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A Schematic Review on Solid Lipid Nanoparticles Targeting to Brain

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ABSTRACT

Targeting drug to brain is becoming a challenging task for inventors of advanced drug delivery systems. Because the blood brain barrier acts as a barricade for many chemical moieties to cross it for treating CNS disorders. Solid lipid nanoparticles (SLNs) are the effective lipid based colloidal carriers which were introduced as an alternative to the conventional carriers such as micro emulsions, liposomes, microparticles and nanoparticles based on synthetic polymers or natural macromolecules. SLNs were introduced to overcome problems of polymeric nanoparticles by putting forward physiological safe lipids in place of polymers to prepare lipid nanoparticles, a novel formulation technique came into light. An approach undertaken here is to focus on various production methods for preparation of SLNs.

Keywords: Introduction; Blood Brain Barrier; Colloidal Carriers; SLNs; Methods of preparation

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INTRODUCTION

Drug delivery to brain is a complicated phenomenon in which the blood brain barrier deprives the movement of many pharmaceutically active agents to the brain. Regarding to the inadequate combative research efforts have recently focused on the development of new strategies to more effectively deliver drug molecules to the CNS[1]. Serious CNS diseases, including depression, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, brain cancer, and cerebrovascular diseases have needs medication. Furthermore, the incidence of CNS disorders increases with age. As the proportion of people aged over 60 years keeps growing, neuropharmaceuticals will become more important in the future [2].Therefore, research is required to ameliorate delivery of CNS drugs across the blood-brain barrier.

Blood brain barrier

Blood brain barrier consists of mainly three components; endothelial cells, astrocytes and pericytes[3, 4]. Endothelial cells of blood brain barrier are having tight junctions between them. Astrocytes activity as a barrier is unknown for protecting the brain. Endothelial tight junctions do not permit the large molecules into brain. This drives the molecules to pass through the cell membranes of the endothelial cells. Cell membranes of endothelial cells are lipophilic in nature. So the chemical moieties with lipophilic properties can easily traverse the blood brain barrier.

Strategies for drug delivery to the brain

Several drugs do not have adequate physiochemical characteristics such as

- High lipid solubility,
- Low molecular size and
- Positive charge which are essential to succeed in traversing BBB.

Colloidal Drug Carriers

Colloidal carriers are particles ranging in size From 1 nm to 1000 nm. They consist of materials in which the active agents (drug or biological active material) is dissolved, entrapped, encapsulated, and or to which the active agent is adsorbed or attached. Modification of properties of these carriers such as particle size, particle rigidity and surface charge and surface hydrophobicities can lead to the development of suitable carrier systems. Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10-400 nm diameter show great promise as drug delivery systems. The goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the

microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and or mesogenic properties.

