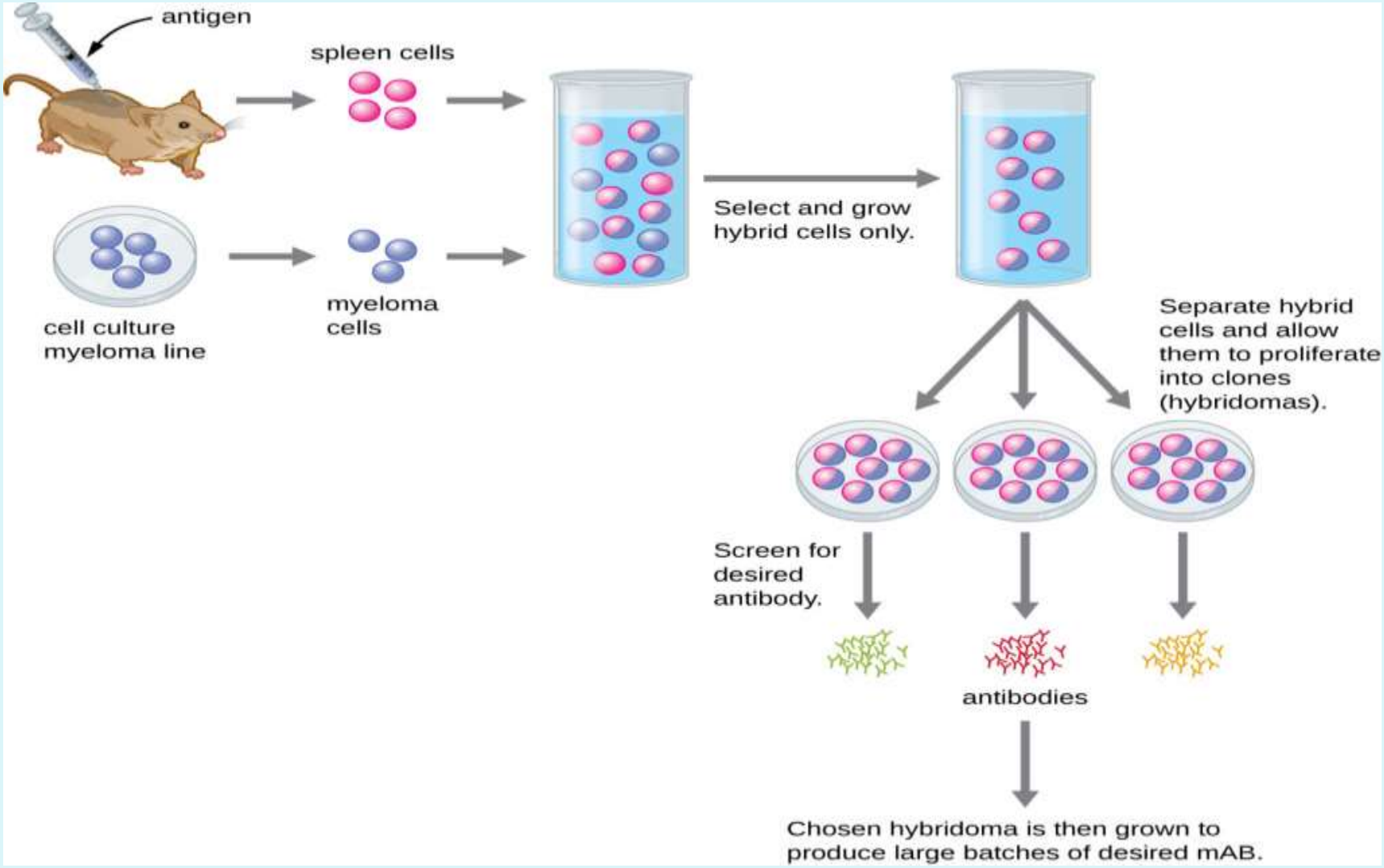
# Advantages

- Cheaper to develop than conventional drugs
- Side effects can be treated and reduced
- Bind to specific damaged cells
- Treat wide range of conditions

# Disadvantages

- Time consuming method
- Expensive method
- System is developed for limited animals not for other animals
- Hybridoma cultures may be subjected to contamination

# Production of Monoclonal antibodies



# Applications

**A] Diagnostic applications**

**1]** Biochemical analysis:- RIA & ELISA

**2]** Diagnostic imaging

**B] Therapeutic agent**

**C] Protein purification**

# THANK YOU….