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LIPOSPHERE - LIPID BASED DRUG DELIVERY SYSTEM FOR DELIVERY OF POORLY WATER SOLUBLE COMPOUNDS: A REVIEW

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ABSTRACT

Researchers face difficulties in designing effective formulation and improving the bioavailability of poorly water-soluble medications to therapeutic uses. The development of new drug molecule alone is not sufficient to ensure extensive pharmacotherapy for various diseases. Due to inadequate concentrations of plasma drugs, significant results obtained from in-vitro studies are not supported by in vivo data. This can be due to the limited solubility and absorption of drugs. Developing new drug delivery systems will be a promising approach to overcome these problems. Lipid microspheres, often called lipospheres, are among the promising systems of delivering particulate drugs to improve water-insoluble drug dissolution. Lipospheres are a drug encapsulation system composed of water-dispersible small particle size microparticles of between 0.01 and 100µm in diameter with a rigid hydrophobic lipid center (triglycerides), protected by a coating of phospholipid molecules embedded in their surface. The bioactive compound dissolves or disperses within the internal core's solid lipid matrix. Since lipospheres were developed in the early 1990s, they have been used by different routes of administration for the delivery of several forms of drugs. Lipospheres have several advantages over other delivery systems, such as improved physical stability, low ingredient costs, ease of preparation and scale-up, high dispersibility in an aqueous medium, high entrapment of hydrophobic drugs, controlled particle size and extended release of trapped drugs after administration, from a few hours to several days. This review article focuses on updated information on several aspects of liposphere including liposphere formulation, factors influencing liposphere quality attribute, mechanisms behind drug loading, liposphere assessment and challenges in liposphere development are discussed in detail. Besides, this

review also briefly enlisted the various applications of lipospheres in medical and biomedical fields.

KEYWORDS: Lipid microspheres, Lipospheres, Drug delivery, Delivery approaches, Formulation techniques.

INTRODUCTION

The advent of combinatorial chemistry followed by developments in in-vitro high-performance screening methods has led to the rapid discovery of many extremely active but poorly water-soluble drug candidates. In fact, to date, over 40 % of new chemical substances are lipophilic and display low water solubility.[1] The development of such poorly water-soluble compounds towards clinically available drugs presents the pharmaceutical scientists with a big challenge. Consequently, there was widespread acceptance of the understanding that the development of new active compounds alone is not sufficient to guarantee adequate pharmacotherapy of various disease states. Promising results obtained very often in invitro studies are not corroborated by in vivo data which is successful. Many explanations for these findings are in vivo. Due to limited solubility, poor absorption and extensive first-pass metabolism some drugs do not reach sufficient plasma concentrations. Some are characterized by impredictable fluctuations in the levels of plasma drugs and therefore lack an effective correlation between dose and response. Poor solubility in water could also exclude the possibility of IV administration. Aside from the site of action, other drugs are distributed to additional tissues and cause harsh adverse effects or toxicity. Toxicity and lack of therapeutic effect could also result from the decomposition of a drug during its voyage from the intestinal lumen to the systemic circulation of blood. Developing suitable drug delivery systems is a promising strategy to overcome those obstacles. Multiple-unit drug delivery systems such as nanoparticles, microparticles, microemulsions and liposomes give greater benefits than single-unit systems in terms of their consistent distribution in the gastrointestinal tract resulting in consistent drug absorption. The disadvantage of those particulate systems is the polymer degradation,[2] organic solvent residues present in the delivery system that could result in severe acceptability and toxicity problems.[3] To solve these problems, lipid microspheres, often referred to as lipospheres, were proposed as a new type of fat-based encapsulation system to deliver bioactive compounds to drugs. For the first time, lipospheres were described as a dispersion of solid spherical particles into solid hydrophobic fat core (triglycerides), stabilized by a monolayer of particle size between 0.01

