

LIOSPHERE: A NOVAL APPROACH OF DRUG DELIVERY

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ABSTRACT

Lipids usually enhance drug absorption in the gastrointestinal tract (GIT), and when formulated as nanoparticles, these molecules improve mucosal adhesion due to small particle size and increasing their GIT residence time. 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. 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. Various 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.

KEYWORDS: Liposphere, lipid drug delivery system, Solvent emulsification–diffusion technique.**INTRODUCTION**

Lipids usually enhance drug absorption in the gastrointestinal tract (GIT), 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.

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 0.2-100 μ m 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. 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 as carrier 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-

- Improving drug stability
- Possibility for controlled drug release
- Controlled particle size
- 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.^[1]

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) and lipospheres are now being studied widely.
- Solid lipid nanoparticles are nanosized lipid carriers in which lipidic core contain the drug in dissolved or dispersed 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.^[2]
- Extended release of entrapped drug after single injection.
- Lipospheres exhibit enhanced physical stability due to avoidance of coalescence
- Ease of preparation and scale up.
- Low cost of ingredients.
- High entrapment of hydrophobic drugs.
- Controlled particle size.
- Reduced mobility of incorporated drug molecules responsible for reduction of drug leakage, circumvention of instabilities due to interaction between drug molecules and emulsifier film.
- Static interface facilitates surface modification of carrier particles after solidification of the lipid matrix.
- Lipospheres well comply with the needs of the drug development process, as for instance safety, stability, different application's fields (pharmaceutical, veterinary, cosmetic as well as food additives) and administration pathways (oral, mucosal and topical delivery), ease of modifying the release of APIs, taste masking ability, rapidity and availability of several processing techniques. Moreover, advances in solvent free process technologies have greatly improved the potential for successful lipid based formulations without surfactants included.

Lipospheres

Lipospheres were first reported as a particulate dispersion of solid spherical particles between 0.2-100 µm in diameter consisting of solid hydrophobic fat core

such as triglycerides or fatty acids derivatives, stabilized by monolayer of phospholipids.^[4] The internal core contains the drug dissolved or dispersed in solid fat matrix. Lipospheres represent a new type of fat based encapsulation system developed for parenteral and topical delivery of bioactive compounds. Inconsistent nomenclature is found in relation to lipospheres as nano-scale particles termed solid lipid nano particles (SLN).^[5,7]

- Agents for agricultural applications such as herbicides, fungicides and fertilizers can also be incorporated into lipospheres.^[5] Lipospheres are distinct inner cores at room temperature. The lipospheres are distinct from microspheres of uniformly dispersed material in homogenous polymer since they consist of at least two layers, the inner solid particle and the outer layer of phospholipids.^[5]
- The combination of solid inner core with phospholipid exterior confers several advantages on the lipospheres compared with conventional microspheres and microparticles, including high dispersability in aqueous medium, and a release rate for the entrapped substance that is controlled by the phospholipid coating and the carrier. There are also many advantages of lipospheres over the dispersion based delivery systems. Lipospheres have increased stability as compared to emulsion based systems, including vesicles and liposomes, and are more effectively dispersed than most suspension based systems. Further, the substance to be delivered does not have to be soluble in the vehicle since it can be dispersed in the solid carrier. Lipospheres also have a lower risk of reaction of substance to be delivered with the vehicle than in emulsion system because the vehicle is a solid material. Moreover, the release rate of the substance from the liposphere can be manipulated by altering either or both the inner solid vehicle or the outer phospholipid layer. Lipospheres are also easier to prepare than delivery vectors such as liposomes and are inherently more stable. Stability has become the major problem limiting the use of liposomes, both in terms of shelf life and after administration in vivo. Liposomes and vesicles do not remain intact or available in vivo after injection for more than a few hours to a couple of days. Unlike many of the biodegradable polymeric systems, the lipospheres not made with biodegradable polymers are stable in aqueous solutions. As importantly, the cost of the reagents for making the lipospheres (food grade) is significantly less than the cost of reagents for making liposomes, which require very pure lipids.

Advantages of liposphere drug delivery system

- High dispersability in aqueous medium
- Ease of preparation and scale up
- High entrapment of hydrophobic drugs.