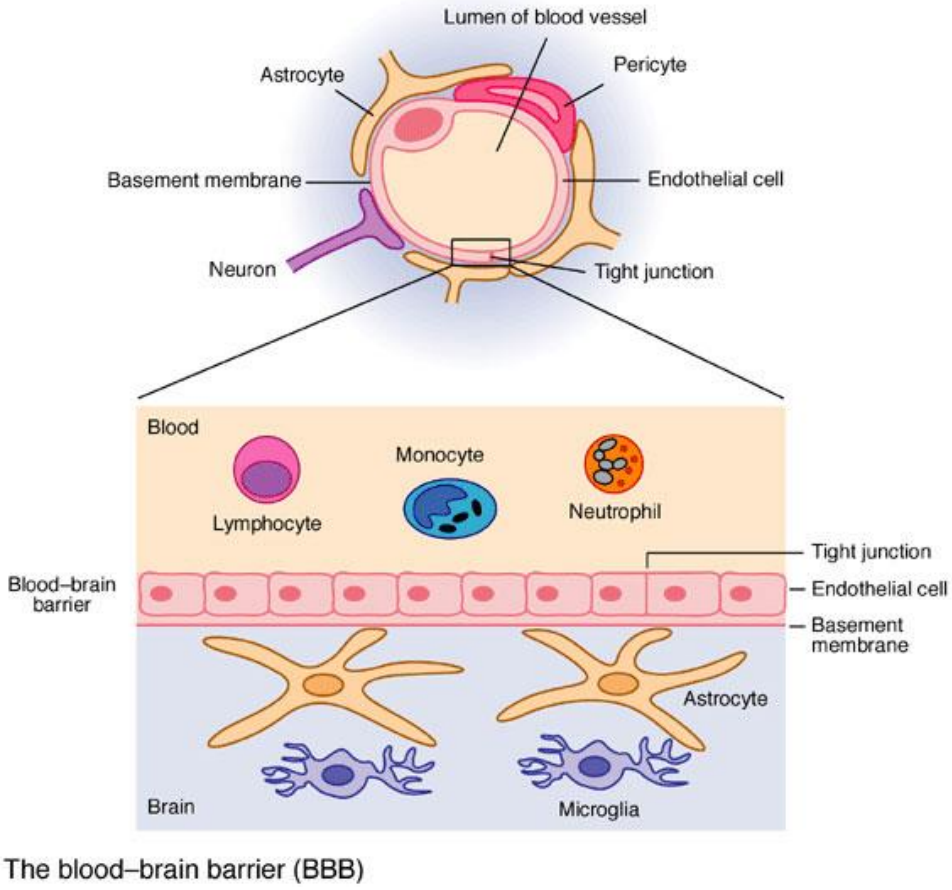

Figure 1: The blood-brain barrier.

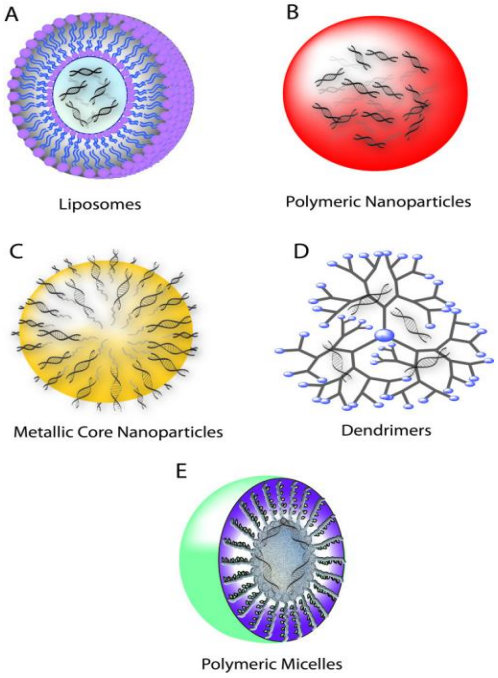

Figure 2: Colloidal drug carriers.

Solid Lipid Nanoparticles[19]

Solid lipid nanoparticles generally are spherical in shape and are comprised of a solid lipid core stabilized by a surfactant interfacial region with an average diameter between 10 to 1000 nm. Solid lipid nanoparticles can masquerade the blood brain barrier because they are highly lipophilic and they can entraps high amounts of lipophilic drug.

Table 1: List of drugs, lipids and surfactants used for the preparation of SLNs using different methods.

Drug	Lipids and surfactants used	Method	References
5-fluorouracil	Dynasan 114 and 118,Soya lecithin 30%	Solvent evaporation	24
Aceclofenac	Poloxamer188, Glyceryl behenate (Compritol888 ATO) and Tween 80	Solvent injection method	25
Artemether	Tripalmitin, Cremophor EL 0.25%w/w	Hot homogenization	26
Bromocriptine	Tristearin, Compritol 888 ATO	Hot homogenization	27
Cyclosporine	Glyceryl behenate (Compritol ATO 888) and lauroyl macrogolglycerides (Gelucire 44/14)	Emulsification-diffusion	28
Diazepam	Compritol ATO 888, Tween 80	Modified high-shear homogenization and ultrasound techniques	29
Dithranol	Tristearin, Tween 80	Hot homogenization	30
Domperidone	Glyceryl mono stearate, and soya lecithin	Hot homogenization	31
Doxorubicin	Capmul MCM C10, Solutol HS15	Solvent emulsification-diffusion	32
Flurbiprofen	Dynasan 114, Captex 355 EP/NF	Hot homogenization	33
Meloxicam	Geleol, Poloxamer 188	High shear homogenization	34
Mepivacaine	Tripalmitin, Poloxamer 188	Hot homogenization	35
Nisin	Imwitor 900, Poloxamer 188	High shear homogenization	36
Raloxifene hydrochloride	Compritol 888 ATO, Pluronic F68	Solvent emulsification/evaporation	37
Ramipril	Glyceryl monostearate and glyceryl monooleate, Tween 80, poloxamer 188, and span 20	Hot homogenization	38
Repaglinide	Tristearin, poloxamer 188	Microemulsion	39
Stavudine	dynasan 114, Solutol HS 15, Plurol Oleique CC 497, Poloxamer 188 Tween 80	High shear homogenization	40
Triamcinolone acetonide	Dynasan114, Gelusire50/13, Poloxamer188,	Solvent emulsification- solvent diffusion	41

Advantages of SLNs[18,20,21,22,23]:

Controlled and targeted release of the assimilated drug can be obtained

Increased scope of drug targeting can be achieved by coating with or attaching ligands to SLNs

Development of new formulation, which are safer

Prolonged circulation time

Good biocompatible

More sensible for higher drug loading

Improve the stability of bioactive compounds

Augment the bioavailability of entrapped pharmaceuticals

Better control over release kinetics of encapsulated compounds.

