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Review on the Novel Drug Delivery System

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Abstract: *Novel drug delivery system is the new system recent advances in the understanding of pharmacokinetic and pharmacodynamic behaviour of drug have offer a more rational approach to the development of optimal drug delivery system. Novel therapeutic approaches such as nanotechnology have opened a new direction in biochemical sciences.(1)*

Keywords: Novel drug delivery system

I. INTRODUCTION

Novel drug delivery system is the new system recent advances in the understanding of pharmacokinetic and pharmacodynamic behaviour of drug have offer a more rational approach to the development of optimal drug delivery system. Novel therapeutic approaches such as nanotechnology have opened a new direction in biochemical sciences.**(1)**

Novel drug delivery system (NDDS) refers to the approaches , formulations technologies, and the systems for transporting a pharmaceutical compounds in the body as, needed to safely achieve its desired therapeutic effect. It may involve scientific site targeting with8 the body or it might involve facilitating systemic pharmacokinetics ,in any case it is typically concerned with both quantity and duration of drug presence.**(2)**

- NDDS is a system for delivery of drug other than conventional drug delivery forms.
- NDDS is a combination of advance technique and new dosage forms which are far better than conventional dosage forms.

1.1 Advantages

- Optimum therapeutic -Drug concentration in the blood or in tissue may be maintained over a prolonged period of time.
- Predetermined release rates of extended period of time may be achieved.
- Duration for short half-life drug may be increased.
- By targeting the site of action side effects may be eliminated.
- Frequent dosing and wastage of the drug may be reduced or excluded .
- Better patient compliance may be ensured .
- Optimum dose at the right time and right location.
- Efficient use of expensive drugs, excipients and reduction in production cost.
- Beneficial to patients, better therapy , improved comfort and standard of living.**(3)**

A. Nanosomes

Non -ionic surfactants vesicles are now widely studied as an alternative to liposomes .Non-ionic surfactants vesicles results from the self-assembly of hydrated surfactants manomers.

Non-ionic surfactants of wide variety of structural types have been found to be useful alternatives to phospholipids . Through the terminology suggests that distinctions exists between the Niosomes and liposomes of which the former is having chemical differences in the manomers- units. Niosomes possess physical properties.**(1)**

Methods

1. Vesicles and Non vesicular trafficking are involved in progress of Nanosomes across a biological membranes.
2. Ultrafine Nanosomes are passively imported into cells without surface-specific receptors.

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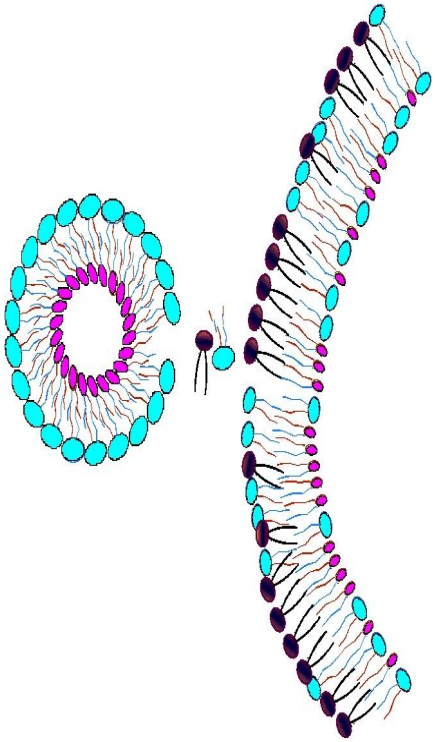
3. Vander Waals forces, electrostatic charges, steric interactions or interfacial tension effects facilitate cell adherence of Nanosomes.
4. Very small nanoparticles such as C60 molecules with a diameter of 0.7 nm penetrate cells via ion channels or pores in the cell membrane.
5. The biogenesis of endocytotic Vesicles requires the action of accessory phospholipids,proteins GTPases,and dynamin and actin polymerization.**(4)**

B. Liposomes

Liposomes were discovered in the early 1960s by the Bingham and Co- workers and subsequently became the most extensive explored drug delivery system.

