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NANOPARTICLES: A NEW APPROACH

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ABSTRACT

The application of nanotechnology in pharmaceutical industries has received great attention from last decade. A lot of research work is going on in this field due to its safety, efficacy and better patient compliance. Different production methods have been developed for nanoparticles and most of the methods use two basic steps; emulsification and size reduction to Nano size. Homogenization techniques are most frequently employed using hot and cold homogenization or ultra-sonication for the production. Few methods based on emulsification are also applied used earlier for polymeric nanoparticle production. Hot high pressure homogenization and ultra-sonication are most commonly used method with scale up workability but costly equipment is biggest drawback. Other methods used to produce lipid nanoparticles are possible in a laboratory setup with no expensive equipments are needed but scale up is still a problem with such method along with regulatory problems associated with high surfactants concentrations in these formulations. This review focus on different methods used for lipid nanoparticles production with their procedure, advantages and disadvantages associated with them.

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INTRODUCTION

Nanoparticles are sub- nanosized colloidal structures composed of synthetic and semi synthetic polymers. The continual quest and manoeuvering towards physical stability improvisation of liposomes resulted into development solid core nanoparticles in eighties as an alternative drug carier. The first reported nanoparticles based on non-biodegradable polymeric systems (polyacrylamide, polymethyl, polystyrene etc.) The colloidal carriers based on biodegradable and biocompatible polymeric systems have largely influenced the controlled and targeted drug delivery concepts .It was realized that the nanoparticles loaded bio-actives could not only deliver drug(s) to specific organs within the body but delivery rate in addition could be controlled as being bystanders ,burst , controlled, pulsatile or modulated.(1)Nanoparticles size within the range of 10-1000nm.

Solid lipid nanoparticles were developed in early 1990s as an alternative to other traditional colloidal carriers like liposomes, polymeric nanoparticles and emulsions as they have advantages like controlled drug release and targeted drug delivery with increased stability. Lipid nanoparticles with a solid matrix, such as solid lipid nanoparticles (SLNS), are an alternative nanoparticulate carrier system to polymeric nanoparticles, liposomes and o/w emulsions. Aqueous SLNS dispersions are composed of a lipid which is solid both at body and room temperature, being stabilized by a suitable surfactant.(2,4 With regard to developing commercial products for the therapy, SLNs possess distinct advantages compared to other carriers, e.g., polymeric nanoparticles. Especially for topical and oral administration, all lipids can be used as matrix material, which are currently in use for creams, ointments, tablets, and capsule formulations including the long list of different surfactants/stabilizers employed in these traditional formulations. Thus, there is no problem with the regulatory accepted status of excipients **.** SLNS also enjoy more advantages over other colloidal delivery systems with regard to biocompatibility and scale up, also the release of drugs from SLNS can be modulated in order to optimize their blood levels. These features together make lipid nanoparticles an interesting carrier system for optimized oral delivery of drugs. Reports on the use of SLNS for avoiding first pass metabolism of drugs are scanty [,5,6].

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agent in order to achieve the site specific action of the drug at the therapeutically active rate and dose regimen. For instance ,they help to increase the stability of drug/proteins and possess useful controlled release properties. Nanoparticles are defined as particulate dispersions or solid particles with a size in the entrapped ,encapsulated or attached to a nanoparticles matrix .depending upon method of preparation ,nanoparticles, nanosperes or nanocapsules can be obtained.nanocapsule are system in which the drug is confined to a cavity surrounded by a unique polymer membrane, while Nano spheres are matrix systems in which the drug is physically and uniformly dispersed . Biodegradable polymeric nanoparticles ,particularly those coated with hydrophilic polymer such as poly ethylene glycol (PEG) known as long-circulating particles ,have been used as potential drug delivery devices of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy ,and their ability to deliver proteins, peptides and genes[8,9,10,12).

