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An Overview Showing Recent Studies on Nano Medicines for the Treatment of Hyperlipidemia

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Abstract
Hyperlipidemia refers to a group of inherited and acquired illnesses that are characterized by high lipid levels in the body. It has been established that high cholesterol and LDL in the blood are the primary causes of atherosclerotic arteries, while high concentrations of HDL in the blood are beneficial. Many drug are available to lower the lipid level but they are associated with lots of side effects like myopathy, rhabdomyolysis, myalgia and arthralgia, to overcome this problem there are many oral conventional dosage forms. But there is a problem associated with that is poor bioavailability. In order to overcome that bioavailability problem associated with the less soluble drugs there are some novel drug delivery systems which can be formulated as nano medicines with novel nano techniques employed to enhance the pharmacokinetic parameters of the antihyperlipidemic drugs. The present review includes an overview showing recent studies on nano medicines for the treatment of hyperlipidemia.

Keywords
hyperlipidemia, novel techniques, nanomedicines, conventional dosage forms, bioavailability.

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INTRODUCTION:
Hyperlipidemia is one the major risk factor for the cause of cardio vascular diseases which leads to 1/3rd deaths in the world. [1]Abnormalities may lead to cardiovascular, cerebrovascular, peripheral vascular arterial diseases. Raised levels of plasma sterol and triglycerides were treated by statins and fibrates. The lipid metabolism occurs in many ways but enzymes are considered to be most important regulators for the lipid metabolism. [2]The story of lipids in humans started in the year 1769 as solid cholesterol in gall stones. Genetic disorders and lifestyle diet rich in calories, fats may also lead to hyperlipidemia but the main factor that causes hyperlipidemia is change in the lifestyle i.e., diet or poor food intake. Several antihyperlipidemic drugs have poor bioavailability and have many disadvantages but some nan particulate drugs which have approval from USFDA shows more effective in action against hyperlipidemia.

Mainly hyperlipidemia is of two types:

1. Primary hyperlipidemia
2. Secondary hyperlipidemia

Primary Hyperlipidemia: It is caused due to genetics.
Secondary Hyperlipidemia: It is caused as a result of many diseases like diabetes, thyroid, renal diseases, liver problems, etc. It does not show any symptoms,

but it is very dangerous as leads to heart attack or heart stroke.

TYPES OF LIPOPROTEINS:

There are different types of lipoproteins based on their densities. They are as follows:

1. Chylomicrons
2. Very Low-Density Lipoproteins
3. Low Density Lipoproteins
4. Intermediate Density Lipoproteins
5. High Density Lipoproteins

1.Chylomicrons:

Chylomicrons are the largest triglycerides both in size and density which are rich in lipoproteins produced namely fatty acids and cholesterol.

2.Very Low-Density Lipoproteins:

Here the size of lipoproteins is too small and are produced in the liver and then released into the blood stream. VLDL is also known as bad cholesterol. Normal VLDL levels are from 2 to 30 mg/dL or below 30mg/dL but also increase in levels of VLDL leads to heart problems.

3.Low Density Lipoproteins:

Low density lipoproteins are the same as VLDL. They are also known for bad cholesterol. High levels of LDL may lead to heart attack and heart stroke by blocking arteries.

4.Intermediate Density Lipoproteins:

These are formed by the lysis of high-density lipoproteins such as low-density lipoproteins. It is responsible for exporting triglycerides and cholesterol.

5.High Density Lipoproteins:

High density lipoproteins are also known as good cholesterol. These lipoproteins are synthesized in the liver and carry cholesterol and other lipids back to the liver from tissues for degradation.

CAUSES OF HYPERLIPIDEMIA:

There are two main causes of hyperlipidemia. They are familiar and acquired. The familial type is the one which is acquired from the parents.

Acquired type is a result of:

- Underlying health conditions- like smoking, drinking a lot of alcohol, sitting too much instead of being active, etc.
- Medications you take –for hypothyroidism, lupus, diabetes, HIV, hepatitis, obesity, pregnancy, etc.
- Lifestyle choices-cheese, egg yolks, pastries, red meat, ice creams, fried and processed food, etc.

RISK FACTORS OF HYPERLIPIDEMIA:

- Hyperlipidemia is common metabolic Disorder and are risk factors for cardiovascular disease clinical studies have proven hyperlipidemia increases the risk of non- ischemic heart failure while decreasing serum lipids can reverse heart dysfunction.
- Hyperlipidemia risk factors in three types.
- Cardiovascular risk analysis.
- Novel risk factors.
- Alternative risk factors.

Cardiovascular risk analysis:

Traditional risk factors for CVD include older age, smoking, high blood pressure being overweight, obese, diabetes, high cholesterol, heart disease, higher risk of CVD benefit screening and treatment cardiovascular disease are habits behaviors circumstances are risk of developing cardiovascular disease including lack of exercise, unhealthy eating, smoking, diabetes age and family history.

Novel risk factors:

Plasma concentration of c- reactive protein IL- 6 and membrane- bound IL receptors increased levels of the leukocyte enzyme Myeloperoxidase HIV positive status Metabolic syndrome micro albuminuria Remint lipoproteins.

Alternative risk analysis:[3]

Found across multiple assay clones must just equities and bonds implemented through a long, short approach across asset clone but an academic and empirical research that can be applied and replaced in markets pressure.

HYPERLIPIDEMIA TREATMENT:

There are two different types of treatment, they are nonpharmacological treatment and pharmacological treatment.

1. Non-Pharmacological Treatment:1ST line therapy

a) Diet modification

- Decrease intake of fat
- Increase fiber intake.
- Also increase omega -3- fatty acid intake
- Take less sugar.
- Take more fruits and vegetables HMG CoA reductase inhibitors,

b) Exercise

2. Pharmacological Treatment:

It includes drug therapy i.e., treatment with HMG CoA reductase inhibitors, Fibric acid derivatives, bile acid sequestrants, pyridine derivatives, cholesterol absorption inhibitors, LDL oxidation inhibitors, miscellaneous.

CLASSIFICATION OF HYPERLIPIDEMIC DRUGS:

Sl.no	Class	Drug	Mechanism of action
1	Statin	Atorvastatin[1, 3, 4] Pravastatin sodium	3-Hydroxy-3methylglutaryl-Coenzyme A(HMG-CoA) reductase competitively inhibited by atorvastatin. By preventing conversion of HMG-CoA to mevalonate this is rate limiting step in cholesterol synthesis. Cholesterol production in liver is decreased by statin medications. The drug also enhances number of LDL receptors on the surface of hepatic cells.
2	Fibrates	Fenofibrate[5] Gemfibrozil	Cellular fatty acid uptake stimulated by fibrates, conversion to acyl-CoA derivatives and catabolism by the beta-oxidation pathways, which combined with reduction in triglyceride and fatty acid, results in decreased the VLDL production.
3	Cholesterol absorption inhibitors	Ezetimibe[6]	Cholesterol absorption inhibitors acts preferentially at the level of luminal brush border of enterocytes in the upper intestine reducing cholesterol content of CMs while maintaining absorption of lipids – Soluble steroid hormones vitamins
4	Nicotinic acid group	Niacin Nicotinic acid Vit B3	Hepatocyte diacylglycerol acytransferase-2 inhibited by Niacin. This action results in preventing the final step of synthesis of triglyceride in hepatocytes, limiting available triglycerides for VLDL (very low-density lipoproteins.
5	Bile acid sequestrants	Colestipol hydrochloride Cholestyramine Colesevelam	Bile acid sequestrants bind bile acids in the intestine and enhance the excretion of bile acids in this stool. This reduces the returning amount of bile acids to the liver. e acids to the liver and forces the liver to produce more bile acids to replace the bile acids lost in the stool.

Table 1 classification of hyperlipidemic drugs

NANOPARTICULATE CARRIER SYSTEM:

Nanotechnology is one of the most important branches of science and engineering which has been widely developed from the past decades in our daily life[7]. Nano technology is a Greek word in which nano means dwarf. The term nanotechnology was first used in the year 1974 by Norio Taniguchi. The application of nanotechnology in medicinal purpose is known as nano medicine where the particle size ranges between 1-100nm and consists of different biodegradable materials like synthetic and natural polymers and lipids or metals. Nano medicine is widely used in medical field for diagnosis, treatment, cure, prevention and control of various diseases.

Nanomaterials possess novel physical and chemical properties different from those of other chemical substances so they have good pharmacokinetic actions such as absorption, distribution, metabolism and elimination. Nano particles can be used in target drug delivery system to improve the solubility, bioavailability and targeting of drugs to specific site. Physicist Richard Feyman is known as the father of nanotechnology. Nowadays nanotechnology is used in everyday life i.e., in food industry, pathogen detection, cosmetics and sunscreens, treatment of a disease, etc. Size reduction is the major advantageous factor in nanoparticles so widely used in pharmacy. Also, there are advantages of nanoparticles such as bioavailability, inexpensive, stable dosage forms, reduce particle size, reduce toxicity, i.e., smaller tablet faster dissolution, etc.

Classification Of Nanomaterials:

Nanomaterials are unit sized particles between 1 to 100nm in at least one external or internal dimension. Examples of nanoparticles include: Titanium dioxide, silver, iron oxide, etc.

Nanomaterials are classified into three different categories. [8]

They are:

Nanoparticles

Nano clay

Nano emulsion

Nanoparticles:

Nanoparticles are also known as ultrafine particles where the particle size ranges between 1 to 100nm[9].Nanoparticles are divided into two categories: A) Inorganic nanoparticles B) Organic nanoparticles

A) Inorganic nanoparticles: It comprises of metal or nonmetal element or take the form of hydroxide,

oxide or phosphate compound. Inorganic nanoparticles are sub divided into:
Mesoporous silica nanoparticles
Gold nanoparticle
Quantum dots
Super paramagnet nanoparticles

B) Organic nanoparticles: These are templated upon synthetic or natural organic molecules. These are fabricated from carbohydrates, lipids, proteins and other organic compounds. Organic nanoparticles are sub divided into:
Liposomes
Micelles
Cyclodextrin
Dendrimers

Nanoclay: These are the minerals which have high aspect ratio and with at least one dimension of the particle in the range of nanometer. It contains polypropylene-nanoclay systems.

Nano emulsions: These are nanosized emulsions, which are manufactured for improving the delivery of active pharmaceutical ingredients. Here two immiscible liquids are mixed to form a single phase by using emulsifying agent i.e., surfactant and co-surfactant. It contains lipophilic nano emulsion.