Liposomes are structurally phospholipids-based on colloidal vesicles structure in which hydrophilic core is vesicular structure in which membraneous lipid bilayers.**(1).**



Methods

1. Physical Dispersion Technique

a. Lipid film hydration by hand shaking/non-hand shaking.
b. High shear homogenization /sonication.
c. Membrane extrusion.
d. Micro fluidizer technique for micro emulsification.
e. French pressure cell.
f. Dried reconstituted vesicles.
g. Fusion method.

2. Solvent dispersion technique-

a. Ethanol injection.
b. Ether injection.
c. Reverse phase evaporation vesicle.
d. Emulsion and double emulsion vesicles.
e. Detergent Solubilization technique.(5)

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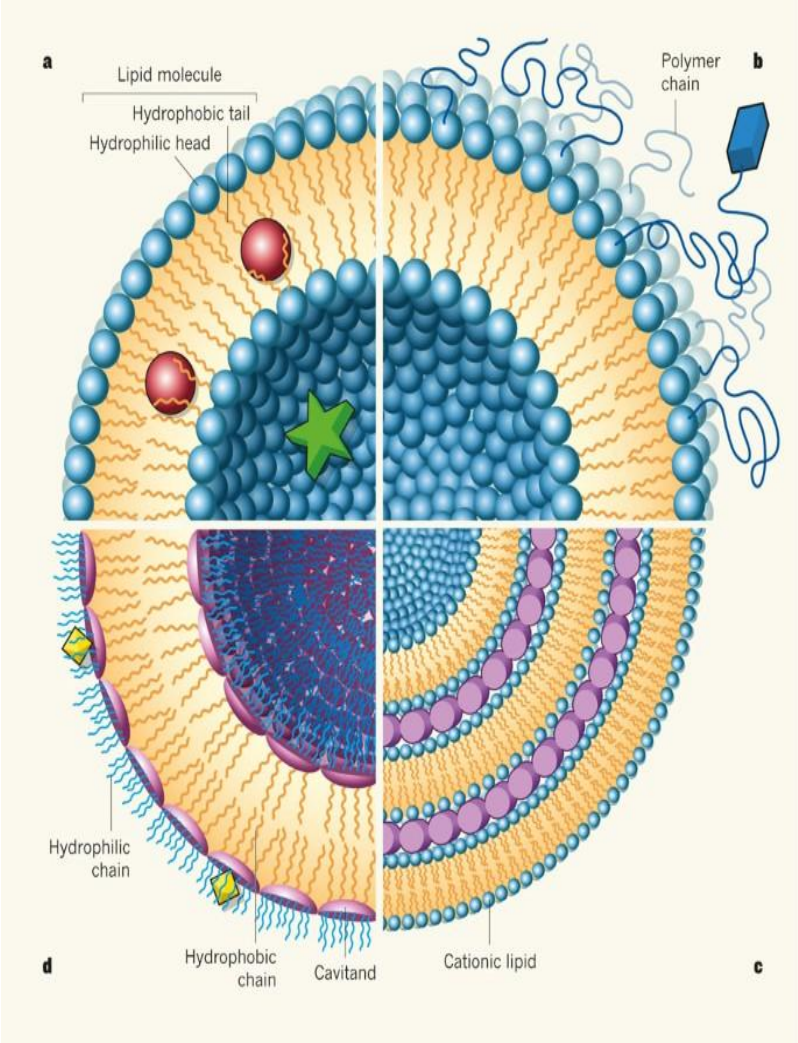
1. Physical Dispersion Technique

Lipid film hydration by hand shaking Non-hand shaking-

1. Lipid + Organic solvent (Chloroform/ Chloroform: Methanol) 10-20mg lipid/ml =Mic throughly.
2. Lipid film is dried to eliminate, residual organic solvent by placing in vaccum over night.
3. Lipid film can be also prepared by freezing in dry ice/dry ice acetone/alcohol bath.
4. Dry lipid film removed from vaccum container closed tightly, taped and stored frozen.



