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An Overview on A Nanolipid Carrier System

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Abstract:

Nanotechnology is one of the leading technology due to its physical, chemical and biological properties with improved biopharmaceutical consideration. Nanoparticles are distinguished according to their size, shape, composition. The review represents the overview about the nanotechnology aplications , history of nanoparticles with their types and different method of preparations of nanoparticles such as solvent evaporation method, Emulsion diffusion method, salting out method , high sheer homogenisation method, polymerisation and coacervation method . It also highlights the different characterisation methods and a focused on need for nanoparticles explained as per their applications in variety.

Keywords: Nanoparticles, history of nanoparticles, method of preparation, characterization techniques.

1. INTRODUCTION:

Recent years have tremendous growth of research and application in the area of nanotechnology. Naontechnology is advanced branch of science applied to medicine , will being significant advances in diagnosis and treatment of various diseases. Engineered Nano lipid carriers are important tool to realise the number of its application in most life threatening diseases like cancer.

The colloidal carriers based on biodegradable and biocompatible polymeric systems have mostly influence the controlled and targeted drug delivery concept. The drug delivery system such as emulsion, liposomes and Nano particulate system are generally designed the improved drug release at target site with minimised side effects. The controlled release of pharmacologically active agents to the specific site of action at the therapeutically optimal rate and dose regimen has been the major gaol while formulating the nanoparticlea as a new drug delivery system.

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The branch of nanotechnology is divided intpo two main categories nanodevices and nanomaterials . Nanodevices are miniature devices at nanoscale including microarrays.[1,2] and some intelligent machines like respirocytes . Nanomaterials contains particles smaller than 100 nm in atleast one dimension.

The composition of the engineered nanoparticles may vary. Source materials may be of biological origin like phospholipids, lipids , lactic acid, dextran, chitosan, or have more chemical characteristic as like various polymers, carbon silica and metals. The interaction with cell for some biological components is quite different with comparison to non biological components like metals.

Nanotechnology is the manipulation of matter on an atomic, molecular, and supramolecular scale involving the design, production, characterization and application of different nanoscale materials in several key areas providing novel technological advances mainly in the category of medicine (so called Nanomedicine) [6, 18-20]. The development and optimization of drug delivery approaches based in nanoparticle deal with early detection of cancer cells and improvement in the efficacy of the treatments applied and also useful for specific cancer biomarkers [21]. The most important biomedical applications of nanoscale materials can be organized as shown in Figure 1.

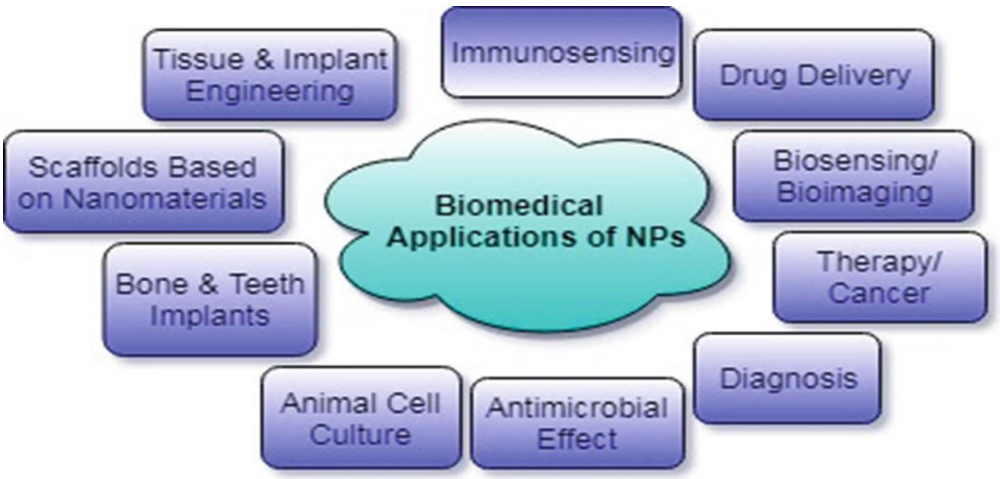

Fig. 1 : Biomedical applications of Nanoparticles.

Recently, there has been enormous developments in the feld of delivery systems to provide therapeutic agents or natural based active compounds to its target location for treatment of various aliments [3, 4]. There are a number of drug delivery systems successfully employed in the recent times to achieve more effective therapies while eliminating the potential for both under and over dosing , however there are still certain challenges that need to be addresses and an advanced technology need to be developed for successful delivery of drugs to its target sites. Hence the nano based drug delivery systems are currently been studied that will facilitate the advanced system of drug delivery.

The novelty of nanoparticle related to the biomedical and therapeutic fields was not because of their size and shape , but a progressive changein the therapeutic paradigm: a designed , functional , usually carrying a drug that could reach the systemic circulation of the patient along with the drug.

