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LIPOSPHERES

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ABSTRACT

Lipospheres are novel lipid-based drug delivery systems developed to address the limitations of poorly water-soluble drugs, which frequently exhibit low bioavailability and inconsistent therapeutic response. They consist of a solid hydrophobic lipid core in which the active drug is dispersed or dissolved. They have been employed for the controlled delivery of a wide range of drugs, including anti-inflammatory medications, antibiotics, and anticancer agents, and as carriers for vaccines. This review emphasizes the formulation methods, advantages, limitations, and diverse applications of lipospheres, highlighting their potential as a simple, cost-effective, and versatile lipid-based carrier system in drug delivery.

KEYWORDS: Lipospheres, Drug delivery, Bioavailability, Controlled release, Lipid carriers.

INTRODUCTION

The formulation of poorly water-soluble drugs remains one of the most critical challenges in pharmaceutical development, as limited solubility often results in low oral bioavailability and variable therapeutic response. It is estimated that nearly 40–45% of newly developed drug candidates are highly lipophilic, exhibiting poor solubility in aqueous media and consequently poor absorption.[1] To address these issues, several carrier-based systems, such as liposomes, nanoparticles, microparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), microemulsions, and self-emulsifying drug delivery systems (SEDDS), have been developed. While these systems have shown potential in improving solubility and bioavailability, they are often limited by issues such as polymer degradation, organic solvent residues, stability concerns, and complex manufacturing processes. To overcome these issues, lipospheres have emerged as a promising platform owing to their ability to enhance the solubility and bioavailability of poorly water-soluble drugs. The lipidic matrix provides a favourable microenvironment for the drug, improving its wettability and dissolution while simultaneously ensuring stability and patient safety.[13]

Lipid microspheres, often called lipospheres (LS), have been proposed as a new type of fat-based encapsulation system for drug delivery of bioactive compounds (especially lipophilic compounds).[2]

Lipospheres are lipid-based, water-dispersible solid microparticles (0.01–100 µm) consisting of a solid hydrophobic lipid core in which the active drug is dissolved or dispersed. They serve as versatile carrier systems for both hydrophilic and hydrophobic drugs and are particularly effective in enhancing the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs. Owing to their fat-based composition, lipospheres have been developed as promising particulate delivery systems suitable for oral, parenteral, and topical administration.[3]

Lipospheres (LS) have been widely used as carriers for the controlled delivery of various therapeutic agents, such as vasodilators, antiplatelet drugs, anti-inflammatory agents, local anesthetics, antibiotics, and anticancer compounds. Furthermore, they have demonstrated effectiveness as delivery systems for vaccines and also serve as adjuvants to enhance immune responses.[2]

Types of Lipospheres[5]

Based on matrix composition, lipospheres are classified as.

Classical Lipospheres: These lipospheres consist of a lipid-based matrix, primarily composed of neutral lipids that facilitate the formation of a lipophilic core. Common examples include triglycerides such as tricaprin, trilaurin,

tristearin, and other lipids like stearic acid, ethyl stearate, and hydrogenated vegetable oils.

Polymer Lipospheres: In this type, the matrix is formed using biodegradable polymers such as polylactic acid (PLA), polycaprolactone (PCL), and polylactic-co-glycolic acid (PLGA). Polymeric lipospheres are explored for achieving prolonged and controlled drug release. However, their use is sometimes limited due to concerns related to polymer degradation and potential toxicity.

Benefits of the liposphere drug delivery system[4]

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

In addition, the use of lipospheres for oral administration can protect the drug from hydrolysis and improve the bioavailability of poorly water-soluble drug moieties, thus making them ideal carriers for problematic drugs.

Advantages[5]

- Easy to prepare and scale up
- Made from low-cost materials
- Good physical stability
- Can trap a large amount of hydrophobic drugs
- Easily disperses in water when carrying lipophilic drugs
- Reduces the movement of the trapped drug inside
- Allows for slow and extended drug release
- Highly biocompatible
- Suitable for oral, intramuscular (IM), intravenous (IV), and topical use

Disadvantages[5]

- Low drug loading capacity for hydrophilic compounds.
- Variable kinetics of distribution processes.
- High-pressure induced drug degradation.