- Lipospheres exhibit enhanced physical stability due to avoidance of coalescence.
- Reduced mobility of incorporated drug molecules responsible for reduction of drug leakage, circumvention of instabilities due to interaction between drug molecules and emulsifier film.
- Static interface facilitates surface modification of carrier particles after solidification of the lipid matrix.
- Low cost of ingredients.^[4]

Disadvantages

- Low drug loading capacity for protein.^[8]
- Insufficient stability data
- High pressure induced drug degradation.
- Variable kinetics of distribution process.

Method for preparation of Lipospheres

Melt dispersion technique

A mixture containing all the phospholipids, cholesterol etc, are 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 60-70°C containing suitable surfactant. The emulsion is mechanically stirred by using mechanical stirrer equipped with alternate impellers and maintained at 70°C. And a hot buffer solution is added at once, along with the phospholipid powder. The hot mixture is homogenized for about 2 to 5 min, using a homogenizer or ultrasound probe, after which a uniform emulsion is obtained. 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.^[9,10]

Solvent emulsification–diffusion technique

In solvent emulsification-diffusion technique, the solvent used (e.g. benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate) must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil. Initially, both the solvent and water were mutually saturated in order to ensure the initial thermodynamic equilibrium of both liquid. When heating is required to solubilise the lipid, the saturation step was performed at that temperature. Then the lipid and drug were dissolved in water saturated solvent and this organic phase (internal phase) was emulsified with solvent saturated aqueous solution containing stabilizer (dispersed phase) using mechanical stirrer. After the formation of o/w emulsion, water (dilution medium) in typical ratio ranges from 1:5 to 1:10, were added to the system in order to allow solvent diffusion into the continuous phase, thus forming aggregation of the lipid in the nanoparticles. Here the both the phase were maintain at same elevated temperature and the diffusion step was performed either at room temperature or at the temperature under which the lipid was dissolved. Throughout the process constant

stirring was maintained. Finally, the diffused solvent was eliminated by vacuum distillation or lyophilisation.

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 50-60°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 hr till complete evaporation of the solvent. The LS are recovered by filtration through a filter paper, dried and stored.^[11]

Roto evaporation method

In this technique, lipid solution with drug is prepared in a round bottom flask containing 100 grams of glass beads (3mm 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 vessel 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.

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 vortexes 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.^[9]

Multiple microemulsion method

This method in which a solution of peptide is dispensed in stearic acid melt at 70°C followed by dispersion of this primary emulsion into aqueous solution of egg lecithin, butyric acid and taurodeoxycholate sodium salt at 70°C. 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.

Ultrasonication or High Speed Homogenization

This ultrasonication technique is a dispersing technique, which was initially used for the production of solid lipid

micro or nano dispersion. Ultrasonication based on the mechanism of cavitations. Step wise procedure for ultrasonication is: The drug was added to previously melt solid lipid then the heated aqueous phase (heated to same temperature) was added to the melted lipid and emulsified by probe sonication or by using high speed stirrer or aqueous phase added to lipid phase drop by drop followed by magnetic stirring. The obtained pre-emulsion was ultrasonicated using probe Sonicated with water bath (at 0°C). Production temperature kept at least 5°C above the lipid melting point in order to prevent recrystallization during the process. The obtained nanoemulsion (o/w) is then filtered through a 0.45µm membrane in order to remove impurities carried in during ultrasonication. The obtained SLN is stored at 4°C. To increase the stability of the formulation it is necessary to lyophilize with the help of lyophilizer to obtain freeze-dried powder and sometime mannitol (5%) was added into SLNs as cryoprotector.

Polymeric Liposphere

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 (PLD) or PCL substitute the triglycerides. Both types of lipospheres are thought to be stabilized by one layer of phospholipid molecules embedded in their surface.^[12]