2. HISTORY OF NANOPARTICLES:

The prefix ‘nano’ is referred to a Greek prefix meaning ‘dwarf’ or something very small and depicts one thousand millionth of a meter (10−9 m). We should distinguish between nanoscience, and

nanotechnology. Nanoscience is the study of structures and molecules on the scales of nanometers ranging between 1 and 100 nm, and the technology that utilizes it in practical applications such as devices etc. is called nanotechnology [5].

The American physicist and Nobel Prize laureate Richard Feynman introduce the concept of nanotechnology in 1959. During the annual meeting of the American Physical Society, Feynman presented a lecture entitled "There's Plenty of Room at the Bottom" at the California Institute of Technology (Caltech). In this lecture, Feynman made the hypothesis "Why can't we write the entire 24 volumes of the Encyclopedia Britannica on the head of a pin?", and described a vision of using machines to construct smaller machines and down to the molecular level [7]. This new idea demonstrated that Feynman's hypotheses have been proven correct, and for these reasons, he is considered the father of modern nanotechnology.

After Feynman had discovered this new field of research catching the interest of many scientists, two approaches have been developed describing the different possibilities for the synthesis of nanostructures. These manufacturing approaches fall under two categories: top-down and bottom-up, which differ in degrees of quality, speed and cost.

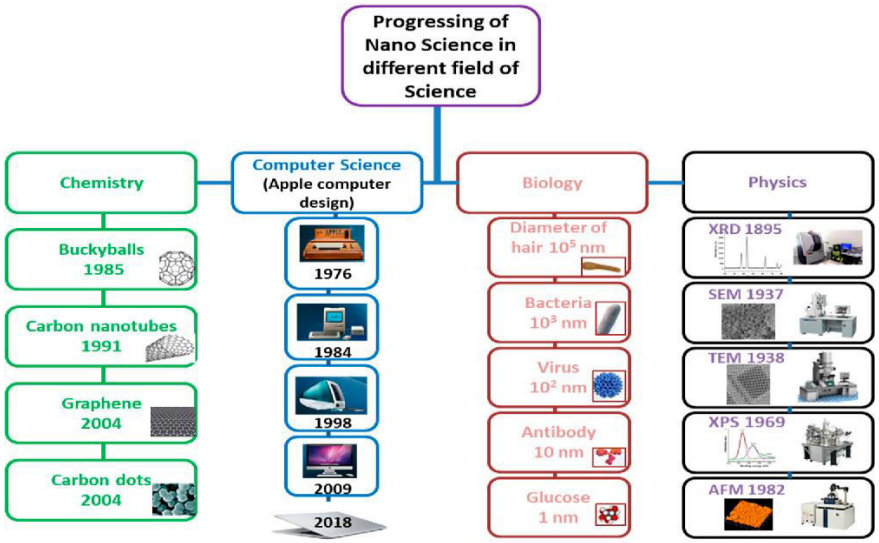

Fig 2 : Progress in nanoscience and nanotechnology in different fields of science.

3. TYPES OF NANOPARTICLES [16,17]:

Nanoparticles are classified according to their size, morphology , physical and chemical properties. These are as follows :

3.1. Carbon based nanoparticles:

Carbon nanotubes (CNTs) and fullerenes are main material of carbon based nanoparticles. CNTs are nothing but graphene sheets rolled into a tube. Due to 100 times stronger than steel these materials are used for structural reinforcement.

CNTs can be classified into single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). Carbon nanotubes are unique in nature as they are thermally non-conductive across the tube and conductive along the length.

3.2. Lipid based Nanoparticles:
Lipid nanoparticles are generally spherical in shape with a diameter ranging from 10 to 100nm. It consists of a solid core made of lipid and a matrix containing soluble lipophilic molecules. The external core of these nanoparticles is stabilized by surfactants and emulsifiers.

3.3. Ceramic Nanoparticles
These are made up of oxides, carbides, carbonates and phosphates. They are mostly high heat resistant and chemical inertness. They are used in the photo catalysis, photo degradation of dyes, drug delivery, and imaging.

3.4 Metal Nanoparticles:
Metal precursors are used to prepare metal nanoparticles . These nanoparticles can be synthesized by chemical, electrochemical, or photochemical methods. By reducing the metal ion precursers in solution chemically metal nanoparticles are prepared. These have the ability to adsorb small molecules and have high surface energy.

3.5. Polymeric Nanoparticles:
These are organic based nanoparticles. Depending upon the method of preparation, these have structures shaped like nanocapsular or nanospheres. A nanocapsule particle has core shell structure while a nanosphere has a matrix like structure. The active constituents and polymer are uniformly dispersed while in latter the active constituent are confined and surrounded by a polymer shell.

4. LIPID BASED NANOPARTICLES:
These are classified into following areas.

4.1. Liposome:
Liposomes are the most studied delivery systems due to the biocompatibility and biodegradability that they present. The main components of these nanoparticles are phospholipids, which are organized in a bilayer structure due to their amphipathic properties.They form vesicles, improving the solubility and stability of anticancer drugs once they are loaded into their structure in presence of water. They are capable of encapsulation of either hydrophobic or hydrophilic drugs [8].