and 100µm.[4] The lipospheres are suitable for the oral, parenteral and topical delivery of bioactive compounds and are designed to overcome the disadvantages of traditional colloidal systems, such as emulsions, liposomes and polymeric nanoparticles.[5,6] Since its implementation in the early 1990s, lipospheric use has been well illustrated by numerous routes of administration for the delivery of local anesthetics, anti-inflammatory agents, antibiotics, anticancer agents, vaccines, enzymes, and peptides, insect repellents, etc.[7,8] However, a pro-nanolipospheres (PNL) self-assembling encapsulation system was developed for oral drug delivery of poorly water-soluble drugs.[9] Techniques such as melt dispersion, evaporation of solvent emulsification, homogenization by hot and cold, ultrasonics and homogenization by high pressure are used for lipospheres production. A variety of advantages of the lipospheres drug delivery system include increased drug safety, bioavailability, drug hydrolysis protection, managed release of drugs, freezing hot, reconstitution properties, regulated particle size, high drug load, well-controlled release of drugs, no carrier toxicity and managed particle size with high drug load efficiency.[10] Furthermore, lipospheres protect drug candidates from hydrolysis; confirm shelf-life facilitating high bioavailability and prolonged plasma levels.[11] This review article focuses on updated information on several aspects of lipospheres including lipospheres formulation, factors influencing lipospheres quality attribute, mechanisms behind drug loading, lipospheres assessment and challenges in lipospheres development are discussed in detail. Besides, this review also briefly enlisted the various applications of lipospheres in medical and biomedical fields. These dispersions of lipids can be used for multiple routes of administration.

Advantages and Disadvantages of lipospheres

Advantages

Due to the convenience of several processing techniques such as safety , stability, route of drug administration (oral, parenteral, mucosal and topical delivery), targeting, controlled release of drugs, various fields of application (pharmaceutical , cosmetic, veterinary and food additives) and taste masking capabilities etc.[7] In addition, process innovation in solvent-free technologies has greatly enhanced the potential for successful lipid based formulations without surfactant inclusion.[10,12] The drug's polymorphic phase transitions are now being studied extensively to improve the physical stability of solid lipid nanoparticles and other lipospheres types. Lipospheres formulations have the major advantages are:

1. Nanosized carrier contains medications that are absorbed or spread in a lipid center in such a manner that the surface of the drug is coated with an emulsifier.

2. To avoid its inherent toxicity, polymeric carriers can be substituted.
3. High dispersibility in a windy medium.
4. The size of the lipid particles in the ranges from 0.2 to 100 μm can be controlled or reduced.
5. High entrapment of hydrophobic drugs.
6. Reduced or no leakage due to less sensitivity from the inserted drug.
7. Extended release of trapped drug following single injection can be obtained.
8. Increased physical stability which evades coalescence.
9. Preparation and scale-up easiness.
10. Low cost to manufacture.
11. The solidification of the lipid matrix facilitates the static interface of the carrier particles (surface modifications).
12. High stability and dispersibility in an aqueous medium, low reagent costs, ease of fabrication and high dispersibility in an aqueous medium.
13. A release rate for the trapped material which is regulated by the phospholipid and carrier coating. Effective administration of drugs such as anesthetics, antigens, and insect repellent (DEET) etc.
14. Reduced mobility of built-in drug molecules responsible for reducing drug leakage and avoiding instability due to interaction between drug molecules and emulsifier films.[4,5,8,9]

Disadvantages

The major disadvantages of liposphere are

Liposphere often undergo unpredictable gelation, particle size growth and poor drug loading for hydrophilic compounds; re-crystallize during storage due to polymorphic transition of triglycerides to the β-form via a metastable intermediate leading to drug expulsion and loss of controlled release; gel formation (changed morphology); change of lipid and colloidal species may cause differences in solubility and melting point of active and auxiliary species; low drug loading capacity for hydrophilic compounds; variable distribution kinetics; insufficient stability data and high pressure induced drug degradation.[10,13,14]

