World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Review Article

An overview on lipospheres

C.H. Sirisha[1], B. Chaitanya*[2], Lakshmi Naganathan[3], J.V.C. Sharma[3]

[1] Department of Pharmacy, [2]Department of Pharmaceutics, [3] Department of Pharmacognosy, Joginpally B.R. Pharmacy College, Moinabad, 501504

Received: 11-11-2019 / Revised Accepted: 10-12-2019 / Published: 02-01-2020

ABSTRACT

Recent advances in pharmaceutical research focuses 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. Lipospheres are amongst the promising particulate drug delivery systems for improving dissolution of water insoluble drugs. They were initially reported as 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 mono layer of phospholipids. Lipid based drug delivery system (LDDS) or lipospheres are extensively employed as oral delivery systems for drugs and other active ingredients in the field of pharmaceutical, food, agriculture and cosmetic technology. This article presents various aspects of lipospheres like its types, formulation, techniques employed in preparation, evaluation techniques and applications.

Keywords: Lipid based Drug Delivery System, Lipospheres, Lipid carrier, Solid-Lipid nanoparticle

Address for Correspondence: B. Chaitanya, Department of Pharmaceutics, Joginpally B.R. Pharmacy College, Moinabad, 501504; **E-mail:** chaithu.15june@gmail.com

How to Cite this Article: C.H. Sirisha, B. Chaitanya, Lakshmi Naganathan, J.V.C. Sharma. An overview on lipospheres. World J Pharm Sci 2020; 8(1): 6-12.

INTRODUCTION

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 100µm [1]. They represent a new type of fat based encapsulation system developed for parentral and topical delivery of bioactive compounds [2, 3]. This system was designed to protect the substance from the environment during delivery and provide controlled release of substances to targeted areas. Solid Lipid Microparticles (SLMs) is a typical example of lipospheres and combine many advantages of drug carrier systems. Techniques such as Melt dispersion, co-solvent method, multiple microemulsion method, supercritical fluid method, spray drying and spray congealing method, ultra sonication method.

Lipid based Drug Delivery System (LDDS) is broadly grouped into four: solid lipid particulate dosage forms, emulsion based systems, solid lipid tablets, and vesicular systems. Modifications from these four types include: lipospheres, solid lipid nanoparticles (SLNs), lipid drug conjugate nanoparticles (LDC), Solid Lipid Microparticles (SLMs) [4].

CORE PRINCIPLE FOR FORMATION OF LIPOSPHERES

Distribution of drug in the SLMs was found to be in three ways, such as homogeneous matrix, drug-enriched shell and drug-enriched core. Cold and hot homogenization processes led to homogeneous matrix in which the active moiety was dispersed in SLM either in molecular form or amorphous cluster. In drug-enriched shell, lipids get precipitated without drug and then drug filled shell got crystallizes on the lipid core and lead to burst release of drug from lipospheres. Drug-enriched core formed by precipitating the drug followed by lipid shell containing less amount of drug. This model obeys Fick's law of diffusion and releases the drug in a controlled manner. Drug distribution patterns in SLM were depended on the structure of matrix, chemical properties of the drug, excipients and their magnitude of interaction and also on production conditions. The drug distribution in SLM cannot be determined by lysis owing to a smaller size of particles and low melting points of lipids. Simulation methods were employed to analyse the drug distribution in SLMs and thereby release characteristics of the drug were assessed. In the compritol SLM, ibuprofen molecules were distributed in outer matrix formed by the polar hydroxyl groups of compritol, which interact with carboxyl groups of ibuprofen. Hence, the hydrophobic groups of the ibuprofen molecules remain in the body of the carrier with their carboxyl groups at the oil/water interface along with the hydroxyl groups of compritol. By this distribution of drug molecules in the lipid matrix was demonstrated [5].

TYPES OF LIPOSPHERES

a) Based on matrix composition lipospheres are classified as:

Classical lipospheres: These comprises lipid based matrix and mostly neutral lipids used in their penetration of lipophilic core e.g. TriCaprin, Tri Lauren, Stearic acid, Hydrogenated vegetable oil, TriStearin, Ethyl Stearate.

