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Lipospheres

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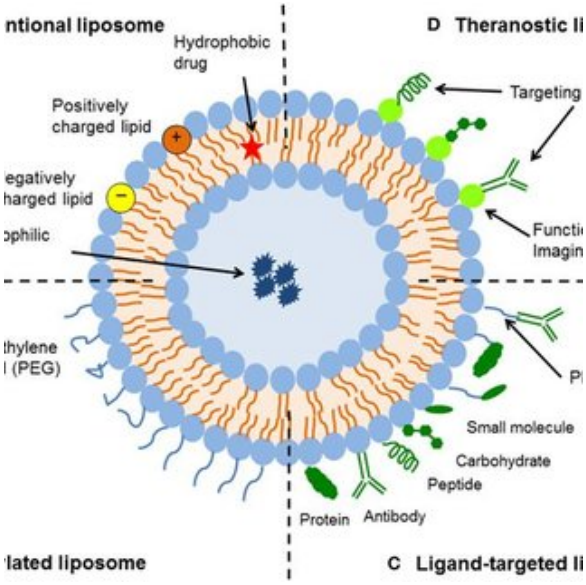
INTRODUCTION:

Lipospheres represent a new type of fat based encapsulation system developed for parenteral and topical delivery of bioactive compounds and have been utilized in the delivery of anti- inflammatory compounds, local anaesthetics; antibiotics, anticancer agents, insect repellent, vaccines, proteins and peptides. The lipospheres are distinct from microspheres of uniformly dispersed material in homogenous polymer since they consist of two layers, the inner solid particle that contains the entrapped drug [1].Liposphere formulation is appropriate for oral, parenteral and topical drug delivery systemwith phospholipids outer layer.

Benefits of liposphere drug delivery system are;

a) Improving drug stability;
b) Possibility for controlled drug release;
c) Controlled particle size;
d)High drug loading.



Advantages of Lipospheres

- Liposphere exhibit enhanced physical stability due to avoidance of coalescence.
- High dispersability in an aqueous medium.
- Low cost of ingredient.
- Ease of preparation and scale up.
- High entrapment of hydrophobic drugs.
- Controlled particle size.
- Extended release of entrapped drug after a single injection.
- Static interface facilitates surface modification of carrier particles after of the lipid matrix.

Dis –Advantages of Lipospheres

- Different lipid modifications and colloidal species coexist that may cause differences in solubility and melting point of active and auxillary species.
- Low drug loading capacity for hydrophilic proteins.
- Variable kinetics of distribution processes.
- High-pressure induced drug degradation.
- Insufficient stability data
- Toxic effects of organic residues after the production of polymers, Lack of large industrial scale production

Application of lipospheres

1) Parenteral Route

Lipospheres have been exploited for the delivery of anesthetics like lidocaine bupivacaine , for the parenteral delivery of antibiotics like ofloxacin, norfloxacin, chloramphenicol palmitate and oxytetracycline, and antifungal agents, such as nystatin and amphotericin B ; for the parenteral delivery of vaccines and adjuvant[2].

2)Transdermal route

Properties of lipospheres like film forming ability, occlusive properties; controlled release from solid lipid matrix resulting in prolonged release of drug and retarded systemic absorption of drugs; increasing the stability of drugs which are susceptible to extensive hepatic metabolism, make them attractive candidates for topical delivery.[2]

3)Oral delivery

Several categories of drugs like antibiotics, anti-inflammatory compounds, vasodilators, anticancer agents, proteins and peptides are being formulated as oral lipospheres

Formulation of liposphere [2] Triglycerides:

- Witepsol W35
- Witepsol H35
- Compritol 888 ATO (Glycerylbehenate)
- Dynasan 112
- Precirol (Glycerylpalmito stearate)
- Tricaprin, trilaurin, tripalmitin, tristearin, trimyristin.

Monounsaturated fatty acid:

Cis forms of monounsaturated fatty acids have lower melting point than triglycerides hence used as a mixture with higher saturated fatty esters

Partially hydrogenated vegetable oils Soybean oil, coconut oil, cotton seed oil.Oils olive oil, wheat germ oil, evenin primrose oil, arachis oil, safflower oil, corn oil, rice bran oil.

WAXES:
- Bees wax,
- spermaceti,
- cetylpalmitate,
- arachidyloleate,
- carnauba wax,
- cetyl alcohol,
- cholesteryl butyrate

Active Pharmaceutical ingredient Emulsifiers:
- Phospholipids pure-egg phosphatidyglycerol,
- Dimyristoylphosphatidylglycerol,
- soybean phosphatidylcholine
- Surfactants Tween-80,
- Butyl alcohol

Stabilizers:
Gelatin, pectin, carrageenan, polyvinyl alcohol, polyoxyethylenesorbitantrioleate, Pluronic PE 8100, lauryl sarcosine.

Method of Preparation:
1**)Melt dispersion technique**
The physical mixture is melted at 70ºC and then emulsified into a hot external aqueous phase maintained at 70ºC containing suitable surfactant. The emulsion is mechanically stirred by using stirrer equipped with alternate impellers and maintained at 70ºC. Then, the emulsion formulation is rapidly cooled to about 20ºC by immersing the formulation into a 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[3].

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 thermolabile 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 50ºC 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].

3)**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 (Morel et al., 1994). 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 (Morel et al., 1996). Polymeric lipospheres have also been reported by double emulsification for encapsulation of antigen (Amselem et al., 1996)[3].

4) **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.

5) **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 (PVA) 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[3]

Storage of lipospheres:
The liposphere formulations are stored in aqueous buffer, freeze dried, or in an ointment or cream base, in the freezer, refrigerator or room temperature. It is preferred to store the formulations suspended in an aqueous solution in the refrigerator for immediate use[3].

Factors Influencing Quality Attributes of Lipospheres:
1. Morphology of lipospheres[2]
a) Drug loading
b) Type of lipid
c) Type of impeller

2 .Entrapment efficiency[2]
a) Type of lipid
b) Amount ofPhospholipid:
c) Effect ofmethod ofpreparation:

3. Drug release[2]
a) Releasepattern
b) Effect ofparticlesize
c) Type oflipid.
d) Effect ofstabilizer

Evaluation
1)Morphology
The size and surface characteristics of lipospheres can be determined by methods like electron microscopy, atomic forcemicroscopy (AFM), nuclear magnetic resonance (NMR) and acoustic methods.[2]

2)Entrapment efficiency:
Amount of drug loaded into lipospheres can be determined by first extracting the free drug (unencapsulated) bycentrifugation into a suitable buffer. The encapsulated drug is then determined by dissolution-extraction of drug loadedMicroparticles in Triton solution or in a solvent which can dissolve the Microparticles. [2]

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