2. High Shear Homogenization/Sonication

1. Sonication is perhaps most extensively used method for the preparation SUV.
2. The main advantage of this method are very low internal volume/ excapsulation effciency.
3. The lipid Suspensions of LMV clarifies to yield SUV of 15-50nm.

3. Membrane Extrusion

1. Used for preparation of LUV and MLV's .
2. The size of liposomes is reduced by gently passing through polycarbonate membrane filter of defined as pore size at lower pressure.
3. Filter with 100nm pores yeild LUV of 120-140nm.

4. Micro fluidizer technique for micro emulsification-

1. Micro fluidizer used to prepare small ULV/MLV's from concentrated lipid dispersion.

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2. Micro fluidizer pumps the fluid at very high pressure through a 5um orifice
3. The lipids are introduced into fluidizers , either as a dispersion of large MLVs or as a slurry of unhydrated lipids in organic medium.

5. French pressure cell

1. French pressure cell is invented by 'CHARLES STACY FRENCH'.
2. The method has several advantages over sonication method.
3. The method is simple rapid , reproducible and involves gentle handling of unstable Material.

6. Dried reconstituted vesicles

1. Useful for preparation of small uni lamellar and oligo lamellar Vesicles.
2. This method involves freeze drying the dispersion of empty SUV followed by rehydration with aqueous fluid which have material to be entrapped.
3. In SUV's with DRV freeze dried aqueous solute to be membrane phase entrapped solutes with oligo and uni lamellar freeze membrane rehydration.

7. Fusion Method

1. This method lipids and entrapped material from harmful physicochemical environment.
2. Used for preparation of LUV in large quantities.

2. Solvent Dispersion Method

Ethanol Injection-

1. A solution of lipids dissolved in dimethyl ether or ether -methanol mixture is gradually injected to an aqueous solution of the material to be encapsulated at 55°c to 65°c or under reduced pressure.
2. Suitable for incorporating hydrophobic and amphibolic drugs in to liposomes.

This is suitable for preparing small and large unilemellar vesicles.

Ether Injection-

1. This was developed by Deamer and Bangalan similar to ethanol injection.
2. The lipid solution is added at the vapourizing temperature of organic phase.**(6),(7)**

C. Niosomes

- Niosomes are the multilamellar vesicles formed from Non-ionic surfactants of the alkyl or di alkyl polyglcerol ether class and cholesterol .
- Niosomes are the now widely studied as an alternatives to liposomes.
- Niosomes are prepared from uncharged single- chain surfactants and cholesterol.**(1)**
- Niosomes May be used as the HB Carrier.
- Niosomes were used as iobitridol carrier a screening agent for x ray imaging.**(11)**

Methods

- Ether injection.
- Hand shaking method.
- The bubble method.
- Reverse phase evaporation.
- Sonication.
- Multiple membrane extrusion method.
- Micro fluidization method.
- Formation of Niosomes from proniosomes.**(8)**