Classification of nanoparticulate carrier system with preparation methods:

LIPOSOMES:

Liposomes are spherical in shape and can be created from cholesterol and natural nontoxic phospholipids. Because of their size, hydrophilic, hydrophobic characters these are promising systems for drug delivery.[10]

Liposomes with particle size ranging from 30nm to several micrometers. These consists of one or more lipid bilayers encapsulated the aqueous units, where polar head group-oriented interior and exterior aqueous phase.

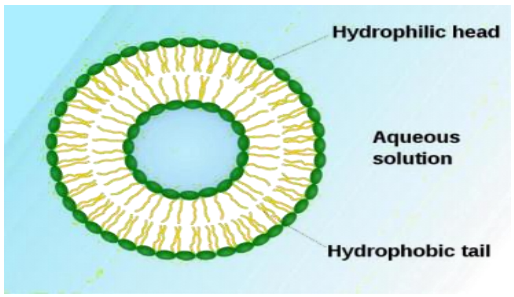


Fig.1 liposomes

Advantages and disadvantages of liposomes:

Liposome increased stability via encapsulation.	Short half-life
Liposomes are non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations.	Sometimes phospholipid undergoes oxidation and hydrolysis-like reaction
Liposomes reduce the toxicity of the encapsulated agent (amphotericin B, Taxol)	Leakage and fusion of encapsulated drug/molecules
Liposomes help reduce the exposure of sensitive tissues to toxic drugs.	Production cost is high.
Site avoidance effect	Fewer stables

Table-2 pro's and con's of liposomes

❖ **Methods of preparation of liposomes:**

There are two techniques for the preparation of liposomes:[11]

- Passive loading technique
  - ✓ Mechanical dispersion method
  - ✓ Solvent dispersion method
  - ✓ Detergent removal method
- Active loading technique

Mechanical dispersion method:

It includes different types of mechanical dispersion methods:

- Hand shaking method
- Micro emulsion
- Sonication
- French pressure cell
- Membrane extrusion

- Dried reconstituted vesicles
- Freeze thawed liposomes
- **Hand shaking method:** This is the most widely used method in the preparation of liposomes[11]. In this method the lipids are first dissolved in an organic Solvent mainly ethanol in a round bottom flask by continuous stirring in a circular motion. So, the organic Solvent evaporates and forms a thin film on the RBF which on treating with water forms liposomes.

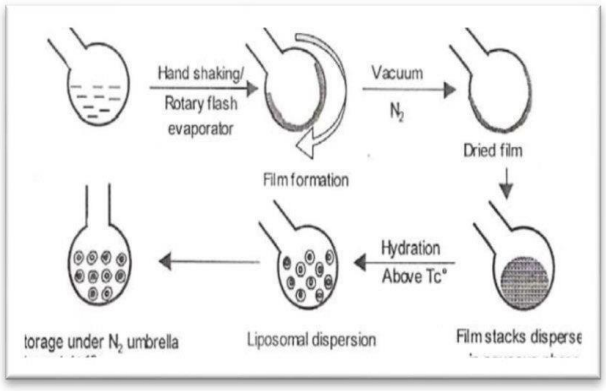
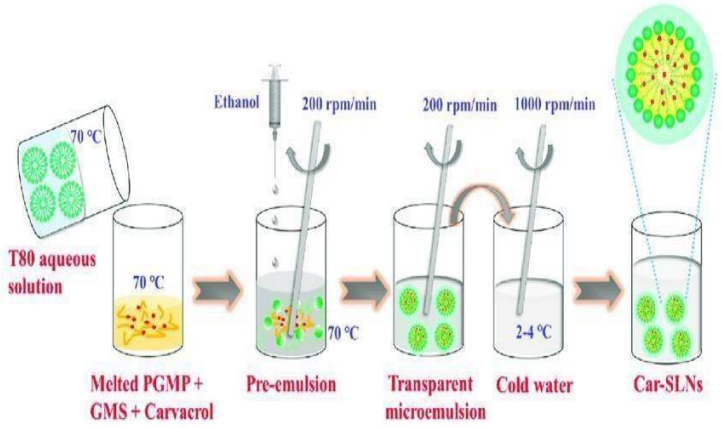


Fig.2 Hand shaking method
Mostly MLV (multilamellar vesicles) liposomes are produced by this method.

- **Micro emulsion:** At first the drug is dissolved in a lipophilic Solvent then add aqueous surfactant by continuous stirring under room temperature, it results in the formation of nanoparticles by removal of Solvent by evaporation method under low pressure and excess surfactants by precipitation. Then apply centrifugation is done along with freeze drying.



Showing process of microemulsion
Fig.3

- **Sonication:** It is also one of the most widely used method. There are two types of Sonication methods, they are:

Probe Sonication method
Bath Sonication method

Probe Sonication Method: In this method the tip of the probe is directly engrossed into the liposome dispersion. The energy input in this method is very high due to the generation of heat, to control the heat the dispersion is placed in an ice bath.

Bath Sonication Method: In this method the liposome dispersion is placed in a bath sonicator where the control of temperature is easy.

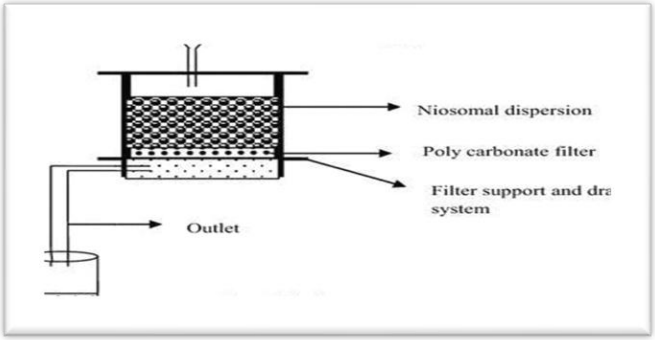
Fig.4 Probe Sonicator

Fig.5 Bath Sonicator

- **French Pressure Cell:** It is a method where unstable MLVs (medium sized unilamellar vesicles) are converted to SUVs (small unilamellar vesicles) and LUVs (large unilamellar vesicles). It is more appropriate method as it has more stability compared to Sonication method. But the main drawback in this method is it has small volume to work and also it is hard to manage high temperatures.

French Pressure Cell
Fig.6

- **Membrane Extrusion:** This method is used for the preparation of MLVs and SLVs, also the size of the liposomes is reduced by passing them through polycarbonate membrane filter.



Membrane Extrusion
Fig.7

- **Dried Reconstituted Vesicles:** It is shortly known as DRV. Here the liposomes are formulated under mild conditions, they have the capability to entrap hydrophilic solutes when compared with the other liposomes.

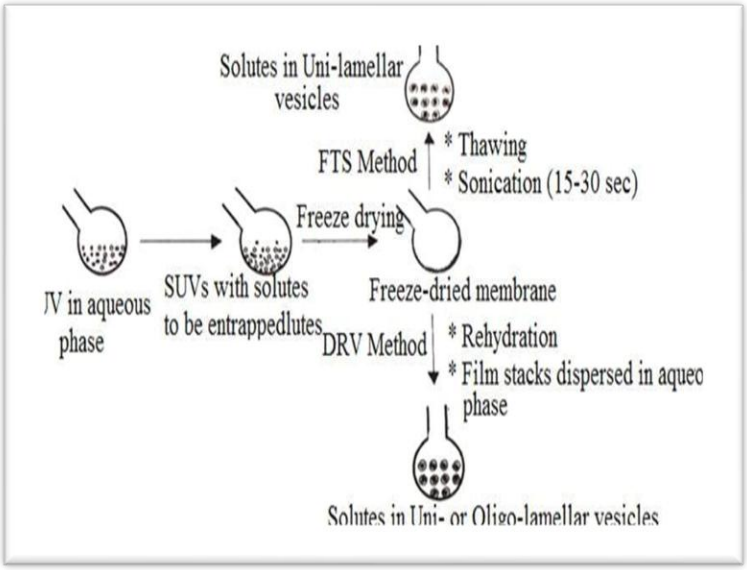


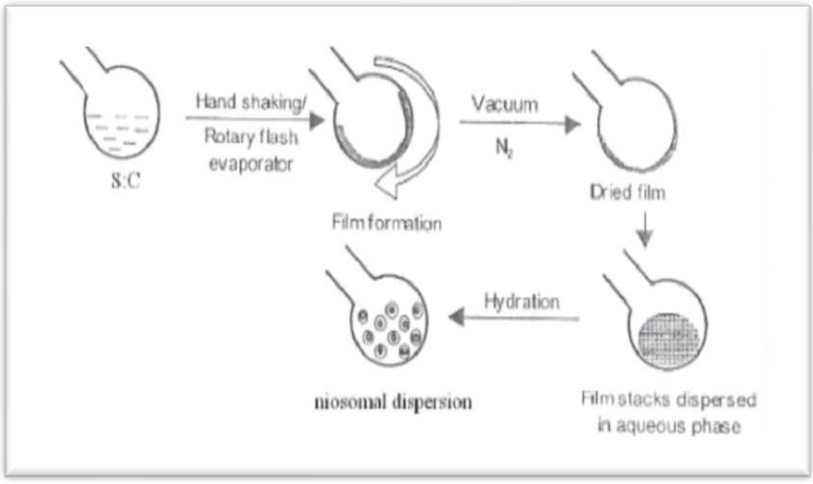
Fig.8
Dried Reconstituted Vesicle Preparation of Dried Reconstituted Vesicles And Freezed Thawed Liposomes

Freeze Thawed Liposomes: The SUVs formed in the Sonication method are freezed and thawed to form LUVs. LUVs are formed due to the aggregation of SUVs during thawing process.

Solvent Dispersion Methods: There are different Solvent dispersion methods which are as follows:

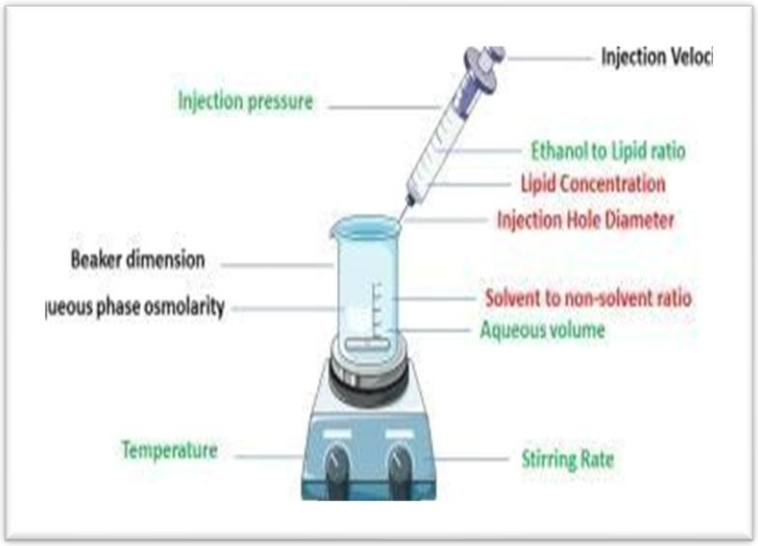
- Ether injection
- Ethanol injection
- Double emulsion
- Reverse phase evaporation vesicles
- Stable pluri lamellas vesicles

Ether Injection: In this method, surfactant cholesterol solution is slowly injected in ether through 14-gauge needle into a preheated aqueous phase maintained at 60°c.Ether vaporization results in formation of ether gradient at ether-water. Diameter of vesicle range from 50-1000nm depending on the conditions used.