Application versatility

Lyophilisation feasible

Disadvantages of SLNs:

Particle growth and crystallization of drugs

Unreliable gelatin tendency

Unpredicted dynamics of lipid transitions

Drug expulsion from lipids

Table 2: Lipids and emulsifiers used for preparation of SLNs[20]

Lipids	Emulsifiers / coemulsifiers	Surfactants
Mineral oils	Soya lecithin	PEG-8 glyceryl caprylate/caprate (Labrasol)
Sucrose poly esters	Egg lecithin	PEG-32 glyceryl laurate (Gelucire 44/14)
Triglycerides	Phosphatidyl choline	PEG-32 glyceryl palmito stearate (Gelucire 50/13)
Tricaprin	Poloxamer 188, 182, 407, 908	Caprylic/Capric Glycerides (Acconon MC8-2, EP/NF)
Trilaurin	Tyloxapol	Polyoxyl 35 castor oil (Cremophor EL)
Trimyristin (Dynasan 114)	Polysorbate 20	d-Alpha-Tocopheryl Polyethylene Glycol-1000 Succinate (TPGS)
Tripalmitin	Polysorbate 60	Lecithin, Modified Lecithin
Tristearin(Dynasan 118)	Polysorbate 80	Sorbitan monolaurate (Span 20)
Diglycerides	Sodium cholate	Sorbitan monostearate (Span 60)
Fatty acids	Sodium glycocholate	Sorbitan monooleate (Span 80)
Waxes	Sodium taurocholate	Polyoxyethylene 20 sorbitan monolaurate (Tween 20)
Cyclic complexes	Sodium taurodeoxycholate	Polyoxyethylene 20 sorbitan monostearate (Tween 60)

Methods of Preparation of Solid Lipid Nanoparticles[18,20,21,23]:

High pressure homogenization

Hot homogenization

Cold homogenization

Ultrasonication/high speed homogenization

Probe ultrasonication

Bath ultrasonication

Solvent evaporation method

Solvent emulsification-diffusion method

Supercritical fluid method

Microemulsion based method

Spray drying method

Double emulsion method

Precipitation technique

Film-ultrasound dispersion

Using Membrane Contractor

High pressure homogenization (HPH):

It is a reliable and powerful technique, which is used for the first time for production of SLNs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high Shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated. HPH is of two types-hot homogenization and cold homogenization. In both cases, a preparatory step involves the drug incorporation into the bulk lipid by dissolving or dispersing the drug in the lipid melt.

Hot Homogenization

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device (Ultra-Turrax). The quality of the final product is affected by the quality of pre-emulsion to a large extent and it is desirable to obtain droplets in the size range of a few micrometers.

Cold Homogenization

In contrast, the cold homogenization is carried out with the solid lipid and represents, therefore, a high pressure milling of a suspension. Effective temperature control and regulation is needed in order to ensure the unmolten state of the lipid due to increase in temperature during homogenization. Cold homogenization has been developed to overcome the following three problems of the hot homogenization technique.

1. Temperature-induced drug degradationable equipment.

2. Drug distribution into the aqueous phase during homogenization

3. Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts pressure.

The first step is same as in hot homogenization which includes the solubilisation or dispersing of the drug in the melt of the bulk lipid. The drug containing melt is rapidly cooled which favours the homogeneous distribution of drug in the solid matrix. Low temperatures increase the fragility of the lipid and, therefore, particle comminution. The solid lipid micro particles are dispersed in a chilled emulsifier solution. The pre-suspension is subjected to high pressure homogenization at or below room temperature. In general, compared to hot homogenization, larger particle sizes and a broader size distribution are observed in cold homogenized samples.

Advantages[22]

Low capital cost.

Demonstrated at lab scale.

Disadvantages

Energy intensive process.

Demonstrated at lab scale

Bio molecule damage.

Polydisperse distributions.

Unproven scalability.