Composition of lipospheres

Lipospheres consist of a solid lipid core surrounded by a single unit of phospholipid layer that] clog the drug or fill its coat with the drug [Fig. 1]. Yes. The emulsifier or stabilizer is used to form a uniform coat around the raw substance and to promote the separation of the

product between the lipid and the aqueous phases.[15,16] Low molecular polyethylene glycols (PEGs), as plasticizers could impart the external lipid coat tensile strength. The strong affinity between progesterone, lipophilic drug and lipid was observed and evidenced by 70% high-trapment efficiency (EE) resulting in sustained release.[17] In the other hand, in order to help entrap a hydrophilic substance, w / o / w emulsion method was employed. The release of sodium cromoglycate has been shown to be based on the stabiliser principle. Different stabilizers such as gelatin and poloxamer 407 used in liposphere formulated hydrophilic drug have shown sequential release of sigmoids and biphasic release. Excipients are affected by morphology and the lipospheric characteristics. This was exemplified by a highly lipophilic allopurinol drug that contains lipid systems. In combination with pluronic-68, the lipids such as beeswax, stearic acid, cetyl alcohol, stearyl alcohol and cetostearyl alcohol as excipients were used as dispersants at different ratios. The size of allopurinol found to be small with wax lipid particles from bees followed by stearyl alcohol.[18] In the development of liposphere formulations liposphere compounds such as tristearin, tripalmitin, trilaurin and tricaprin were used as major lipid composition to establish lipid core and allow drug moiety interaction. The phospholipids were used to create the external liposphere coat found to be biosimilar to the components of the cell. The essential phospholipids used in liposphere formulations are naturally distilled ones, such as soybean phosphotidyl choline and its derivative soybean hydrogenated phosphotidyl choline. The phospholipids synthesised are viz. As coat materials, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, and distearoyl phosphatidylcholine[19] have been proven effective. The thickness of the lipid molecule and its surface charge contributed to the durability and physical consistency of the lipospheres. The effect of nonionic surfactants such as Tween 20 and Tween 80 on particle size control and reduction of the surface charges of lipid crystal particle formulations resulted in an extended period of stability.[20]

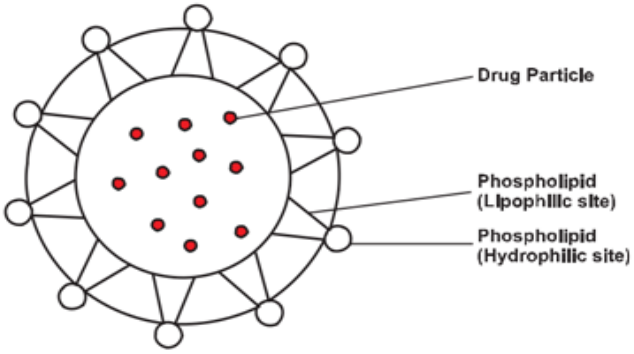

Fig. 1: Structural composition of lipospheres.

Selection criteria of Drugs and Excipients

The main theme for liposphere formulation was delivery of lipophilic drugs to the target site, where the phospholipid coat causes increased permeability by minimizing the lipophilic moiety's solubility problem. In the case of moieties of hydrophilic substances, the permeability across the biomembrane is limited; this can be solved effectively by inserting the active moiety into the lipid core. It is therefore possible to incorporate both types of drugs in the liposphere, whereas the lipophilic drug encapsulation has been reported to be higher up to date. Effective delivery of peptides was achieved through lipospheres with increased peptide stability by reducing their exposure to various pH environmental conditions. Thus, demerits from other site-specific / targeted drug delivery systems could be minimized by proper liposphere carrier selection, which enables the drug moiety to be delivered effectively to the specific tissue / organs.[21] Physicochemical properties, compatibility between drug and carrier, and drug distribution in the solid lipid matrix (SLM)[22] are the key factors to be considered for carrier selection. The selection priority belongs to the carrier's melting point amongst the physical characteristics. To minimize the stability problems, the carrier melting point should be >45°C.[23] Core materials will have a hydrophilic lipophilic equilibrium value of < 2, because they are more lipophilic and have better chances of forming stable matrices over the hydrophilic materials that form colloidal dispersions. The carrier should be capable of solubilizing the drug and shaping particles of optimal size and strength allowing the release of the drug at the desired site.[24]