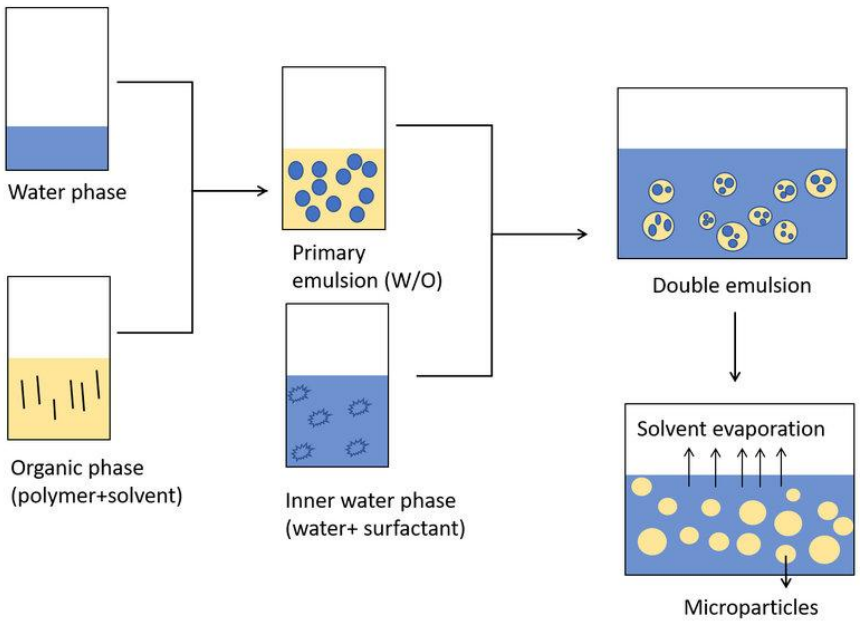
Ether Injection Method
Fig.9

Ethanol Injection: It is a simple and safety technique where liposomes can be easily produced. Here the ethanolic solution of lipid is injected into aqueous medium through a needle by dispersing the phospholipids from the medium and promotes the formation of vesicles.



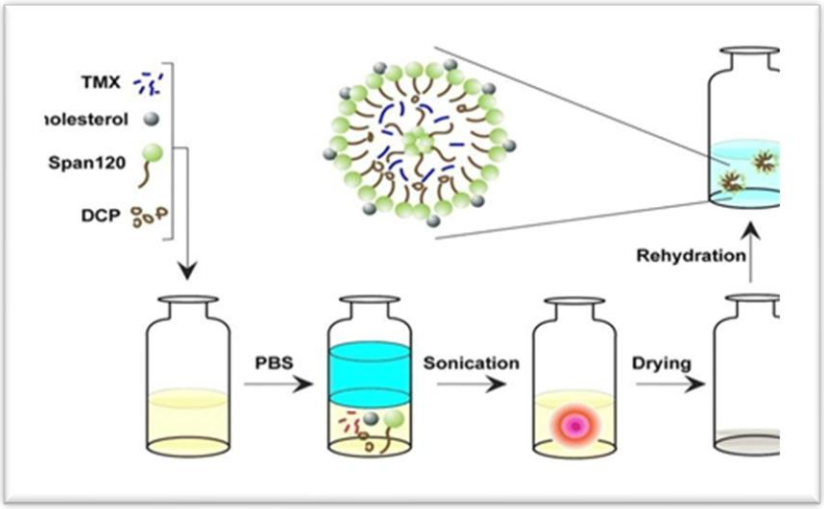
Ethanol Injection Method
Fig.10

Double Emulsion Technique: Double emulsion technique is a novel technique where the drug is dissolved in aqueous medium then added into the organic phase and stabilized so primary emulsion is formed. Later aqueous medium along with nonionic surfactants are added results in the formation of double emulsion
.



Double Emulsion Technique
Fig.11

Reverse Phase Emulsion Techniques: It is also known as backward emulsion or invert emulsion. The continuous phase is oil and the dispersed phase is water. Phase inversion is attained by shifting the emulsifier affinity from one phase to the other



Reverse phase emulsion technique
Fig.12

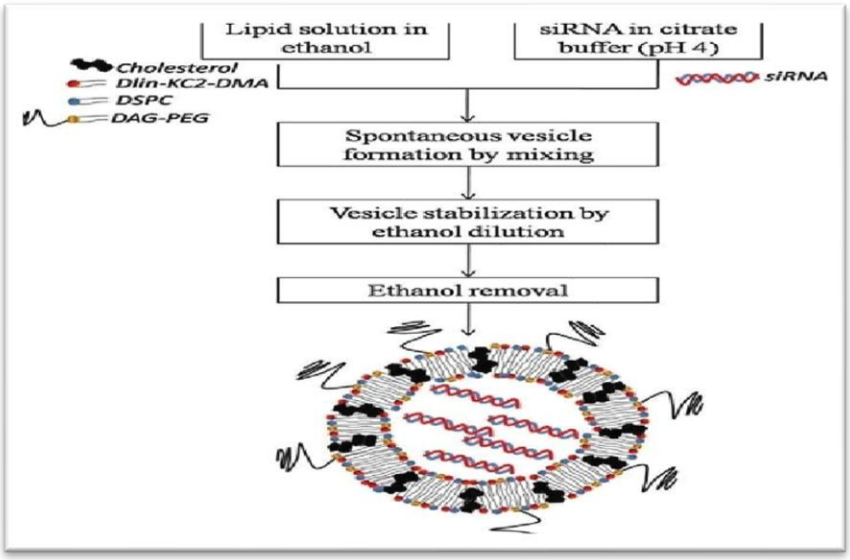
Stable Pluri Lamellar Vesicles: This is a new model technique which is used for the preparation of multi-layer vesicles. The vesicles which are prepared by this method differ from other vesicles instability, entrapment efficiency, electronic spin, etc.

Detergent Removal Method:

Detergent (cholate, alkyl glucoside, triton x-100) removal from mixed micelles by:

- Dialysis
- Column chromatography
- Dilution
- Reconstituted sendai virus enveloped

- **Dialysis:** In this method detergents are used to dissolve the lipids at CMC i.e. Critical Micelles Concentration. So detergent is removed by using different equipment's such as LipoPrep.
- **Column Chromatography:** In column chromatography separation mostly used material is sephadex G-50Dilution: In this method lipid solution is mixed in ethanol along with citrate buffer where spontaneous vesicles are formed by mixing continuously, then vesicles stabilized by ethanol later on ethanol is removed.

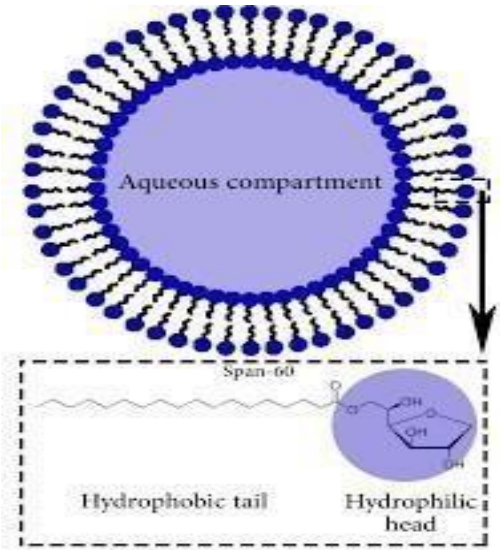


The process involved Column chromatography.
Fig.13

Reconstituted Sendai Virus Enveloped: In this method Triton x-100 is used. It has low CMC value, so it is considered as the best detergent for reconstituted studies.

NIOSOMES

Niosomes are the best among all these. Niosomes are Nonionic surfactant vehicle(tweens and spans) [12]. In niosomes the drug is enclosed in a vesicle. These have good opportunities in research and pharma industry.



Structure of niosomes

Fig.14

Advantages:

- Enhance the penetration of drugs i.e. through skin
- They are active, stable, biodegradable, etc.

Disadvantages:

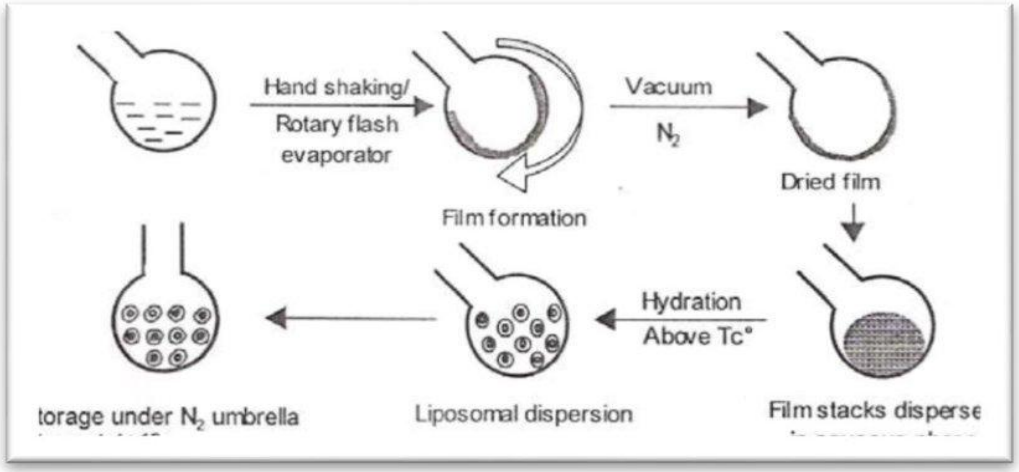
- Leakage of drug from vesicles
- Hydrolysis of encapsulated drug

Methods of preparation of Niosomes:

- Ether injection method
- Hand shaking method
- The bubble method
- evaporation technique
- Trans membrane pH gradient (inside acidic) uptake process(remote loading)
- Multiple membrane extrusion method
- Sonication
- Formation of Niosomes from proniosomes

✓ **Ether Injection Method:**

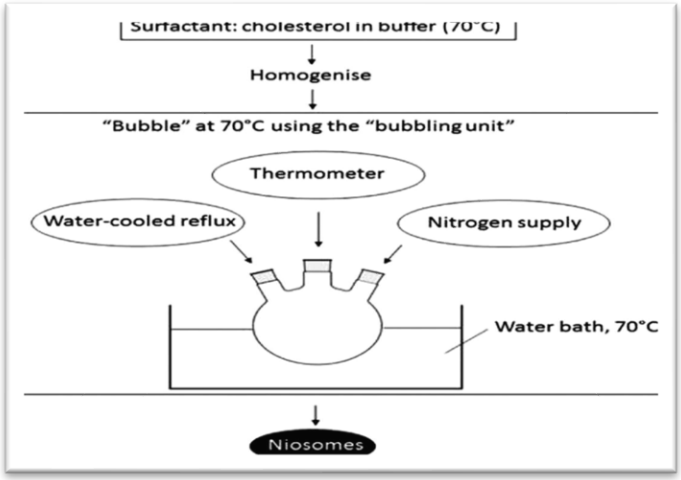
In this method, surfactant cholesterol solution is slowly injected in ether through 14 gauge needle into a preheated aqueous phase maintained at 60°c.Ether vaporization results in formation of ether gradient at ether-water. Diameter of vesicle range from 50-1000nm depending on the conditions used.



Ether Injection Method

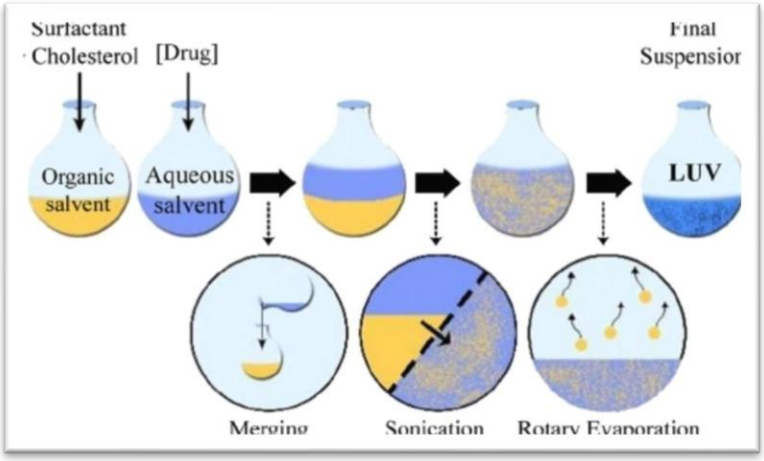
Fig.15

The 'Bubble' Method: The bubbling unit consists of round bottom flask with three necks positioned in water bath to control the temperature. In the first and second neck water-cooled reflux and thermometer is positioned and through the third neck nitrogen is supplied. At 70°c cholesterol and surfactant are dispersed together in this buffer (pH 7.4), with the high shear homogenizer and by using nitrogen gas immediately afterwards bubbled at 70°c.



Process involved in bubble method.
Fig.16

✓ **Reverse Phase Evaporation Technique:**
In a mixture of ether and chloroform the cholesterol and surfactant (1:1) are dissolved.
The aqueous phase containing drug is added to this and resulting in two phases are sonicated at 4-5°c. Clear gel formed is further sonicated after the addition of small amount of phosphate buffered saline (PBS). The removal of organic phase occurs at 40°c under low pressure. With the PBS the resulting viscous niosome suspension is diluted and heated on a water bath for 10 minutes at 60°c to yield the niosomes.
Methods: Ether injection method: In this method, surfactant cholesterol solution is slowly injected in ether through 14-gauge needle into a preheated aqueous phase maintained at 60°c.
Ether vaporization results in formation of ether gradient at ether-water. Diameter of vesicle range from 50-1000nm depending on the conditions used.



The reverse phase evaporation technique
Fig.17

Trans Membrane Ph Gradient (Inside Acidic) Uptake Process (Remote Loading):
In chloroform surfactant and cholesterol are dissolved. Under reduced pressure the solvent is evaporated to get thin film on the wall of the round bottom flask. Film is hydrated with 300mM citric acid (pH 4) by vortex mixing. Frozen the multilamellar vesicles and thawed 3 times and then sonicated.

Aqueous solution containing 10 mg/ml of drug added to this niosomalsuspension and vortexed.The pH of sample is raised to 7.0-7.2 with 1M disodium phosphate. This mixture is then heated for 10 minutes at 60°c to give niosomes.

✓ **Multiple Membrane Extrusion Method:**

This method involves a mixture of cholesterol, surfactant and diacetyl phosphate is prepared and by using rotary vacuum evaporator the solvent is evaporated to leave a thin film. The obtained film is then hydrated with aqueous drug solution and suspension thus obtained is extruded through polycarbonate membrane (mean pore size 0.1 mm) and placed in series upto eight passages to get uniform size niosomes . This is good method of controlling size of niosome.

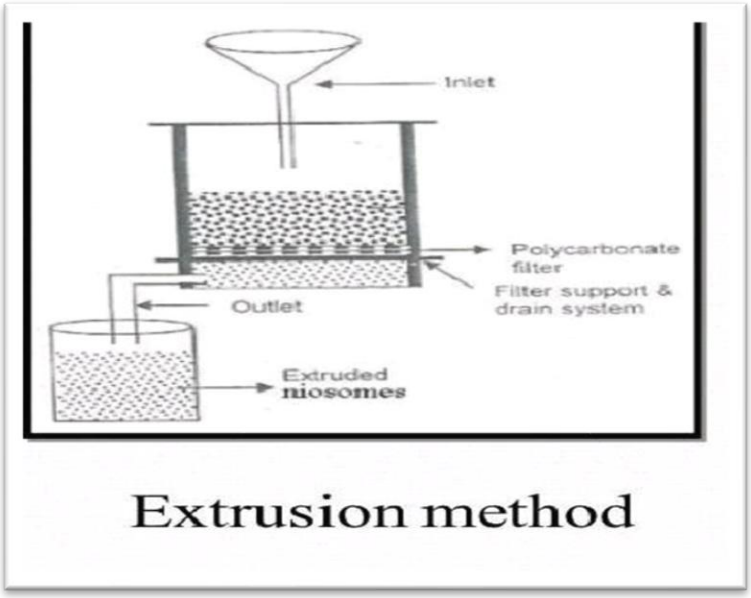
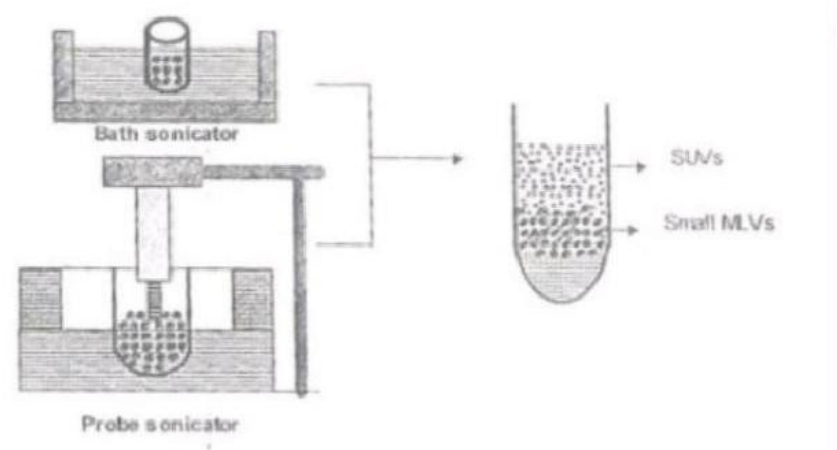


Fig 18 extrusion method

A 10 ml glass vial containing surfactant/cholesterol mixture, to this an aliquot of drug solution in buffer is added. Using a sonicator this mixture probe sonicated at 60°c for 3 minutes. The resulting vesicles are of small unilamellar type niosomes.



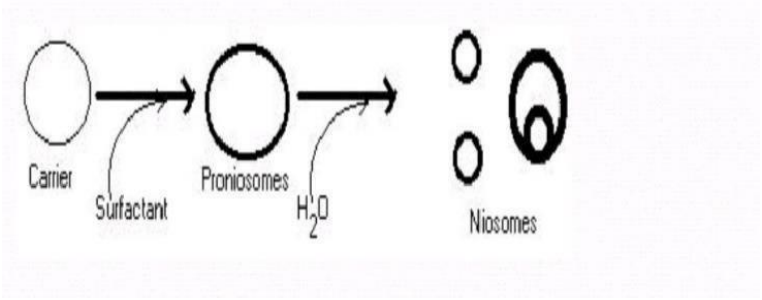
Sonication

Fig.19

✓ **Formation Of Niosomes from Proniosomes:**

This is another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. Dry formulation is a result of coating process. In which thin film of dry surfactant is covered each water- soluble particle. This preparation named as proniosomes. By t the addition of aqueous phase niosomes formed at Tm<T and brief agitation.

T = Temperature.
T_m = mean phase transition temperature



showing formation of niosomes
Fig.20

NANOPARTICLES:
These are not simple molecules. They are made of three different layers a) surface layer which is made of different metal ions, surfactants, etc. b) shell layer it is chemically different from core c) the core this is the center portion of the nanoparticles[13].
Nanoparticles are most widely used in nanotechnology. Again, nanoparticles are of different types. They are:

- Gold nanoparticles
- Quantum dot
- Nano capsules
- Carbon nanotubes liposomes

Advantages:

- These are less toxic.
- Has multiple molecular targeting

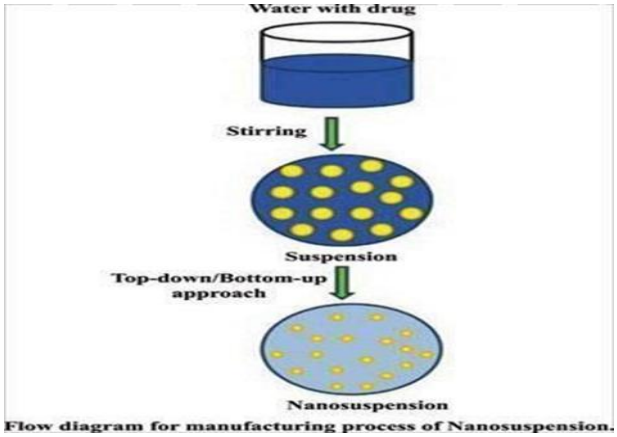
Disadvantages:

- They cause lung damage.
- They have limited loading drug capacity.