LITERATURE REVIEW

- **Umesh et al (2016)** formulated pioglitazone hydrochloride lipospheres by melt dispersion technique using 32 full factorial design. Optimized formulation of pioglitazone hydrochloride (PLS 5) shows 79.69± 1.35% entrapment efficiency, 94.63± 2.10% drug content and particle size was found to be 23.74± 0.35µm with spherical shaped free flowing particles. In vitro release was carried out using dissolution apparatus in 0.1N HCl and optimized formulation shows 96.06 ± 0.54 % drug release within 8 hrs. Which follows quasi-fickian type of transport and was characterized by the Korsmeyer-Peppas model. Formulation was stable at 5 oC ± 3 oC for two months. Developed liposphere formulation was able to sustain the drug release and entrap the pioglitazone hydrochloride drug at high level.^[13]
- **Satheesh et al (2016)** developed ofloxacin loaded lipospheres as a drug delivery system to improve the oral bioavailability, reduce toxicity and achieve better patient compliance. The ofloxacin loaded lipospheres were formulated by melt dispersion technique using cetyl alcohol; poly vinyl alcohol (0.1% w/v) and pectin (1% w/v) act as lipid carrier, surfactant and co-surfactant respectively. The in vitro release kinetic studies were carried out for lipospheres loaded with ofloxacin and the value of R² in Higuchi model is greater than 0.99 and release exponent (n), was found to be more than 0.5 that is Non-Fickian type. The in vitro release kinetic followed dissolution and then Korsmeyer–Peppas models. The bioavailability of ofloxacin loaded lipospheres was performed in rabbits after oral administration was studied. The plasma drug concentration was estimated by using a simple, accurate and precise high performance thin layer chromatographic technique. The pharmacokinetics studies demonstrated that the liposphere system enhance the bioavailability of ofloxacin by 2.45 fold after oral administration. Based on these results, we concluded that lipospheres might be a promising lipid based colloidal carrier system to enhance the bioavailability of ofloxacin.^[14]
- **Upendra et al (2015)** formulated Glimepiride Lipospheres using 3² full factorial design. They Glimepiride optimized formulation was evaluated for entrapment efficiency, drug content, particle size analysis, surface morphology, percentage drug release and stability study. For formulation GLS 4, drug content 85.13 ± 2.35 %, entrapment efficiency 85.37 ± 2.50 % and particle size 25.68 ± 0.18 µm was observed with spherical shaped free flowing particles. Percentage drug release was carried out using USP type II dissolution apparatus in 0.1N HCl medium and drug release of glimepiride lipospheres within 8 hrs was found to be 81.19 ± 3.91 % for GLS 4 batch. Formulation was able to sustain the drug release. Drug release follows non-fickian super case II type of transport and Korsmeyer- Peppas was the best suited model for drug release. Stability study of optimized glimepiride lipospheres formulation revealed that the formulation was stable at 5oC ± 3oC for two months.^[15]
- **Satheesh et al (2015)** formulated naproxen loaded lipospheres. The lipospheres were characterized for particle size, photo microscopy, scanning electron microscopy, FT-IR spectroscopy, drug entrapment efficiency, in vitro release studies, and in vitro release kinetics. The shape of microspheres was found to be spherical, drug entrapment efficiency of various batches of microspheres was found to be ranging from 80 to 90 %. The in vitro drug release studies of optimized batches were carried out for up to 24 h using phosphate buffer pH 7.4 showed 80-85% drug release. The optimized formulation batch was considered for scale up process. The lipospheres obtained from the scale up were then characterized for particle size, drug loading and morphology and compared with non-scaled up optimized batch, thereby establishing successful process scale-up.^[15]
- **Alladi et al (2015)** formulated lamivudine lipospheres by means of pegylation. n. The method involved to formulate pegylated lipospheres is melt dispersion method by using paraffin wax, stearic acid, tween80,lecithin and PEG (Poly ethylene

glycol) 4000. The lipospheres of lamivudine was pegylated using a biocompatible polymer lecithin which was proved to be efficient in achieving delayed and targeted drug release. From the dissolution studies F3 formulation was optimized for characterization studies. Long circulating lipospheres of lamivudine were spherical and free flowing. Characterization studies with FT-IR do not showed any interaction between drug and polymer. The investigated study can be an effective therapeutic approach for the treatment of AIDS.^[16]