Core principles for formation of lipospheres

There were three ways of distributing drug in the SLMs, such as homogeneous matrix, drug-enriched shell, and drug-enriched core [Figure. 2]. Cold and hot processes of homogenization led to homogeneous matrix in which the active moiety was distributed in either molecular form or amorphous cluster in SLM. In drug-enriched shell, lipids are precipitated without drug, and then drug-filled shell has crystallized on the lipid core, causing drug release from lipospheres to burst. Drug-enriched core formed through precipitation of the drug followed by lipid shell containing lesser drugs. This model obeys Fick 's diffusion rule and releases the drug in a controlled manner. The patterns of drug delivery in SLM were based on matrix composition, drug chemical properties, excipients and their magnitude of activity, and also on the conditions of development. Due to a smaller particle size and weak lipid melting points, the drug distribution in SLM cannot be calculated by lysis.[25] Simulation methods were used to analyze the distribution of drugs in SLMs, thereby evaluating the drug's release

characteristics.[26] In the compritol SLM, ibuprofen molecules were distributed in external matrix formed by compritol polar hydroxyl groups, which interact with ibuprofen carboxyl groups. The hydrophobic groups of the ibuprofen molecules then reside in the carrier body along with their carboxyl groups at the oil / water interface along with the compritol hydroxy groups. Matrix was proved by this distribution of drug molecules in the lipid.

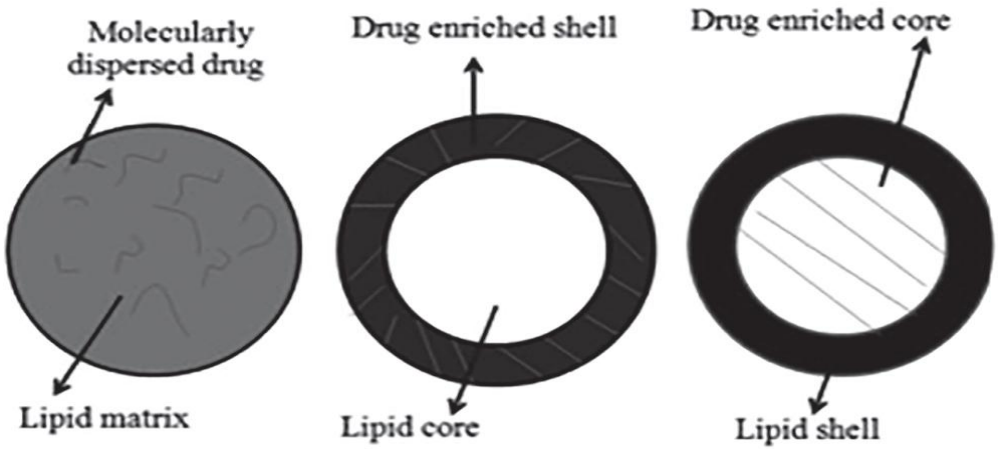

Fig. 2: Drug incorporation models in solid lipid matrix.

Lipospheres are prepared by various techniques includes

Melt dispersion technique

Initially the lipid physical mixture containing lipids, phospholipids, and cholesterol with or without a lipophilic drug will be prepared. After mechanical stirring with alternating impellers at the same temperature, the physical mixture is melted at 70 ° C and then emulsified into a hot external aqueous phase in the presence of a surfactant. The resultant emulsion is then rapidly cooled at about 20°C, while continuous agitation to obtain a uniform dispersion. The dispersion is then washed with water and filtered.[27]

Solvent evaporation technique

Unlike the method of melt dispersion, an alternative procedure known as liquid evaporation technique may be used with the goal of reducing exposure to thermolabile compounds (proteins and nucleic acids) to high temperature. The later allows solid microparticles to be formed based on organic solvent evaporation, in which lipids are dissolved. In particular, the lipidic matrix dissolved in an organic solvent (ethyl acetate) is emulsified with an external aqueous phase containing surfactant and 50°C temperature is maintained throughout the process. The resulting oil-in-water (o/w) emulsion is continuously stirred for 6 to 8 hr till complete evaporation of the organic solvent following filtration to recover the lipospheres.[27]

