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A STUDY ON: TYPES, CHARACTERISTICS, METHOD OF PREPARATION AND APPLICATIONS OF NANOPARTICLE DRUG DELIVERY SYSTEM

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ABSTRACT

The goal of the drug therapy is to achieve a steady state blood level that is therapeutically effective for an extended period. Targeted drug delivery where a drug carrier complex/conjugate delivers drug exclusively to the pre-identified targeted cells in a specific manner. The targeting methods may be classified as chemical methods, by covalent bonding and physical methods. Chemical methods consists of chemical modification of the parent compound to a derivative, which was activated only at the target site. Various physical methods made use of the carriers such as liposomes, niosomes, erythrocytes, platelets, magnetic microspheres, nanoparticles, and monoclonal anti-bodies. There is an enhancement in the activity due to increased surface area that would directly increase the absorption of the drug and hence enhanced bioavailability can be achieved. This review will focus onto the key properties of nanoparticles, their methods of preparation and its application in medicine, diagnostics and pharmaceutical industry. The review will also focus on the surface chemistry of the nanoparticle, which may interact with a range of molecules. It concludes that the nanoparticles emerge of great importance because of their unique surface characteristics and variability of applications.

KEYWORDS

Nanoparticles, Nanotechnology, Synthesis and Characteristics.

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INTRODUCTION

The most important difficulty in cure of various disorders is that the drug fails to reach the targeted organ. The drawbacks for the medications used in earlier days were[1].

- Low Bioavailability.
- Restricted Effectiveness.
- Unwanted Side Effects.

To outdo these problems scientists tried to search and develop newer techniques and approaches which helped the drug and its components to reach the particular organ and show the effects therein[1].

By formulation of timed release system the drawbacks like degradation and elimination of the active pharmaceutical ingredient were blown away[1].

Due to the timed release action the volume of drug at the particular site increases which directly helps to reduce the frequency of dosing.

Scaling down the size of the preparation with properties like timed release and targeted actions helps to achieve more efficacy and improved bioavailability[1].

This reduction in size helps in the emergence of the nanotechnology.

These facts help us to understand that nanoparticles inherent huge potential in transporting the active pharmaceutical ingredient towards the targeted organ or tissue[1].

Nano technology has been advantageous in decreasing the lethal effects, boosting the bioavailability, augmenting the solubility etc.

Merits of Nano particles over conventional system:[1]

- Elevating the solubility profile of an API.
- Enhanced bio-distribution thereby uplifting the bioavailability of the drug.
- Helps in raising dissolution rate of the drug.
- It also leads to the escalation of the surface area of a particle thereby making dissolution faster.
- Reduced frequency of dosing.
- Quick commencement of the action.

The word NANO has its roots in Latin, defining as "DWARF".

The optimal size dimensions explained in the nanotechnology states that it is one thousand million of a desired unit. Hence one million unit of a meter is NANO. NANOTECHNOLOGY finds its applications in different technological territories like electronics, engineering, biomedical sciences, molecularsciences, biophysics and many more. It also finds its use in vital functioning areas like brain targeting, tumor targeting, and gene transport. Nanotechnology also termed as NANOMEDCINE[1].

DEFINITION

Drug developed from nanotechnology refers to site specific medication at a Nano scale for prevention, cure, mitigation of disease and disorder and buildup of tissues like bone, muscle etc[1].

Major principles involved in nanotechnology

1. Analytical tool
2. Nano imaging tools
3. Toxicology studies
4. Nano devices
5. Novel drug delivery formulation

These principles are interconnected to each other. The benefit of nanoparticles in various divisions of medication has brought about revolutionary changes in field of medical sciences. With the aid of nanoparticles it is now feasible to provide remedies at micro cosmic levels which further aids in curing and mitigation of disease[1].

The use of nanostructures as fluorescent materials, therapeutic agents which have an action against specific antigens and antibodies are used in cancer therapy. Newer modifications in the Nano particulate formulations are:

1. Quantum dots.
2. Nano shells.
3. Nanosomes etc.

These are used for therapeutic purposes. Optimization of nanoparticles formulation mainly are occupied for identification of cancerous cells and improve the affectivity of formulation[1].

The prominent mechanism of transport of nanoparticles is by passive diffusion which thereby reduces the chances of adverse drug reaction[1].

TYPES OF NANOPARTICLES

One Dimension Nanoparticles

1-100nm – these are first type of nanoparticles used. These are used in solar cells, microchips, biosensors, fiber optic cables etc[1].

Two Dimension Nanoparticles – eg. nanotubes[1]

Three Dimension Nanoparticles[1]

- Quantum dots
- Fullerenes

Silvernanoparticles

It possess the antimicrobial against the bacteria and viruses and also with other eukaryotes. Because of this property these are very useful and efficient nanoparticles. Due to this antimicrobial properties these nanoparticles find their application in the textile industry, for water treatment, preparation of sunscreen lotions etc. These are the frequently used nanoparticles. This approach has been successfully formulated in various preparations by using active ingredients from Azadirachta indica, capsicum annum, cacrica papaya etc[3].