Advantages of Nanoparticles

- Particle size and surface characteristics of nanoparticle easily manipulated to achieve both passive and active drug targeting after parenteral administration.
- They control and sustain release of the drug during the transportation and at the site of localization.
- They increase in drug therapeutic efficacy and reduction in side effects.
- Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.
- Drug loading relatively high and drug can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
- The system can be use for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

Disadvantages of nanoparticle

- Their small size and large surface area can lead to particle-particle aggregation, making handling of nanoparticles difficult in liquid and dry forms.
- In addition, small particles size large surface area readily result in limited drug loading and burst release.

APPLICATIONS OF SLNs:

- SLNS for Parenteral Application.
- SLNS for Nasal Application.
- SLNS for Ocular Application.
- SLNS for Respiratory Application.
- SLNS for Rectal Application.
- SLNS for Topical application.
- SLNS for potential agriculture application.
- SLNS in Cancer chemotherapy.
- Oral SLNS in antitubercular chemotherapy

Methods of Preparation of Nanoparticles

Different methods of SLNS/NLC formulation are described here-

1. Homogenization techniques
i. Hot high pressure homogenization technique
ii. Cold high pressure homogenization technique
iii. Melt emulsification ultrasound (ultra sonication) homogenization technique (High shear homogenization and/or ultrasound technique)
2. Microemulsion technique
3. Emulsification-solvent evaporation technique
4. Solvent displacement or injection technique
5. Emulsification-solvent diffusion technique
6. Phase inversion technique
7. Film ultrasonication dispersion technique
8. Multiple emulsion technique
9 .Membrane contactor technique

S.No	Method	Compounds loaded	Application	Reference
1	Melt emulsification ultrasonication	KetoprofenNaproxen	Topical	6
2	Melt emulsification	Progesterone	-	7
3	Solvent Diffusion	Progesterone	-	7
4	HPH	Ratinol	Topical	8
5	Solvent Diffusion	Valproic Acid	Nasal to Brain	9
6	Microemulsion	Celecoxib	Topical	10
7	Melt emulsification ultrasonication	Nitrendipine	Oral(SLP)	11
8	Hot HPH	Clotrimazole	Topical	12
9	Microemulsion	Minoxidil	Topical	13
10	Hot HPH	Flurbiprofen	Transdermal	15
11	Solvent Diffusion	Clobetasol propionate	-	16-17
12	Hot HPH	Nile Red	Topical	
13	Melt emulsification ultrasonication	Tiolated PEG stearate	Ocular(NLC)	18
14	Solvent Diffusion	Tretinoin	Topical (SLNS)	19
15	Microemulsion	Tretinoin	Topical (S +-LNS)	20
16	Hot HPH	Coenzyme Q10	Topical (NLC)	21
17	Microemulsion	Pepsin A, Pancreatin, Insulin	Oral (SLNS)	24-25

High Pressure Homogenization Technique

High pressure homogenization is a well established technology for the production of emulsions for parenteral nutrition, such as Intralipid and Lipofundin, and it can also be adapted for scale-up production of lipid nanoparticles. The preparation of lipid nanoparticles applying the high pressure homogenization techniques has been developed and practiced extensively. Hot as well as cold homogenization processes can be used for the preparation of lipid nanoparticles. In both processes the active compound is dissolved or dispersed in the melted lipid prior to the high pressure homogenization. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (having size of few microns). Particles formed are in submicronrange due to very high shear stress and cavitation forces generated in the homogenizer. Large scale production of lipid nanoparticles are possible with this technique with regulatory acceptance as production lines are very much in use for manufacturing of parenteral lipid emulsions since long period. This is the main advantage of this method as compared with other available technique but high energy conditions of temperature and pressure questioned its applicability in certain conditions.