Nanoparticles are of different types they are:

1. Nano suspensions
2. Nano emulsions

<u>Nanosuspensions:</u>
It is defined as very finely disperse solid drug particles in aqueous phase stabilized by surfactants[14]. The diameter of suspended particle is less than 1um in size (i.e.,0.1 to 1000nm). These are used for either oral and topical use or parenteral and pulmonary administration[15, 16].



Flow diagram shows manufacturing of nanosuspension.
Fig.21

Advantages:

- These can be given by any route
- In case of subcutaneous or intramuscular the tissue irritation can be reduced
- It can be applied for poorly water-soluble drugs.
- These can be easily manufactured.
- Reduction in amount of dose

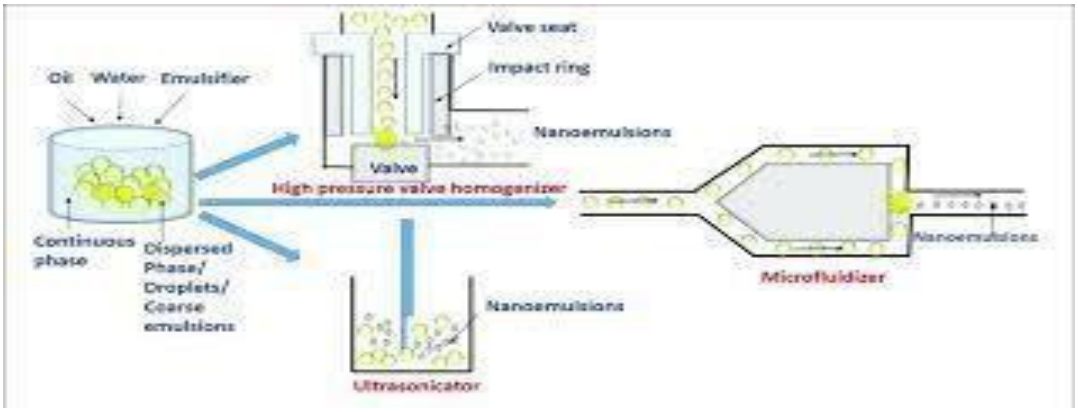
Disadvantages:

- Sedimentation, compaction and physical stability cause problems
- Accurate and uniform dose cannot be achieved.

Methods of preparation of Nano suspension:

- High pressure homogenization
- Media milling
- Emulsification
- Melt emulsification • Solidification.
- **High Pressure Homogenization:**

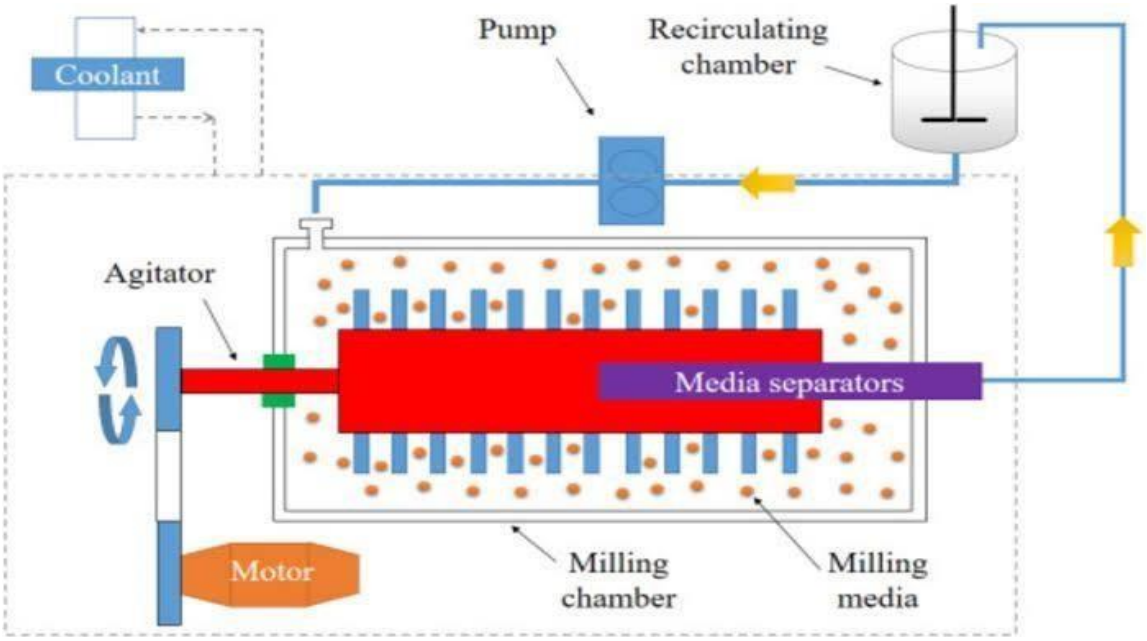
High pressure homogenization is the most widely used method for both small- and large-scale neck production due to its high efficiency, simplicity and low cost compared to other
alternative it passing the cellulose fiber water suspension very narrow channel under high pressure homogenization is the preferable method ability to reduce particle sizes more significantly blending.



High Pressure Homogenization Media
Fig.22

- **Milling Method:**

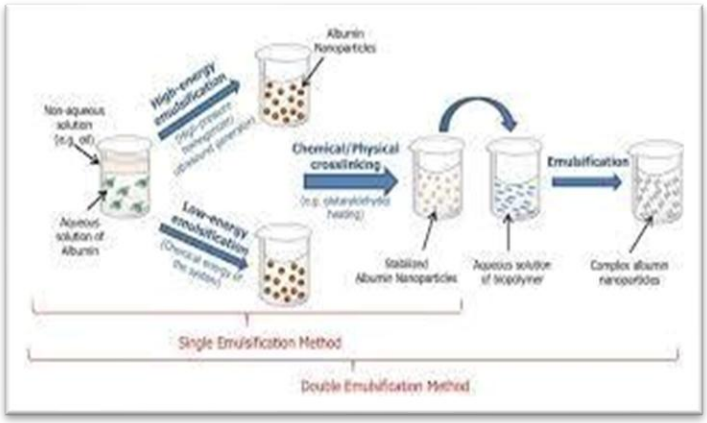
Frequently used in technique in pharmaceutical industry. The particle size reduction is mainly through abrasion., cleavage, and fracturing.



Media Milling Method
Fig.23

- **Emulsification Method:**

Emulsification dispersing two are more immiscible liquids to get her to form a semi stable mixture food application. These two liquids generally consists of an organic oil phase aqueous water phase addition of food- grade emulsifier.



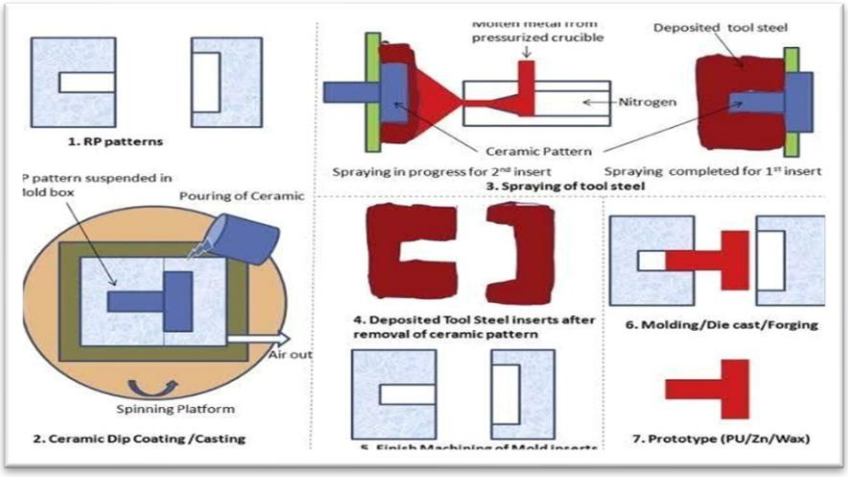
Emulsification Method
Fig.24

- **Melt Emulsification:**

Spherical particles and thus widens the availability of polymer feed materials for additive manufacturing the process the polymer is molten in a continuous phase.

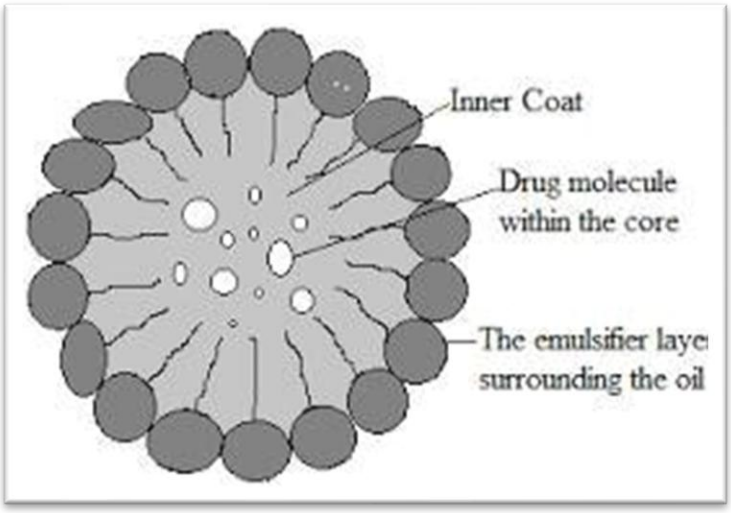
- **Solidification Method:**

Solidification technique either mixing cement or other additives into either mixing cement or other additives into the soil to bind the soil particles to get her this are five type solidification kinetic under cooling, thermal under coaling, Constitutional under cooling, curvature under cooling and pressure under cooling.



Solidification Method
Fig.25

Nano emulsion: Nano emulsions[17, 18] are the colloidal particles where the size ranges from 10 to 1000nm i.e. submicron type. These are kinetically stable. These are the heterogeneous dispersions of two non-miscible liquids[19].



Structure Of Nano Emulsion
Fig.26

Advantages:
- It is applied for poorly water-soluble drugs.
- Dissolution is rapid.
- These are incorporated in tablets, pellets and hydrogel

Disadvantages:
- Its physical stability, compaction may cause problems.
- Uniform and accurate dose cannot be achieved unless it is suspension.