Gold particles

Gold nanoparticles are termed as AuNPs find their major use in the immunochemical reactions used for the detection of the proteins. It also finds use as the lab tracer in DNA fingerprinting in the identification of DNA in sample .NANORODS have been used in the identification of the cancerous stem cells[3].

Alloy nanoparticles

These exhibits distinct structural characteristics from their bulk samples. Bimetallic alloys have a very good properties of both the metals used and possess more efficient use than other metallic nanoparticles[3].

Magnetic nanoparticle

The magnetite F3O4 and maghemite F2O3 magnetic nanoparticles are found to be biocompatible. These have been studied for the application in the targeted cancer treatment (magnetic hyperthermia), stem cell sorting, DNA analysis, and MRI[3].

CHARACTERISTICS OF NANOPARTICLES

The general characterization of nanoparticles include size, density, electrophoretic properties, contact angle, specified surface area etc.

Size and morphology

In nanoparticles the size is prime important characteristics. Sizing of the particles and sub optical particulates have different procedures and it does not only have changes in procedure but also the procedure of sizing affects the surface associated properties. Two main techniques are used in assuring the particle size distribution.

Photon co-relation spectroscopy

Electron microscopy

Electron microscopy is comparatively less time consuming and if used with freeze fracture method it can be used for determining the inner structure of nanoparticles[9].

Scanning Electron Microscopy (SEM)

In this technique the liquid solution is converted into dry powder and then visualization takes place. The dry powder is mounted on sample holder followed by coating with conductive metal. The electrons are excited using a fine focused beam and then electrons are emitted from surface of the sample and then surface characterization is possible[1].

Tem

It uses high energy electron of very short wavelength. The energy of electron is up to 300kv and this electrons are emitted from a tungsten filament and accelerated nearly to speed of light. Air is evacuated from the column and a vacuum is created and the collision of electrons with air particles is avoided. When an electron beam passes through a thing section of specimen scattering of electrons takes place. A sophisticated system of electromagnetic lenses focuses the scattered electrons into an image[1].

Density

The internal arrangement of the nanoparticles consists of some defects which gives the evidence of the density parameter in the matrix. The density of the nanoparticles is calculated by using the helium or air by gas pycnometer[9].

Electrophoretic properties and surface charge

The constitution and the magnitude of the surface charge present on the nanoparticles is essential because of this parameter it affects the reaction of the nanoparticles with its surrounding biological climate and the electrostatic reactions with the other bioactive compounds. The surface charge present on the nanoparticle can be calculated by the measurement of the velocity of the particle in an electric field. To calculate the velocity the

instrument used is Laser Doppler Anemometry or also known as Velocitymetry. The surface charge of the nanoparticles can be also calculated by the electrophoretic mobility apparatus. It is measured by using the phosphate saline buffer of pH 7.4 and human serum. The zeta potential can also be calculated by using the Helmholtz- Smoluchowski equation[9].

Molecular weight measurement

The molecular weight of the nanoparticles is calculated by using the Gel permeation chromatography (GPC) using the refractive index detectors[9].

Specific surface area

The specific surface area of the nanoparticles can be measured by the Sorptometer. The equation given below helps to measure the surface area of the nanoparticles.

A= 6/ density. d

Where,

A= Specific surface area

d = diameter

The determined and measured specific surface areas are moderately comparable but in the case of residual surfactants deviation is seen in the observed and calculated surface area. The surface area tends to reduce in the case of surfactant coating[9].

NANOPARTICLE RECOVERY AND DRUG INCORPORATION EFFECIENCY

The nanoparticle recovery is also termed as the nanoparticle yield can be calculated by using the following formula.

$$\text{Recovery (\%)} = \frac{\text{Concentration of the drug in nanoparticles}}{\text{Concentration of nanoparticles recovered}} \times 100$$

Drug incorporation efficiency is also known as the drug content or drug loading. It is then calculated by the given formula.

$$\text{Drug content (\%)} = \frac{\text{Concentration of drug in nanoparticles}}{\text{Concentration of nanoparticles recovered}} \times 100$$

Surface hydrophobocity

The surface hydrophobicity of nanoparticles shows the effect of the nanoparticles and its reaction with the biological climate. The two parameters i.e. hydrophobicity and hydrophilicity decides the effect and stay of the nanoparticles in the body. The hydrophobicity governs the hydrophobic interactions of the nanoparticles with the blood constituents. The surface hydrophobicity is measured by the following methods i.e. hydrophobic interaction chromatography, two phase partition, adsorption of hydrophobic fluorescent or radio labeled probes and contact angle measurement[9].