Hot High Pressure Homogenization Technique

Melting of lipid
↓
Dissolution of the drug in the melted lipid
↓
Mixing of the preheated dispersion medium and the drug lipid melt
↓
Premix using a stirrer to form a coarse pre-emulsion
↓
High-pressure homogenization at a temperature above the lipid melting point
↓
O/W – Nanoemulsion
↓
Solidification of the nanoemulsion by cooling down to room temperature to form SLNS
↓
SLNS prepared using hot homogenization technique

Cold High Pressure Homogenization Technique

Melting of the lipid
↓
Dissolution/solubilisation of the drug in the melted lipid
↓
Solidification of the drug loaded lipid in liquid nitrogen or dry ice
↓
Dispersion of the lipid in the cold aqueous dispersion medium
↓
Homogenization at room temperature or below
↓
Solid lipid nanoparticles

Microemulsion Technique

This method is adapted by different research groups since the early start of lipid nanoparticle formulation . Nanoemulsion are formed when excess of water is added during cooling phase to a Microemulsion, the systems breaks converting it into nanoemulsion which recrystallize internal oil or lipid phase forming particles. Briefly, the melted lipid containing drug mixed with surfactant, cosurfactant containing aqueous phase prepared at the same temperature as of the lipid in such a ratio to form . The hot Microemulsion is diluted with excess of cold water. Sudden reduction in its temperature causes breaking ,converting it to a nanoemulsion .which when recrystallized forms lipid particles.

Advantages

No need of specialized equipment ,energy for the process is not required while scalup production of lipid nanoparticles can be achieve

Disadvantages-

The process demands more time as the dilution of the particles suspension is high concentrations of raise regulatory concern, removal of surfactant by ultra filtration or dialysis takes a lot of time and are costly.

Emulsification-Solvent Evaporation Technique

This method is at its ease when incorporation of highly suitable for the thermolabile drug is needed, due to avoidance of heat during its process. But solvent residuals in the final dispersion can create problems due to regulatory concerns. Limited solubility of lipids in organic material demands ultra filtration or evaporation to raise concentration .On the other hand small particle a size around the 100nm width can be achieved through this process

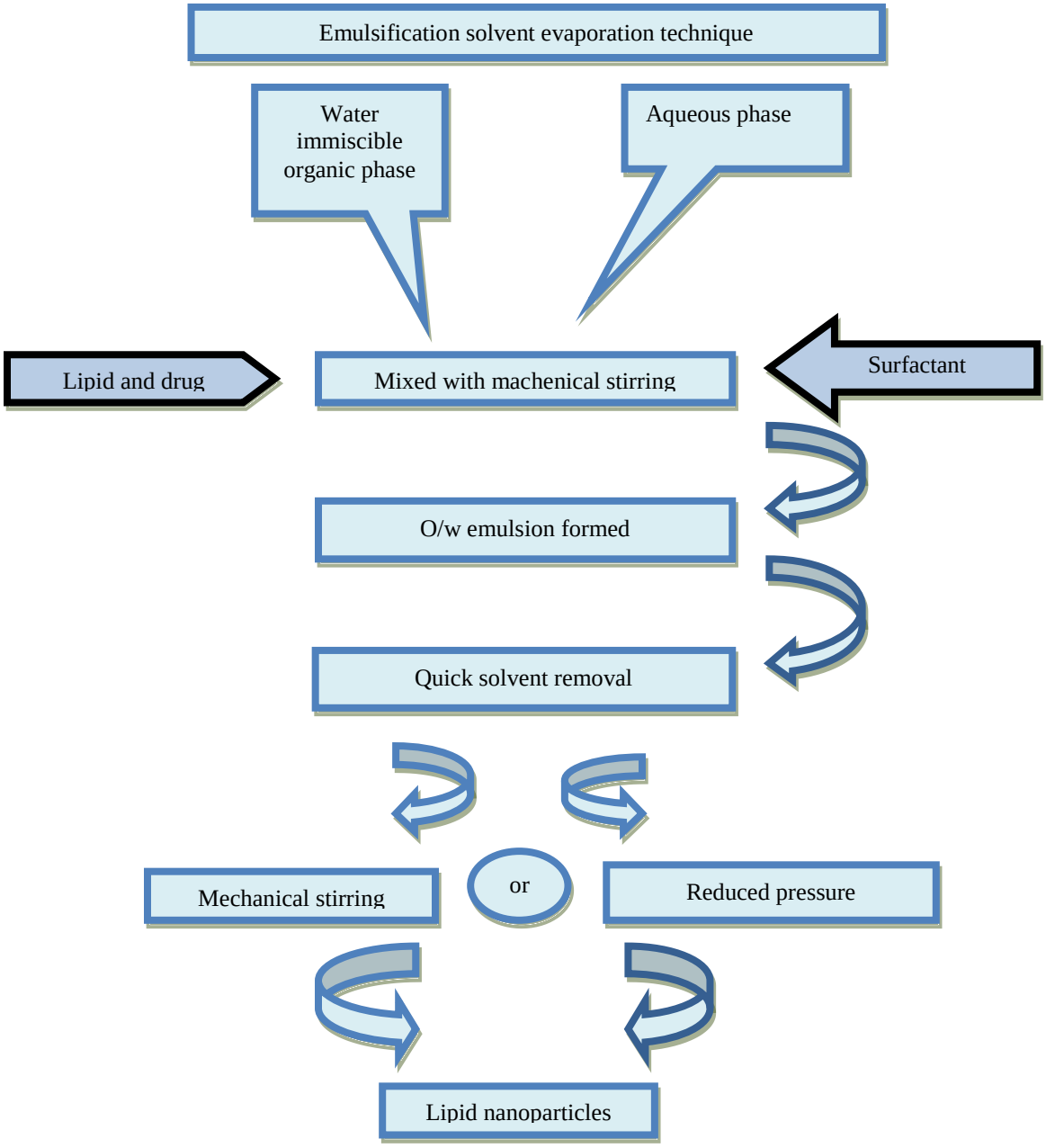
Solvent Displacement or Injection Technique