Co-Solvent-Solvent evaporation technique

Chloroform and N-methyl pyrollidone are used in co-solvent-solvent evaporation techniques to obtain a clear solution. The yield and particle size of the formed lipospheres may be altered by the different solvents used. The use of polar or / and non-polar lipids and synthetic stabilizers for such formulation, however, leads to a deviation from conventional liposphere definitions. Although, their work is not related to protein delivery, when trialed with hydrophilic drugs around 50% entrapment has been reported.[28]

Multiple microemulsion technique

In this technique, a peptide solution mixed with stearic acid is dispersed at 70oC into aqueous butyric acid, egg lecithin, and taurodeoxycholate sodium salt to obtain a multiple emulsion. The resulting multiple emulsion is subsequently quickly cooled to obtain the solid lipospheres with 90% entrapment of peptide. Inclusion of lipophilic counter ion has been reported to form lipophilic salt of peptide, which exhibits sustained release. Polymeric lipospheres have also been reported by double emulsification for encapsulation of antigen.[29]

Sonication technique

In this technique, a scintillation vial which is pre-coated with phospholipids mixes the drug with lipid. The vial is heated until the lipid has melted, and then vortexed for 2 minutes to ensure the ingredients are properly mixed. In the above mixture a 10 ml hot buffer solution is added and sonicated with intermittent cooling for 10min.[29]

Rotoevaporation technique

In this technique, lipid solution is thoroughly mixed with the drug in a round bottom flask of 3 mm diameter, containing 100 grams of glass beads until a clear solution is found. The solvent from the mixture is then evaporated by means of a roto-evaporizer at reduced pressure at room temperature. A thin film is formed around the glass beads and round bottom flask inside wall. A known quantity of 0.9% w/v saline is added to the round bottom flask soon after complete evaporation of the organic solvent, and the contents are mixed at room temperature for 30min. The flask is then cooled to 10 ° C by putting it in an ice bath with constant mixing for an additional 30 minutes until liposphere is formed.[29]

Microfluidizer technique

Microfluidizer equipped with two separate ports of entry may be used for lipospheric preparation. A homogenous melted solution or drug suspension with carrier is pumped from

one port, whilst an aqueous buffer is pumped from the other. All the liquids can be mixed in the instrument at elevated temperature followed by rapid cooling to form the lipospheres. The particle size and distribution of lipospheres can be manipulated by changing the temperature of the microfluidizer at any stage during the processing stage.[29]

Solvent extraction technique

In this procedure, using a static microchannel mixer, the solution of cationic lipid and triglyceride (tripalmitin) in an organic solvent (dichloromethane) is mixed with an extraction fluid [0.5 per cent w / w aqueous polyvinyl alcohol solution] and an o/w emulsion is obtained. The mixing aids in the production of fine lamellae that subsequently disintegrate into droplets to allow the dispersion of lipid microspheres in the aqueous medium.[28]

Polymeric lipospheres technique

Solvent or melt processes can be used to manufacture polymeric biodegradable lipospheres. Unlike standard lipospheres, the neutral triglycerides are replaced by biodegradable polymers such as polylactide (PLD) or poly-epsilon-caprolactone (PCL) for internal core composition. As conventional lipospheres, polymeric lipospheres can be stabilized by a phospholipid layer embedded on to the surface.[29]

Supercritical fluid technique

Recent advances in the field explored the use of supercritical fluids to circumvent organic solvent contamination during preparation or storage of lipospheres. In this technique, the resulting emulsion (including organic solvent, drug and lipid) from the conventional procedure is appropriately treated with a supercritical fluid that facilitates organic solvent extraction to permit precipitation of solid composite lipid drug particles (nano-sized) in aqueous dispersion.[9]

Sterilization of lipospheres

Sterile liposphere formulations are prepared during preparation using a 0.2-mm filter at a temperature 5 °C above the melting point of the core composition of the liposphere by sterile filtration of the dispersion in the hot stage. Heat sterilization using standard formulations of the liposphere did not affect its physical properties.[30]