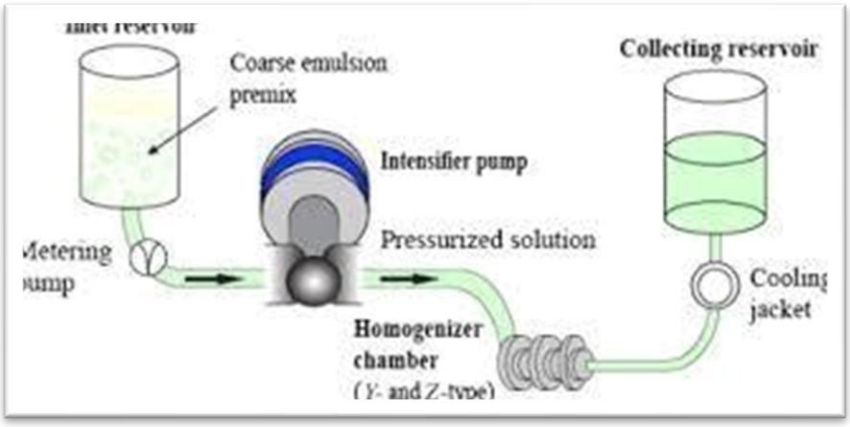
Methods of preparation of Nano emulsion:
- High energy method.
- Micro fluidization method.
- Ultra-sonication method.
- Nano emulsification method.

- **High Energy Method:**

Most used for creating emulsions and cell lysis when relatively volumes are being processed, they are also kinds of homogenizers used dairy industry albeit an a large scale.

- **Micro Fluidization:**

Is used for production of micro and nanoscale size materials it is commonly used in pharmaceutical industry to make liposomal products emulsion and in food industry to produce dairy products micro fluidization also widely used to NFCs.



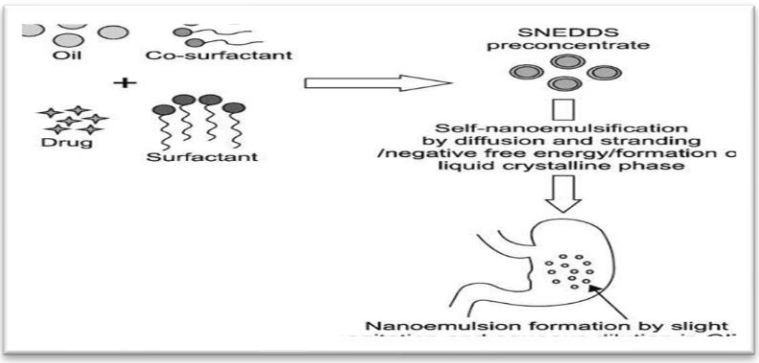
Micro Fluidization
Fig.27

- **Ultrasonication Method:**

Ultra-sonication is based on the phenomena of sludge disintegration ultra and waves development of the compression and Rarefaction while transmitting medium microbubbles are farmed in the few microsecond's threshold size.

- **Nano emulsion Method:**

Nano- sized emulsions ingredients these are thermodynamically stable isotropic system two immiscible liquids are mixed to form a single phase by means an emulsifying agent.
Example: surfactant and co- surfactant.



Self Nanoemulsion Technique
Fig.28

Marketed Nanomedicines:

S.No	Class	Drugs	Formulation	Dose
1	Statin	Atorvastatin	Tablet	80mg/day
		Pravastatin sodium	Tablet	40mg/day
		Fluvastatin	Tablets/extended release capsule	80mg/day 40mg capsule
		Lovastatin	Mevacor tablet/immediate release Altoprev(extended release)	
		Simvastatin	Tablet/oral disintegrating Tablet	
2	Fibrates	Fenofibrate oral	Tablet/Capsule	160mg/day 200mg capsule
		Gemfibrozil	Tablet	600mg twice a day
3	Cholesterol absorption inhibitors	Ezetamide[1]	Tablet	10 mg daily
4	Nicotinic acid group	Niacin, nicotinic acid,Vit B3	Tablet (controlled/extended release) Capsules	250,500 and 750 tablets;250 and 500mg capsules three times a day
		Colestipol hydrochloride	Tablets Oral suspension	2-16gm/day once or twice a day
5	Bile acid sequestrants	Cholestyramine	Oral suspension	4-8gm once or twice daily Max dose-24gm/day
		Colesevelam	Tablet and oral suspension	625mg colesevelam HCl tablet,1.875gm or 3.75gm oral suspension three tablets twice a day

Table-3

Importance Of Nanoparticles:[20, 21]

- Nanotechnology is the science the details with the processes that the occur at molecular level and of nano length scale size. example: DNA, water molecules.
- Pharmaceutical nanotechnology provides two basic types.

Nano materials.

Nono - devices.

- Nano materials are biomaterials used. example: ortho pedicortho pediorthopedic or dental implants and scaffolds and tissue- engineered products.
- They are surface modifications are or coatings night greatly enhance the biocompatibility by flavoring the interaction at living cells with the biomaterial.
- These materials can be sub classified into nano crystalline and nano structure materials.
- Nano- crystalline materials are readily manufactured and can substitute the less performing bulk materials.
- Raw nano materials can be used in Drug encapsulation bone replacements prostheses. example: artificial limbs, facial prosthetics, Neuroprosthetics, etc.
- Nanostructured materials are processed
- Forms of raw nano materials that provide special shapes of functionality. Example: Futlerences and carbon nanotubes.

Toxicity associated with nanoparticles

Nanotoxicology:

It is study of toxicity of nanomaterials[22]. The toxicity of nanoparticles increased with increase in surface charge. If the nanoparticle has higher positive charge, then it had greater electrostatic interactions with the cell and thus greater endocytic uptake[22, 23]. With the decrease in particle size, there is an increase in the inherent toxicity of nanoparticles. The metals silver, aluminum, gold and copper these metal- based nanoparticles exhibit increased toxicity with decreases the particle size.

Toxicity of nanoparticles depending upon:

- Type of precursor
- Concentration of precursor
- Nature of chemical used for the synthesis
- Duration of exposure
- Personal susceptibility
- Mode of entry
- Size of nanoparticle
- Environmental factors
- Threshold value

The toxicity of nanomaterials was broadly classified into two: -

1. Biological toxicity
2. Environmental toxicity

1.Biological toxicity:

- Nanostructures can enter the body via principal routes – dermal, subcutaneous, intravenous, inhalation, intraperitoneal and oral.
- The nanostructure entered into the body can distribute to various organs and may remain structurally same, be modified or metabolized.
- Nanoparticles firstly target at respiratory organs and gastrointestinal tract.
- They first interact with biological compounds like cells and proteins.
- The toxic effects are:
  - Allergy
  - Fibrosis
  - Deposition in different organs (lead to organ failure)
  - Inflammation
  - Cytotoxicity
  - Tissue damage
  - ROS generation
  - DNA damage

2.Environmental toxicity:

- By deposition of nanoparticle in ground water and soil nanoparticle pollution occus.
- It also affects the ecosystem.
- The effects of nanoparticles on microbes and plants are also rare.
- There pumps lot of nanoparticles to the environment during the outburst of nanomaterial research.

Different Antihyperlipidemic Nano medicines with Their Formulations

1. Drug: Atorvastatin Calcium[24]

Atorvastatin Calcium belongs to the statins group of class HMG CoA reductase inhibitors. It is used along with the proper diet where it lowers the bad cholesterol in the body such as LDL and triglycerides and increases the level of good cholesterol i.e. HDL. This drug is also used to prevent heart attacks and heart strokes.

Formulation: Chitosan nanoparticles

Chitosan nanoparticles is the ratio of Nitrogen of chitosan to Phosphate of DNA. Chitosan nanoparticles have various applications in both animal system and plant system. In animal system it includes: drug delivery, tissue engineering, antimicrobial activity, cancer diagnosis, vaccine delivery, gene therapy, encapsulation, enzyme immobilization, etc.

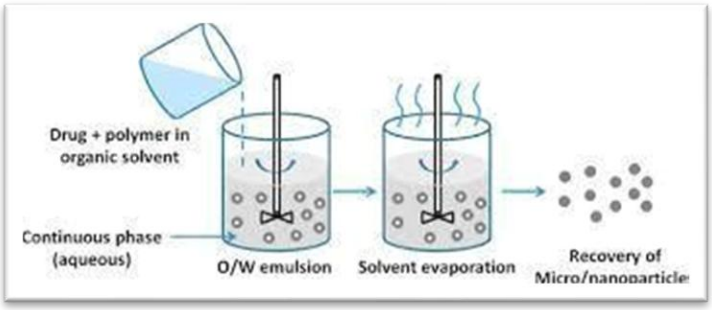
In plant system it includes: antimicrobial activity, pesticide delivery, fertilizer delivery, herbicide delivery, see germination, antioxidant activity, micronutrient delivery, delivery of plant growth promoters, etc.

Polymer/lipid: Chitosan

Chitosan is the polymer or lipid which is used in the preparation of Atorvastatin Calcium. Chitosan is a sugar molecule which is present in skeleton of shellfish, crab, lobster, etc. It has many medical uses and is a fibrous substance which is helpful to reduce fat.

Method of preparation: Solvent evaporation method

Solvent evaporation method involves the emulsification of proteins into the aqueous phase and then dispersed into a volatile solvent like dichloromethane, chloroform, etc. Then the solvent is evaporated using vacuum, high temperature, or by continuous stirring. Then the nanoparticles are obtained.



Solvent evaporation method
Fig.29

Size: It ranges from 150.5 to 1.24nm.

Inference: It acts as an effective carrier for the controlled drug delivery system.

2. Drug: Atorvastatin calcium[24, 25]

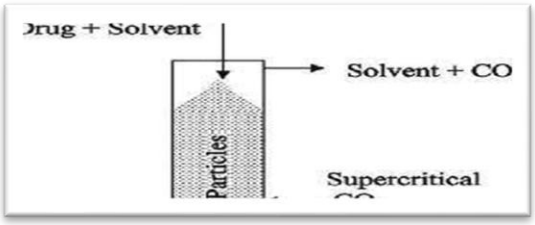
Atorvastatin Calcium belongs to the statins group of class HMG CoA reductase inhibitors. Itis used along with the proper diet where it lowers the bad cholesterol in the body such as LDL and triglycerides and increases the level of good cholesterol i.e. HDL. This drug is also used to prevent heart attacks and heart strokes.

Formulation: Amorphous Atorvastatin calcium nanoparticles

Amorphous Atorvastatin has greater performance in solubility and intrinsic dissolution rate while compared to crystalline form. So, they have higher solubility and greater dissolution rate. It is prepared by using supercritical antisolvent process (SAP).