Polymer lipospheres: These comprises matrices made from biodegradable polymer e.g. poly lactic acid (PLA), polycaprolactone (PCL), poly lactic-co-glycolide (PLGA). Lipospheres of polymeric matrix have been investigated to achieve longer release periods and considered as an efficient tool for controlled delivery.

b) Based on the size and composition of lipids:

- Solid lipid microparticles (SLMs) SLMs are micro – and nanoscale drug carries possessing matrix made from fatty acid glyceride, fatty alcohols, and solid wax with high melting points. SLMs combine many advantages as drug carrier systems.
- The amount of drug encapsulated can vary up to 80 % for lipophilic compound and they are well tolerated in living systems because they are made from physiological or physiologically related material.
- The solid matrix protects loaded labile substances against degradation and they offer the possibility of controlled drug release and drug targeting [6]

Advantages

- High dispersibility in an aqueous medium.
- Extended release of entrapped drug after single injection.
- Ease of preparation and scale up.
- High entrapment of hydrophobic drugs.
- Controlled particle size.
- Lipospheres enhances physical stability due to avoidance of coalescence [4].
- 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.

Disadvantages

- SLNs dispersions often undergo unpredictable gelation tendency, particle size growth, and poor drug loading.

- Formation of perfect crystalline structure during storage: Triglycerides crystallize in different polymorphic forms such as α, γ, β' and β - forms. Recrystallization from the melt results in the metastable α -polymorph which subsequently undergoes a polymorphic transition into the stable β -form via a metastable intermediate. Transition to the β - form via a metastable intermediate form leads to drug expulsion and inability to protect or prolong the release of the encapsulated drug.
- Gel formation: The change in morphology of lipid nanoparticles from spheres to platelets is responsible for the gelation of solid lipid nanoparticle dispersion. Different lipid modifications and colloidal species coexist that may cause differences in solubility and melting point of active and auxiliary species.
- Low drug loading capacity for hydrophilic compounds.
- Variable kinetics of distribution processes.
- High-pressure induced drug degradation.
- Insufficient stability data [7, 8].

Purpose for developing particulate drug delivery system: Main purpose of developing a LDDS is to target different carriers without causing harm to different organs, avoid first pass metabolism hence enhanced bioavailability, sustained and controlled drug delivery, enhance solubility of poorly water drugs, carriers can improve the 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 (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 [9].

SELECTION CRITERIA OF DRUGS AND EXCIPIENTS

Delivery of lipophilic drugs to the target site was the main theme of liposphere formulation, where the phospholipid coat causes increased permeability by minimizing the solubility problem of the lipophilic moiety. In the case of hydrophilic drug moieties, the permeability through the biomembrane is limited and this can be successfully overcome by incorporating the active moiety in the lipid core. Hence both types of drugs can be incorporated in the lipospheres, whereas till date the lipophilic drug encapsulation was reported to be higher. The effective delivery of peptides was achieved by lipospheres with enhanced stability of peptides by reducing their exposure to different pH environmental conditions. Thus, the demerits of other site specific/targeted drug delivery systems could be minimized by proper selection of Liposphere carrier, which enables the delivery of the drug moiety effectively at the specific tissue/organs. The key factors to be considered for selection of the carrier are physicochemical properties, compatibility between drug and carrier and drug distribution in solid lipid matrix (SLM). Among the physical characteristics, the selection priority belongs to the melting point of the carrier. The melting point of carrier should be >45°C to minimize the stability problems. The hydrophilic lipophilic balance value of core materials should be <2, since they are more lipophilic and have high chances to form solid matrices over the hydrophilic materials which form colloidal dispersions. The carrier should have the capability to solubilize the drug and to form particles of optimum size and strength enabling the drug release at the desired site [10].

FORMULATION OF LIPOSPHERES

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 cores of the lipospheres.

LIPID STABILIZERS

- Glyceryl monostearate, Glyceryl monooleate, Ethyl stearate, Trilaurin
- Tristearin, Tribehenin, Tripalmitin, Trimiristin, Cetyl alcohol, Cholesterol
- Stearic acid Hydrogenated vegetable oil
- Gelatin 200 Bloom
- Pectin Carrageenan, Polyvinyl alcohol, Polyoxyethylene sorbitan
- Trioleate
- Pluronic PE 8100 Lauryl sarcosine

Various lipids and stabilizers used in the formulation of lipospheres lipids.