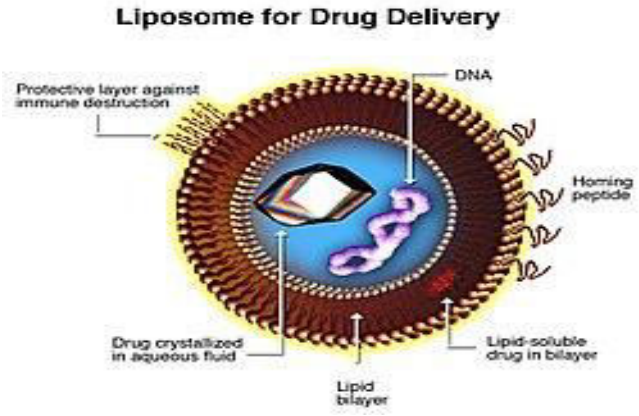

Fig. 3 Structure of Liposome

4.2 Solid Lipid nanoparticles (SLN):
SLNs represent a relatively new colloidal drug delivery system, composed of physiological lipids that remain in a solid state at both room and body temperature. These particles are in the size range of 50–1000 nm. The solid lipid used forms a matrix material for drug encapsulation and include

mono-, di- or triglycerides, fatty acids and complex glyceride mixtures. This matrix is stabilized by a mixture of surfactants or polymers. SLNs have significant advantages, such as site-specific targeting, physical stability over a long period, possibility of controlled release of both lipophilic and hydrophilic drugs, protection of labile drugs, low cost, ease of preparation and nontoxic. Furthermore, in reference to toxicity, SLNs have exceptionally low toxicity effects against human granulocytes. All these outstanding advantages make them an important candidate for drug delivery systems [23].

4.3 Nanosructured Lipid Carriers [NLC]:

NLCs represent a second generation of lipid-based nanocarriers, developed from SLN, which comprise a combination of solid and liquid lipids. This system was developed in order to overcome the limitations of SLNs; hence, NLCs have higher drug loading capacity, and could also avoid drug expulsion during storage by avoiding lipid crystallization due to the presence of liquid lipids in the NLC formulation. NLCs are a mixture of solid and liquid lipids, such as glyceryl tricaprylate, ethyl oleate, isopropyl myristate and glyceryl dioleate. The mean particle sizes are highly similar to SLNs, generally in the range of 10–1000 nm.

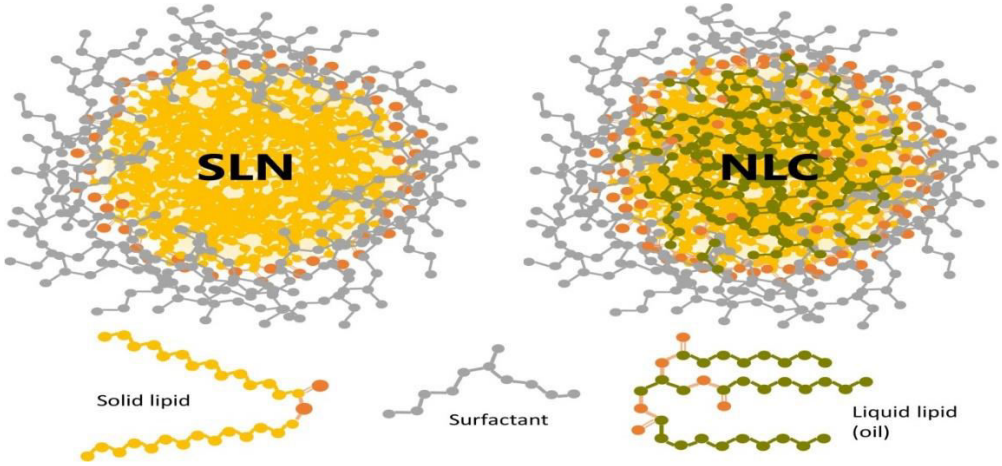

Fig 4: SLN and NLC as a biopharmaceutical consideration.

5. METHOD OF PREPARATION OF SLN/NLC:

5.1 Emulsion Precurser:

This is the most important technique of SLN/NLC preparation .

An **emulsion** is a colloid of two or more immiscible liquids where one liquid contains a dispersion of the other liquids. In other words, an emulsion is a special type of mixture made by combining two liquids that normally don't mix. The word emulsion comes from the Latin word meaning "to milk" (milk is one example of an emulsion of fat and water). The process of turning a liquid mixture into an emulsion is called **emulsification**.

Emulsion can be used for SLN preparation as lipids are solid at room temperature, can be heated 5-10^{0}C above their melting point to get a liquid lipid which is emulsified with water at same temperature and the droplets solidify in the form of solid lipid particles.

5.1.1 Hot Homogenisation:

High pressure homogenization of the pre-emulsion is done above the lipid melting point. Usually, lower particle sizes are obtained at higher processing temperatures because of lowered viscosity of the lipid phase [10].