***In vitro* release**

The in-vitro drug release of the nanoparticles can be measured by using standard dialysis, diffusion cell or ultra-filtration technique[9]

Preparation of nanoparticles

Synthesis of the nanoparticles can be achieved by using different chemical compounds such as the synthetic polymers, polysaccharides and proteins. The choice of the matrix materials which are stated above relies on the certain parameters which are stated below:[4,8]

- Desired size range of the nanoparticles to be synthesized
- Physicochemical properties of the drug e.g. Solubility , stability
- Surface characteristics of the nanoparticles
- Extent of biodegradability , biocompatibility and toxicity
- Antigenicity associated with drug
- Release characteristics of the drug.

Nanoparticles are generally being synthesized by 3 methods.

- Dispersion of the preformed polymers
- Monomer polymerization
- Coacervation or ionic gelation method[8]

DISPERSION OF THE PREFORMED POLYMERS

This is most general method for the synthesis of the nanoparticles. This technique provides the formation of the biodegradable nanoparticles with the use of the following polymers[8].

- Poly (lactic acid) (PLA)
- Poly (D, L- lactide-do-glycolide) (PLGA)
- Poly (cyanoacrylate) (PCA)

This technique is used by following approaches.

Spontaneous emulsification or solvent diffusion method

This is the altered version of the solvent evaporation method. These are following steps involved in this method.

i. Water miscible solvent + water immiscible solvent (oil phase)
ii. Instinctive diffusion of solvents take place which leads to occurrence of the interfacial turbulence between the solvents
iii. Leads to the synthesis of the small or nano particles
iv. As the concentration of the water miscible solvent increases the size of the nanoparticles reduces the above methods can be used for the hydrophilic as well as hydrophobic drugs[8].

Polymerisation

The polymerization of the monomers takes place in the aqueous medium to synthesize nanoparticles. The drug is embedded in nanoparticles by 2 ways i.e. by dissolving in polymerization matrix or by adsorption on nanoparticles after the polymerization is complete. The nanoparticle suspension is decontaminated by various methods including ultra-filtration to remove the different kinds of surfactants and stabilizers used for the polymerization method. This method is listed in literature for the preparation of the polybutylcyanoacrylate and poly (alkylcyanoacrylate) nanoparticles. The size of the nanoparticles is dependent on the amount of the surfactants used[8].

COACERVATION OR INONIC GELATION METHOD

Calvo and co-workers found a newer approach to synthesis the hydrophilic chitosan nanoparticles by ionic gelation method. This approach includes the preparation of the mixture of aqueous phases in which one is the polymer chitosan and other is the polyanion sodium tripolyphosphate. The chitosan consists of the amino group of the chitosan which is positively charged. This group reacts with the negatively charged group tripolyphosphate to form coacervates of nanometer scale. Coacervates i.e the nanoparticles form from the coacervation technique basically results from the electrostatic interaction between the 2 aqueous phases. But this is not the case with the ionic gelation method. Here the compound or the material gets transformed from liquid state to gel state because of the ionic interaction at the room temperature[9].

Other techniques used for the preparation of nanoparticles:

Other method of preparation of the nanoparticles

Synthesis of nanoparticles by using cross linking of the amphiphilic Macromolecules

The nanoparticles can be prepared by an alternative method by using the cross linking of the amphiphilic macromolecules, proteins and polysaccharides. The word amphiphilic states that the macromolecules have both lipid as well as the aqueous solubility. The method involves following steps:[9]

This process takes place in biphasic medium i.e. O/w or W/O dispersed system, which causes the division of the amphiphiles before the stabilization process. This process can also take place in the aqueous medium, where the removal, extraction or diffusion of solvents leads to the formation of the aggregates which are small in size and then these are stabilized by the chemical cross linking.

Cross linking in w/o emulsion

This technique is usually used for the Nano-encapsulation of the drugs.

This process includes following steps[9].

EMULSION CHEMICAL DEHYDRATION

This method is genrally used for the preparation of the BSA nanoparticles with small size range. The researchers Bhargava and Aindo, 1992 gave the alternative and less complicated cross linking method[9].

The process includes:

Synthesis of nanoparticles by polymer precipitation methods

This process includes following steps[9].

The external phase also consists of the stabilizer. There are two solvent micsiblity methods including the solvent extraction and solvent evaporation techniques. This two techniques are accomplished by follwing:

- Addition of the alcohol to rise the solubility of the organic solvent in the external medium.
- By increasing the amount of the water into ultraemulsion(to extract or to diffuse the solvent)
- Thesolevnt is rapidly evaporated at the room temperature or at accelerated temperatures.
- Or adopting such a organic solvent which is completely soluble in continous aqueous phase

APPLICATIONS IN THERAPEUTICS AND COSMETICS

Intra cellular targeting

Treatment of obligate and facultative intra cellular microorganism is difficult hence Nano particles are proving a boom to the use of antibiotics. These antibiotics mimic the entry path way of bacteria by penetrating the cells into phagosomes and lysomes. These nano particles when administrated intra venously they rapidly accumulate in spleen and liver which are main organ of reticuloendothelial system associated infection.

e.g.- Ampicillin loaded polyhexylc yanoacrylate (PIHCA)-Nano particles were prepared and was tested against salmonellosis in mice[8]

Nano particles in cancer treatment

The most encouraging application of nano particles is their fruitful achievements in chemotherapy. The drug targeting to tumour tissue, the "stealth" behaviour using polyoxyethylene polymer has successfully increased the extravasation[8]

e.g.- Aclacinomycin A in polyisobutylcyanaacrylate nano particles.