Applications of Lipospheres[6]

Lipospheres have gained wide attention as a promising lipid-based carrier system, and their applications have been reported across various routes of administration and therapeutic areas. In general, they are employed to improve the solubility, stability, and bioavailability of poorly water-soluble drugs and to provide controlled or sustained release. Major applications include.

1. Oral delivery

Lipids and lipid-based nanoparticles are commonly used as carriers for oral delivery of drugs and bioactive compounds. They facilitate better drug absorption in the gastrointestinal tract (GIT), and when converted into nanoparticles, their reduced particle size enhances mucoadhesion and prolongs residence time in the GIT. Various classes of drugs—including antibiotics, anti-inflammatory agents, vasodilators, anticancer drugs, and therapeutic proteins or peptides—have been successfully incorporated into oral liposphere formulations. These systems improve the dissolution of poorly soluble (BCS Class II and IV) drugs, shield sensitive molecules from gastric degradation, and enhance intestinal uptake, resulting in greater oral bioavailability.

2. Parenteral delivery

Due to their aqueous dispersibility and biocompatibility, lipospheres serve as carriers for hydrophobic drugs in injectable formulations. They reduce local irritation, enable depot formulations, and prolong systemic circulation. Lipospheres have been exploited for the parenteral delivery of some anesthetic drugs like lidocaine, bupivacaine, antibiotics like ofloxacin, norfloxacin, chloramphenicol palmitate and oxytetracycline and antifungal agents, such as nystatin and amphotericin B, vaccines and adjuvant etc.

3. Topical and transdermal delivery

The occlusive and film-forming nature of lipospheres enables the design of sustained or controlled-release drug formulations, where the solid lipid matrix delays systemic absorption and enhances the stability of the drug. They also facilitate deeper skin penetration of lipophilic drugs, providing targeted therapeutic effects with minimal systemic exposure, and support prolonged delivery of agents such as anti-inflammatory, analgesic, and dermatological drugs.

4. Ocular drug delivery

For ophthalmic delivery, lipospheres should have a small particle size, with a narrow size range, should be non-irritant, compatible with ocular tissue, and should not cause blurred vision. The colloidal character of a drug carrier such as nanosized lipospheres improves drug penetration by prolonging the ocular residence time, reducing the nasolacrimal drainage and increasing interaction with corneal surface, combined with the advantage of being an easy-to-use liquid dosage form.

5. Pulmonary delivery

The dispersible nature of lipospheres makes them suitable for inhalation-based formulations, offering localized treatment for respiratory diseases and systemic delivery of biomolecules such as peptides.

6. Gene Delivery

Lipospheres also serves as a gene vector. There are several recent reports of liposphere carrying genetic or 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 (TAT 2) into liposphere gene vector.

Factors affecting lipospheres formulation[3]

- **Type of lipid:** A combination of non-polar lipids, such as tristearin, tripalmitin, or tribehenin, with polar lipids like glyceryl monostearate or glyceryl

monooleate resulted in lipospheres exhibiting desirable particle size, shape, and yield.

- **Drug loading:** Increasing the amount of drug led to the formation of larger particles. At a higher drug-to-lipid ratio (1:1), the lipid coating around the drug became inadequate, causing aggregation during the cooling stage and producing irregular, fragile, and fluffy lipospheres.
- **Type of impeller:** Lipospheres were prepared using various impeller designs to evaluate their influence on particle characteristics. The impellers tested included rotor types with two and three blades, a helicoidal rotor with four blades, and a double truncated cone rotor. Among these, the two-blade rotor was found to effectively produce lipospheres.

Factors influencing entrapment efficiency

- **Type of lipid:** The degree of drug entrapment in lipospheres is influenced by the lipophilicity of the active pharmaceutical ingredient (API). Long-chain triglycerides such as tristearin and triarachidin, being more hydrophobic, generally offer higher drug entrapment compared to short-chain triglycerides like tricaprin and trilaurin.
- **Effect of method of preparation:** The melt dispersion technique has been shown to provide better entrapment efficiency than the solvent evaporation method. This is because, in the melt dispersion process, the drug tends to be incorporated into the lipid core, whereas in solvent evaporation, the drug is mainly distributed in the outer coat.