An important problem rises while preparing SLN by hot homogenisation is drug expulsion from nanoparticles, which happen during process of lipid re-crystallisation when cooling of the hot nano emulsion carried out. [11]

Hot Homogenization is carried out by two methods.

i. High pressure homogenisation
ii. High Speed Homogenisation and Ultrasonication:

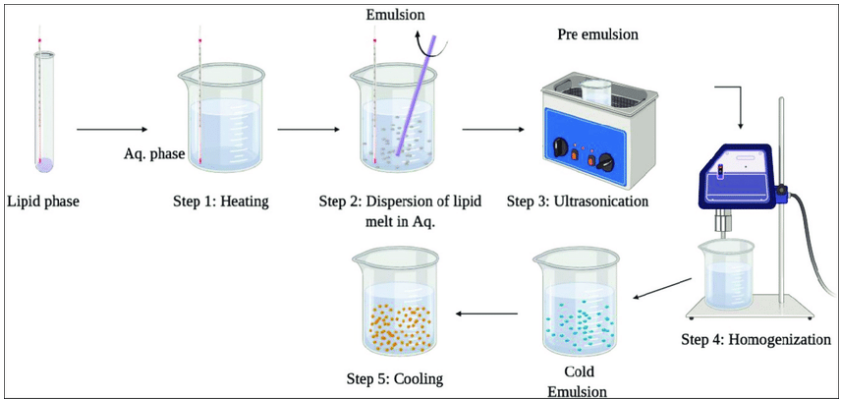

Fig 5: Hot Homogenization Technique

High pressure Homogenisation:

This method initially was used for the preparation of Solid lipid Nano dispersion. For this method various lipids are used like trimyristin, tripalmitin, a mixture of mono, di and triglycerides. However, dispersion quality is often compromised by the presence of micro particles. High-speed homogenization method is used to produce SLN by melt emulsification [12]

High Speed Homogenisation and Ultrasonication:

These are dispersing techniques are generally used for the preparation of SLN. Both methods are widespread and easy to operate . The impedimenta used for this method is prevalent in every single laboratory. The main drawback of this technique is wider particle size distribution ranging into micrometer range which is the main cause for physical instability .[13]Particle gain on storage and potential metal decay are acute problems in this method. After many studies and intense research, it was proved that high-speed and ultrasonicate stirring when operated combinedly at high temperatures, yield a steady formulation.[14]

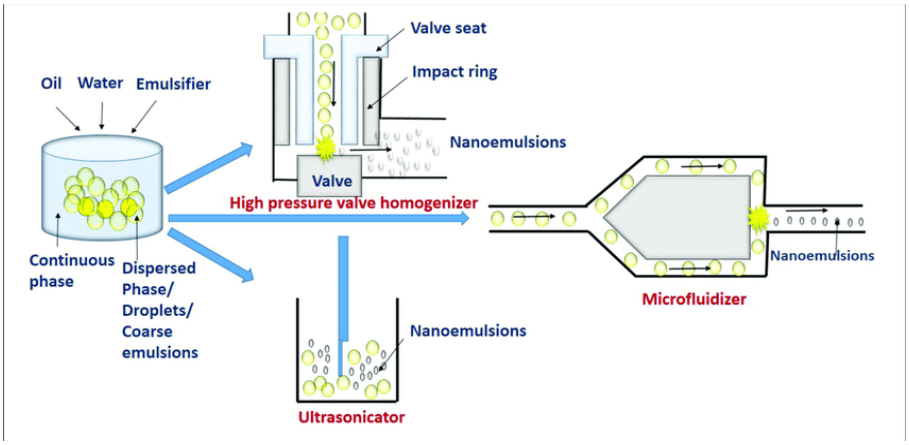

Fig 6: High pressure Homogenisation

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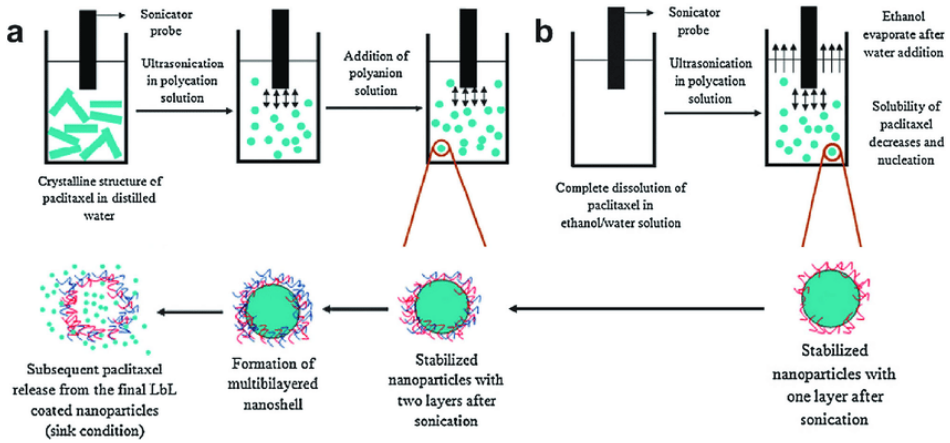