For gene carting

DNA is produced cheaply and has state of art storage and handling properties. However there are various problems affiliated with the carting of polynucleotides. The major section is ensuring that integrity of polynucleotide during the carting at target site. This therapy can be used for bone healing using PLGA Nano particles containing genes like bone morphogenic protein[8].

Tissue rejuvenation

Tissue rejuvenation can be done with the help of iron oxide. Now this can be done using two techniques:

1. Welding
2. Soldering.

Welding includes separating the two tissues or moving them apart and then heating them so that they could get tightly bound to each other.

Whereas in soldering the polymer coated nanoparticles are placed at the joints present in the tissue thereby making strong bonds between them.

Gold and silver nanoparticles are widely used for this technique as they absorb higher amount of light and this absorbed light is used for protein entanglement which helps to improve the binding of the tissue. Stem cells that are bounded to Gold nanoparticles are widely used and can be proved to be useful in regeneration and rejuvenation of the cells[8].

For diagnostic and bio-imaging purpose

Techniques like Ultrasound Imaging, Magentic Resonance Imaging, Optical Imaging, Positron Emission Tomography are being used widely for *in-vivo* and *in-vitro* drug release profile. There are two kinds of nanoparticles available for imaging purpose:

1. Luminescent Nano probes- used for optical imaging.
2. Magnetic nanoparticles- used for magnetic resonance imaging (MRI).

Here due to technological development dual modes can also be used that is optical imaging and MRI can be done all together. Nanobots are labelled with nanoparticles and then they help to recognize the content of blood[8].

Thrombolysis

Nanobubbles when combined with ultrasound technique are widely used for removing clots or emboli and thereby reducing the chances of stroke

and reducing the costs of angiography and angioplasty[12].

Vaccine adjuvant

The vaccine developed using nano particles are basically matrix entrapped and surface absorbed.

Eg: polymethylmethacrylate nano particles having influenza antigen helps to induce antibody response. Reducing the size and raising the hydrophobicity causes the enhancement in the adjuvant effect[8].

NANO PARTICLES IN VARIOUS ORGANS

Pulmonary drug delivery system

Lungs targeting has been done because of its prime advantage i.e the elimination of the first pass effect. Solid lipid nanoparticles and liposomal formulations are mostly preferred for delivery of insoluble drug particles to the target site. Due to the nano size of the particle and the larger surface area of the lungs the effect or the absorption of the drug is directly increased due to larger surface area and thereby increasing the potential action. The use of nebuliser and focusing effect of the stream must be enhanced so as to deliver the nanoparticle in sufficient amount at a faster rate[11].

Eg. Beclomethasone - Anti asthmatic / Anti-inflammatory drug is formulated as lipid nanoparticles.

Gastrointestinal drug delivery system

Use of nanoparticles for drug carting to the GI tract has been under investigation. Two basic mechanism are used in this kind of drug carting they are:[4]

1. Use of specific binding ligands.
2. Use of nonspecific adsorption.

Eg. The absorption of vitamin B12 is done by using specific binding ligands that directly binds to M-receptors present in the stomach and gut lining.

Ocular drug delivery system

The ophthalmic drug delivery system are mainly used for the glaucoma therapy. The drug used in this therapy are cholinergic agonist like pilocarpine. Pilocarpine having short elimination half life in eye drop formulation (due to lacrimal secretion) can be extended using nanoparticle system[11].

Eg. Polyalkylcyanoacrylate nanoparticles, Albumin nanoparticles.

They also can be used against inflamed eyes.

Intra-arterial drug delivery system

Advantages of the intra-arterial nanoparticles system are subcellular size, good suspendibility, uniform dispersion, target specific and ease of penetration without causing trauma. Intra-arterial interventional procedure like angioplasty, atherectomy causes RESTENOSIS to prevent this or treat this therapeutic agents must be present at the site of action rather than whole systemic administration[11].

