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Corresponding Author:

*Wattamwar Mayur Madhukarrao

Department of Pharmaceutics,
Marathwada MitraMandals College of Pharmacy,
Theragaon (Kalewadi), Pune-411033
India.
Mob.no:9921986281

QR Code AJPTI

*Email Id-Mayurwattam@gmail.com

Liposphere - Lipid Based Drug Delivery System :A Review

Wattamwar Mayur Madhukarrao*,Ratnaparkhi Mukesh P, Chaudhari Shilpa P

ABSTRACT

New chemical entities (NCEs) in modern discovery libraries and development programs have an ever-increasing number of unconventional physical and chemical properties. In particular, up to 70% of discovery compounds and 40% of pipeline candidates are insoluble in water. These promising molecules present unique formulation and development challenges and often suffer from poor bioavailability. Therefore, conventional formulation systems cannot be employed. Techniques available for scientists to increase the bioavailability of poorly soluble drugs are either increasing their solubility in biological media of choice, or increasing their dissolution kinetics. The use of advanced lipid-based drug delivery systems (LBDDS) is a strategy to design pharmaceutical dosage forms with improved therapeutic benefits.

Key-words: lipospheres, lipids, method of preparation, formulation aspects.

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Introduction:

Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug. Solid dispersion, drug micronization, lyophilisation, microencapsulation, inclusion of the drug solution or liquid drug into soft gelatin capsules are some of the methods that have been used to enhance dissolution characteristics of water insoluble drugs. Among them, lipospheres are amongst the promising particulate drug delivery systems for improving dissolution rate of water insoluble drugs that were initially reported as a particulate dispersion of solid spherical particles between 0.2-100µm in diameter consisting of solid hydrophobic fat core such as triglycerides or fatty acids derivatives, stabilized by monolayer of phospholipids. 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 with phospholipids outer layer. The combination of solid inner core with phospholipid exterior confers several advantages on the lipospheres as compared with conventional microspheres and microparticles, including high dispersibility in aqueous medium, and a release rate for the entrapped substance that is controlled by the phospholipid coating and the carrier. Further, the substance to be delivered does not have to be soluble in the vehicle since it can be dispersed in the solid carrier[1].Liposphere formulation is appropriate for oral, parenteral and topical drug delivery system. The solid core containing a drug dissolved or dispersed in a solid fat matrix and used ascarrier for hydrophobic drugs. Several techniques, such as solvent emulsification evaporation, hot and cold homogenization and high pressure homogenization have been used for the production of lipospheres.

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.

In addition, use of lipospheres for oral administration, it can protect the drug from hydrolysis, as well as improve drug bioavailability. Therefore, the present review article is focused on achievements of lipospheres formulation to deliver the drugs in the targeted sites.

Due to several limitations with polymeric delivery systems, extensive attempts are being made to develop alternate carriers. Lipids especially, are now being studied widely due to their attractive properties namely physicochemical diversity, biocompatibility, biodegradability, ability to increase the oral bioavailability of poorly water soluble drug moieties, thus making them ideal candidates as carriers for problematic drugs[2].

Advantages of lipid based delivery systems:

Physical stability of lipid dosage forms like polymorphic phase transitions of drug and Lipid based drug delivery systems like solid lipid nanoparticles (a technology owned by Skye Pharma) andlipospheres are now being studied widely. Solid lipid nanoparticles arenanosized lipid carriers in which lipidic core

contain the drug in dissolved ordispersed state. These systems were designed to substitute polymeric carriers due to the inherent toxicity. Lipospheres are lipid based dispersion systems in which drug is dissolved or dispersed in lipidic core, the surface of which is embedded with emulsifier layer. Particle size of such lipid particles ranges from 0.2-100 micrometer (μm)[2].

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.[2]

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, phosphatidylethanolamine, 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 lipidic physical mixture containing lipid, phospholipids, cholesterol, etc., is prepared with and without a lipophilic model drug. 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. 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 reported by Domb in his patent (Cortesi et al., 2003). 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[3].

