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A DETAILED REVIEW ON LIPID BASED CARRIER DRUG DELIVERY SYSTEM: LIPOSPHERES

Pharmacy

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ABSTRACT

Lipospheres are lipid-based water dispersible solid particles of particle size between 0.01 and 100 µm in diameter composed of a solid hydrophobic lipid core (triglycerides), stabilized by a layer of Phospholipid molecules embedded in their surface. Lipospheres delivery system is a suitable carrier system for the delivery of both hydrophobic and hydrophilic drugs. Much of research is now focused on using lipids as novel carriers for drug moieties. Lipid based drug delivery systems like solid lipid nanoparticles, lipospheres (LS) are being developed as substitutes for "polymer based delivery systems" due to the increasing toxicity related concerns of monomers after intracellular processing of polymers and attractive benefits offered by lipids as carriers. Lipospheres are new type of drug delivery system developed mainly for parenteral system. As most of the recent drugs discovered (nearly 40-45 %) are lipophilic in nature having poor water solubility and less bioavailability. This article explains about formulation of lipospheres, factors influencing the quality attribute of lipospheres, mechanisms behind drug loading, evaluation of lipospheres and challenges in the development of lipospheres are discussed in detail.

KEYWORDS

Lipospheres, Phospholipid, hydrophobic, hydrophilic drugs, polymers, Encapsulation.

INTRODUCTION:

The first approach of using lipid microparticles was described by Eldem *et al*. The liposphere drug delivery system is an aqueous micro dispersion of solid water insoluble spherical micro particles of a particle size between 0.2 and 200 µm. Lipospheres were firstly reported by Domb and Maniar as scattering of strong circular particles of molecule size between 0.2-500 µm in breadth. Recently, advances in pharmaceutical research is focused on new delivery systems utilizing new devices to achieve modification of delivery time, targeting, as well as improve the *in-vivo* solubility and hence bioavailability of poorly soluble drugs. The particulate drug carriers that have been investigated for sustaining the therapeutic activity are based on the synthetic polymers or natural macromolecules. The drawback of these particulate systems, being the degradation of the polymer, organic solvent residues present in the delivery system that could result in severe acceptability and toxicity problems. To resolve these issues, lipid microspheres, often called lipospheres, have been proposed as a new type of fat-based encapsulation system for drug delivery of bioactive compounds. Lipospheres are lipid based water dispersible solid particles bearing particle size between 0.01 and 100 µm in diameter, composed of a solid hydrophobic lipid core containing active drug moiety dissolved or dispersed in a solid fat matrix, which is stabilized by a layer of phospholipid molecules as external coat.

LIPOSPHERES:

Lipospheres represents a type of fat based encapsulated system developed for parenteral, topical delivery of bioactive compounds. Lipospheres are lipid-based water dispersible solid particles of particle size between 0.01 and 100 µm in diameter composed of a solid hydrophobic lipid core, stabilized by a layer of phospholipid molecules embedded in their surface.

Many existing drug candidates have poor solubility in biological fluids, which results in low and highly variable bioavailability and a high food dependency after oral administration. Lipospheres are single unit system with respect to their uniform drug dispersion, maintain the uniform absorption of drug at gastrointestinal tract and more advantages than multiple unit drug delivery systems like Nanoparticles microparticles, microemulsions, and liposomes. The amount of drug encapsulated can vary up to 95% for lipophilic as well as for hydrophilic drugs and because they are made from physiological or physiologically related materials, they are well tolerated in living systems.

Comparison of Lipospheres and Liposomes

Table 1: Comparison of Lipospheres and Liposomes

	Lipospheres	Liposomes
Components	Soybean oil, Lipid. Water	Phospholipid, Water
Lipid membrane	Monolayer single membrane	Mono- or multi-layer double membrane
Emulsion form	O/W	W/O/W
Incorporable drugs	Compounds soluble in soybean oil and retainable in lipids.	Water soluble compounds and compounds retainable in lipids.
Particle diameter	200 – 300 nm	Various sizes
Safety in vivo	Safe Clinically used as intravenous nutrition in 100 ml doses	Liposomes made of some lipids are toxic
Stability	Stable for 24 months at room temperature. Lipo preparation are stored at 4°C	Rather unstable

CHARACTERIZATION OF LIPOSPHERES:

Morphology:

- Lipospheres are characterized in the terms of morphology by various microscopic techniques such as optical and electron microscopy.
- Lipospheres are prepared by melt dispersion method, it shows unimodal shape with average particle size between 5-15µm with less than 2% of particles greater than 100µm.
- Polymeric Lipospheres consisting of PLA and lecithin shows very board particle distribution from 2-100µm.