This technique was first illustrate for the formation of liposomes and polymeric nanoparticles from pre-formed polymers. Recently, this technique has also beings used to prepare lipid nanoparticles. The basis of this process is to dissolve is a lipid precipitation in a solution the process fallow s a rapid injection of mixture lipid in a water miscible solvent into a aqueous phase. The process result in the o/w emulsion formation by injecting organic phase into aqueous phase under magnetic stirring.

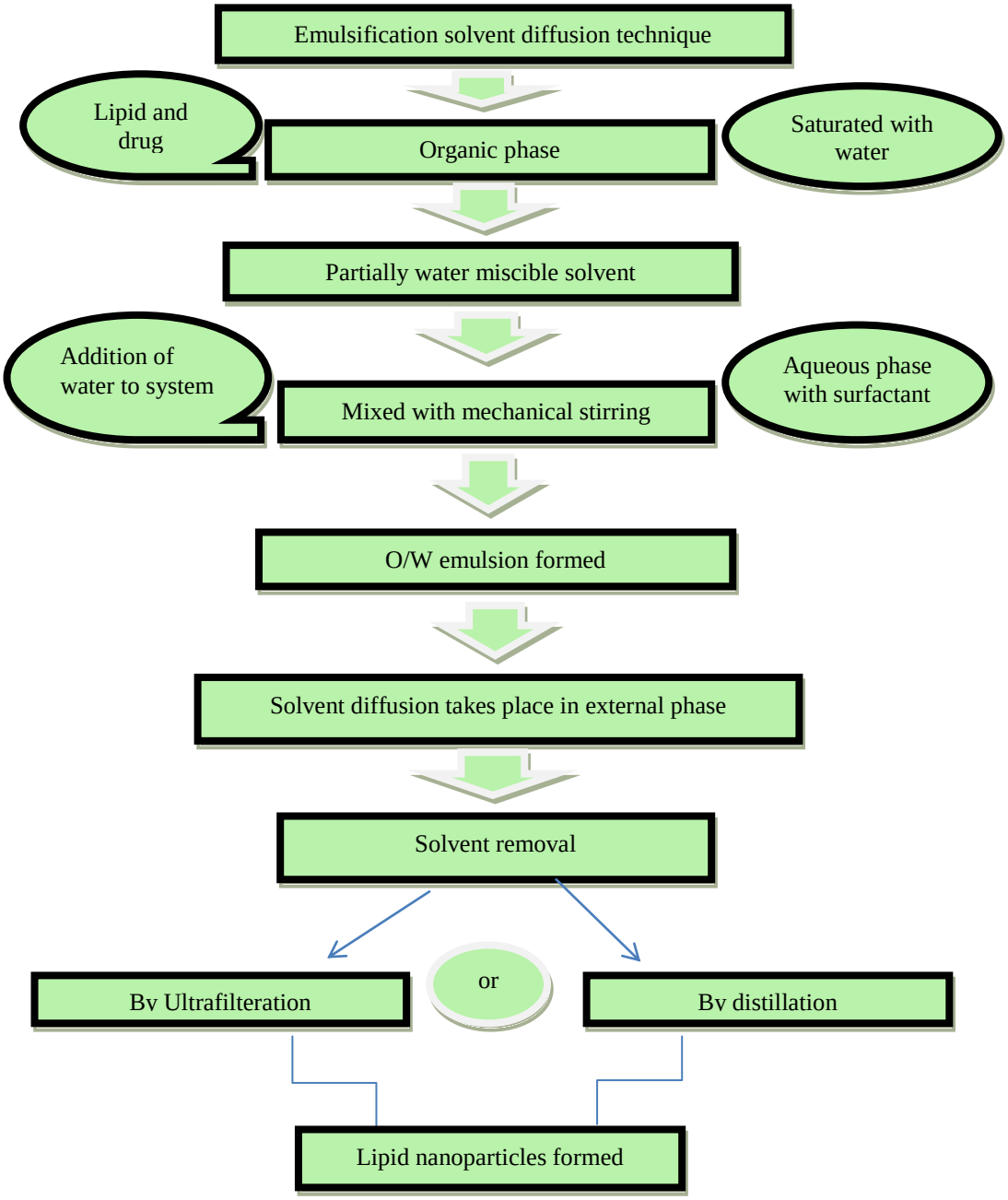
The oil phase is a semi polar water miscible solvent such as methanol ethanol or acetone ,the active compound lipid is dissolved in this phase .Aqueous phase consist of surfactant .In this procedure solvent displacement of diffusion takes place giving fresh lipid precipitate. Lipid nanoparticles are formed after total evaporation of a water miscible organic solvent, hence water removal is necessary and can be performed by distillation. The result particle size is dependent on the distillation condition such as amount to injected ,concentration of lipid and solvent.

This method clearly overpower the existing methods such as the use of organic solvents, although they are pharmaceutically accepted and used. Clearly traditional process are not required as the handling and less time consuming methods with ease equipments are discovered ,Disadvantage clearly evident in using organic solvent .Although used frequently in formulation.

Schematic representation of the emulsification- solvent evaporation technique for the production of lipid nanoparticles.