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 used to form the surrounding layer of lipospheres include:

- Phosphatidylethanolamine (PE)
- Soybean phosphatidylcholine (PCS)
- Dimyristoyl phosphatidylglycerol (DMPG)
- Pure egg phosphatidylcholine (PCE)
- Food grade lecithin (96% acetone insoluble)

- Lipospheres for topical and veterinary applications [9]

Factors affecting lipospheres formulation:

- **Type of lipid:** Combination of a polar (tristearin, tripalmitin or tribehenin) with polar lipids (glyceryl monostearate, glyceryl monooleate) gave lipospheres good size, shape and recovery.
- **Drug loading:** When Proportion of larger particles formed was high on increasing the drug amount. At maximum drug: lipid (1:1) insufficient coating of drug by lipid leads to the formation of aggregates during cooling phase resulting in irregular, fluffy and fragile particles.
- **Type of impeller:** Lipospheres were produced using different impeller types and particle characteristics of formed lipospheres were studied. Impellers used were of rotor (2-blade, 3blade) type, helicoidal rotor (4-blade) type, double truncated cone rotor. 2-blade rotor could produce elliptical particles of Lipospheres [9]

Factors influencing entrapment efficiency:

- **Type of lipid:** Entrapment in lipospheres is promoted by lipophilicity of API. Long chain triglycerides (tristearin and triarachidin) are generally more hydrophobic than short chain triglycerides like tricaprin and trilaurin.
- **Amount of phospholipid triglyceride:** As the phospholipid (coat) amount increases, formation of alternative systems like liposomes was observed which will compromise drug entrapment. Phospholipid at a 1:0.5 to 1: 0.25 w/w revealed that 70-90% of phospholipid polar heads were accessible on liposphere surface thus enhancing the entrapment of drug [6]
- **Effect of method of preparation:** Melt dispersion method was found to be superior over solvent evaporation method in terms of entrapment efficiency as melt method promotes drug incorporation core where as solvent evaporation promotes drug incorporation in coat.
- **Effect of stabilizer:** Lipospheres formulated with gelatin as stabilizer released 80% of total drug in 8hrs whereas formulations with Poloxamer 407 resulted in a biphasic pattern (burst release followed by slow release) [9]

TECHNIQUES EMPLOYED IN PREPARATION OF LIPOSPHERES

Melt method: The lipophilic drug was melted along with the lipid material, and the temperature was maintained at slightly higher than the melting point of the lipid or lipid mixture to maintain in the molten state. Phospholipids such as soya lecithin were added to the phosphate buffer or the aqueous phase, which was maintained at a temperature near or slightly higher than the lipid phase. The lipid mixture and the aqueous phase containing phospholipids were mixed together. In addition, emulsifier at required concentration can be added to form uniform sized spheres at range of 38-50 µm. Melatonin lipospheres of melt method for topical application was proved to be effective compared to that of gels or lotions. Several drugs like bupivacaine, glipizide, aceclofenac, retinyl acetate, progesterone, sodium cromoglycate, diclofenac, carbamazepine, C14-diazepam, proteins like somatostatin, casein, bovine serum albumin, R32NS1 malaria antigen, tripalmitin based lipospheres for lab-on-chip applications have been prepared by melt dispersion methods [11]

Co-solvent method: Use of co-solvent in liposphere development facilitates the enhanced solubility of lipids and lipophilic drugs and to obtain clear homogeneous solutions. This was evident when chloroform was used as co-solvent to prepare peptide loaded lipospheres and to solubilize polylactic acid, hydrogenated soya bean phosphatidylcholine and thereby to obtain a clear solution of N-methyl pyrrolidone containing peptide. [7] Selection of solvents and cosolvents was the result of miscibility which affects the output. The highly hydrophobic drugs viz. somatostatin, triptorelin, leuprolide were formulated as lipid systems in the presence of co-solvents such as dichloromethane, ethyl acetate, acetone, methyl ethyl ketone, tetrahydrofuran and acetonitrile and made them to solubilize along with phospholipids and polymers [12]

Multiple micro emulsion method: The uniform size of about 300 nm with 90% EE was reported with multiple microemulsion method. In this approach, the hydrophilic drugs were dissolved in an aqueous phase, and this solution was added to the lipid phase to yield primary emulsion at high temperatures. Then, the solution was added to the oil phase containing hydrophobic emulsifier to yield uniform size lipospheres. The same technique was employed on thymopentin encapsulation using sodium hexadecyl phosphate, a lipophilic counter ion [13].

