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Liposphere: A Comprehensive Review

Ramesh Ahirwar, Mr. Ashish Chaurasia, Dr. Vijay Nigam, Dr. Anil kumarChourasiya,MuskanKankane, Pooja Adhikari
Daksh Institute of Pharmaceutical Science, Chhatarpur (M.P.)

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ABSTRACT
Lipospheres are meant to deliver both therapeutic moieties with enhanced efficacy and added stability to reach out intended tissue areas. Both hydrophobic and lipophilic therapeutics can be delivered successfully into deep and peripheral tissues by encapsulating them with crystalline lipids as liposphere. In this articlewe are compiling the key points for the formulation of liposphere and discussed about the methods of preparation, evaluation, application of liposphere. Composition and factor affecting the quality of liposphere has also been discussed. Lipospheres have been successfully utilized for the delivery of variety of substances with the potential of targeting while avoiding systemic side effects. The internal hydrophobic core of the liposphere is composed of fats, mainly solid triglycerides, whereas the surface activity of liposphere particles is provided by the surrounding lecithin layer composed of phospholipid molecules.

KEYWORDS – Liposphere**,** lipid drug delivery system, encapsulation technique, targeted drug deliverysystem

I. INTRODUCTION

Lipids usually enhance drug absorption in the gastro intestinal tract (GIT), and when formulated as nano particles, these molecules improve mucosal adhesion due to small particle size and increasing their GITresidence time. In addition, lipid nano particles 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. The various technique has been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug. Liposphere are amongst the promising particulate drug delivery system for improving dissolution rate of water insoluble drugs.[5]

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. Lipospheres also known as solid lipid microparticles are the formulations that can administer biological, synthetic, and semisynthetic drugs. [9,6]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. [22,23]

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 drugs with phospholipids outer layer. The combination of solid inner core with phospholipids exterior of several advantages on the lipospheres as compared with conventional microspheres and microparticles, including high dispersibility in aqueous medium,better physical stability, low cost of ingredients, ease of preparation and scale-up, [7] and release rate for the entrapped substance that is controlled by the phospholipid coating and the carrier. Lipospheres also have a lower risk of drug reaction than with emulsion systems because the vehicle is inert solid material. [4,8]Liposphere formulation is appropriate for parenteral and topical drug delivery system. The solid core containing a drug dissolved or dispersed in a solid fat matrixand used as carrier for hydrophobic drugs. [5] A new dimension in this area is delivery of peptides and oral delivery of drugs. [17]

Benefits of liposphere drug delivery system [1]

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 drug from hydrolysis, as well as improve drug bioavailability. To increase

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the oral bioavailability of poorly water-soluble drug moieties, thus making them ideal candidates as carriers for problematic drugs.[34]

Advantages of liposphere

1. High dispersibility in aqueous medium
2. Ease of preparation and scale up
3. Particle size of such lipid particles ranges from 0.2-100 micrometer.[35]
4. Low cost of ingredients.[36]
5. Reduced mobility of entrapped drug.
6. Protection of incorporated active compounds against degradation. [11]
7. Solid matrix is composed of well tolerated lipids
8. Extended release of loaded drug.
9. High entrapment of hydrophobic drug.
10. Better physical stability.[11]
11. Extended release of entrapped drug after single injection. [12]

The main advantage of lipospheres is that it offers better biocompatibility and being physiological substance. They are comparatively polymers but offers high degree of variability due to different degree of esterification and chain lengths or even mixtures of lipid components. Lipospheres can be administered by various routes such as oral, I.V, I.M and topical route. [11]

Disadvantages of liposphere

1. Low drug loading capacity for protein.[37]
2. Insufficient stability data.
3. High pressure induced drug degradation. [24]
4. Variable kinetics of distribution process.
5. Different lipid modifications and colloidal species coexist that may cause differences in solubility and melting point of active and excipients. [11]
6. Toxic effects of organic residues after the production of polymers, Lack of large industrial scale production.[15]

Classification of lipospheres

A) Based on matrix composition lipospheres are classified as

- **Classical Lipospheres:** These comprises lipid-based matrix and mostly neutral lipid used in their penetration of lipophilic core. E.g., Tri Caprin, Tri Lauren, Stearic acid, hydrogenated vegetable oil, Tri Stearin, Ethyl Stearate.
- **Polymer Lipospheres:** This comprises matrices made from biodegradable polymer.E.g., poly lactic acid (PLA), poly caprolactone (PCL), poly lactic-co-glycolide (PLGA). Lipospheres of polymeric matrix have been investigated to achieve longer release periods andconsidered as efficient tool for controlled delivery. This suffers from major drawback including potential toxicology.

B) Based on 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 system.