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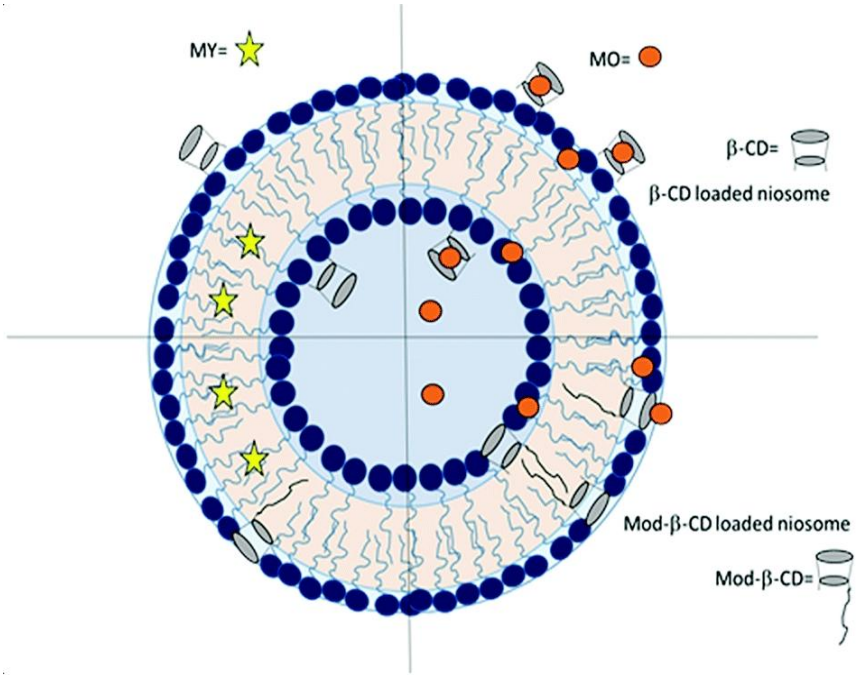
Ether Injection Method

1. This method is based on slow injection of surfactants: cholesterol solution in either through 14 gauge needle into preheated aqueous phase maintained at 60°c.
2. The particle size of the Niosomes formed depends on the condition used and can range anywhere between 50-1000um .
3. Vapourization of ether leads to formation of single layered Vesicles.**(9)**



Hand shaking Method

1. Surfactants and Cholesterol are dissolved in a volatile organic solvent.
2. This process forms large multilamellar Niosomes .
3. The mixture of vesicles forming ingredients like surfactants and Cholesterol are dissolved in a volatile organic solvent (Diethyl ether, chloroform a Methanol) in around bottom flask.

Bubble Method

1. The bubbling unit consist of round bottom flask with three necks positioned in water bath to control the temperature.
2. It is a novel techniques for the one step preparation of liposomes and Niosomes without the use of organic solvents.

Reverse Phase Evaporation

1. Cholesterol and Surfactants are dissolved in a Mixture of ether and chloroform.
2. The preparation of Dichlofenac Sodium Niosomes using tween 85 by this method.

Sonication

1. In this method an aliquate of drug solution in buffer is added to the surfactant/ Cholesterol Mixture in a 10 ml glass vial.
2. A typical method of production of the Vesicles is by sonication method.
3. In this method an aliquate of drug solution in buffer is added to the surfactant/Cholesterol Mixture in a 10ml glass vial.

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Micro Fluidization Method-

1. Micro Fluidization is a recent technique to prepare unilemellar vesicles of defined size distribution.
2. In this method,a mixture of surfactant and diacetyl phosphate is prepared and then solvent is evaporated using rotary vaccum evaporator to leave a thin film.
3. Film is then hydrated with aqueous drug Solution and the suspension thus obtained is extruded through the polycarbonate membrane and then placed in series up to eight passages to obatin uniform size Niosomes.

Formation Of Niosomes from Proniosomes-

1. Another method of producing Niosomes is to coat a water-soluble carrier such as sorbitol with surfactant.
2. Niosomes are formed by the addition of aqueous phase at T>Tm and brief agitation.**(10)**

D. Nanoparticles

Nanoparticles are the solid state and they are either amorphous or in crystalline form.
Nanoparticles have 2 types.

Nano spheres

Matrix type structure in which a drug is dispersed.