Storage of liposphere

The liposphere formulations are stored in aqueous buffer, freeze dried, or in an ointment or cream base, in the freezer, refrigerator or room temperature. It is preferred to store the formulations suspended in an aqueous solution in the refrigerator for immediate use.[31]

Technique for manufacturing of nanosize lipospheres

A recently developed alternative method uses dispersible concentrate oil system to prepare nanosize lipospheres in situ (particle size less than 100 nm). The process adopts homogenisation by a series of reduced pore size filters. In this system, a mixture of surfactants (tween and span series) and suitable organic solvent [*e.g*. ethanol, propanol, propylene glycol, N-methyl pyrrolidone (NMP), low molecular weight–polyethylene glycol (PEG), ethoxilated castor oil (Cremophor), PEG conjugated α-tocopherol, or propylene–ethylene glycol copolymers (Poloxamer)] are chosen to dissolve the drug, triglyceride, phospholipid, and other additives. The resulted anhydrous and clear solution upon mixing with an aqueous solution spontaneously forms nanosize particles. The size and nature of the particles can be controlled by careful modification of the formulation compositions. Addition of a cationic (stearyl or phosphatidil ethanol amine) or anionic (stearic or phosphadilic acid) lipid can form cationic or anionic nanolipospheres respectively.[9]

Factors affecting Formulation and Entrapment efficiency of lipospheres

Type of lipids

Combinations of non-polar (tripalmitin, tribehenin, or tristearin) and polar (glyceryl monooleate, or glyceryl monostearate) lipids typically allow the development of good liposphere shape, scale, and recovery, while lipophility of the drug greatly affects the entrapment efficiency. Lipophilic drugs have greater capacity for better entrapment. The bioavailability of the drug greatly depends upon the hydrophobicity of triglyceride. At variance to short chain triglycerides (trilaurin and tricaprin) and longer chain fatty acids (triarachidin and tristearin) are normally more hydrophobic and attribute to increase the gastrointestinal residence time, thereby increasing the drug bioavailability to a greater extent. Lipidic excipients essentially contribute to lower the activity of P-glycoprotein and multi drug resistant associated proteins by down regulating the protein expression and enhanced the cell membrane permeability including lymphatic uptake. Increasing the amount of phospholipid coat may alternately lead to form liposomes, where the drug entrapment would be significantly compromised. From a case study, it was revealed that upon lowering the

triglyceride: phospholipid ratio from 1:0.5 to 1: 0.25 w/w; a significant increase in phospholipid polar heads form 70 to 90% remained accessible to drug.[32]

Drug loading

Increasing the amount of the drug can cause larger particles to form. The proportion of drugs and lipids can play an important role, where maximum drugs tend to result in insufficient lipid coating and aggregate formation (during the cooling phase), fluffy, irregular and fragile particles.[32]

Types of impeller

Impeller types can influence the characteristics of the particles in the liposphere. Particle characteristics experimented with the use of several impellers such as: type of rotor (2-blade, 3-blade), type of helicoidal rotor (4-blade) and type of double-truncated cone rotor, proving that a 2-blade rotor could produce elliptical liposphere particles.[32]

Effect of method of preparation

In comparison to the two most common methods of liposphere preparation, the technique of melt dispersion was found to be superior to the technique of solvent evaporation in terms of entrapment efficiency because the former facilitates the absorption of drugs into the center while the latter in the coat.[32]

Effect of types of stabilizer

The types of stabilizer used in formulating lipospheres can influence the pattern of drug release. Gelatin promotes 80% drug release in 8hrs, while Poloxamer 407 has led to a biphasic pattern of drug release (slow release followed by burst release).[32]

Charaterization of lipospheres

Determination of drug entrapment efficiency

The concentration of entrapped drug was determined by chloroform lysis of the lipospheres. Accurately weighed amount of liposphere loaded drug (50 mg) was dissolved in 10 ml chloroform. To obtain a clear solution the solution was sonicated for 5min.The solution was sonicated for 5min to obtain a clear solution. The concentration of drug in chloroform was determined by spectro-photometrically at particular wavelength of drug.