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 possibility of controlled drug release and drug targeting. [11]

Critical composition of lipospheres

Lipospheres are composed of solid lipid core surrounded by a single unit phospholipid layerthat may entrap the drug or enrich its coat with drug. The emulsifier or stabilizer is used to form uniform coat around the core material and to facilitate partition of drug between the lipid and aqueous phases. [38,39] The strong affinity between progesterone, a lipophilic drug and lipid was observed and evidence with high entrapment efficiency (EE) of 70% which resulted in sustained release.[40] On the other hand, w/o/w emulsion system was employed for a better entrapment of a hydrophilic drug. The lipids such as beeswax, stearic acid, cetyl alcohol, stearyl alcohol and cetostearyl alcohol as excipients were used in combination of pluronic-68 as dispersant at different ratios. The size of allopurinol with bee'swaxes lipid particles found to be small followed by stearyl alcohol.[41]

The development of liposphere formulations to establish lipid core and allows interaction of the drug moiety. The phospholipid was being establish to the external coat of lipospheres which are found to biosimilar to cell components. The synthesized phospholipids are viz. Dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine and distearoyl phosphatidylcholine were proved effective as coat materials.[42]

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Phosphatidylcholine, dipalmitoyl phosphatidylcholine and Di stearoyl phosphatidylcholine were proved effective as coat materials. The integrity and physical stability of lipospheres were contributed by the size of lipid particle and its surface charge. Effect of the non-ionic surfactants such as Tween 20 and Tween 80 on controlling particle size and reducing thesurface charges of lipid crystal particle formulations led to prolonged stability period.[43]

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 bio membrane is limited; 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 pHenvironmental 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.[19] 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).[20] 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.[21] The hydrophilic lipophilic balance value of core materials should be less than 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 desired site. [16]

Core principle for formation of lipospheres

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 led to burst release of drug from lipospheres. Drug-enriched core formed by precipitating the drug followed by lipid shell containing less amount of drug.

The drug distribution in SLM cannot be determined by lysis owing to a smaller size of particles and low melting points of lipids.[11] Simulation methods were employed to analyse the drug distribution in slms and thereby release characteristics of the drug were assessed.[12] 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.

FORMULATION OF LIPOSPHERE

1. Triglycerides:

- Witepsol W35
- Witepsol H35
- Compritol 888 ATO (Glyceryl behenate)
- Dynasan 112
- Precirol (Glycerylpalmito stearate)
- Tricaprin, trilaurin, tripalmitin, tristearin, trimyristin. [15]

2. 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, evening primrose oil, arachis oil, safflower oil, corn oil, rice bran oil.

3. Waxes:

- Bees wax,
- Spermaceti,
- Cetylpalmitate,
- Arachidyloleate,
- Carnauba wax,
- Cetyl alcohol,
- Cholesteryl butyrate
- Active Pharmaceutical ingredient Emulsifiers:
- Phospholipids pure-egg phosphatidylglycerol,
- Dimyristoylphosphatidylglycerol,
- Soybean phosphatidylcholine
- Surfactants Tween-80,

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- Butyl alcohol

4. **Stabilizers:** Gelatin, pectin, carrageenan, polyvinyl alcohol, polyoxyethylenesorbitan trioleate, Pluronic PE 8100, lauryl sarcosine.[15]

Factors Affecting Quality Of Lipospheres [11]

1. **Morphology of lipospheres [19]**
- Drug loading
- Type of lipid
- Type of impeller

2. **Entrapment efficiency**
- Type of lipid
- Amount of phospholipid
- Effect of method of preparation

3. **Drug release**
- Release pattern
- Effect of particle size
- Type of lipid.
- Effect of stabilizer [15]

1. **Morphology of lipospheres:** Morphology related drug loading at maximum drug lipid ratio (1:1) insufficient coating of drug by lipid forms aggregate during cooling phase which results in irregular, fluffy and fragile particles.
- **Size analysis:** Particle size and size distribution studies can be performed using coulter counter method to correlate the size and drug release from lipospheres. The lipid particles showed burst release profile for compritol lipospheres loaded with tetracaine, which was due to more surface area of exposure.
- **Type of Lipid:** Polar (glyceryl monostearate, glyceryl monooleate) and a polar (tristearin, tripalmitin or tribehenin) lipids combinations gave lipospheres satisfactory in respect of size, shape and recovery.
- **Type of impeller:** Lipospheres could not be formulated using 2-blade rotor and resulted in the formation of elliptical particles. Different impellers used are rotor (2-blade, 3-blade) type, helicoidal rotor (4-blade) type, double truncated cone rotor.