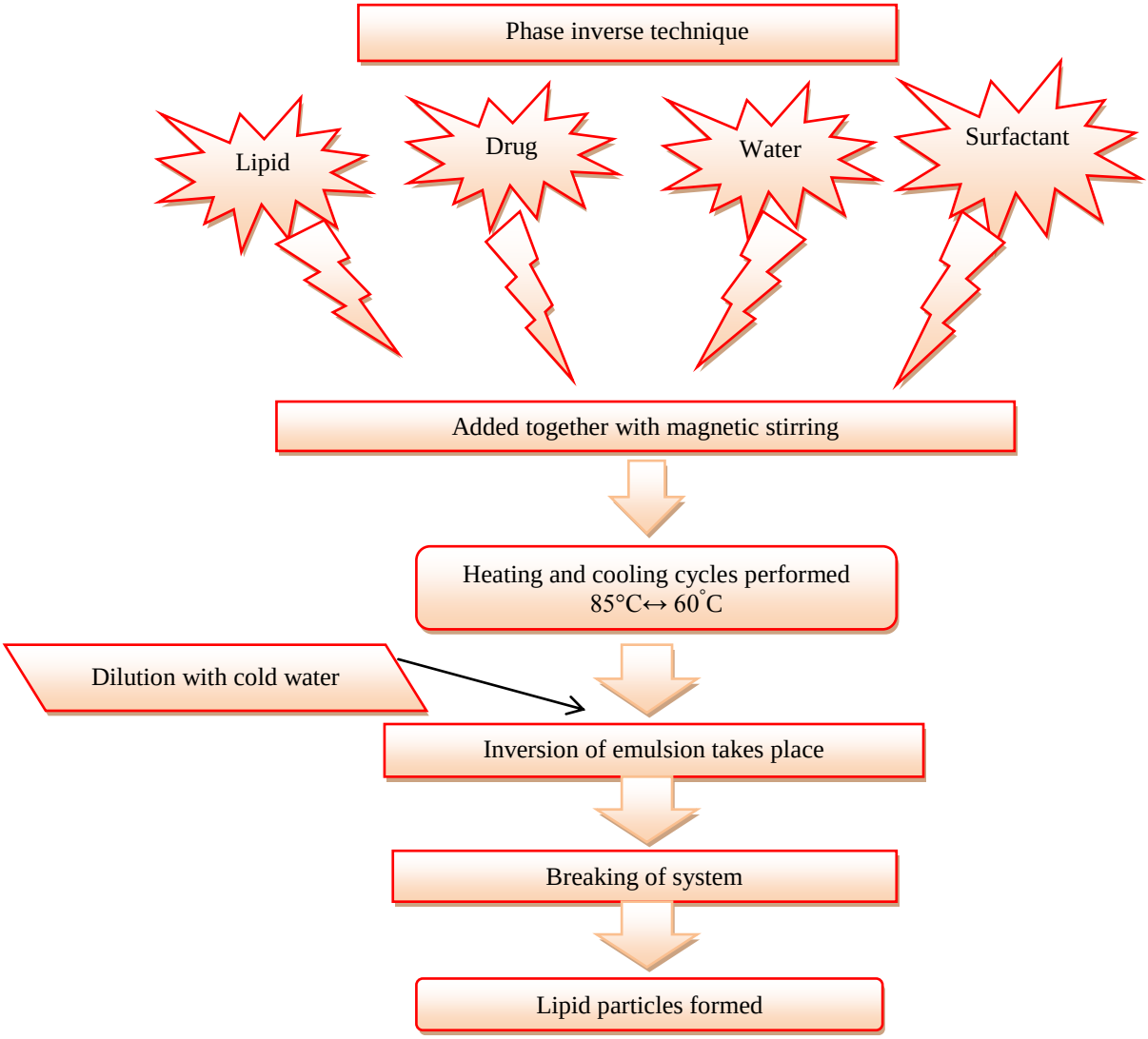
Schematic representation of the emulsification-solvent diffusion technique for the production of lipid nanoparticles