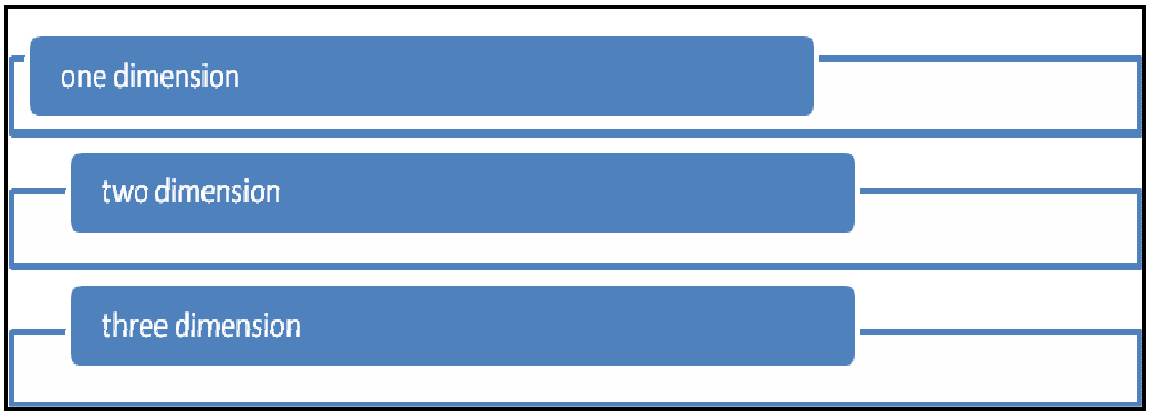
Eg. Dexamthasone and heparin were formulated with prolonged retention in the arteries and thereby preventing restenosis.

Lymph target drug delivery system

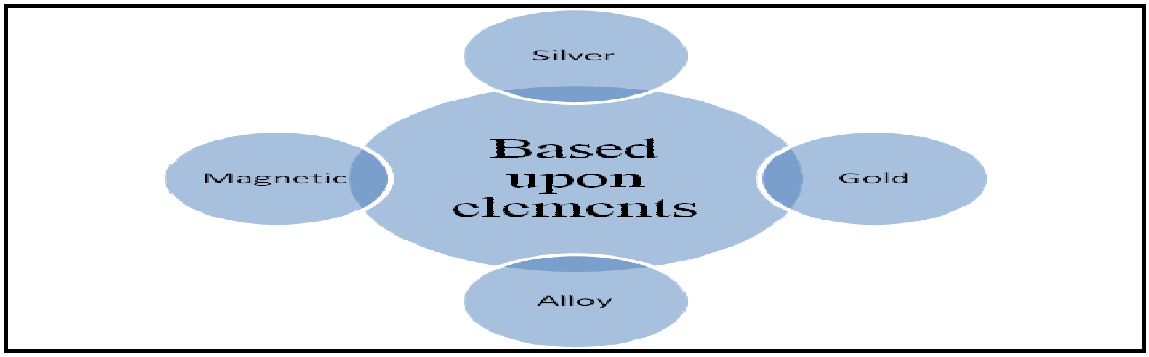
Major application is for prevention of metastasis of tumour cells accumulating in the lymph node. The major objective of carting the drug into lymph node is localization of diagnostic agent to the lymph node and lymph vessels[11].

Eg. Polyalkylcyanoacrylate nanoparticles having anticancer drug against tumour in peritoneal cavity.