PREPARATION METHODS[6,9,10,11]

1. Melt dispersion technique

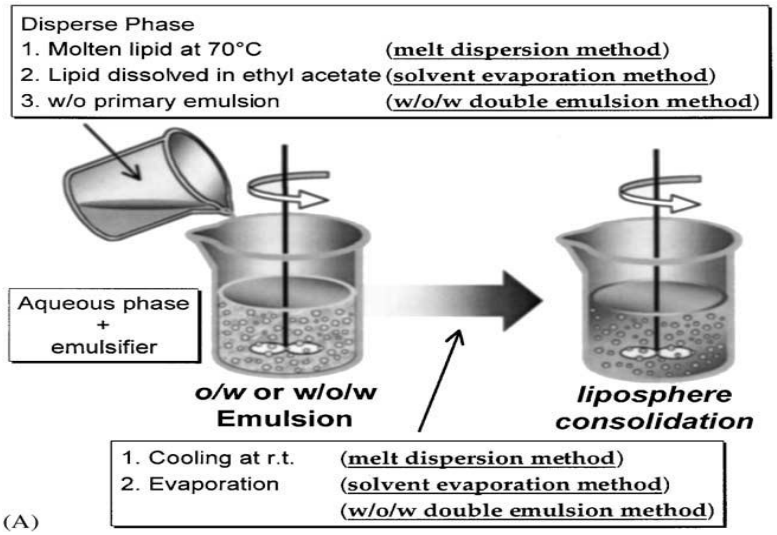
The lipidic mixture was melted at 70°C, and the lipophilic model drug was then incorporated into the molten lipid phase and then emulsified into an external aqueous phase containing a suitable surfactant. The emulsion was mechanically stirred by a stirrer equipped with alternative impellers. Afterward, the emulsion was heated to the same temperature as the melted lipidic phase. The milky formulation was then rapidly cooled to about 20°C by immersing the formulation flask in a cool water bath without stopping the agitation to yield a uniform dispersion of LS. The obtained LS were then washed with water and isolated by filtration through a paper filter.

2. Solvent evaporation technique

This method serves as an alternative to the melt dispersion technique and is specifically designed to minimize heat exposure for thermolabile drugs. It relies on the evaporation of an organic solvent in which the lipid material is dissolved to form solid microparticles. In this process, the lipid matrix is dissolved in an organic solvent such as ethyl acetate at approximately 50 °C and then emulsified into an external aqueous phase containing a surfactant. The resulting oil-in-water emulsion is continuously stirred for 6–8 hours until the solvent completely evaporates. The formed lipospheres are then collected by filtration using filter paper.

3. Water-in-oil-in-water double emulsion (w/o/w) method

In this technique, the drug is dissolved in the internal aqueous phase of a water-in-oil-in-water (w/o/w) double emulsion, together with a stabilizer that minimizes drug diffusion into the external phase during solvent evaporation. An aqueous drug solution is first emulsified into the molten lipid phase maintained at about 70 °C using a high-shear homogenizer (Ultra-Turrax) to produce a uniform dispersion. The primary emulsion is stabilized by incorporating gelatin (250 bloom) or poloxamer 407, which is dissolved in the aqueous phase. This emulsion is then dispersed at 70 °C into 150 mL of an external aqueous phase containing 0.25% (w/v) polyvinyl alcohol (PVA) and stirred at 300 rpm using a four-blade turbine impeller. After continuous stirring for 3–5 hours, the resulting microparticles are collected by filtration.



(A)

4. Multiple microemulsion technique

In this method, hydrophilic drugs are first dissolved in the aqueous phase, which is then incorporated into the molten lipid phase maintained at around 70 °C to form the primary emulsion. This emulsion is subsequently introduced into an oil phase containing a nonpolar emulsifier, resulting in the formation of uniformly sized lipospheres.