Particle size analysis

Particle size analyser will calculate the total particle size of the liquid liposphere packed. Often, the liquid composition is needed to achieve a concentration of 5 percent v / v for further dilution by distilled water. The distribution of particle size can be estimated by setting the scattered light intensity at 750 nm wavelength and the scattering angle (θ) at 900 respectively.[33]

Differential Scanning Calorimetry (DSC)

The drug excipients compatibility can be studied by interpreting the thermograms obtained from the measurements on a differential scanning calorimeter. During the measurements, inert atmospheric condition is maintained by purging nitrogen gas. All accurately weighed (about 3-5mg) samples are placed in a sealed aluminum pan, and heated at a scanning rate of 10ºC per min from 40 to 240ºC. An empty aluminum pan is used as reference.[33]

Scanning Electron Microscopy (SEM)

The surface morphology of the lipospheres can be analyzed with the aid of SEM. The samples are mounted on an aluminum stab by a double-sided adhesive tape and placed in the ion coater unit for gold coating under vacuum of 10-50mm. Subsequently, an accelerating voltage (10-15 kV) is applied and the image is photographed by a camera.[33]

Powder X-ray diffraction study

X-Ray diffraction studies provide information about the crystallinity of the sample, which is revealed by a characteristic fingerprint region in the diffraction pattern. Studies are carried out using a diffractometer with a definite resolution. Vacuum grease is applied over the glass slide to stick the sample. About 10mg of sample s sprinkled over the slide to make a layer (thickness of ~0.5mm). The samples are radiated using a Cu target tube and exposed to all lines of wavelength. Scanning angles ranged from 5° to 40° of 2θ, current of 30mA and voltage of 40KV can be suitably used.[33]

***In vitro* drug release study**

Amount of lipospheres equivalent to 100 mg of total drug, is filled in a capsule and *in vitro* drug release is performed in both acidic mediums i.e. 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) using an USP type I dissolution tester at a stirring rate of 75rpm. Samples are withdrawn periodically (0, 30min, 1hr up to 8h) and the volume is replaced immediately by fresh medium. The sample solution is filtered and analyzed for drug content. The study is

essentially meant for reduction of drug leakage, circumvention of instabilities due to interaction between drug molecules and emulsifier film.[33]

Applications of lipospheres

Parenteral drug delivery

Lipospheres have been exploited for the parenteral delivery of some anesthetics drugs like lidocaine, bupivacaine, antibiotics like ofloxacin, norfloxacin, chloramphenicol palmitate and oxytetracycline and antifungal agents, such as nystatin and amphotericin B, vaccines and adjuvant *etc*. For intravenous administration, the small particle size is a prerequisite as passage through the needle and possibility of embolism.[34]

Transdermal drug delivery

Film forming ability and occlusive properties of lipospheres help to formulate control or prolong release formulation of drugs from solid lipid matrix resulting retardation of systemic drug absorption and improvement of drug stability. Through this route, drugs susceptible to extensive hepatic metabolism can be designed as attractive candidates for topical delivery using lipospheres.[34]

Oral drug delivery

Lipids and lipid nanoparticles are extensively employed as oral delivery system for drugs and other active ingredients. Lipids usually enhance drug absorption in GIT and when formulated as nanoparticle, these molecules improve mucosal adhesion due to small particle size and increasing their GIT residence time. In addition, lipid nanoparticle may also protect the loaded drugs from chemical and enzymatic degradation and gradually release drug molecule from lipid matrix into blood, resulting in improved therapeutic profiles compared to free drug. Therefore, due to their physiological and biodegradable properties, lipid molecules may decrease adverse side effects and chronic toxicity of the drug delivery systems when compared to others of polymeric nature. Several categories of drug like antibiotics, anti-inflammatory compounds, vasodilators, anticancer agents, proteins and peptides are being formulated as oral lipospheres. Gastro-intestinal irritation by indomethacin is the major side effect being safe for use by lipid based formulation and lipid as vehicle for drug delivery.[35]