Structure:

- Lipospheres are lipid-based water dispersible solid particles, composed of a solid hydrophobic lipid core, and stabilized by a layer of Phospholipid molecules embedded in their surface.
- Phospholipid content on the surface of lipospheres is determined by 31P-NMR, before and after complexation of manganese (Mn2+) or proseodimium (Pr+3) ion with tri- nitrobenzene sulfonic acid labeling using liposphere formulations containing phosphatidyl ethanolamine.

Entrapment efficiency:

- Loading capacity of drug in lipid carriers depends on the type of lipid matrix, solubility of drug in melted lipid, miscibility of drug melt and lipid melt, chemical and physical structure of solid lipid matrix and the polymorphic state of the lipid material.

Stability:

- Numerous research works has been done and they explain the dealing with protein delivery through Lipospheres.
- Preservation of the integrity of protein can be maintained by avoiding exposure to higher temperatures using low melt lipid carriers.
- Stability of proteins in terms of physical, chemical and conformational features is an important prerequisite to establish the utility of the procedures adopted for encapsulation. The extent

to which they occur is dependent on the temperature and pH of the solution.

Release Kinetics:
Release of a hydrophilic substance from a lipophilic matrix depends on matrix material composition, properties of the incorporated drug such as solubility in lipid and aqueous medium, drug carrier interaction, drug loading, presence of surfactants, particle size, and method of preparation.

Purpose of developing particulate drug delivery system:
Main purpose of developing a LDDS is to target different carriers without causing harm to different organs, avoid first past metabolism hence enhanced bioavailability, sustained and controlled drug delivery, enhance solubility of poorly water drugs, carriers can improve stability of drug, enhanced drug absorption as surface area gets increased can be obtained by micro & nano sized particles. Lipids usually enhance drug absorption in the gastrointestinal tract, and when formulated as nanoparticles, these molecules improve mucosal adhesion due to small particle size and increasing their GIT residence time. In addition, lipid nanoparticles may also protect the loaded drugs from chemical and enzymatic degradation and gradually release drug molecules from the lipid matrix into blood, resulting in improved therapeutic profiles compared to free drug.

FORMULATION OF LIPOSPHERES:
Classical lipospheres consist of lipid based matrix. The neutral fats used in the preparation of the hydrophobic core.

The formulation of lipospheres approach utilizes naturally occurring biodegradable lipid constituents. The internal hydrophobic core of lipospheres is composed of lipids, especially triglycerides, while the surface activity of liposphere is provided by the surrounding phospholipid layer. The neutral fats, stabilizers are additionally used in the preparation of the hydrophobic core of the Lipospheres.

Table-2: Various lipids and stabilizers used in the formulation of Lipospheres:

Lipids	Stabilizers
Glyceryl monostearate	Gelatin 200 Bloom
Glyceryl monooleate	Pectin
Ethyl stearate	Carrageenan
Trilaurin	Carrageenan
Tristearin	Carrageenan
Tribehenin	Polyvinyl alcohol
Tripalmitin	Polyoxyethylene sorbitan trioleate
Trimiristine	Pluronic PE 8100
Cetyl alcohol	Lauryl sarcosine
Cholesterol	

Some biodegradable polymers also used in the preparation of polymeric lipospheres to enhance the stability of lipospheres, which includes:
- Low molecular weight poly (lactic acid)
- Poly (caprolactone).

The phospholipids are used to form the surrounding layer of lipospheres includes:
- Phosphatidylethanolamine
- Soybean phosphatidylcholine
- Dimyristoyl phosphatidylglycerol
- Pure egg phosphatidylcholine

PREPARATION METHODS:
1. Melt dispersion technique
The lipidic physical mixture containing lipid, phospholipids, cholesterol, etc., is prepared with and without a lipophilic model drug. The physical mixture is melted at 70°C and then emulsified into a hot external aqueous phase maintained at 70°C containing suitable surfactant. The emulsion is mechanically stirred by using stirrer equipped with alternate impellers and maintained at 70°C. Then, the emulsion formulation is rapidly cooled to about 20°C by immersing the formulation into an ice bath and continuing the agitation to yield uniform dispersion of LS. The obtained LS is then washed with water and isolated by filtration through a paper filter.