5. Sonication method

In this method, the drug is combined with the lipid in a phospholipid-coated scintillation vial. The vial is heated until the lipid melts, followed by vortexing for about 2 minutes to achieve uniform mixing. Subsequently, 10 mL of a hot buffer solution is added to the mixture and subjected to sonication for 10 minutes with intermittent cooling, allowing the formulation to gradually reach room temperature.

6. Microfluidizer method

Lipospheres can also be prepared by using a microfluidizer which is equipped with two separate entry ports. From one entry port, a homogeneous melted solution or suspension of the drug and carrier is pumped, and from the 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.

7. 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.

EVALUATION OF LIPOSPHERES[6,7,8,10,13]

Particle Size

Particle size of lipospheres was determined by photo microscopic studies. About 1 mg of the lipospheres formulation was placed on a clean glass slide and covered with a coverslip to form a thin layer. The prepared sample was then examined under an optical microscope equipped with a calibrated eyepiece, using 45× magnification for observation.

Percentage Yield of Lipospheres

The yield of Lipospheres percent w/w was calculated according to the formula.

% Yield = Weight of lipospheres /Wt. of Drug + Wt. of Excipients

Drug loading and Entrapment efficiency

The amount of drug present in lipospheres was determined by taking the known amount of lipospheres in which 20 mg of drug should be present theoretically. Then the lipospheres were crushed and the powdered microspheres were taken and dissolved in 10 ml of methanol, and stirred for 15 minutes with an interval of 5 minutes, and allowed to keep for 24 hours. Then the solution was filtered through Whatman filter paper. Then the absorbance after appropriate dilution was measured spectrophotometrically by a UV-visible spectrophotometer.

Drug entrapment efficiency (%) = (Experimental drug content/Initial drug content in the formulation) × 100

Drug Loading (%) = (Quantity of drug present in the Liposphere/Weight of Lipospheres) × 100

Electron Microscopy

Electron microscopy techniques, including Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM), are employed to study the morphology and overall shape of lipid particles. These methods also enable the measurement of particle size and distribution. In SEM, electrons are reflected from the sample surface to generate an image, whereas TEM utilizes electrons that pass through the sample to reveal internal structural details.

Crystallinity and Polymorphism

o study the crystallinity and polymorphic behavior of lipospheres, techniques such as X-ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC) are employed. DSC is a useful tool for confirming the solid state of lipid particles by identifying their melting transitions.

XRD provides information about the crystalline structure of the microparticles and helps to evaluate how formulation composition and processing conditions influence their polymorphic form.

Zeta Potential

Colloidal particles carry surface charges either due to the presence of ionizable groups or through the adsorption of ions from the surrounding dispersion medium. These surface charges, along with the intensity and range of the resulting electric field, are crucial in preventing particle aggregation by promoting electrostatic repulsion, thereby enhancing the stability of lipospheres.

In-Vitro drug release study

The in vitro release of lipospheres is usually evaluated using a suitable dissolution medium with a USP type II (paddle) apparatus at a constant stirring speed. A quantity of formulation equivalent to a known amount of drug is used for the study. Samples are collected at specific time intervals, and the withdrawn volume is replaced with fresh medium to maintain sink conditions. The samples are then filtered and analyzed for drug content using an appropriate method.

CONCLUSION

Lipospheres are emerging as a promising lipid-based carrier system capable of improving the solubility, stability, and bioavailability of poorly water-soluble drugs. Their simple preparation methods, cost-effectiveness, and biocompatibility make them attractive for various routes of administration such as oral, parenteral, topical, ocular, and pulmonary delivery. In addition to enhancing dissolution and absorption, they also allow sustained and controlled release, thereby improving therapeutic outcomes.

Although challenges like limited drug loading for hydrophilic compounds and variable release kinetics remain, advances in formulation techniques continue to address these drawbacks. Moreover, the ability of lipospheres to encapsulate not only small molecules but also biomolecules and genetic materials highlight their broad application potential. With ongoing research and optimization, lipospheres are expected to become a reliable platform for next-generation drug delivery, offering better patient compliance and improved clinical efficacy.

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