Fig 7: Ultrasonication Method of preparation of SLN

5.2 Solvent Based Method:

Solvent based methods have been proposed in order to encapsulate NP with stability and problems associated with biopharmaceutical consideration by minimising the toxicity associated therewith. Main advantage of this method is the mild operating temperature, which is the key step of encapsulation of thermosensitive materials. According to different precursor method used , solvent based method can be divided in:

Solvent Injection:

The lipid and active constituent is dissolved in organic solvent and this solution is injected by a syringe needle in water with continuous stirring. In this process lipid is precipitate as nanoparticles when comes in contact with water and same time encapsulation of drug is carried out. Particle size get influenced by type of lipid, surfactant and solvent used and viscosity of outer phase.[15]

Solvent Evaporation- Diffusion from emulsion: O/W or W/O/W emulsions can be prepared; O/W emulsions are suitable for lipophilic drugs are dissolved in the inner organic phase of the system [15], together with the lipid. W/O/W emulsions are suitable for hydrophilic drugs, that are dissolved in the inner aqueous phase, while the lipid is dissolved in the intermediate organic phase of the multiple system [24]

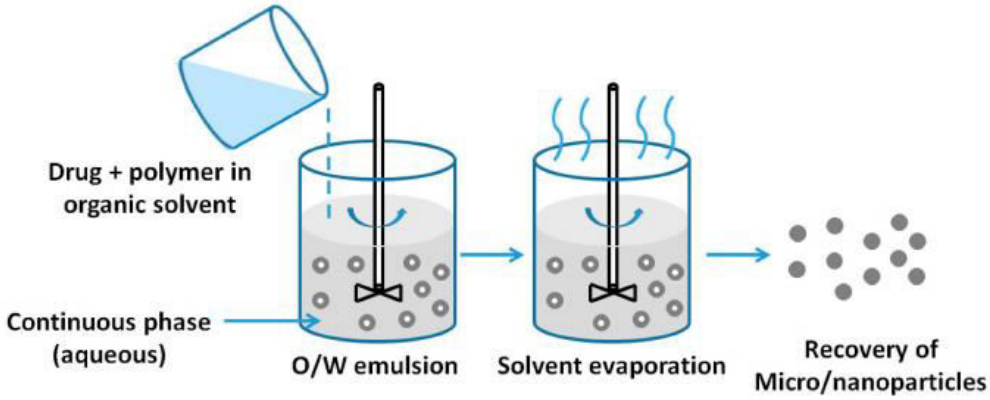

Fig 8: Solvent evaporation method

5.3 Coacervation Method:

This was a new method developed to prepare a controlled way SLN. This method allows the incorporation of drugs in a very simple manner, without using complex equipment hence it is the

inexpensive method for SLN preparation. It is based on the interaction between a micellar solution of a fatty acid alkaline salt and a acid solution in the sight of amphiphilic stabilizing agents. [25,26]

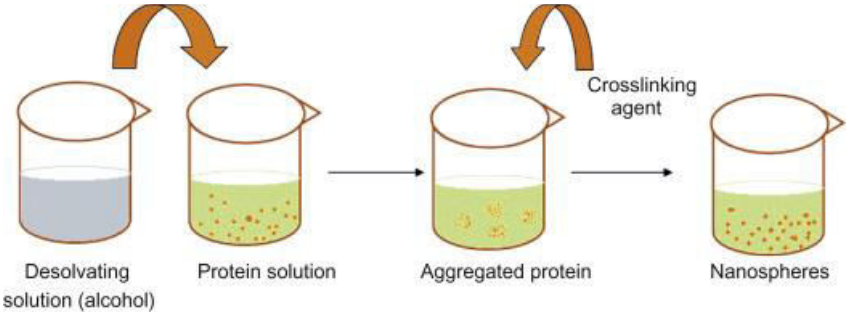

Fig 9 : Coacervation Method

5.4 Supercritical fluid (ScF)

This is a comparatively advanced technique for the manufacturing of SLNs. The supercritical fluid has distinct thermo physical properties which can be finely adjusted by minute modifications in the pressure. It is solvent-free processing [27] With the elevation in pressure, the density and capability of fluid to liquefy compounds enhance, whereas the velocity remains the same. ScF is a substance above its pressure and critical temperature. The fluid has properties with density , viscosity and larger diffusivities .