- **Kar et al (2015)** developed mucoadhesive buccal tablet of Itraconazol. Various approaches to combine hydrophilic (HPMC, chitosan) polymers have been made to prepare total six formulations. Further, these formulations were subjected to different evaluation studies like content uniformity, surface pH, friability, bio adhesiveness and dissolution tests. Results for in vitro drug release and bio adhesiveness studies suggest that the formulation (F5) containing chitosan (20%w/w) and HPMC (80%w/w) has shown better mucoadhesive property. Thus, the present investigation suggests the combination of HPMC and chitosan, as hydrophilic polymers for preparation of Itraconazole mucoadhesive tablets.^[17]
- **Wattamwar et al (2014)** studied Liposphere as a Lipid Based Drug Delivery System. 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.^[18]
- **Sandeep et al (2014)** studied about methods and its applications in bio-compatible drug delivery system of liposphere. Lipospheres are made of solid hydrophobic triglycerides containing active moiety either dissolved (Lipophilic) or dispersed (Hydrophobic) & having a monolayer of phospholipids embedded on the surface of the particle. Lipospheres derived their name from lipid microspheres. These are generally used as carrier vehicle for hydrophobic drugs. However hydrophilic moieties such as Proteins & Peptides can be effectively delivered. Lipospheres are mainly composed of materials like triglycerides, waxes, oils etc. which avoids the toxicity than that bearing with the use of synthetic polymers concerns of monomers after intracellular processing of polymers and attractive benefits offered by lipids as carriers. This article reviews lipospheres in particular as delivery system.^[19]
- **Malarvizi et al (2014)** formulated "Itracinazole nanosuspension as aerosol foam formulation" for the treatment of skin diseases such as Cellulitis, Erysipelas, Impeigo and Blastomycosis, Histoplasmosis, Onchomycosis, etc. The solubility of poorly soluble itraconazole can be improved through nanosuspension process and also the absorption rate and bioavailability of drug can be enhanced by means of aerosol foam dispersion at the site of application.^[20]
- **Anna et al (2012)** studied Lipospheres and pro-nano lipospheres for delivery of poorly water soluble compounds. This study focuses on updated information on several aspects of lipospheres and PNL, including preparation techniques, physicochemical properties and in vitro evaluation methods. Additionally, it covers lipospheres and PNL utilization for oral, ocular, and parenteral delivery, with special attention to unique considerations and aspects for each route of administration.^[21]
- **Avi et al (2012)** formulated pro-dispersion liposphere for delivery of cyclosporine. Prepared pro-dispersion liposphere formulation is a homogeneous solution of a lipophilic drug such as cyclosporin in a mixture of surfactants, lipids and ethyl lactate proved to spontaneously form dispersion when added to aqueous media. This formulation concept has a potential clinical use for improved bioavailability of water insoluble drugs.^[22]
- **Nasr et al (2008)** developed lipospheres of Aceclofenac for topical skin delivery by using different lipid cores. Lipospheres were prepared using different lipid cores and phospholipid coats adopting melt and solvent techniques. The anti-inflammatory effect of liposphere systems was assessed by the rat paw edema technique and compared to the marketed product. Results revealed that liposphere systems were able to entrap aceclofenac at very high levels (93.1%). The particle size of liposphere systems was well suited for topical drug delivery. DSC revealed the molecular dispersion of aceclofenac when incorporated in lipospheres. Both entrapment efficiency and release were affected by the technique of preparation, core and coat types, core to coat ratio and drug loading. Lipospheres were very stable after 3 months storage at 2–8°C manifested by low leakage rate (less than 7%) and no major changes in particle size. Finally, liposphere systems were found to possess superior anti-inflammatory activity compared to the marketed product in both lotion and paste consistencies. Liposphere systems proved to be a promising topical system for the delivery of Aceclofenac.^[23]
- **Hagalavadi et al (2007)** formulated glipizide loaded lipospheres using response surface methodology. Numerical optimization using the desirability approach was employed to develop an optimized formulation by setting constraints on the dependent and independent variables. The experimental values of dg, % EE, rel12 and t50 values for the optimized formulation were found to be 57.54 ± 1.38 mm,

86.28 ± 1.32%, 77.23 ± 2.78% and 5.60 ± 0.32 h, respectively, which were in close agreement with those predicted by the mathematical models. The drug release from lipospheres followed first-order kinetics and was characterized by the Higuchi diffusion model. The optimized liposphere formulation developed was found to produce sustained anti-diabetic activity following oral administration in rats.^[24]