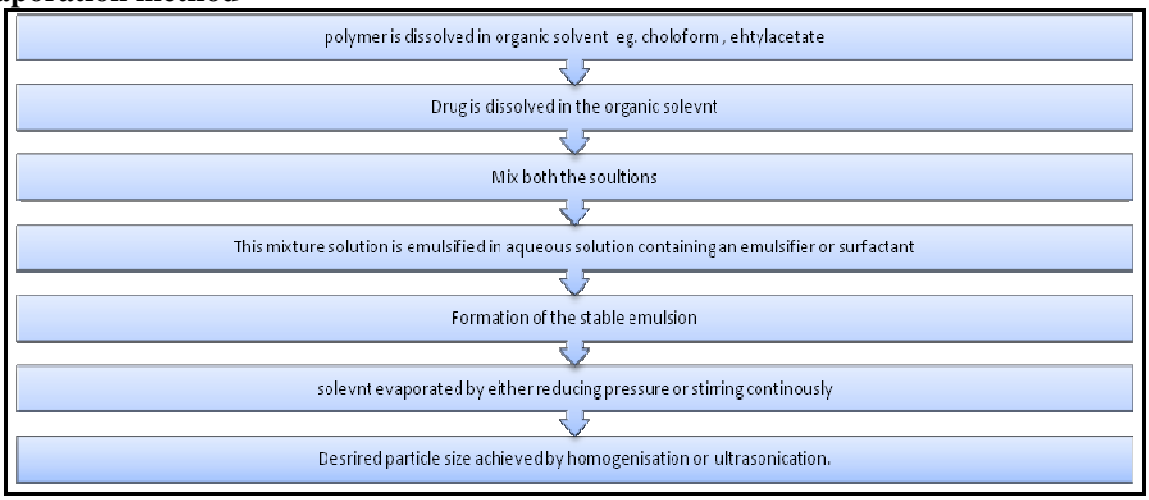
Based upon dimensions

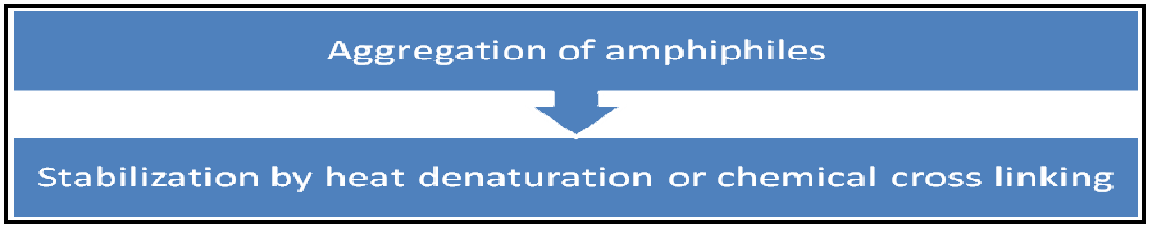


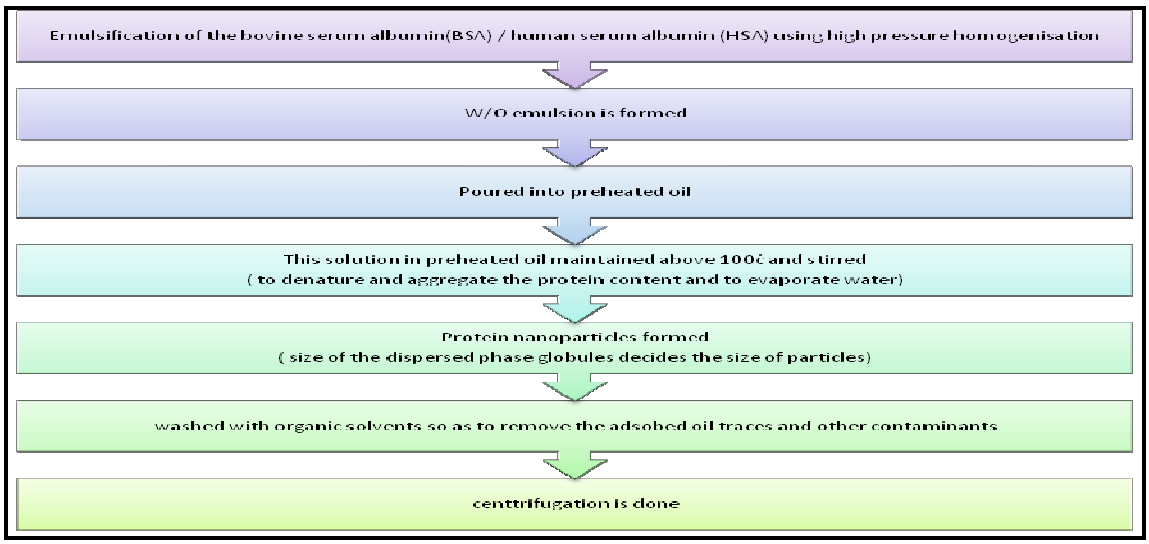
Based upon elements used

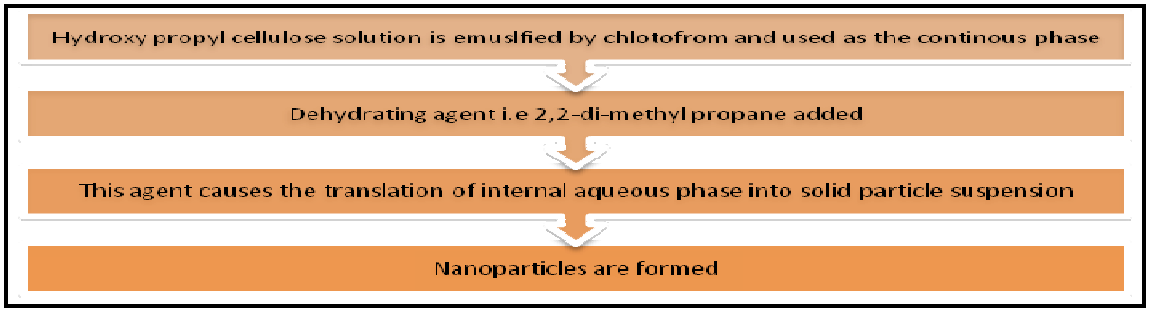