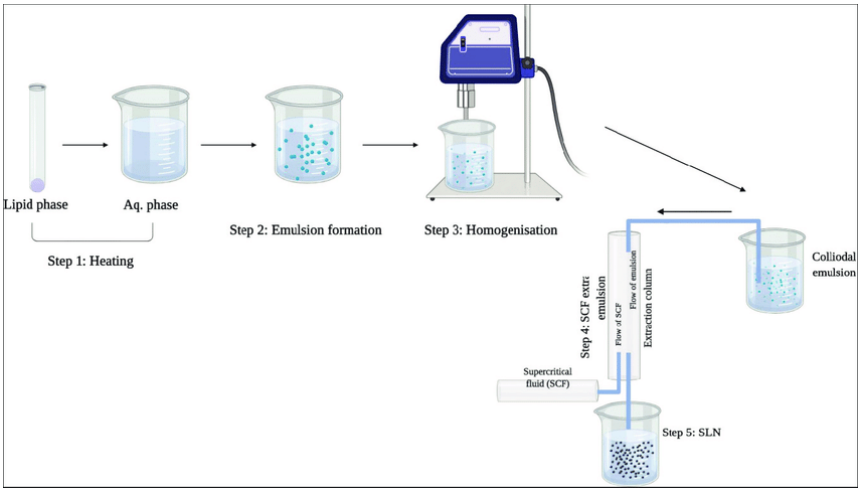

Fig 10. Supercritical fluid method

5.5 Microemulsion:

Microemulsions are one of the best candidates as novel drug delivery system because of their long shelf life, improved drug solubilization with ease of preparation and administration. Microemulsions are thermodynamically stable and optically isotropic liquid solutions of oil, water and amphiphile. They have emerged as novel vehicles for drug delivery which allow controlled or sustained release for ocular, percutaneous, topical, transdermal, and parenteral administration of medicaments. Microemulsions can be easily distinguished from normal emulsions by their low viscosity, transparency and more accurately their thermodynamic stability.

The drug is be dissolved in the lipophilic part of the microemulsion i.e. oil and the water phases can be combined with surfactant and then cosurfactant is added at slow rate with constant stirring until the system is transparent. The amount of surfactant and cosurfactant to be added and the percent of oil phase that can be incorporated is determined with the help of pseudo- ternary phase diagram. To

achieve desired morphological characteristics ultrasonicator is used. It is then allowed to equilibrate. Gel may be prepared by adding a gelling agent to the above micro emulsion. [29]

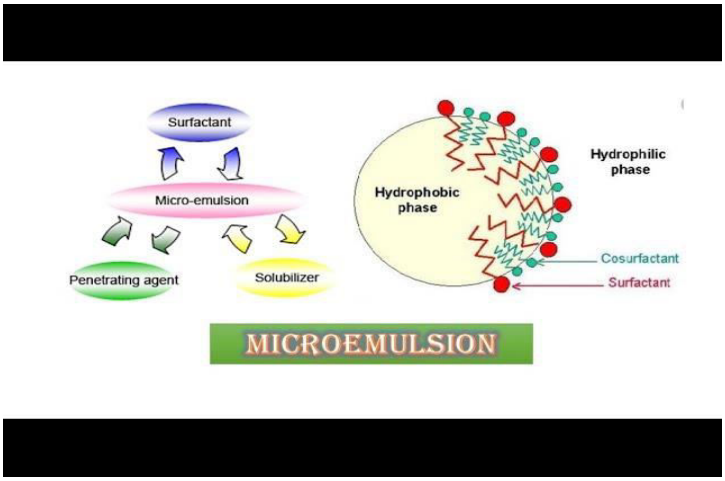

Fig 11 Microemulsion method

5.6 Spray drying

It is the subsequent modified economical method to lyophilisation of an aqueous dispersion into a drug. The particles are gathered due to elevated temperature, shear forces, and incomplete melting of the particles .[30]

Freitas et al. (1998) recommended that the lipids selected for spary drying having boiling point more than 70°C. The best result was procured by spray drying with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol–water mixtures (10/90 v/v).

Spray drying is a single-step manufacturing process where a liquid feed is converted to a dried particulate form. The principle involved in spray drying is atomisation of feed into fine droplets and at the same time evaporation of solvent is takes place with hot drying gas.

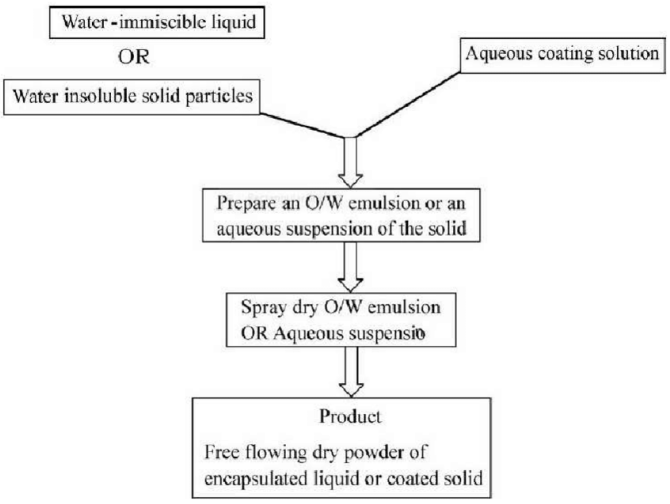

Fig 12 flow chart of spray drying method

5.7 Double emulsion method:

For the preparation of hydrophilic loaded SLN, a novel method based on solvent emulsification-evaporation has been used[32]. Here the drug is encapsulated with a stabilizer to prevent drug

partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion.