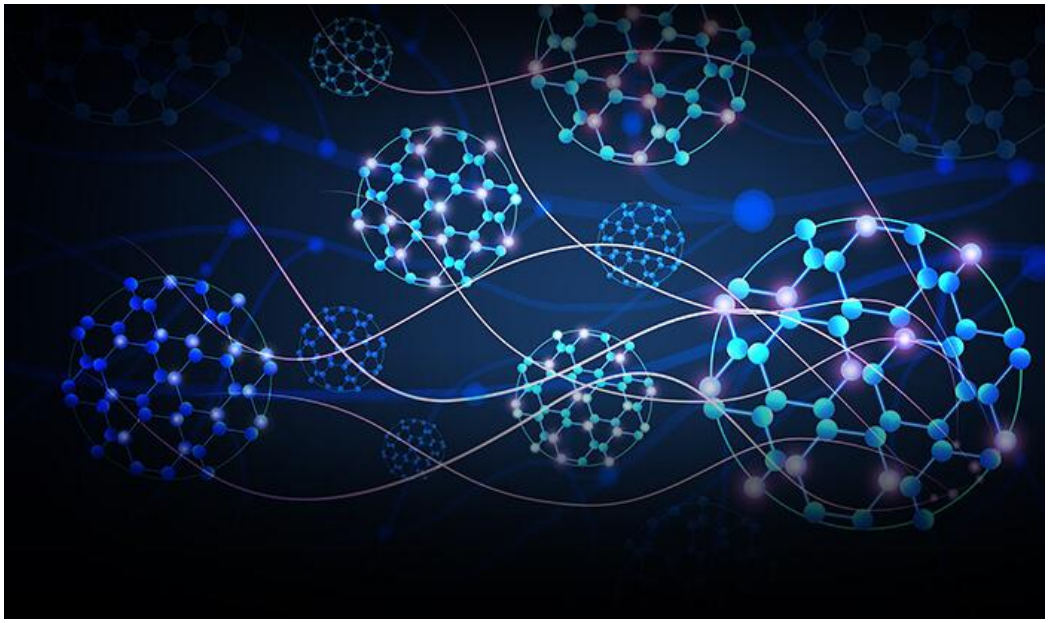
Nano capsule

Membrane wall structure in with an oil core containing drug.

Methods

1. Emulsion polymerization.
2. Dispersion polymerization.
3. Interfacial polymerization.
4. Interfacial complexion.**(13)**

Various polymers used in the method of Nano particles preparation.



1. Manomers Polymerization =1. Poly (alkyl Cyanocrylate)
2. Poly (alkyl Methacrylate)
3. Poly (Styrene)

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2. Solvent Evaporation=1. Poly(Lactic Acid)
2. Poly (Lactic – Co – Glycolic acid)
3. Ethyl cellulose.

3. Desolvation, Denaturation, Ionic gelation =Albumin, casein, Gelation, Alginate **(12)**

4. Emulsion Polymerization-

1. Emulsion polymerization is one of the fastest method for nanoparticles preparation and is readily scalable.
2. The polymerization process can be initiated by different mechanisms.
3. The major emulsion polymerization technique involves conventional Emulsion polymerization, Surfactants, free emulsion polymerization.

5. Dispersion Polymerization-

1. In case of Dispersion Polymerization however the monomer instead of emulsified is dissolved in aqueous medium which acts as a precipitant for the subsequent formed polymer.
2. Nucleation is directly induced in aqueous monomer solution and the presence of stabilizer or surfactants is not necessary for the formation of stable Nano spheres.

6. Interfacial Polymerization

1. It is one of the well established method used for the preparation of polymer Nanoparticles.
2. It involves step polymerization of two reactive monomers or agents which are dissolved respectively into 2 phase (Dispersed and Continuous phase.)

7. Interfacial Complexion

1) The method is based on the process of Micro Encapsulation introduced by Lin and Sun,1969.
2) In case of Nano particles preparation aqueous polyelectrolyte solution is carefully dissolved in reverse micelles in an apolar bulk phase with the help of an appropriate surfactant.**(14)**

E. Microsphere

- Microsphere are the solid spherical particles made up of polymeric substances in which the drug is dispersed throughout the microscopic matrix.
- It's size ranges from 1-1000um .
- They facilitate accurate delivery of small quantities of potent drug and reduced concentration of drug at site other than the target organ or tissue.
- It provide constant and prolonged therapeutic effect.

Methods

1. Spray Drying

1. In the spray drying Techniques , firstly the entire polymer are dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. and then drug in solid form is dispersed in polymer solution with high speed homogenization.
2. One of the major advantage of this process is feasibility of operation under aseptic condition.