Supercritical fluid method: The lipid and drug dissolved in a suitable organic solvent to form a solution which was emulsified in an aqueous phase to form an emulsion containing a discontinuous phase of micelles comprised of organic solvent, drug and lipid. Finally, the emulsion was treated with a supercritical fluid (SCF) under suitable conditions, which results in the extraction of the organic solvent from the micelles and precipitation of solid composite lipospheres in the aqueous

dispersion. Rapid removal of pressure causes the supersaturation of particles leading to enhanced stability. Use of CO2 as an SCF was favored due its low cost, nontoxicity, a critical point at 31°C and 74 bars of pressure. Insulin SLM was followed SCF method for pulmonary delivery [14].

Spray drying method: Spray drying provides smaller size particles with homogeneous distribution compared to other methods. The shape of particles was affected by drying rate, viscosity and surface tension of the drying liquid. The key parameters involved with this method were inlet and outlet temperatures, feeding rate, drying gas medium, gas flow rate, gas humidity and residence time. The rate of particle formation was controlled by these key parameters. As complete removal of solvent was observed, the chance of toxicity was also minimized. This technique was highly applicable in food industry in producing peptide loaded liposphereS [15].

Spray congealing method: Spray congealing was successfully employed for preparing lipid microparticles loaded with therapeutics such as clarithromycin, theophylline, verapamil and indomethacin. The molten lipid-containing dispersed drug at 70°C was made to flow into the spray congealer specifically into cyclone which was maintained at −20°C, which led to separation of solid particles that were again made to atomize to remove adhered condensed water. The atomization pressure and spraying temperature affect the particles size distribution and also product yield. It was noticed that the increased spraying temperature and pressure in spray congealing cause the result of reduced particle size. This method can be recommended for scale-up process of sensitive drugs like peptides to favor the stability of the active moiety and to sustain the release. Lipospheres are differing from other nanolipid carrier systems in terms of preparation itself. The solid lipid nanoparticles can be prepared by double emulsification method whereas nanostructured liquid crystals can be obtained by emulsification of cubic lipid (e.g., glyceryl monooleate) phases in aqueous buffers [16].

Ultra Sonication: 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 a 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^oC). Production temperature kept at least 5^oC 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 4oC. 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 cryo protector [17].

Sterilization of lipospheres: Sterile liposphere formulation are prepared by sterile filtration of dispersion in hot stage during preparation using 0.2 μm filter at temperature that is 50 C above the melting point of liposphere composition. Heat sterilization using a standard autoclave cycle is reliable procedure. However, it might decompose the formulation γ -sterilization of liposphere formulation did not affect their physical properties. γ - Irradiation sterilization of liposphere formulations on the other hand, did not affect their physical properties [18].

IN VITRO EVALUATION TECHNIQUES

The entrapment efficiency is defined as the drug entrapped in the lipid based particles, relative to the total amount of drug added, that is percent of drug included in the particles versus percent of drug remaining in the dispersion medium, which can be calculated from Equation 1. The EE increases with drug concentration. The EE depends on the polymer concentration as well. This was evident with that of EE of gentamycin, which was depended on PEG and EE and subsequent microencapsulation were increased gradually with PEG concentration. The EE was also affected by the lipid composition/ratio used in formulating the lipospheres. The reason behind it may be due to the presence of small amounts of fat in the inner core of the lipospheres which lead to saturation of the fat core of the lipospheres by the drug incorporated in dispersion. The EE also depends upon the drug solubility in the solvent system used for processing. Various co-solvents such as ethanol, dimethylsulfoxide and dimethylformamide are often used in the formulation of lipospheres since they aid in a higher drug entrapment. Ultra filtration and micro dialysis were considered as the most reliable techniques for EE quantification, while results obtained by ultracentrifugation, the fastest and easiest technique, but not always accurate. Loading capacity (LC) was the percentage of drug entrapment. Ultra filtration and micro dialysis were considered as the most reliable techniques for EE quantification, while results obtained by ultracentrifugation, the fastest and easiest technique, but not always accurate. Loading