2. **Entrapment Efficiency Related**
- **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. Long chain triglycerides increase the gastrointestinal residence of API compared to medium and short chain fatty acids thus increases the bioavailability. Lipid excipients reduce the activity of P-glycoprotein and MDR (multi drug resistant) associated protein by down regulating the protein expression and increase in cell membrane permeability in addition to lymphatic uptake.
- **Amount of Phospholipid:** Triglyceride: 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.
- **Method of Preparation:** Melt dispersion technique was found to be superior than solvent evaporation in terms of entrapment efficiency as melt method increases drug incorporation core where as in solvent evaporation promotes drug incorporation in coat. [11]

Preparation Methods Of Lipospheres

1. **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 lipospheres were then washed with water and isolated byfiltration. [25,26, 3]
2. **Solvent emulsification- diffusion technique:** In solvent emulsification- diffusion technique, the solvent used must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil. (e.g., benzyl alcohol, butyl acetate, ethyl acetate, isopropyl acetate, methyl acetate). Initially, both the solvent and water were mutually saturated in order to ensure the initial thermodynamic equilibrium of both liquids. When heating is required to solubilise the lipid, the saturation step was performed at the

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temperature. Then the lipid and drug were dissolved in water saturated solvent and this organic phase was emulsified with solvent saturated aqueous solution containing stabilizer using mechanical stirrer. After the formation of o/w emulsion, water is 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 phases were maintained at same elevated temperature and the diffusion step was performed either at room temperature or at 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.

3. **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 labilecompounds, such as proteins and nucleic acids. This technique is based on the evaporation of organic solvent in which lipids are 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 from 6 to 8hr till complete evaporation of the solvent. The LS are recovered by filtration through the filter paper, dried and stored.[15]
4. **Rotary 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 roto evaporizer under reduced pressure at room temperature and a thin film is formed around at the round bottom flask and glass beads. Raise the temperature up to 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.
5. **Sonication method:** In this technique, the drug is mixed with lipid in a scintillation which is precoated with phospholipids. It is heated until the lipids melts, and then vortexes for 2 minto 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.[16]
6. **Multiple microemulsion method:** In this method the 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 tauro deoxycholate 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.
7. **Ultrasonication or highspeed 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 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 nano emulsion (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 lyophilize with the help of lyophilizer to obtain freeze- dried powder and sometime mannitol (5%) was added into slnsas cryoprotector.
8. **Super critical fluid method:** The lipid and drug are dissolved in a suitable organic solvent to form a solution which was emulsified in aqueous phase to form an emulsion containing a discontinuous phase of micelles comprised of

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organic solvent, drug, and lipid. The emulsion was treated with a super critical 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.[17] Rapid removal of pressure causes the supersaturation of particles leads to enhance the stability. Use of co2 as CSF was favored due to its low cost, nontoxicity, a critical point at 31°C and 74 bars of pressure.[18]

9. **Spray drying method:** Spray drying provides smaller particle size with homogenous distribution compared to other methods. The shape of particle was affected by drying rate, viscosity and surface tension of the drying liquid.[19] This method was inlet and outlet temperatures, feeding rate, drying gas medium, gas flow rate and gas humidity and residence time. The rate of particle formation was controlled. The 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 liposphereres.[20]
10. **Spray congealing method:** Spray congealing was successfully employed for preparing lipid microparticles loaded with therapeutics such as clarithromycin, theophylline and verapamil. 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 particle 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.[21] This method can be recommended for scaleup process of sensitive drugs like peptides to favor the stability of the active moiety and to sustain the release.

Lipospheres are differing from other nano lipid carrier system in terms of preparation itself. The solid lipid nanoparticles can be prepared by double emulsification method whereas nanostructure liquid crystals can be obtained by emulsification of cubic lipid (e.g., glyceryl monooleate) phases in aqueous buffers. [22]

11. **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. [27]
12. **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.
13. **Co solvent Method**: Cosolvent-solvent evaporation method employ in chloroform and N-methyl pyrrolidone to create a clear solution. Although low yield and large particle size was obtained, which was altered by variation in the solvent used. Lipospheres made up of polar and non-polar lipids using synthetic stabilizers instead of phospholipids which were the deviation from the definition of lipospheres. Although their work is not related to protein delivery but they tried with hydrophilic drug and reported around 50% entrapment by double emulsification method. [11]

EVALUATION OF LIPOSPHERE[44,45,46]

1. **Particle Size Analysis and Photo Microscopic Evaluation**: Particle size of different batches of lipospheres was determined by photo microscopic studies (DMWB1-123 MOTIC MICROSCOPE). Analysis was carried out by observing randomly selected 100 particles under a microscope. Mean particle size of all formulations were determined.
2. **Yield of Liposphere**:The liposphere formed were filtered from the medium, dried and

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weighed to get the yield of the lipospheres formulated per batch.