2. Solvent Evaporation

1. This Process are carried out in vehicles in the 2 phases aqueous and organic phase that process called as Emulsification.

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3. Single Emulsion Technique

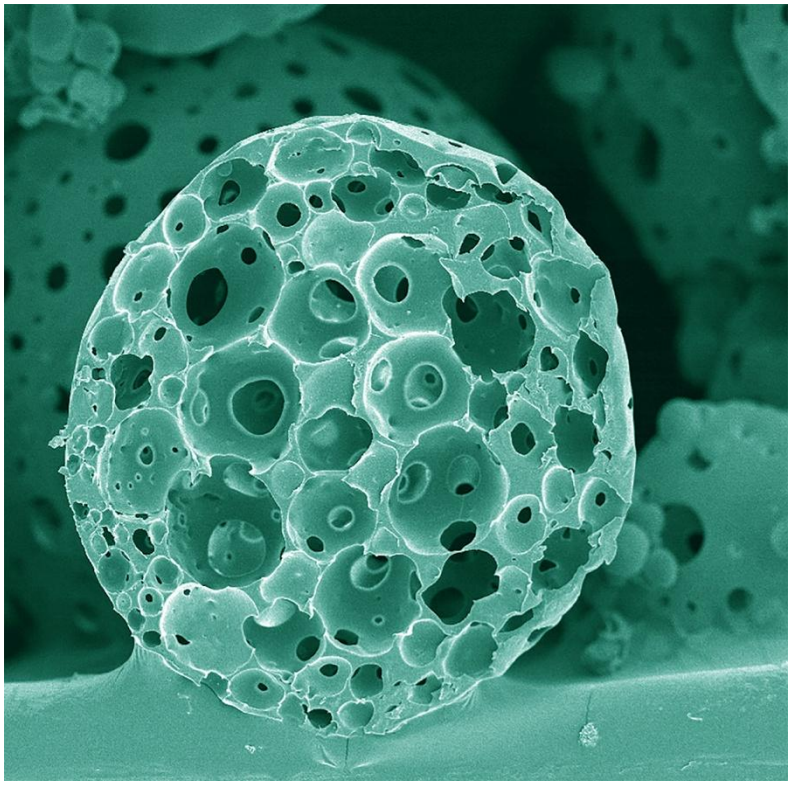
1. In this Technique aqueous solution of polymer are dispersed in organic phase oil/ Chloroform with continuous stirring this process is called as sonification.

4. Double Emulsion

1. In this method aqueous solution of polymer and drug are Dispersed in organic phase which produce 1st emulsion after addition of aqueous solution of PVA and make multi emulsion in solution separation, washing, drying to produce microspheres.

5. Phase Separation Coacervation technique

1. In this technique aqueous/organic solution that forms polymer rich globules or droplets and hardling in aqueous/ organic phase, separation of microspheres washing and then drying to pure form of microspheres.**(15)**



F. Micro Particles

Micro particles are defined as particulate dispersion or solid particles with size in the range 1-1000um.
The drug is dissolved , entrapped, encapsulated or attached to a micro particle matrix.

Methods

- Technique of micro particles preparation
- Emulsion- solvent Evaporation

Phase Separation

1. The process consists of decreasing the solubility of the encapsulating polymer by addition of a 3rd component to the polymer solution.
2. The Coacervation process consist of following 3 steps-
    - Phase separation of the coating polymer solution.

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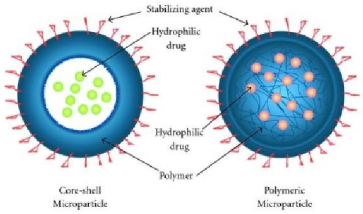
- Solidification of the Micro spheres.
- Adsorption of the coacervate around the drug particles.

Spray drying

- Spray drying is a widely used method for formulating bio degradable micro particles.
- The method typically uses drug dissolved or suspended in polymer solution.**(16)**



G. Micro-Emulsion

Micro-Emulsion is a system of water ,oil and an amphibole which a a single optically isotropic and thermodynamically stable liquid solution.