- **Bhatia et al (2007)** developed lipospheres of benzocaine to improve the local anesthetic performance using different combinations of lipids/oils (e.g castor oil, arachis oil, and soybean oil), with surfactant (lecithin) and co surfactant (polyoxyethylene sorbitan monooleate). Following selection of suitable oil phase, surfactant, and cosurfactant, the composition of the lipospheres was optimized to obtain maximum drug loading and sustainability. The formulations were further evaluated for *ex vivo* drug permeation and retention behaviour in mice skin. The optimum formulation with the highest skin permeation rate and retention consisted of benzocaine (0.1 g), soybean oil (25 g), lecithin (0.15 g), and Tween 80 (0.025 g) with aqueous: non-aqueous phase volume ratio as 5:1. The onset of anesthetic effect in rabbit cornea was found to be 6 min with lipospheres vis-à-vis 17 min and 13 min, observed with the classical emulsion system and plain drug solution, respectively. Analogously, the anesthetic effect lasted much longer for 53 min with lipospheres in comparison to 11 min and 18 min with classical emulsion and plain drug solution, respectively. Another study on human volunteers using pin-prick method also corroborated improved pharmacodynamic activity of lipospheres over classical conventional emulsion system. Accordingly, the *in vivo* results were quite in accordance with the *ex vivo* findings, as the lipospheres exhibited quicker onset of action and longer duration of anesthesia.^[25]
- **Toongswana et al (2004)** developed Bupivacaine lipospheres were prepared as a parenteral sustained-release system for post-operative pain management. Bupivacaine free base was incorporated into micron-sized triglyceride solid particles coated with phospholipids, which were formed via a hot emulsification and cold resolidification process. The bupivacaine liposphere dispersions were characterized with respect to drug loading, particle-size distribution, and morphology. Gelation of the fluid liposphere dispersions was observed at different time intervals upon storage. The type of phospholipids used in the formulation was found to have a major impact on the gelation of the dispersion. The use of synthetic phospholipids instead of the natural phospholipids in the formulation yielded bupivacaine liposphere dispersions exhibiting prolonged gelation time. The addition of a hydrophilic cellulosic polymer can

further improve the physical stability of the dispersion.^[26]

- **Siriporn et al (2004)** lipospheres were prepared as a parenteral sustained-release system for post-operative pain management. They observed Gelation of the fluid liposphere dispersions at different time intervals upon storage. The type of phospholipids used in the formulation was found to have a major impact on the gelation of the dispersion. The use of synthetic phospholipids instead of the natural phospholipids in the formulation yielded bupivacaine liposphere dispersions exhibiting prolonged gelation time. The addition of a hydrophilic cellulosic polymer can further improve the physical stability of the dispersion.^[27]

Application

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 adjuvants.^[12]

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.

Oral delivery

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

REFERENCES

1. Mohammed N, Bhise K. Formulation and development of fenofibrate loaded liposphere, *Journal of Drug Delivery & Therapeutics*, 2013; 3(1): 1-10.
2. Leeladhar P. lipospheres: recent advances in various drug delivery system, *International Journal Of Pharmacy & Technology*, 2013; 5(1): 2446-2464.
3. Müller RH, Maeder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery-a review of the state of the art. *Eur J Pharm Biopharm*, 2000; 50(1): 161-177.
4. Mangenheim B., Levy M.Y., Benita S. An in vitro technique for evaluation of drug release profile from colloidal carriers – ultrafiltration technique at low pressure. *Int. J. Pharm.*, 1993; 94: 115–120.
5. Domb A.J., Manier M. Lipospheres for controlled delivery of Pharmaceuticals, pesticides, fertilizers. *Nova pharmaceuticals, pesticides, fertilizers. Nova*