Method of preparation: Super critical antisolvent process

It is a process where the sample is dissolved in an organic or inorganic solvents and then injected into supercritical fluid which is held under pressure which results in decrease in solution density.



Super critical antisolvent process
Fig.30

Size: Its size ranges from 152 -863nm.

Inference: Talented approach to dissolution, absorption and super saturation of atorvastatin calcium.

3. Drug: Chitosan [25]

Chitosan is safe and nontoxic polymer which is made of chitin. It has many medicinal activities and is the 2nd most abundant biopolymer that is found. Also, it has the ability to absorb liquids and can form a

protective layer. It is sparingly soluble in water also insoluble in ethanol and other organic solvents.

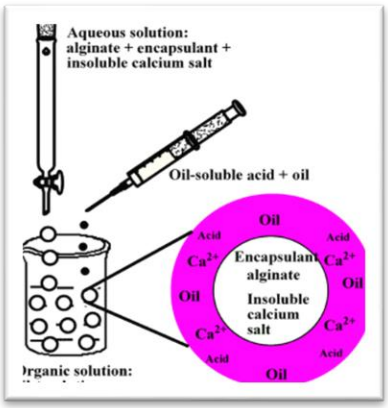
Formulation: Chitosan nanoparticles [26]

Chitosan nanoparticles is the ratio of Nitrogen of chitosan to Phosphate of DNA. Chitosan nanoparticles have various applications in both animal system and plant system. In animal system it includes: drug delivery, tissue engineering, antimicrobial activity, cancer diagnosis, vaccine delivery, gene therapy, encapsulation, enzyme immobilization, etc.

In plant system it includes: antimicrobial activity, pesticide delivery, fertilizer delivery, herbicide delivery, see germination, antioxidant activity, micronutrient delivery, delivery of plant growth promoters, etc.

Method of preparation: Ionotropic gelation, rotary evaporation, spray drying

Ionotropic gelation: It is shortly known as IG. This technique is used for the production of nanoparticles by electrostatic force of attraction between two ionic species.



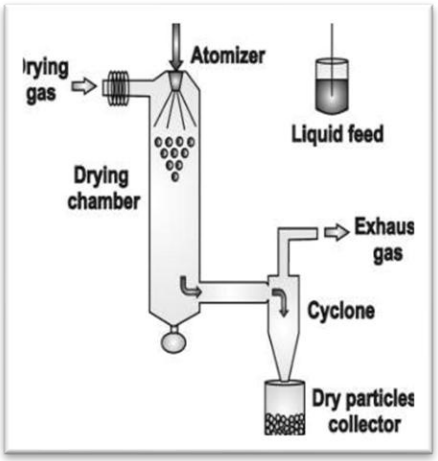
Ionotropic gelation
Fig.31

Rotary evaporation: It is a device used in the laboratories for the evaporation of solvent from the liquids or slurry.

Rotatory evaporator
Fig.32

Spray drying: It is a device used for producing dry powder from the liquid or slurry by passing hot air through it

.



Spray dryer
Fig.33

Size: Its size ranges from 500-1000nm
Inference: Chitosan nanoparticles, these are non-toxic and useful in lowering body weight. [27]

4. Drug: Atorvastatin calcium

Atorvastatin Calcium belongs to the statins group of class HMG CoA reductase inhibitors. It is used along with the proper diet where it lowers the bad cholesterol in the body such as LDL and triglycerides and increases the level of good cholesterol i.e. HDL. This drug is also used to prevent heart attacks and heart strokes.

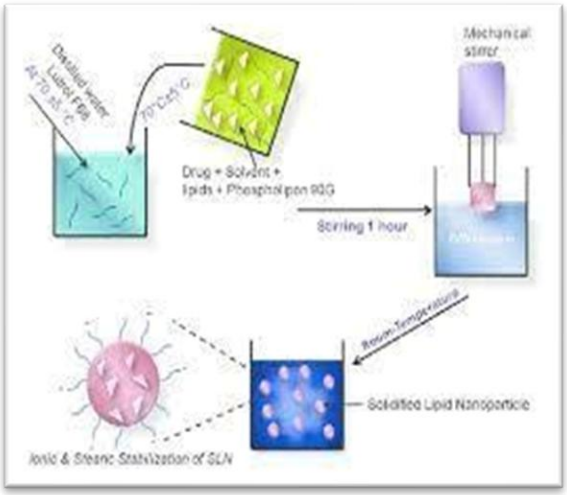
Formulation: Oral Nano particulate atorvastatin calcium

Oral given atorvastatin calcium nano particles enhance their bioavailability and shows more effective action. Also, it is safe to use.

Method of preparation: Emulsion-Diffusion-Evaporation method

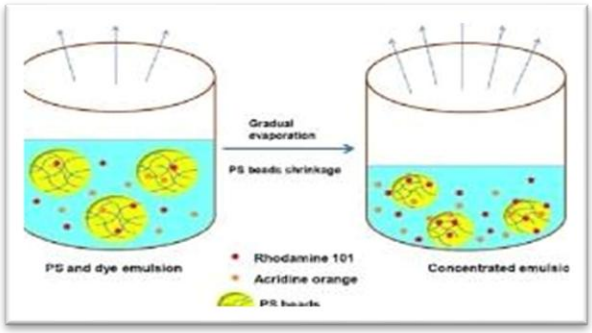
Emulsion: It is most commonly used technique for the preparation of nanoparticles which aims at high stability, high encapsulation and efficacy with low toxicity.

Diffusion: Diffusion is the movement or transport of molecules where the nanoparticles can be separated according to different sizes.



Solvent diffusion technique
Fig.34

Evaporation method: The drug is dissolved or dispersed in an organic polymer solution, and then emulsified into an aqueous medium, then the nano particles are formed after the diffusion and evaporation of the solvent.



Solvent evaporation method
Fig.35

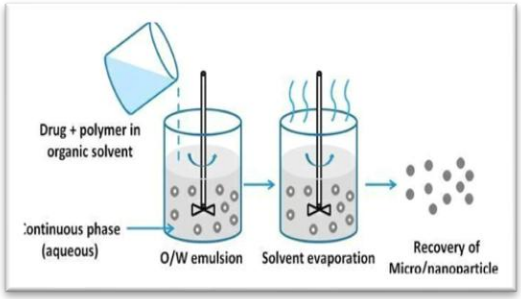
Size: Here the particle size ranges from 120.0-4.2nm and 140.0-1.5
Inference: Improves the safety and efficacy of the drug.

5. Drug: Estradiol[28]

Estradiol is Bioidentical estrogen and naturally occurring. Estradiol has antigonadotropic effects Due to its estrogenic activity. It can Inhibit fertility and suppress sex hormone production in both men and women.

Formulation: Oral estradiol nanoparticles
Method of preparation: Emulsion-diffusion-evaporation

By using emulsion- diffusion- evaporation method nanoparticles were prepared. In this PLGA is used as polymer. Therefore particles were prepared by PLGA 50:50 as well as PLGA 65:35 and PLGA 85: 15.PLGA and estradiol solution in ethyl acetate added to the aqueous phase (1%w/v DMAB) undergo stirring results in o/w emulsion. The ratio of o/w emulsion was 1:2. By using high speed homogenizer the o/w emulsion was homogenizer. Water was added by constant stirring that facilitated diffusion and evaporation of organic solvent occur. This results in nanoprecipitation and formation of nanoparticles contain estradiol.



Double emulsion technique
Fig.36

Inference: Reduced dose and frequency in comparison to that of drug suspension administrated orally.

6. Drug: Simvastatin [29]

Formulation: Simvastatin- loaded lipid nanoparticles Simvastatin is a cholesterol lowering agent used in the treatment of hypercholesterolemia. Experimental results show that simvastatin loaded lipid nanoparticles were spherical nano – sizes particles with high encapsulation efficiency.

Method of preparation:

Simvastatin:

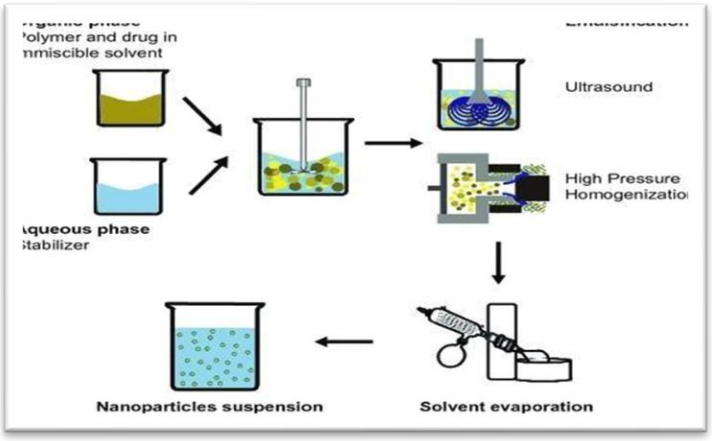
Simvastatin is a cholesterol lowering agent. Lipid nanoparticles enhance the oral bioavailability of simvastatin. Compared to free simvastatin the absorption of simvastatin loaded lipid nanoparticles have greater absorption.

Polymer:

Tween-20 and oleic acid

Method: Emulsification solvent evaporation technique

Emulsification solvent evaporation technique used to prepare simvastatin loaded lipid nanoparticles. IN this method emulsification of polymer in aqueous phase and dispersion in volatile solvent like chloroform, ethyl acetate etc.. solvent as evaporated by using vacuum, continuous stirring or high temperature.



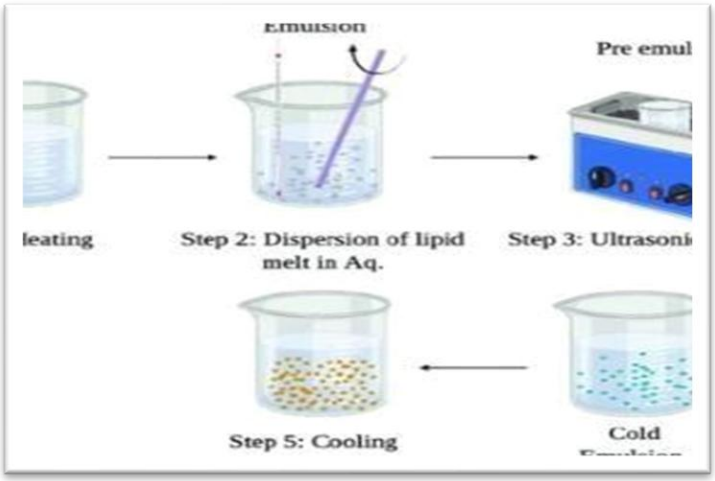
Emulsification solvent evaporation technique
Fig.37

Size: 48.9 and 68.3 nm
Inference: Promising delivery system to enhance the oral bioavailability of simvastatin.