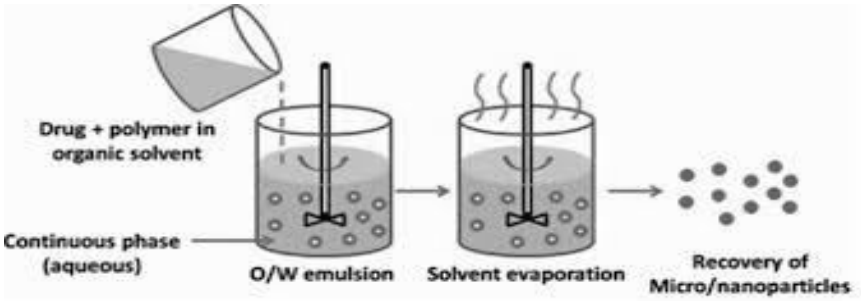

Fig 13 Double emulsion method

6. CHARACTERISATION OF NANOPARTICLES: [33]

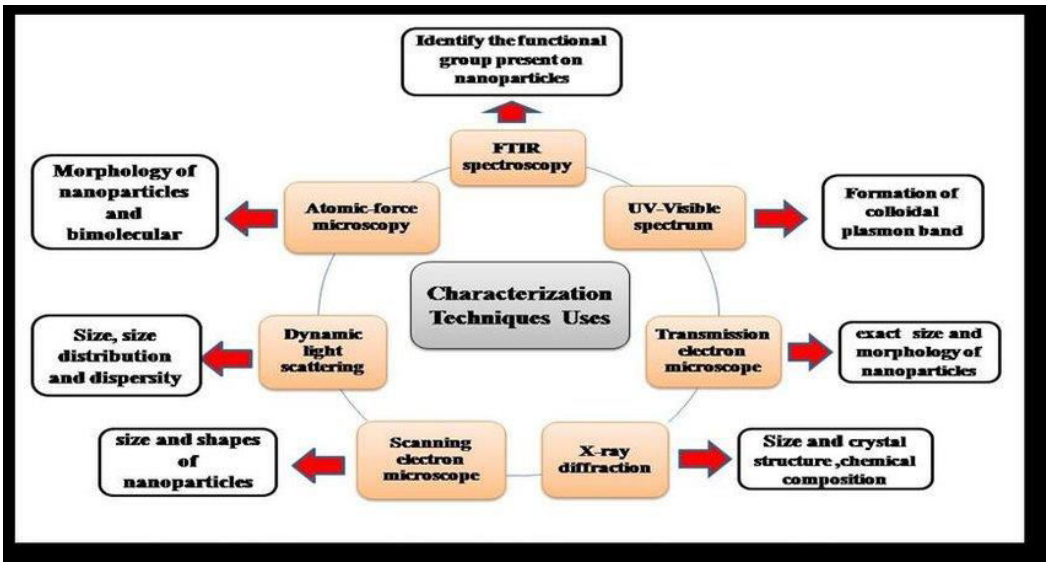

Fig 14: few characterization techniques of NP's

Nanoparticles are generally characterised by particle size, morphology , surface charge using advanced microscopic techniques such as scanning electron microscopy(SEM), transmission electron microscopy (TEM) and atomic force microscopy(AFM). The average particle size distribution, particle diameter and the surface charge affect the stability and in-vivo distribution of nanoparticles. Electron microscopy is useful to determine the toxicity .

6.1. Scanning electron microscopy

Scanning electron microscopes have a wide range of magnifications, ranging from several times to hundreds of thousands of times, covering the magnification range of optical magnifiers to transmission electron microscopes. The scanning electron microscope has a large focal depth of than that of an optical microscope with higher resolution. For complex and rough sample surfaces, clear and focused images can still be obtained. The signals are derived from electron- sample interactions which gives information about morphology, chemical composition and crystalline structure of the simple.

6.2. Transmission electron microscopy

Transmission electron microscopy can be used to observe the morphology, dispersion of nanoparticles, and measure and evaluate particle size. Atomic-level appearance can be obtained by

TEM, and its resolution is about 1 nm. The combination of line-scan mode transmission electron microscopy and electron energy loss spectrometer (EELS) can be used to analyse nanoscale multilayer structures. When electrons illuminate the specimen, the resolution power increases with increase in wavelength of transmitted electrons.

6.3. Atomic force microscopy: [34]

This technique works on a principle of scanning a probe over the surface or just across the sample building up a topological map, with the exact nature of the particular force employed serving to distinguish among the sub techniques. The scanning probe and dependant of probe is the only limitations to atomic force microscopy. It is used to imaging proteins sample and also samples of ceramic material, human cells or individual molecules of DNA, dispersion of metallic nanoparticles can be damaged.

6.4. Ray diffraction

Ray diffraction includes powder X-ray diffraction (XRD), small angle X-ray scattering (SAXS), small angle neutron scattering (SANS), and electron diffraction (ED).