capacity (LC) was the percentage of drug incorporated into the lipid particles, relative to the total weight of the lipid phase (drug + lipid) and it would be computed from the Equation 2. LC being an important parameter for characterization and optimization of lipid-based drug carrier depends mainly on the solubility of the drug under investigation in the core lipid/lipid blend, miscibility of drug melt and lipid melt, chemical and physical stature of the SLM and the polymorphic state of the lipid. The reported LC values range between 1% for prednisolone, 20-25% for cyclosporine A (CsA) and up to 50% for extremely lipophilic compound Vitamin E [19].

SIGNS OF INCOMPATIBILITY

The incompatibility between the drug and solid lipid core that cause the escape of drug from lipospheres was observed in bupivacaine lipospheres. Core formed by ethyl stearate could not incorporate bupivacaine due to incompatibility. Bupivacaine migrated out of the particles and got needle-like crystals which were due to a gradual dissolution of the drug by aqueous medium to saturation. The migration occurred due to the presence of water in the liposphere dispersion, which could be avoided by lyophilization using cryo-protectant like sucrose and kept dry until reconstituted before use [20].

SUITABLE FORMULATIONS OF LIPOSPHERES

Lipospheres being possible alternative to avoid the side effects resulting from the oral administration. The aceclofenac was formulated into lipospheres successfully to sustain the release topically. The antigen or immunogen, alone or in combination with a phospholipid carrier were able to form lipospheres with aid of melt method and also with solvent preparation. One of the most promising approaches for the delivery of poor water-soluble drugs is the use of layer-by-layer assembly technology for the encapsulation of the lipid based drugs. This technique permits the step-wise adsorption of the various components as the layer growth is governed by their electrostatic attraction and allows the formation of multi-layer shells with nanometer-scale precision. The application of layer-by-layer assembly for emulsions, nanoparticles and capsule based delivery systems for lipid based drugs were extensively developed. The lipid microparticles as a parenteral controlled release device for peptides were also established [21].

SUITABLE STORAGE CONDITIONS

As the storage conditions are important for lipid dispersion, the formulated lipospheres can be stored at 4°C in order to prevent the degradation of the coat and core material and thereby maintaining the structural integrity. Lipospheres are very stable after 3 months storage at 2-8°C manifested by low leakage rate (<7%) and no major changes in particle size. Oxytetracycline injectable lipospheres meant for veterinary use were analyzed for the injectability when stored at 4°C showed stability irrespective of the lipid used in liposphere formulations. If proper storage conditions were not maintained the problems of stability could be aroused leading to failure and may cause toxicity due to degradation of lipids [21].

STABILITY STUDIES

Many studies have been 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 methoxydibenzoylmethane (BMDBM), a sunscreen agent complexed with hydroxypropyl- β -cyclodextrin (HP- β -CD). The lipospheres of BMDBM were developed with tristearin and hydrogenated soybean phosphatidylcholine. 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 [22].

IN VIVO EVALUATION:

The efficiency of target/site specific delivery of liposphere systems was supported by *in vivo* studies. Out of these evidences, the curcumin loaded lipospheres targeted to colon for treating intestinal bowel disorder were evaluated based on the degree of inflammation and the presence of edema or ulceration, diarrheal score and visible fecal blood. Lipospheres of bupivacaine was pharmacodynamically assessed for its nerve blockade. Both sensory and motor blockade lasted for 11 h on greater side and the least being 1.8 h. The CsA loaded lipospheres were developed by spray drying along with hyaluronic acid and sodium lauryl sulfate and had increased *in vitro* and *in vivo* parameters compared with CsA powder. Such research findings provide strong support to lipospheres as effective oral dosage forms for poorly water-soluble drugs [23].

APPLICATIONS

Parenteral: 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 parenteral delivery of vaccines and adjuvants.

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 [24].

CONCLUSION

The pharmaceutical researchers focused on development of new drug delivery systems which facilitates the modifications of drug delivery time, targeting, in vivo solubility which improves the bioavailability of poorly soluble drugs. In this review article we have reviewed the achievements and importance of lipospheres drug delivery system.