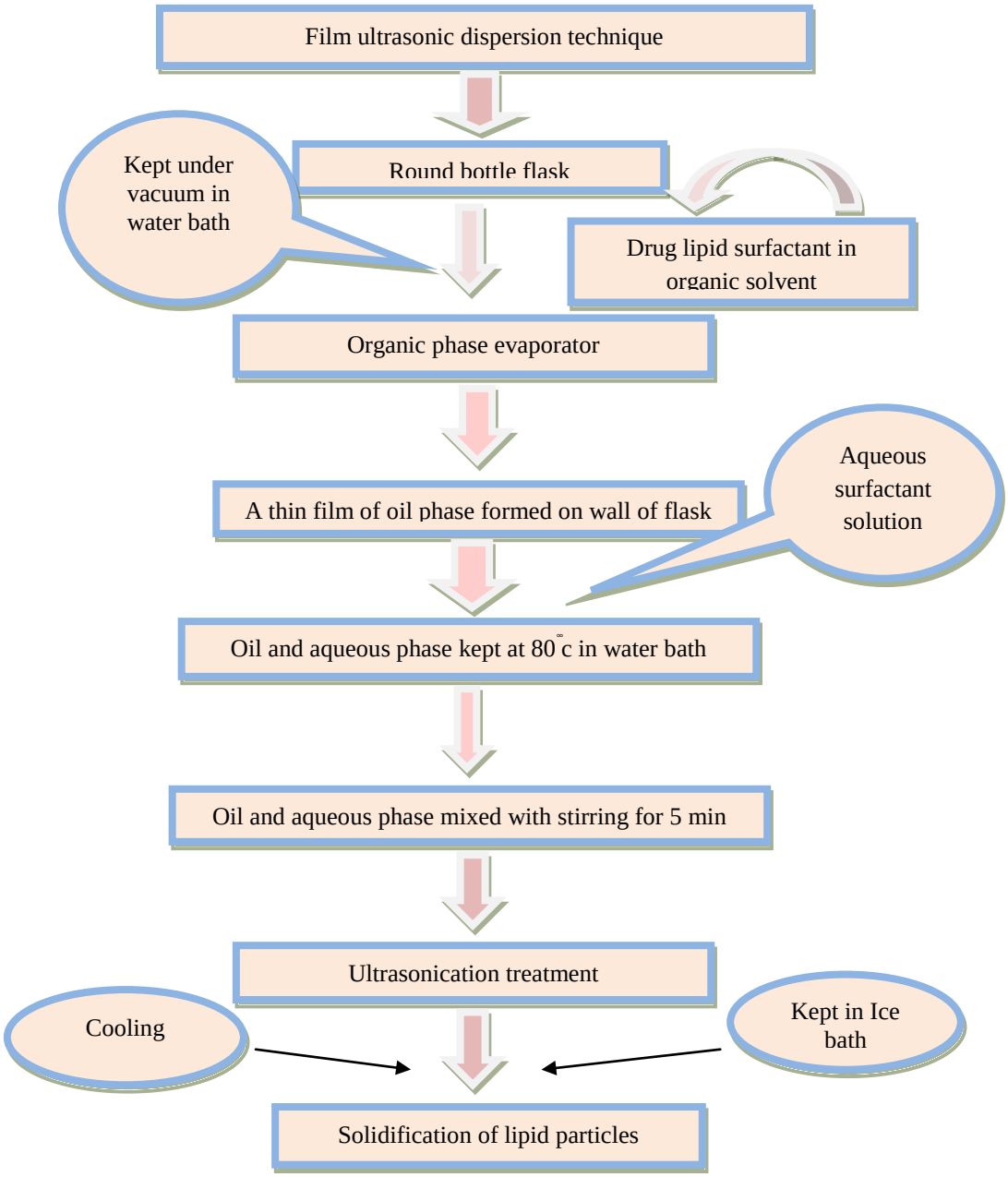
Phase Inversion Technique

This technique has the advantage of the incorporation of thermolabile drugs as thermal degradation is not expected to occur as it has very short heating period. In addition, this technique also avoids the use of organic solvents. Different formulation components proportion influences the size parameters of the obtained particles thus need to be optimized.

Schematic representation of the phase inversion-based technique for the production of lipid nanoparticles.



Schematic representation of the film ultrasonication dispersion technique for the production of lipid



The advantages of this method are use of common lab equipment. Its a hard to range broader particle size distribution in micrometer hence it's a biggest disadvantage of this method .Also it affects physical stability of an element, leads to particle growth when stored. The mental contaminates during ultrasonication, major problem in this process.

Multiple Emulsion Technique

Double emulsion method, w/o/w also known as solvent emulsification-evaporation method. It applied emulsification followed by solvent evaporation for the preparation of hydrophilic drug SLNS. The drug is encapsulated with a stabilizer to during solvent evaporation process to prevent drug from partitioning.

The above process has its limitation and disadvantage as described in the double emulsion process, but it can be applied for preparation of hydrophilic molecules such as peptide and proteins.

Membrane Contactor Technique

In this method work on simple procedure of lipid passing from pores of a membrane with pressure keeping system above the melting temperature of lipid. Pressed the lipid phase through the membrane pores, at a temperature above the melting point of the lipid, lead to formation of small droplets. On the other hand aqueous phase is circulated inside the membrane module, and droplets formed at the pore outlets are sweeps along with this aqueous phase. SLNS are formed by the cooling of the preparation to room temperature. The velocity of aqueous phase flow, temperature of lipid and aqueous phase, membrane pore size and lipid phase pressure is the process variables which affect size and lipid flux of SLNS.