3. **Scanning Electron Microscopical Evaluation (SEM)**: Surface morphology of the specimen was determined by using a scanning electron microscope (SEM), (Model JSM 84 0A, JEOI, Japan). The samples were dried thoroughly in a vacuum desiccator before mounting on brass specimen studies, using double sided adhesive tape. Gold- palladium alloy of 120°A Knees was coated on the sample sputter coating unit (Model E5 100 Polaron U.K) in Argon at ambient of 8-10 with plasma voltage 20Ma. The sputtering was done for nearly 5 min to obtain uniform coating on the sample to enable good quality SEM images. The SEM was operated at low accelerating voltage of about 1515 KV with the load current about 80ma. The condenser lens position was maintained between 4.4 - 5.1. The objective lens aperture has a diameter of 240 µ and the working distance was above 39 mm.
4. **Determination of Drug Content**: Exactly weighed amount of the loaded liposphere (10 mg) was dissolved in 10 ml of phosphate buffer pH7.4 and sonicated for 15 min. The obtained sample was diluted to volume (100 ml) with the buffer (ph 7.4). Then the solution was filtered and assayed by UV spectroscopy at a wave length of 288 nm. (Unloaded lipospheres produced insignificant absorbance values at the same wave length). Each sample were analysed in triplicate.
5. **Invitro Release Studies**: Studies on in vitro drug release profiles require a good sink condition to be maintained.[10] It was a well-known fact that the release of a drug from lipospheres influenced by the composition of the lipospheres. Hence, the in vitro releases of cefixime from the formulation were studied. In vitro drug releases were evaluated by using a dialysis bag diffusion technique. The dialysis bags were hydrated with glycerine overnight before the experiment. Lipospheres equivalent to 100 mg were placed in the dialysis bags. The dialysis bags were tied at both ends and were placed in the basket of USP Type II dissolution apparatus (Lab India disso2000, Mumbai India). The baskets were immersed in 900 ml phosphate buffer (ph7.4) and maintained the temperature at 37.0 ± 0.5°C. The baskets were rotated at100 rpm. At regular intervals, 5.0 ml of dissolution medium was withdrawn and replaced with the fresh buffer to maintain sink condition. The withdrawn samples were filtered through a Whatman filter paper and made appropriate dilution and analysed by using spectrophotometer at 288 nm. [11]
6. **Entrapment efficiency:**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.[28]

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.[29]

The EE also depends upon the drug solubility in the solvent system used for processing. Various co-solvents such as ethanol, dimethyl sulfoxide and dimethyl formamide been often used in the formulation of lipospheres since they aid in a higher drug entrapment.[30]

Ultrafiltration and micro dialysis were considered as the most reliable techniques for EE quantification, while result obtained by ultracentrifugation, the fastest and easiest technique, but not always accurate.[31]

Entrapment efficiency (EE%) = $\frac{\text{mass of drug in liposp heres}}{\text{initial weig ht of drug}} \times 100$

7. **Loading capacity (LC):** LC expresses the ratio between the entrapped API and the total weight of the lipids. It is determined as follows:

$LC = \frac{Wa - Ws}{Wa - Ws + Wl} * 100$

where Wlis the weight of lipid added in the formulation,Wais the weight of API added to the formulation, andWsis the amount of API determined in supernatant after separation of the lipid and aqueous phase.[13]

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8. **In-vivo:** The efficiency of target/site of specific delivery of liposphere systems was supported by in vivo studies. The curcumin loaded lipospheres of 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 sulphate 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.[48]

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. [16]The migration was 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. [14]

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.[49] 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.[50] 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.[18] The lipid microparticles as a parenteral controlled release device for peptides were also established.[6,14]

Storage condition

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.[49] Oxytetracycline injectable lipospheres meant for veterinary use were analysed for the injectability when stored at 4°C showed stability irrespective of the lipid used in liposphere formulations.[47] 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.[14]

APPLICATIONS OF LIPOSPHERES

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.

Transdermal route: The 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: There are several categories of drugs like antibiotics, anti-inflammatory compounds, vasodilators, anticancer agents, proteins and peptides are being formulated aerosol lipospheres.

II. CONCLUSION

Lipospheres consist of water-dispersible solid microparticles of particle size between 0.2–500 μm in diameter and composed of a solid hydrophobic fat core stabilized by one monolayer of phospholipid molecules embedded in their surfaceThough the lipids are prone to degradation, the formulations can be stable and firm with lipids and stabilizers. The liposphere carrier system has

several advantages over other delivery systems, including emulsions, liposomes and microspheres, such as: better physical stability, low cost of ingredients, ease of preparation and scale-up, high dispersibility in an aqueous medium, high entrapment of hydrophobic drugs, controlled particle size and extended release of entrapped drug. liposphere formulation were effective in delivering various drugs and biological agents including local, anaesthetics, antibiotics, vaccines.Lipospheres are able to entrap the drug at very high levels and sustain its release over a prolonged time. Lipospheres possessed a suitable size for topical route and being based on non-irritative and non-toxic lipids, lipospheres seemed to be well suited for use on damaged or inflamed skin.

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.

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