Ultra sonication and high speed homogenisation:

SLNs are also prepared by ultrasonication or high speed homogenization techniques. For smaller particle size combination of both ultrasonication and high speed homogenization is required. It reduces shear stress but has some disadvantages like potential metal contamination, physical instability like particle growth upon storage. In this probe sonicator or bath sonicator is used.

Advantages

Reduced shear stress.

Disadvantages

Potential metal contamination.

Physical instability like particle growth upon storage.

Solvent evaporation method:

The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization.

The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar).

Advantages

Scalable.

Mature technology.

Continuous process.

Commercially demonstrated.

Disadvantages

Extremely energy intensive process.

Polydisperse distributions.

Biomolecule damage.

Solvent emulsification diffusion method

The particles with average diameters of 30-100 nm can be obtained by this technique. Prevention of heat during the preparation is the most important advantage of this technique. In this technique lipid is generally dissolved in the organic phase in water bath at 50 °C and used an acidic aqueous phase in order to adjust the zeta potential to form co acervation of SLN, and then easy separation by centrifugation. The SLN suspension was quickly produced. The entire dispersed system can then be centrifuged and re-suspended in distilled water.

Supercritical fluid method

This is a relatively new technique for SLN production and has the advantage of solvent-less processing. There are several variations in this platform technology for powder and nanoparticle preparation. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) was the good choice as a solvent for this method.

Advantages

Avoid the use of solvents.

Particles are obtained as a dry powder, instead of suspensions.

Mild pressure and temperature conditions.

Carbon dioxide solution is the good choice as a solvent for this method.

Microemulsion based method

Gasco and co-workers developed SLN preparation techniques which are based on the dilution of microemulsions. By stirring at 65-70°C an optically transparent mixture is obtained which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate20,

polysorbate 60, and sodium taurodeoxycholate), co-emulsifiers (sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by the composition of the microemulsion. Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes were obtained with more lipophilic solvents. The hydrophilic co-solvents of the microemulsion play a similar role in formation of lipid nanoparticles as acetone for formation of polymer nanoparticles.

Advantages

Low mechanical energy input.

Theoretical stability.

Disadvantages

Extremely sensitive to change.

Labour intensive formulation work.

Low nanoparticle concentrations.

Double emulsion based method

Warm w/o/w double micro emulsions can be prepared in two steps. Firstly, w/o micro emulsion is prepared by adding an aqueous solution containing drug to a mixture of melted lipid, surfactant and co-surfactant at a temperature slightly above the melting point of lipid to obtain a clear system. In the second step, formed w/o micro emulsion is added to a mixture of water, surfactant and co- surfactant to obtain a clear w/o/w system. SLN's can be obtained by dispersing the warm micro double emulsions in cold then washed with dispersion medium by ultra filtration system. Multiple emulsions have inherent instabilities due to coalescence of the internal aqueous droplets within the oil phase, coalescence of the oil droplets, and rupture of the layer on the surface of the internal droplets. In case of SLN's production, they have to be stable for few minutes, the time between the preparations of the clear double micro emulsions and its quenching in cold aqueous medium, which is possible to achieve.

Precipitation technique

Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. The glycerides will be dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles.

Film ultrasound dispersion

The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed. Site of injection and stabilize SLN until solvent diffusion was complete by reducing the surface tension between water and solvent.

Membrane contractor method

The present study investigates a new process for the preparation of SLN using a membrane contractor, to allow large scale production. The lipid phase is pressed, at a temperature above the melting point of the lipid, through the membrane pores allowing the formation of small droplets. The aqueous phase circulates inside the membrane module, and sweeps away the droplets forming at the pore outlets. SLN are formed by the following cooling of the preparation to room temperature. The influence of process parameters (aqueous phase and lipid phase temperatures, aqueous phase cross-flow velocity and lipid phase pressure, membrane pore size) on the SLN size and on the lipid phase flux is investigated. Also, vitamin E loaded SLN are prepared, and their stability is demonstrated[19].

Spray drying

It is an alternative and cheaper technique to the lyophilization process. This recommends the use of lipid with melting point more than 70^{o}C. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture. The addition of carbohydrates and low lipid content favour the preservation of the colloidal particle size in spray drying. The melting of the lipid can be minimized by using ethanol–water mixtures instead of pure water due to cooling leads to small and heterogeneous crystals, the lower inlet temperatures.

CONCLUSION

Solid lipid nanoparticles offers the best nanoparticulate drug delivery strategy for targeting the drug to brain because they are highly lipophilic and they contain high amounts of lipophilic drug.

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