REFERENCES

1. Satheeshbabu N, Gowthama Rajan K. Overview: Manufacturing techniques of Lipospheres. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3(4): 1-11
2. Cortesi R. Preparation of liposomes by reverse-phase evaporation using alternative organic solvents. J. Microencapsul. 1999; 16: 251-256
3. Masters D B, Domb A J. Lipospheres local anesthetic timed release for perineural site application. Pharm. Res. 1998; 15:1038 – 1045
4. Domb A J, Manier M. Lipospheres for controlled delivery of pharmaceuticals, pesticides, fertilizer. Nova Pharmaceutical Corporation. 90-US6519 (9107171), 1990; 79:8-11
5. Lewis L, et.al. Effect of emulsifier blend on the characteristics of sustained release diclofenac microspheres. J. Microencapsul 1998; 15:283-98
6. Madhu Kanwar Rathore, et.al. A Review on Oral lipospheres of Candesartan cilexetil. International Journal of Pharmaceutical and Biological Science. 2018; 6 (1): 01-04
7. Amselem A, et.al. Emulsions, a novel drug delivery technology. Proc Int Symp Control Rel Mater Bioacts. 1994; 2: 668–69
8. Salome A, Ikechukwu V. Lipid based drug delivery systems (LDDS): Recent advances and applications of lipids in drug delivery. African Journal of Pharmacy and Pharmacology, 2012; 7(48): 3034-59
9. Sandeep Vishnu Jadhav et.al. Liposphere review: Methods and its applications in bio compatible drug delivery system, World Journal of Pharmacy and Pharmaceutical Sciences. 2014; 3(9), 1023-1043
10. Anna Raju Yalavarthi, et.al. A perspective overview on lipospheres as lipid carrier systems. International journal of pharmaceutical investigation. 2014; 4(4): 149-155
11. Domb AJ, Maniar M. Lipospheres for controlled delivery of pharmaceuticals, pesticides, and fertilizers. Nova Pharmaceutical Corp. United States Patent 1990; 90-US6519 (9107171)
12. Mehnert W, Mader K. Solid lipid nanoparticles: Production, characterization and applications. Adv Drug Deliv Rev. 2001; 47:165-96
13. Van Krevelen DW, Hoftyzer PJ. Properties of Polymers. 2009; 4th ed. New York: Elsevier
14. Lewis L, et.al. Effect of emulsifier blend on the characteristics of sustained release diclofenac microspheres. J Microencapsul 1998; 15:283-98
15. Turzilli R, et.al. Enhancement of melatonin photostability by encapsulation in lipospheres. J Pharm Biomed Anal 2006; 40:910-4
16. Maschke A, et.al. Development of a spray congealing process for the preparation of insulin-loaded lipid microparticles and characterization thereof. Eur J Pharm Biopharm 2007; 65:175-87
17. Umesh MB, et.al. Development of pioglitazone hydrochloride lipospheres by melt dispersion technique: Optimization and evaluation, Di Journal of Applied Pharmaceutical Science. 2016; 6(01): 107-117
18. Anna Elgart et.al. Lipospheres and pro-nano lipospheres for delivery, of poorly water soluble compounds, Chemistry and Physics of Lipids. 2012; 165:438-53.
19. Muchow M, et.al. Lipid nanoparticles with a solid matrix (SLN, NLC, LDC) for oral drug delivery. Drug Dev Ind Pharm 2008; 34:1394-405.
20. Jin X, et al. A nanostructured liquid crystalline formulation of 20(S) – protopanaxadiol with improved oral absorption. Fitoterapia. 2013; 84:64-71
21. Reithmeier H, et.al. Lipid microparticles as a parenteral controlled release device for peptides. J Control Release. 2001; 73:339-50
22. Domb AJ. Long acting injectable oxytetracycline – lipospheres formulation. Int J Pharm 1995; 124:271-8.
23. Woo JS et.al. Development of cyclosporine A-loaded hyaluronic microsphere with enhanced oral bioavailability. Int J Pharm 2007; 345:134-41
24. Nancy Dixit, et.al. Liposphere: A novel approach of drug delivery, World Journal of Pharmaceutical and Medical Research, 2017; 3(6):124-130