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 (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].

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[3].

6. Rotoevaporationmethod

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 40ºC 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 10ºC by placing in ice bath and mixing is continued for another 30min until lipospheres are formed[3].

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[3].

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 (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]

Sterilization of lipospheres:

Sterile liposphere formulations are prepared by sterile filtration of the dispersion in the hot stage during preparation using a 0.2-mm filter, at a temperature that is 5ºC above the melting point of the liposphere core composition. Heat sterilization using a standard autoclave cycle decomposed the formulation. Sterilization of liposphere formulations did not affect their physical properties[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].

Recent Advances:

- Production of Lipospheres for Bioactive Compound Delivery
- Lipospheres as Delivery Systems for Peptides and Proteins
- Lipospheres for Vaccine Delivery
- Cationic Lipospheres as Delivery Systems for Nucleic Acid Molecules

Production of Lipospheres for bioactive compound delivery

The solvent evaporation technique is often used for liposome and polyester. Microparticles can be present in the deliverysystem and could result in severe acceptability and toxicity problems.The drug delivery system concept is not new.Great progress has recently been made in the treatment of a variety of diseases. Particulate carriers (e.g., polymericnano-and microparticles, fat emulsion, and liposomes) possess specific advantages and disadvantages. For instance, inthe case of polymeric microparticles, the degradation of the polymer might possibly cause systemic toxic effects throughthe impairment of the reticuloendothelial system or by accumulation at the injection site . To solve these adverseeffects, lipid microspheres, often called lipospheres (LS), have been proposed as a new type of fat-based encapsulation system for drug delivery of bioactive compounds.LS have been used for the controlled delivery of various types ofdrugs, including vasodilator and antiplatelet drugs, anti-inflammatory compounds, local anesthetics, antibiotics, andanticancer agents; they have also been used successfully as carriers of vaccines and adjuvant. Lipospheres (LS), under
appropriate experimental conditions, can entrap both hydrophobic and hydrophilic drugs and can control the release ofthe encapsulated drug. The encouraging results obtained in this study could propose LS for future *in vivo* studies,especially in the delivery of anti-infective and hormone[2].

Lipospheres as delivery systems for peptides and proteins

Delivery systems are designed to protect an incorporated drug from the environment during delivery and to provide acontrolled release. The goal may be either to deliver a drug locally to specific sites in the body or to prepare a drugcarrier system that acts as a reservoir at the site of injection over a certain time period. In recent years, a growingnumber of potential peptide and protein drugs has been discovered as a result of progress in biotechnology and genetic
engineering. Unfortunately, protein drugs are subject to numerous chemical and physical instability mechanisms andrapid enzymatic degradation; therefore, they often show low bioavailability and have short *in vivo* half-lives, thusnecessitating parenteral delivery. To sustain therapeutic effects, these drugs have to be administered by infusion or viafrequent injections.Therefore, alternative carrier substances have been investigated in recent years. Among them, lipidicmaterials have gained growing attention. Successful peptide or protein incorporation and delivery has been reported forliposomes. Multivesicular liposome preparations , cubic phase gels, hollow lipid Microparticles , hollow lipidmicrocylinders, Microparticles, and solid lipid nanoparticles (SLN) for intravenous applications[2].