A micro emulsion is considered to be thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase in a combination with a surfactant .

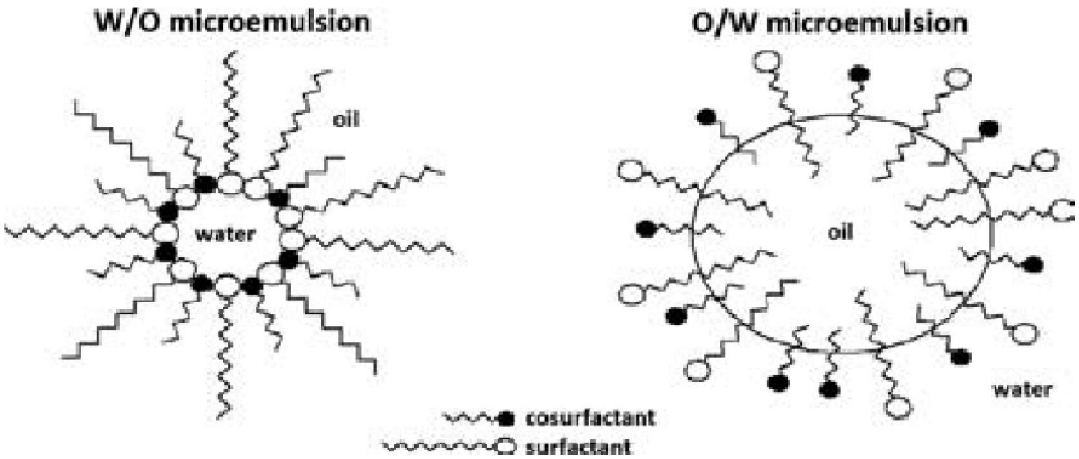
Methods-

Phase Titration Method

1. Micro emulsion are prepared by spontaneous emulsification method which is illustrated with the help of phase diagram
2. Construction of phase diagram is useful approach to study the complex series of interactions that can occur,
3. When different components are mixed.
4. Micro emulsion are formed along with various association.**(17)**

Phase Inversion Method-

1. Phase Inversion of micro emulsion occurs as a result of addition of excess of dispersed phase or in response to temperature.
2. During phase changes in particle size occur including changes in particle size that can affect drug release both in vivo and vitro.
3. Phase Inversion of micro emulsion happens upon addition of excess of dispersed phase.**(18)**



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H. Nano Suspensions

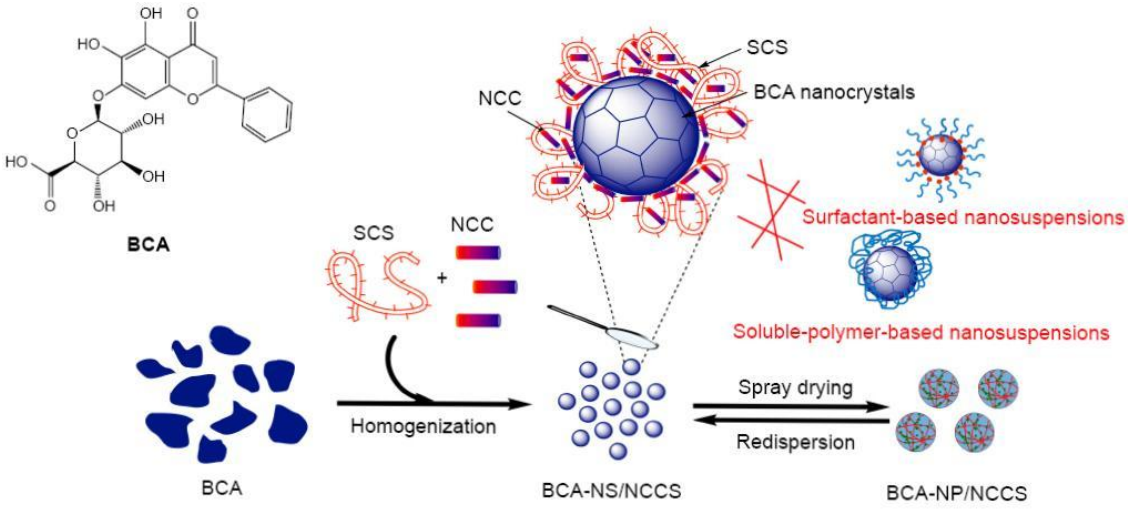
Nano suspensions is defined as very finely dispersed solid drug particles in an aqueous or organic vehicle for either oral and topical use or parental and pulmonary administration .