Every crystalline substance gives a pattern; the same substance always gives the same pattern and in a mixture of substances each produces its pattern independently of the others.

It is used to measure the average spacing's between layers of rows of atoms and also determine the orientation of a single crystal or grain. It is also useful to find the crystal structure of unknown material. It measures the size, shape and internal stress of small crystalline region.

6.5. Thermal analysis

It is the branch of science where the properties of materials are studied as they change with temperature. Thermal analysis includes differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermal gravimetry (TG). The three methods are often combined and also combined with XRD, NMR, etc.

They can be used to characterize: 1) the presence or absence, content, and thermal weight loss temperature of surface-bonding or non-bonding organic groups or other substances; 2) the relationship between the strength of the surface adsorption and the particle size; 3) change in particle size during heating; 4) phase transition and crystallization process at the time of heating.

6. Nuclear magnetic resonance

NMR can be used to determine both the size and the qualitative nature of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle.

It involves the interaction of materials with low energy radio frequency radiation. It is applied for hydrogen bonding. It also used for the identifying drug leads and determining the confirmations of the compound bond to enzymes, receptors and other proteins.

Nuclear magnetic resonance (NMR), as an aid to the study of the structure of nanoparticles, can reflect the dispersion and compatibility of nano emulsions in aqeous phase , as well as the state of each component molecule in the colloidal system.

7. APPLICATIONS OF SLN:

7.1Nanoparticle as a drug delivery system: Solid lipid Nanoparticles possesses a better stability and ease of upgradability to production scale as compared to liposomes. This property may be very important for many modes of targeting. SLNs form the basis of colloidal drug delivery systems, which are biodegradable and capable of being stored for at least one year.

7.1.1 Gastrointestinal tract:

The rate of particle uptake in GI tract depends on diffusion and accessibility through mucus, cellular trafficking and post translocation events. The smaller the particle size greater the extent to diffuse with GI secretion to reach upto the target. Following uptake by GI tract, NP's can reach the blood stream and distribute themselves all over the body.[35,36]

7.1.2 Cell targeting:

SLNs have been reported to be useful as drug carriers to treat neoplasms[37]. Tamoxifen, an anticancer drug incorporated in SLN to prolong release of drug after i.v. administration in breast cancer and to enhance the permeability and retention effect[38].

Targeting of drug molecules at the site of action is resulting in a personalised medicine, Which minimises the untoward effect of the drug on other cells while maximising the therapeutic effect. This objective is mainly achieved by the preparation of smaller size particles which can penetrate though different barriers into target cells.[39]

7.1.3 For Gene delivery:

NP's can provide effective carriers for biomolecules such as DNA , RNA or proteins , protecting these materials from degradation and transporting them across the cell membrane barriers.
The lipid nuclic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nuclic acid nanoparticle (70-100 nm) were formed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

7.1.4 For topical use:

SLNs and NLCs have been used for topical application[40] for various drugs such as tropolide[41], imidazole antifungals[42], anticancers[43], vitamin A[44], isotretinoin[45], ketoconazole[46], DNA[47], flurbiprofen[48] and glucocorticoids[49]. The penetration of podophyllotoxin-SLN into stratum corneum along with skin surface lead to the epidermal targeting[42].

7.1.5 SLNs as cosmeceuticals:

The *in vivo* study showed that skin hydration will be increased by 31% after 4 weeks by addition of 4% SLN to a conventional cream[50]. SLN and NLCs have proved to be controlled release innovative occlusive topicals[51]. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations[52].

7.1.6 Tissue repair:

The nanoparticles are coated onto the surfaces of two pieces of tissue at the site where joining was desired. This technique affords methods to minimise tissue damage by using the least harmful wavelengths of light. Stem cells are the body's master cells and have unique ability to renew them and give rise to othe cell types. These cells are used for the transplantation purposes.
Magnetic nanoparticles can also be used to target stem cells and activate at required sites of injury and repair in diseases such as diabetes, cancer, heart disease, Alzheimer's disease and Parkinson's disease.[53,54]

8. NEED FOR DEVELOPING NANOPARTICLES:

The major challenges in the development of nanoparticles as a delivery system is the control of particle size, surface properties and release of active ingredients to get site specific action at desired

rate and dose. Nanoparticles offer increase the stability of drugs / proteins and possess useful controlled release properties.

CONCLUSION:

To overcome the problems of low solubility and bioavailability various new drug discovery processes are there amongst them one of the method is applications of nanotechnology in various life threatening disease like cancer tremendously applied because of their improved biopharmaceutical nature of particles as they are depenedent of size , shape , structure and nature. This articles explained the various types of nanoparticles along with their different methods of preparation and also the different methods for characterization explained in well manner. This article also attempt to deliver knowledge about the various applications of the nanoparticles .

he role of microemulsion in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability.

Microemulsions can also be used to achieve drug targeting however challenges remain, primarily

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Microemulsion has been shown to be able to protect labile drug, control drug release, and reduce patient variability.

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