Lipospheres for vaccine delivery

The tremendous advances of genetic engineering and the ability to obtain many synthetic recombinant protein antigensderived from parasites, viruses, and bacteria have revolutionized the development of

new generation vaccines.One approach to enhancing the bioavailability and effectiveness of peptide-based vaccines is the use of Microparticlesas vaccine carriers. Several reports describing the improvement of immune response achieved by the association of
antigens with lipid carriers such as liposomes or microparticles like polymeric biodegradable microcapsuleshave been published. The ability of these delivery systems to enhance immunogenicity was related to thephysicochemical characteristics of the particles. Lipospheres are fat-based encapsulation particulate systems developedfor parenteral drug delivery that also have been used successfully as carriers of vaccines and adjuvant
Lipospheres have been used for topical applications, including with insect repellents and moisturizers with extendedaction. Lipospheres consist of water-dispersible solid microparticles composed of a solid hydrophobic fat core stabilizedby one layer of phospholipid molecules embedded in their surface. Manufacture of liposphere–vaccine formulations is
accomplished by gently melting neutral fat in the presence of phospholipid and dispersing the mixture in an aqueoussolution containing the antigen by vigorous shaking. Upon cooling of this mixture, a phospholipid-stabilized solidhydrophobic fat core containing the antigen forms spontaneously. Although the lipospheres seem to fit very well invaccine formulations provided by injection or by oral intake. This chapter is an update of the, emphasis on the possible
use of lipospheres for oral immunization. Particle size is a key factor, and it appears that particles of certaincompositions in the size range of 50 to 3000 nm are capable of uptake and translocation. Uptake increases withdecreasing particle size. Surface hydrophobicity has a direct correlation with the immune response. Although thelipospheres seem to fit very well in vaccine formulations provided by injection or by oral intake[2].

Cationic lipospheres (cls) as delivery systems for nucleic acid molecules

Gene delivery or the release of exogenous genetic material into cells or tissues at a pathological state, has recentlyreceived much attention as a therapeutic methodology for a number of acquired and inherited diseases, including cancer.Thus, the key to success for any gene therapy strategy is to design a vector able to provide safe and efficient genetranscription of the transgene in a variety of cells and tissues. In this view, the development of protocols aimed atobtaining optimal and efficient genetic transfer has been studied and has led to the production of many deliveryvehicles that are able to bind to DNA. The optimal carrier has to accumulate at sites of diseases such as infections,inflammations, and tumors and has to be a small, neutral, and highly serum-stable particle. Moreover, it has to be notreadily recognized by the fixed and free macrophages of the reticuloendothelial system recent years; solid lipidnanoparticles have attracted increasing attention. However, only a few studies that have been aimed to obtain innovativenonviral transfection systems for gene therapy have been performed on CLS. In the last decade, the efficiency ofnonviral transfection systems has improved several orders of magnitude. Although as yet none has proven to be effectiveenough *in vivo*, new developments are still ongoing. Among nonviral transfection systems, colloidal carriers such as
CLS represent an alternative drug delivery system to emulsions, liposomes, and polymeric particles[2].

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 parameters of Lipospheres

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]

3) Release kinetics:

Development of reliable in vitro dissolution testing methodology is important as it aids in selection of excipients,assesses the performance of formulation during different phases of drug development, for regulatory approvals, claimingbiowaivers and substitute clinical studies. For newer formulations like lipospheres for which there are no establishedmethods, a reliable and reproducible dissolution testing method becomes even more important. Methods like "dispersion
test", "digestion test" have been designed for laboratory testing in order to establish *invitro-invivo*correlation (IVIVC).pH stat test or titra-stat test is another development in this direction. In this, a known or measured volume of sodiumhydroxide solution is titrated against formulation containing lipid to which pancreatic lipase and calcium ions (to activate lipase) are added to mimic in *vivo* conditions. Neutralization reaction takes place between sodium hydroxideand fatty acids. As hydrogen ions are consumed or liberated during the course of reaction, amount of reagent added tomaintain deviating pH to

the set pH value is measured. Most of the works reported the use of USP II (Paddle)dissolution apparatus or large pore dialysis tubing to determine release from liposphere formulations. Filtered lipospherepreparation can be filled into hard gelatin capsules and drug release from such capsules can be determined by usingstandard USP II (paddle) apparatus. Alternately, drug release from liposphere dispersions can be determined throughdialysis membrane. Large pore dialysis membrane of 300,000 molecular weight (regular membrane pore size of 12,000was found to affect the drug release) has been used to determine release from several drugs. For example, bupivacinefrom formulations containing 4% free drug was released immediately through dialysis membrane. A 2% loadedlipospheres of etoposide 91 released 90% of drug constantly over a period of 80 hrs.[2]