The advantages of this method are its simple methodology and equipment, SLNS size can be control by an appropriate choice of process parameters, and its scaling-up abilities.

Supercritical PGSS Technique (Particle from gas saturated solution)

This is a nearly new technique for lipid nanoparticle production .This technique based on the use of supercritical carbon dioxide (scCO2). It has been described as a single step method capable of encapsulating drugs into organic solvent-free lipid particles. Carbon dioxide (99.99%) is a good choice as a solvent for this method.

In this method lipid is melted and drug is subsequently dissolved or dispersed in it. Then scCO2 cone shaped nozzle upon pressure release. This event leads to the atomization of the melt, causes evaporation of the gas and the Precipitation of the lipid nanoparticles.

The advantages of this method such as one step procedure, no need of organic solvent and low processing temperature conditions (lower melting temperatures of the lipids obtained from the dissolution of CO2 in the bulk mixture). Disadvantages include frequent nozzle blockage with hydrophilic drug and machinery is cost.

Various nanoparticles based delivery system with their therapeutic and digaonotic uses in cancer therapy.

Nanoparticles based delivery systems	Therapeutic and dioganotic uses
Liposomes	Controlled and targeted drug delivery;Targeted gene delivery
Nanoshells	Tumor targeted
Fullerene based derivatives	As targeting and imaging agent
Carbon nanotube	Drug gene and DNA delivery;Tumor targeting
Dendrimers	Targeted drug delivery
Q uantum dots	As targeteing and imagin agent
Gold nanoparticles	Targeted delivery and imaging agent
Solid lipid nanoparticles	Controlled and targeted drug delivery
Nanowires	As targeteing and imagin agent
Paramagnetic nanoparticle	As targeteing and imagin agent

Recent advancements in nanotechnology

Nanotechnology was first developed in 1959 as a way of manipulating matter at the atomic and molecular level ,it wasn`t until the early 2000s that it really began to flourish .Today ,nanotechnology is one of the most innovative ,cutting-edge areas of scientific study and it continues to advance at staggering rates.

Health: Drug delivery

Today, cancer patients have three treatment option: surgery, chemotherapy or radiation .While the methods vary, the goal for the three treatment options is the same: eradicate the targeted cancer cells with minimal damage to normal tissue.

According to the National cancer Institute, all three methods risk damage to normal tissue or incomplete eradication of the cancer." For example during chemotherapy, cytotoxic drugs are release to kill cancerous cells, but also kill healthy cells during the process. Result in this process can side effects, including hair loss, pain, nausea, nervous system effects, fatigue and appetite loss. Treatment and reaction vary from patient to patient, but these side effects are frequent and common in most cancer patient. Nanoparticles for chemotherapy drug carriers have made some of the greatest advancements in cancer treatment. By nanocarriers using to treat patients, treatments can focus on targeting cancerous cells and limit the damage to healthy cells.

Diseases: Early Detection

Applications of nanotechnology for early disease detection are gaining a significant amount of attention. Essentially exploring the use of nanoparticles to raise a warning or "biomarker" if a cancerous tumor or other disease is found. Since these nanoparticles carry several peptides, in theory, it should send numerous biomarkers to indicate that a disease is present. Early detection of disease like Alzheizer`s and cancer allows treatments and potentially, a cure to being sooner.

Conflict of interests

To design and development of nanotechnology based system for the effective drug delivery the author thought that this cross section research carried out for the development of new formulation and evaluate them .So that author can extrapolate the data obtain by the evaluation of doublet formulation .This type of research studies in future should also being design with assistance in different area of drug delivery system .So that author design the interventional research for the effective drug delivery system.

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List of abreviations

1	SLN_S	Solid lipid nanoparticles
2	NLC	NLC-Nanostructured lipid carriers
3	HPH	high homogenization technique
4	PGSS	Particle from gas saturated solution
5	PEG	Poly ethylene glycol

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