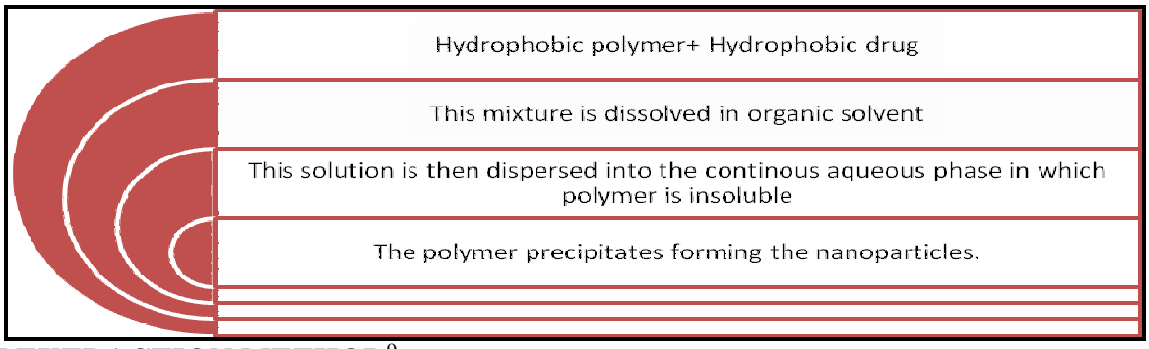
Solvent evaporation method



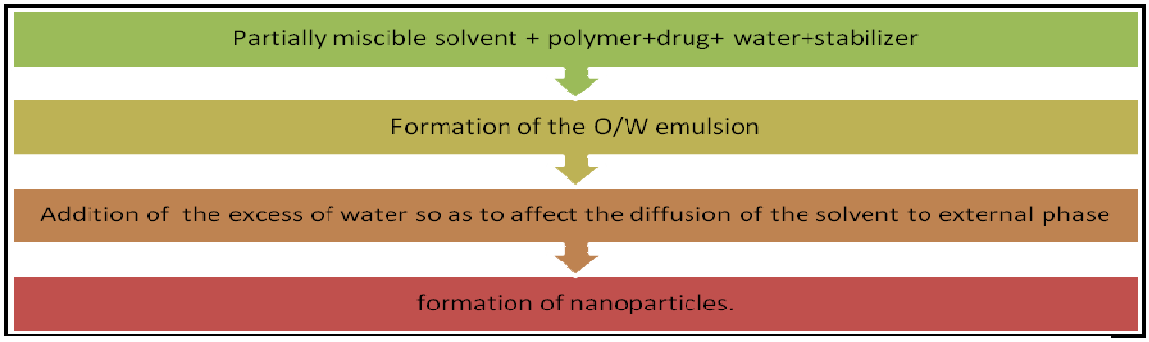






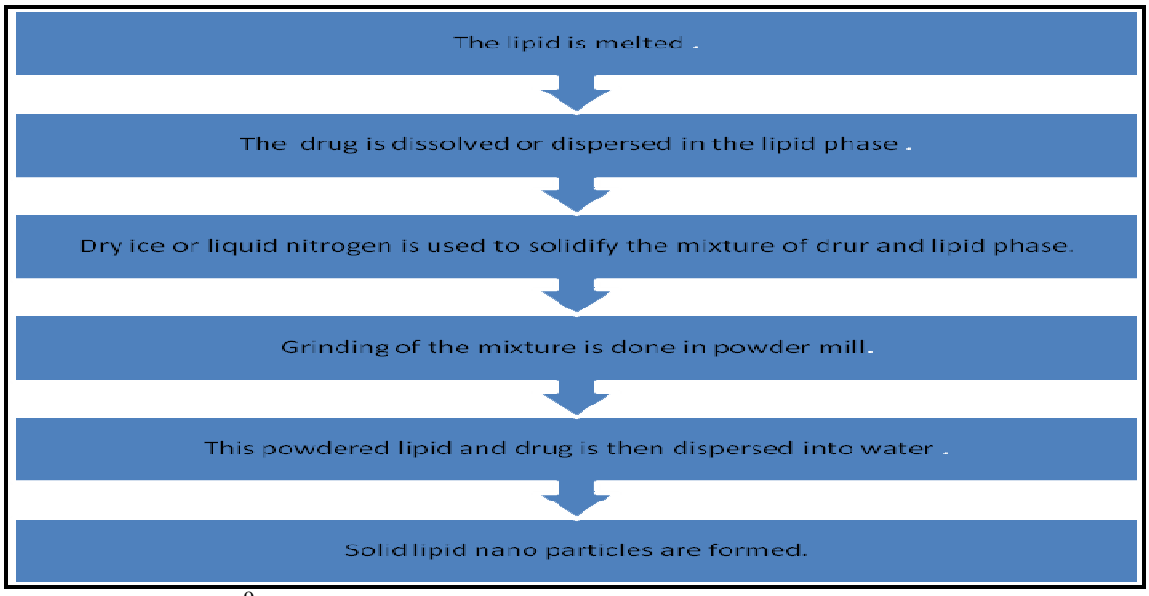


SOLVENT EXTRACTION METHOD[9]