- Pharmaceutical Corporation 90–US 6519 (9107171). 1990; 79: 8-11.
6. Masters D.B., Domb A.J. Lipospheres local anesthetic timed release for perineural site application. *Pharm. Res.*, 1998; 15: 1038–1045.
 7. Khopade A.J., Jain N.K. Long circulating liposphere targeted to inflamed tissue. *Pharmazie*. 1997; 52: 165 – 166.
 8. Amselem S., Alving C.R., Domb A.J. Lipospheres for vaccine delivery. *Drugs Pharm. Sci.*, 1996; 77: 149 – 168.
 9. Rawat M., Saraf S. Liposphere: Emerging carriers in delivery of proteins and peptides. *Int. J. Pharm. Sci. and Nanotechnol*, 2008; 1: 207 – 214.
 10. Lentz B.R., Carpenter T.J., Alford D. R. Spontaneous fusion of phosphatidyl choline small unilamellar vesicles. *Biochemistry*, 1987; 26: 5389–5392.
 11. Morels S., Gasco M.R., Cavalli R. Incorporation in lipospheres of [D – TrP – 6] LHRH. *Int. J. Pharm.*, 1994; 105: R1–R3.
 12. Morel S., Ugazio E., Cavalli R., Gasco M.R. Thymopentin in solid lipid nanoparticles: *Int. J. Pharm.*, 1996; 132: 259–261.
 13. Raisel A., Sheskin, T., Bergelson L., Domb A.J. Phospholipid-coated poly (lactic acid) microspheres for delivery of LHRH analogues. *Polym. Adv. Tech.*, 2002; 13: 127–136.
 14. Umesh MB, Upendra CG, Pravin DC. Development of pioglitazone hydrochloride lipospheres by melt dispersion technique: Optimization and evaluation, *Journal of Applied Pharmaceutical Science*, 2016; 6(01): 107-117.
 15. Sateesh Babu N et al, formulation design and *in vitro* evaluation of azithromycin loaded lipospheres using melt dispersion technique, *Journal of pharmacy research*, 2016; 4(11): 4069-407.
 16. Upendra CG, Umesh MB, Pravin DC. Formulation Development, Optimization and In-vitro Evaluation of Glimepiride Lipospheres, *Int. J. Pharm. Sci. Rev. Res.*, 2015; 34(2): 157-162.
 17. Alladi Saritha, Ponnam Ravi Kumar. Formulation and Evaluation of Pegylated Lipospheric Delivery system of Lamivudine, 2015; 4(1): 44-47.
 18. Satheesh BN, Senthil RD, Prabakaran L, Venkata SM, Suriyakala PC. Formulation Optimization, Scale Up Technique And Stability Analysis Of Naproxen Loaded Lipospheres, *Asian J Pharm Clin Res.*, 2015; 7(2): 121-126.
 19. Kar, S K; Momin, Munira; Joshi, Sonali; Kute, Chaitrali; Jaybhaye, Aart a Formulation Development and pharmacotechnical Evaluation of Mucoadhesive drug delivery system for oral candidiasis. *International J Pharm Sci Res.*, 2015; 6(3): 1156-1160.
 20. Wattamwar MM, Ratnaparkhi MP, Chaudhari SP. Liposphere - Lipid Based Drug Delivery System: A Review, *Asian Journal of Pharmaceutical Technology and Innovation*, 2014: 02(06).
 21. Sandeep VJ, Dipika PS, Moreshwar PP, Rohit MJ. Liposphere Review: Methods And Its Applications In Bio-Compatible Drug Delivery System, *World Journal Of Pharmacy and Pharmaceutical Sciences*, 2014; 3(9): 1023-1043.
 22. K., Malarrvizi, D., Ramaya Devi, Alfred, Raymond, B.N., Vedha Hari. Engineered Nanoparticle Aerosol Foam Formulation for skin Disesses. *International Journal of Scientific Engineering and Technology*, 2014; 3(2): 109-115.
 23. Anna E, Irina C, Yanir A, Abraham J. Domb, AH, Lipospheres and pro-nano lipospheres for delivery of poorly water soluble compounds, *Chemistry and Physics of Lipids*, 2012; 165: 438–453.
 24. Avi Avramoff, Wahid Khan, Aviva Ezra, Anna Elgart, Amnon Hoffman, Abraham J. Domb, Cyclosporin pro-dispersion liposphere formulation, *Journal of Controlled Release*, 160(2012): 401–406.
 25. Maha Nasr, Corresponding author Samar Mansour, Nahed D. Mortada, and A. A. El Shamy Lipospheres as Carriers for Topical Delivery of Aceclofenac: Preparation, Characterization and In Vivo Evaluation. *AAPS PharmSciTech.*, 2008; 9(1): 154-162.
 26. Hagalavadi NS, Pragnesh BP, Bapusaheb GD, Purnima A, Sinnathambi A, Design and statistical optimization of glipizide loaded lipospheres using response surface methodology, *Acta Pharm.*, 2007; 57: 269–285.
 27. Bhatia, Amit; Singh, Bhupinder; Rani, Veena; Katare, O. P. Formulation, Characterization, and Evaluation of Benzocaine Phospholipid-Tagged Lipospheres for Topical Application. *Journal of Biomedical Nanotechnology*, 2007; 3(1): 81-89.
 28. Toongsuwan S1, Li LC, Erickson BK, Chang HC. Formulation and characterization of bupivacaine lipospheres. *Int J Pharm.*, 2004; 1(2): 57-65.
 29. Siriporn T, Luk-Chiu L, Bryan KE , Hung-Chih C, Formulation and characterization of bupivacaine lipospheres, *International Journal of Pharmaceutics*, 2004; 280: 57–65.