2. Solvent evaporation technique
This technique is an alternative to the melt dispersion technique and it is considered with the objective of possibly minimizing the exposure to high temperatures of thermo labile compounds, such as proteins and nucleic acids. This technique is based on the evaporation of organic solvent in which lipids are dissolved and allowing the formation of solid microparticles. In particular, the lipidic matrix is dissolved in an organic solvent such as ethyl acetate and maintaining the temperature about 50°C and then emulsified with an external aqueous phase containing the surfactant agent. The resulting oil-in-water emulsion is stirred for 6 to 8 h till complete evaporation of the solvent. The LS are recovered by filtration through a filter paper.

3. Co-solvent solvent evaporation method
In this co-solvent - solvent evaporation method employing chloroform and N-methyl pyrollidone to create a clear solution, although low yield and large particle size is obtained, which is altered by variation in the solvent used. Lipospheres made up of polar and non-polar lipids using synthetic stabilizers instead of phospholipids which are the deviation from the definition of liposphere. Although their work is not related to protein delivery but they tried it with hydrophilic drug and reported around 50% entrapment by double emulsification method.

4. Multiple microemulsion
This method in which a solution of peptide is dispensed in stearic acid melt at 70ºC followed by dispersion of this primary emulsion into aqueous solution of egg lecithin, butyric acid and taurodeoxycholate sodium salt at 70ºC. Rapid cooling of multiple emulsion formed solid lipospheres with 90% entrapment of peptide. Sustained release is reported by multiple emulsification technique with inclusion of lipophilic counter ion to form lipophilic salt of peptide. Polymeric lipospheres have also been reported by double emulsification for encapsulation of antigen.

5. Sonication method
In this technique, the drug is mixed with lipid in a scintillation vial which is pre-coated with phospholipids. The vial is heated until the lipid melts, and then vortexed for 2min to ensure proper mixing of the ingredients. A 10 ml of hot buffer solution is added into the above mixture and sonicated for 10min with intermittent cooling until it reaches to the room temperature.

6. Rotoevaporation method.
In this technique, lipid solution with drug is prepared in a round bottom flask containing 100 grams of glass beads (3 mm in diameter) mixed thoroughly till a clear solution is obtained. Then, the solvent is evaporated by using rotoevaporizer under reduced pressure at room temperature and a thin film is formed around the round bottom flask and the glass beads. Raise the temperature upto 40°C until complete evaporation of the organic solvent. Known amount of 0.9% saline is added to the round bottom flask and the contents are mixed for 30min at room temperature and then the temperature is lowered to 10°C by placing in ice bath and mixing is continued for another 30min until lipospheres are formed.

7. Microfluidizer method
Lipospheres can also be prepared by using a microfluidizer which is equipped with two separate entry ports. From one entry port, a homogenous melted solution or suspension of drug and carrier is pumped and from second entry port, an aqueous buffer is pumped. The liquids are mixed in the instrument at elevated temperatures where the carrier is melted and rapidly cooled to form the lipospheres. The temperature of the microfluidizer can also be changed at any stage of the lipospheres processing to manipulate the particle size and distribution.

8. Solvent extraction method
The solvent extraction method is based on the dissolution of the triglyceride (i.e., tripalmitin) and the cationic lipid in the organic solvent (i.e., dichloromethane), and on the addition of an aqueous polyvinyl alcohol solution (0.5% w/w) used as extraction fluid. The solution and the extraction fluid are pumped into a static microchannel mixer, leading to the production of an O/W emulsion. The mixing leads to the production of fine lamellae, which subsequently disintegrate into droplets, allowing the formation of lipid microspheres dispersed in the extraction aqueous medium.

9. Polymeric lipospheres
Polymeric biodegradable lipospheres can also be prepared by solvent or melt processes. The difference between polymeric lipospheres and the standard liposphere formulations is the composition of the internal

core of the particles. Standard lipospheres, as those previously described, consist of a solid hydrophobic fat core that is composed of neutral fats like tristearin, while in the polymeric lipospheres, biodegradable polymers such as polylactide or PCL substitute the triglycerides. Both types of lipospheres are thought to be stabilized by one layer of phospholipid molecules embedded in their surface.

EVALUATION

Particle Size

Molecule measuring results are in this way urgent parameter in the improvement and advancement of readiness procedure and also in the assessment of scattering steadiness. Molecule size is controlled by photon connection spectroscopy, laser light dissipating method.

Particle Morphology and Ultra structure of dispersion

Electronic tiny methods have been especially utilized to portray general measurements (structure and shape) of strong lipid molecule. Transmission electron microscopy (TEM) can give significant information on molecule size, shape and structure and in addition vicinity of diverse sorts of colloidal structures inside of scattering. TEM gives 2D pictures while 3D imaging is under scrutiny. Examining electron microscopy (SEM) is utilized for morphological examination of Lipospheres including shape and surface structure regarding change with contact with discharge media. Optical microscopy is valuable in location of stage isolated crystalline bioactive mixes.