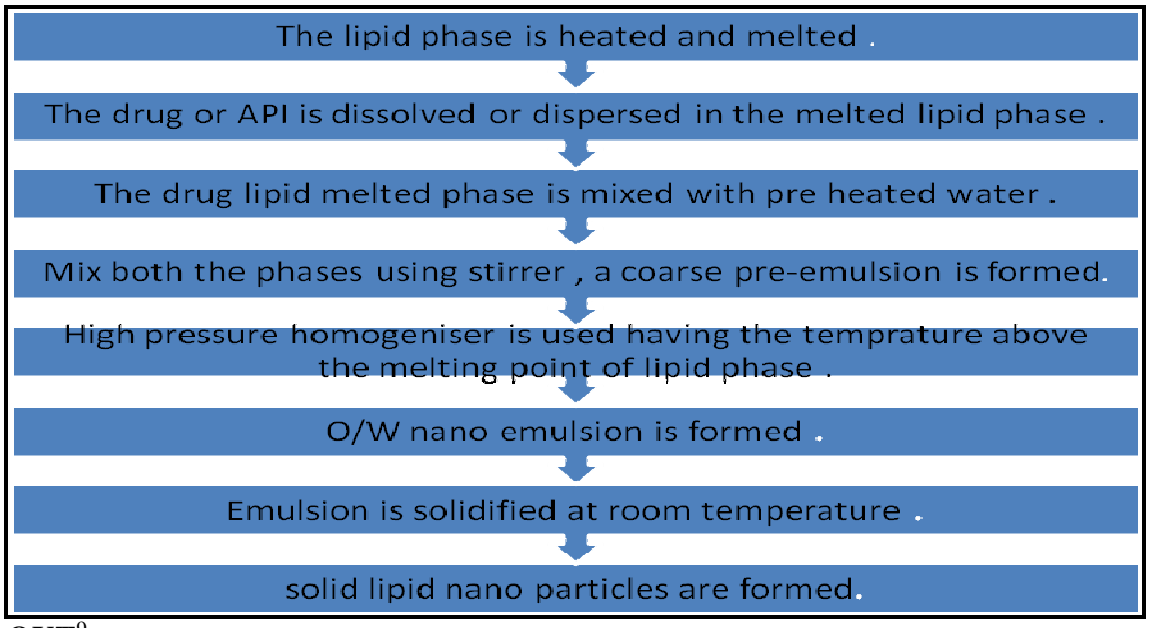


Eg; poly (lactic-*co*-glycolic acid) nano particles have been synthesized with bovineserum albumin

COLD HOMOGENISATION[9]

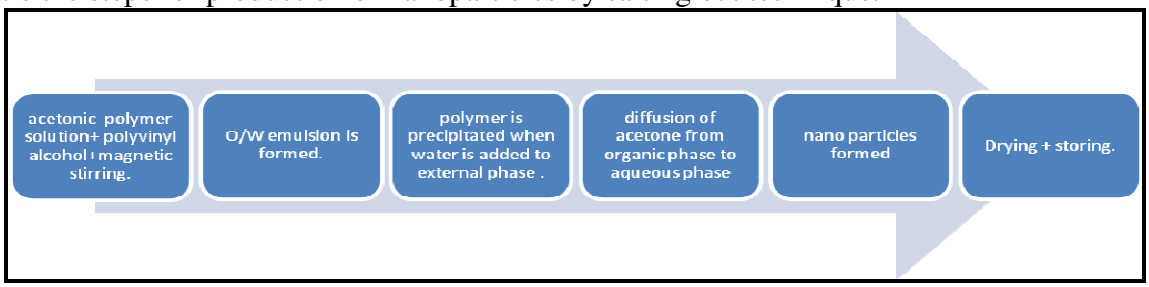


HOT HOMOGENISATION[9]



SALTING OUT[9]

Following are the steps for production of nanoparticles by salting out technique.



CONCLUSION

The customary dosage form are been used for a while and there is an urge to develop modernistic drug delivery system that would vow new and advanced ways for carting the drug in systemic circulation. The properties of many conventional materials including the drugs and various other active ingredients changes when they are converted or their size is been reduced to Nano scale. There is an enhancement in the activity due to increased surface area that would directly increase the absorption of the drug and hence enhanced bioavailability can be achieved. Nanoparticles are the leading edge in the drug delivery system. Nano systems with their altered surface properties help to achieve the targeted site or organ. Various kinds of drugs can be made into nanoparticles and hence depending upon the kind of drug formulation can be made that will have high effectiveness. Nanoparticles due to their site specificity and enhanced solubility profile is an area of intense research and scientific interest .Various characterization tools are been available which would help the individual to study their size, density, electrophoretic property, molecular property, surface area, entrapment efficiency, etc. Scientist have extensively studied and developed variety of methods for production of nanoparticles depending upon the characteristics of the active pharmaceutical ingredient and thereby helping the world to utilize their findings for a better cause. Choice of Method of preparation depends upon size range, solubility, release characteristics etc. In modern day technology nanoparticles will prove or demonstrate its effectiveness and become the part of esteemed inventions. Nanoparticles find a way in both therapeutic as well as the cosmetic industries. Nano technology is been used for diagnostic, mitigation, care and preventive purposes. Distinct route of administrations are being used for the delivery of the nanoparticles to the intentional site. Use of these particles for gene transport, cancer treatment, ocular disease, pulmonary disease, tissue rejuvenation, bio-imaging, treatment for thrombosis, vaccine adjuvant, gastrointestinal disorders, lymphatic diseases, skin care cosmetics etc. Have been increasing the number of advantages day by day.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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