Entrapment Efficiency Percentage = Entrapped drug/Total drug *100

Conclusion

Lipid based delivery systems like lipospheres offer new type of carrier system for lipophilic drugs. Easy availability offormulation ingredients and feasible, simple production techniques offer attractive option for formulation of lipospheresat industrial scale. Owing to the finer particle size of lipospheres and presence of a surface stabilized by emulsifier

particles, bioavailability of several problematic drugs was found to increase. Recent works demonstrate sustained releaseof drugs entrapped in lipospheres. Hence lipospheres can be considered as new formulation approach for drug moieties.Lipid carriers have bright future due to their inherent property to enhance the bioavailability of lipophilic drugs with

poor water solubility. However, the limitations of these carriers like poor physiochemical properties of lipids, lack ofdrug solubility database in lipids and unavailability of standard methodologies for *in-vitro* analysis, need to beaddressed. Liposphere formulations were effective in delivering various drugs and biological agents including: localanesthetics, antibiotics, vaccines, and anticancer agents with a prolonged activity of up to four to five days. Theliposphere approach employs a fat lipid environment to achieve desired goal for controlled and safe delivery of drugs.Lipospheres have the potential to be a major contributor to the search for better oral, parentral and topical drug deliverysystems due to their improved adsorption and penetration. In addition, lipospheres could be suitable for low costproduction, clinical and large-scale production. Therefore, Lipospheres could be considered as a promising deliverysystem for oral, parental and topical delivery of lipophilic drugs.

References:

1.Mohammed Naeem, BhiseKiran,Formulation and development of fenofibrate loaded liposphere,Journal of Drug Delivery & Therapeutics; 2013, 3(1), 1-10

2.LeeladharPrajapati, lipospheres: recent advances in various drug delivery system,International Journal Of Pharmacy&Technology ;2013, 5 (1), 2446-2464

3. Satheeshbabu.n, gowthamarajan.k , Manufacturing techniques of lipospheres: overview International Journal of Pharmacy and Pharmaceutical Sciences ; 3,(4), 2011

4. Ravi Kumar MNV. Nano and microparticles as controlled drug delivery devices, J. Pharm. Pharmaceut. Sci., 2000; 3: 234-258.

5. Gombotz W. Prolonged release of GM-CSF, United States Patent: 5942253; 1995.

6. Wake MC. Effects of biodegradable polymer particles on rat marrow-derived Stromal osteoblasts in vitro, Biomaterials 1998; 19: 1255-1268.

7. Cortesi R. Preparation of liposomes by reverse-phase evaporation using alternative organic solvents, J. Microencapsul 1999; 16: 251-256.

8. Vyas SP, Singh R, Dimitrijevic D. Development and characterization of nifedipinelipospheres, Pharmazie 1997; 52: 403-404.

9. Jenning V, Thünemann AF and Gohla SH. Characterization of a novel solid lipid Nanoparticle carrier system based on binary mixtures of liquid and solid lipids. Int. J. Pharm 2000; 199: 167

10. Claudio Nastruzzi, editor. Lipospheres in Drug Targets and Delivery Approaches, Methods, and Applications. New York: Washington; 2005.

11. Domb, Abraham J, Maniar, Manoj. Lipospheres for Controlled Delivery of Substances. European Patent: EP0502119.

12. Simon Benita Microencapsulation Methods and Industrial Applications. In: Abraham J. Domb, editors. Lipospheres for Controlled Delivery of Substances. 2nd ed. p. 297-315.

13.Ch. NiranjanPatra (2013) Liposphere: A Versatile Controlled Release Carrier for Hydrophobic Drugs. J Pharm Drug Devel 1: e202