Electron Microscopy:

Electron Microscopy methods such as Scanning Electron Microscopy and Transmission Electron Microscopy are used to measure the overall shape and morphology of lipid nanoparticles. It permits the determination of particle size and distributions.SEM uses electrons transmitted from the surface of the sample while TEM uses electrons transmitted through the sample.

Determination of Incorporated Drug:

The amount of drug encapsulated per unit wt. of nanoparticles is determined after separation of the free drug and solid lipids from the aqueous medium and this separation can be done by ultracentrifugation, centrifugation filtration or gel permeation chromatography. The drug can be assayed by standard analytical technique such as spectrophotometer, a spectroflurophotometry, HPLC or liquid scintillation counting.

Micro particulate Contaminant

Particularly trace amounts of microparticles may be difficult to detect in light scattering techniques. The Coutler-Counter method has been used to detect absolute number of particles in the micrometer range. For dispersion of lipid nanoparticles this method has also been applied for particle size determination of solid lipid microparticles.

Zeta Potential

Colloidal particles possess surface charge because of ionized groups or of an ion adsorption from the dispersion medium. These surface charges and the strength and extension of electric field of the surrounding medium play important role repulsion of lipospheres and their stability against aggregation.

Crystallinity and Polymorphism

Characterizing crystallinity and polymorphism of lipospheres X-Ray diffraction and Differential scanning calorimetry are utilized. DSC is convenient method which confirms solid lipid particles by detecting melting transition. XRD is used to analyses microparticles with respect to influence of composition and preparation procedure on resulting polymorphic form.

Entrapment efficiency

The total amount of drug loaded into liposphere can be determined by, first extracting free drug into suitable buffer then encapsulated drug is then determined by dissolution of drug loaded microparticles in Triton solution or in a solvent which can dissolve the Microparticles.

Stability Studies

Many studies have conducted on liposphere stability at various stress conditions. Among them, the photolysis based stability testing was proven to be a benchmark. The photolysis based stability studies were explained with an example of butyl methoxy dibenzoyl methane (BMDBM), a sunscreen agent complexes with hydroxyl propyl-β-cyclodextrin (HP-β-CD). The lipospheres of BMDBM were developed with tristearin and hydrogenated soybean phosphotidylcholine. The resulting cream was undertaken for photo degradation study about 3 months in which permeability of lipospheres and also the release of drug were evaluated. It was learnt that the lipospheres are able to provide further superior protection to the drug in formulation, apart from the protection provided by HP-β-CD inclusion complexation.

APPLICATION OF LIPOSPHERES:

- The use of lipid nanocarriers provides a suitable way for the nasal delivery of antigenic molecules. In this sense, the design of optimized vaccine nanocarriers offers a promising way for nasal mucosal vaccination.
- SLNs offer the opportunity of controlled drug release and the possibility to incorporate poorly soluble drugs.
- The application of lipids as vehicle for the delivery of drugs has revolutionarized drug delivery with some old drugs with very serious side effects being safe for use.
- Some anti-inflammatory drugs for example, indomethacin, have shown that indomethacin lipid formulations could be used with minimal gastro-intestinal irritation.
- Lipospheres also serves as a gene vector carrier SLN can be used in the gene vector formulation. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids. The gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide into SLN gene vector.
- These provide a novel and unique drug-delivery system they evade quick clearance by the immune system. They can target specific cells. Stealth SLNs have been successfully tested in animal models with marker molecules and drugs. Antibody labeled stealth Lipobodies have shown increased delivery to the target tissue in accessible sites.

CONCLUSION

Lipid based delivery systems like lipospheres offer new type of carrier system for lipophilic drugs. Easy availability of formulation ingredients and feasible, simple production techniques offer attractive option for formulation of Lipospheres at industrial scale. Lipospheres have several advantages than other drug delivery systems, including emulsions, vesicles, and liposomes. Lipospheres have high stability, high dispersibility in aqueous medium, and are easy to manufacture at relatively low cost. Lipospheres can be used to control rate of drug release for entrapped substances by altering the phospholipids coating and carrier. The liposphere approach employs a fat lipid environment to achieve desired goal for controlled and safe delivery of drugs. Lipospheres have been successfully utilized for the delivery of variety of substances with the potential of targeting while avoiding systemic side effects. Liposphere formulations were effective in delivering various drugs and biological agents including: local anaesthetics, antibiotics, vaccines, and anticanceragents.

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