7. Drug: Lovastatin

Formulation: Lovastatin nanoparticle
Lovastatin formulations We're designed by Precipitation ultra sonication technique.

Method of preparation:
Precipitation ultrasonication
Precipitation-ultra sonication technique used to prepare nanoparticles. Stability studied were conducted for optimum formulation at 4°c,25°c and 40°c.This method enhancing the solubility and bioavailability of lovastatin.



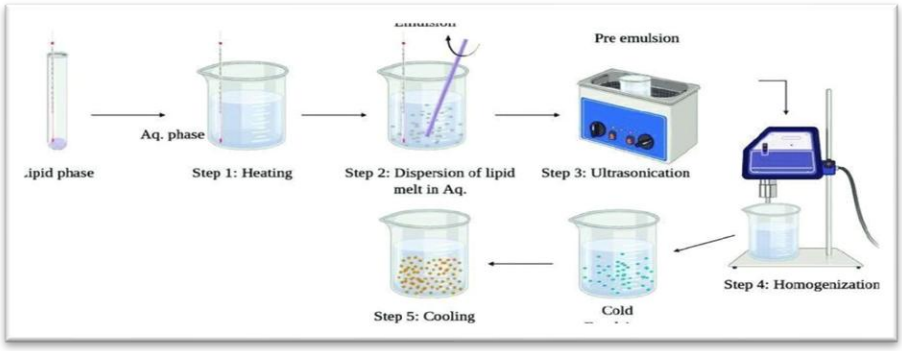
Precipitation ultra sonication
Fig.38

Polymer/ lipid: Precirol and squalene.
Size: 65.6 nm
Inference: Nano aided drug delivery system is a suitable choice For poorly soluble lipophilic drugs.

8. Drug: Atorvastatin

Formulation: Atorvastatin loaded solid – lipid nanoparticles.

Method of preparation: Ultrasonication technique
Ultra-sonication technique used to prepare the Atorvastatin solid lipid nanoparticles. Atorvastatin belonging to the class of HMG- CoA reductase inhibitors. It shows action by slowing the production of cholesterol that builds up on the walls of arteries.

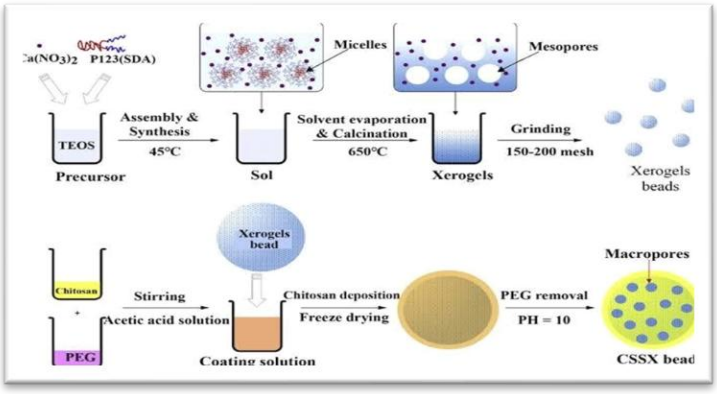


Ultra sonication technique
Fig.39

Size:50.0-6.12nm
Lipid: Trimyristin and soy phosphatidylcholine 90%.
Inference: SLNs are the promising delivery systems for poorly water-soluble drugs.

9. Drug: chitosan

Chitosan is a cationic liner copolymer Polys Chitosanaccharide random distribution 2amino- 2 – deoxy- D- Glucose 2-acetamido- 2-deoxy D-glucose units it is very similar to cellulose C-2hydroxyl groups are replaced by acetamido residue presence of large percentage of Nitrogen 6.89% cellulose 1.2% chitosan chelating properties chitosan deacetylation of chitin Polysaccharide in crustacean shells chitin was identified by henribraconnot director of botanical Garden.
Formulation: Electrostatic interactions two ionic species.
Method of preparation: spray drying technique
Spry drying technique: This is the method of producing dry powder rapidly drying hot gas method of many thermally- sensitive materials food and pharmaceutical or materials.



Spray drying technique
Fig.40

Size: It's size ranges from 650nm.
Inference: Hypercholesterolemia is affected by wsc-nps even more than the wsc.

10. Drug: Lovastatin.

Lovastatin in the literature demonstrate the improve of thermal analysis by
Formulation: water soluble chitosan nanoparticles.
The nanoparticles study was to in vestige potential of water-soluble chitosan protein loaded nanoparticles water- soluble chitosan with ionotropic gelation in sodium thiophosphates bovine serum albumin was applied as a mode drug.
Method: Ionic gelation, spry- drying technique Ionic gelation production of nanoparticles and micro particles thermogravimetry the identification of calorimetry in the characterization polymorphism drugs studies of the pharmaceutical formulation stability and drugs thermal decomposition the plasma levels of low density lipoprotein cholesterol atherosclerosis and risk of cardiovascular disease.
Formulation: nanostructured lipid carriers.
Pharmaceutical formulation physiological and biocompatible lipids surfactants and co- surfactants and are second generation. And lipid nano carrier first generation. Prerequisites in formulating a stable

drug delivery system skin hydration, occlusion, enhanced bioavailability, and skin targeting.

Method: high shear home organization followed by sonication.

Sonication is used to disrupt cellular and membrane release of the cell contents. This is generally referred to as nonoperation sonication primary extracts to break the cell apart.

Size: It's size ranges from 180-290 nm.

Inference: More stable in the gastric environment and improve the clinical efficacy of lovastatin.

11. Drug: protein

Protein is biological macromolecules present in all cells amino acids which are commonly called building blocks of protein. Proteins from of the Greek word proteins of the first rank in j. Berzelius in 1938 protein plays important roles on body building function with all the major components in the carbon, hydrogen, oxygen, and nitrogen. Minor components in phosphorous and sulfur. All proteins are polymer s of amino acids 3000 molecules species of proteins contribute s average 17% of cell mass.

Formulation: Protein – nanoparticles conjugate.

Peptide- nanoparticles conjugates hold great promise in biomedical application nanoparticles – protein conjugates first stable and bio compatible 1.5 nm gold nanoparticles.

Size: It's size ranges from 100nm.

Inference: Digestion of bad cholesterol.

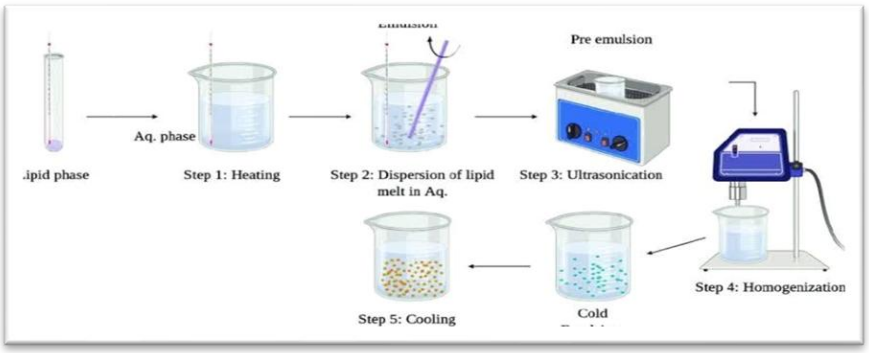
12. Drug: Rosuvastatin calcium

Cholesterol lowering drug commonly referred to as statins was approved for the treatment of dyslipidemia 1-3 Rosuvastatin calcium chemical:4 - flouarophenyl, 6- isopropyl 2- methyl sulfonyl amino pyrimidin-5 5 - dihydroxy hept-6- encocic acid calcium salt 3- hydroxy 3- methyl glutaryl coenzyme A cholesterol Biosynthesis in lover.

Formulation: Solid-state lipid nanoparticles of Rosuvastatin calcium.

Method: Hot homogenization followed by Ultra sonication.

Hot homogenization is carried out temperatures is the melting point of the lipid and is similar to the homogenization of an emulsion are- emulsion of the drug loaded lipid melt aqueous emulsifier phase same temperature obtained by high – shear mixing device.



Hot homogenization followed by ultrasonication
Fig.41

Size: It's size ranges from69-987nm.

Inference: Nanoparticles formulation with least mean particles zine depicted better permeability than the pure drug solution.

13. Drug: Fenofibrate

Fenofibrate belongs to the class of fibrates, and it is fibric acid derivative. Fenofibrate is used along with a proper diet to lower the bad cholesterol and fats (such as triglycerides and LDL) and the good cholesterol in the blood.

Method:

Fenofibrate nanoparticles produced from the Premix solution was prepared by dispersing 12.5wt% hydroxypropyl methylcellulose (HPMC) and 0.1 wt.% sodium dodecyl sulphate (SDS) in 125ml of water (all the concentrations are expressed with respect to amount of drug).

Dose: 145 mg orally once a day.

14. Drug: Ezetamide

Ezetamide belongs to the class of cholesterol absorption inhibitors. It is used to treat high blood cholesterol and certain other lipid abnormalities.

Method:

Solvent-antisolvent precipitation technique:

Nanosuspensions of ezetamide were prepared by this technique using the surfactant, Tween 80 as stabilizer.

Dose:10 mg orally once a day.

15. Drug: gemfibrozil. [30, 31]

Gemfibrozil, solid under the brand name lopid amang is a medication used treat abnormal blood lipid levels.

It is generally less preferred than statins use is recommended to get her with dietary changes and exercise.

It is unclear if it increases the risk of heart disease.

Method: Gemfibrozil usually in 30 mints before breakfast and dinner fallow your doctor's dosing instructions very carefully. gemfibrozil part of treatment program include. Diet exercise and weight control.

CONCLUSION:

This review article finally concludes that the use of present ongoing treatment of hyperlipidemia i.e., conventional dosage forms like tablets and capsules with high doses have poor bioavailability which results in many side effects but the use of advanced technology treatment i.e., with nanotechnology which plays a significant role in pharmacy which are said to be novel drug delivery system and show targeted and controlled action with low doses of drug. Nanomedicines have approval by FDA and show high therapeutic potency with low toxicity and show effectiveness up to 98% by curing the diseases. Nanosuspensions shows rapid onset of action, improved solubility and so improved bioavailability of the poorly soluble drugs. So, the use of nanomedicines is much better than the use of conventional dosage forms for the treatment of hyperlipidemia.

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