Use of Nano suspensions are harsh excipients.

Methods-

1. Precipitation Nano suspensions.
2. Micro emulsion Nano suspensions.
3. Micro Milling Nano suspensions.
4. High pressure homogenization Nano suspensions.
5. Co-grinding Nano suspensions.
6. Solvent Evaporation Nano suspensions.

Precipitation Homogenization



1. The drug is dissolved in an organic solvent and this solution is mixed with a miscible anti solvent for precipitation.
2. In the water -Solvent mixture the solubility is low and drug precipitates.
3. The basic principle of precipitation are the same as that of Nano edge.
4. A combination of these Techniques result in smaller particle size and better stability in a shorter time.

Micro-emulsion as Template/Lipid Emulsion-

1. Micro emulsion are thermodynamically stable and isotropically clear Dispersion of 2 immiscible liquids.
2. Taking advantage of the micro emulsion structure one can use micro emulsion even for the production of Nano suspensions
3. The Nano suspensions Thus formed has to be made free of the internal phase and Surfactants by means of diultrafication in order to make in suitable for administration.

Media Milling

1. In this method the Nano suspensions are produced using high -Shear and the mills or pearl mills.
2. The media mills consist of a milling chamber.
3. The milling chamber charged with polymeric media in the active component of the mill.

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High Shear Homogenization

1. High pressure Homogenization are engineered using piston gap type high pressure homogenizers.
2. High pressure has been used to prepare Nano suspensions of many poorly water soluble drugs .
3. During the Homogenization process the drug suspension is pressed through the Homogenization gap in order to achieve Nano sizing of the drug.

Co-grinding

1. Nano suspensions prepared by high pressure Homogenization and media milling using pearl ball mill are wet-grinding process.
2. Dry Co-grinding can be carried out easily and economically and can be conducted without organic solvents.
3. The co -grinding Technique can reduce particles to the sub-micron level and a stable amorphous solid can be obtained.

Solvent Evaporation Method-

1. This Technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug.
2. Evaporation of the solvent leads precipitation of the drug .
3. Crystal growth and particle aggregation can be controlled by creating High shear forces using a high speed stirrer.**(19)**

I. Micelles

Micelles are formed when temperature of medium is ideal and a certain concentration of electrolytes in the medium.
A micelle is an aggregate of surfactants molecules dispersed in a liquid collide.

Methods

1. Solubility Studies
2. Determination of critical micelle concentration.
3. Preparation of deforaxamine mesylate polymeric micelles.

Solubility Studies

1. Solubility of DFOs was determined in oleic acid,lecithin,castor oil, and isopropyl myristate.
2. An excess amount of DFOs was added to 5ml of the oil and stirred for 30min at 45°c and for 24hr .at room temperature.
3. The equilibrated samples were then was centrifuged to remove undissolved drug.

Determination of critical micelle concentration-

1. Aqueous solution of surfactants and Co-surfactants with different concentrations but constant concentration of polymer were prepared.
2. Surface tension of these solution was measured at 25°c with a torsion balance .Then,the surface tension versus log concentration was plotted.

Preparation of Deforaxamine Mesylate Polymeric Micelles

1. DFO loaded polymeric micelles were prepared by film hydration method.
2. The dried lipid film were hydrated with aqueous solution containing DFO surfactant, polymer ,and co -surfactants at 50°c and 120 rpm and then sonicated in a bath sonicator.**(20)**

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