Nasal drug delivery

The use of lipid nanocarriers provides a suitable way for the nasal delivery of antigenic molecules. In this sense, the design of optimized vaccine nanocarrier offers a promising way for nasal mucosal vaccination.[35]

Ocular drug delivery

For an ocular drug delivery liposphere to be successful because it should have a small particle size, with a narrow size range, should be nonirritant, compatible with ocular tissue, and cause no blurred vision. The colloidal character of a drug carrier such as nanosized lipospheres improves drug penetration by prolonging the ocular residence time, reducing the nasolacrimal drainage and increasing interaction with corneal surface, combined with the advantage of being an easy-to-use liquid dosage form. The small particle size is also advantageous in terms of patient comfort since they do not cause "scratchy" feeling or impaired vision following ocular administration. Submicron sized particles have an extremely high surface to volume ratio, and therefore have an increased dissolution rate, advantageous for absorption of such poor water soluble compounds as paclitaxel, CsA and amphotericin B, which are frequently used in ophthalmic therapy.[35]

Protein and Peptide drug delivery

Proteins are chemically and physically unstable. The main challenge in oral delivery of protein drugs is to enhance their oral bioavailability. Uniform sized liposphere prepared by premix membrane emulsification combined with w/o/w double emulsion method as a potential oral carrier for proteins. The protein loaded liposphere was composed of a hydrophobic poly (D, L-lactide-co-glycolide) core and the lipid molecule self-assembeled at the interface of w/o and o/w. During the preparation, protein structure was effectively maintained. Liposphere also showed high transcytotic efficiency with human microfold cell (M-cell) model, leading to potential enhancement of intestinal absorption.[35]

Gene delivery

Lipospheres also serves as a gene vector. There are several recent reports of liposphere carrying genetic or peptide materials such as DNA, plasmid DNA and other nucleic acids. The gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into liposphere gene vector. The lipid nucleic acid nanoliposphere was prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously

sized lipid-nucleic acid nanoparticle (70-100nm) were formed (genospheres). It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle. These provide a novel and unique drug-delivery system. They evade quick clearance by the immune system. They can target specific cells. Lipospheres have been successfully tested in animal models with marker molecules and drugs. Antibody labeled stealth lipobodies have shown increased delivery to the target tissue in accessible sites.[35]

Agricultural applications

Increasing attention is being directed to reducing the amount of pesticides, herbicides, and other biologically active agents used in modern agricultural crop management. One method for reducing the amount of such agents, while still maintaining effectiveness, is to encapsulate or otherwise incorporate the active agent to form liposphere. Agricultural application includes essential oil extraction from *Artemisia arboreseens* L when incorporated in liposphere, being able to reduce the rapid evaporation compared with emulsions and the systems used in agriculture as a suitable carrier of ecologically safe pesticides.[35]

Brain targeting

Lipospheres are cleared from circulation by the reticuloendothelial system (RES) consisting of phagocytic cells originating from the bone marrow, and are particularly distributed into liver and spleen, tissues enriched with phagocytic cells. Thus, the particles are highly up taken by the RES system before reaching the targeted organ, e.g. the brain. This feature can be utilized in the case of a tumor located in the liver, where nanoparticles can serve as passive targeting for the treatment of hepatic cancer. Otherwise, the application of lipid nanospheres, for instance, for CNS targeting, is rather limited by the relatively intensive clearance from the circulation. Coating the nanoparticles with a hydrophilic coat of polyethylene oxide and blocking polyoxyethylene polypropylene co-polymers, a technique known by the name “stealth technology” creates sterically stabilized lipidbased nanoparticulates which are not recognized by the RES system Avoiding the RES by applying stealth technology prolonged the circulation time of the particles in the systemic blood and enabled to target the delivery of drugs more precisely and to increase drug concentrations in tumors, brain and the cerebrospinal fluid.[35]

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.[36] 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.[37] 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.[38] The lipid microparticles as a parenteral controlled release device for peptides were also established.[39]

Suitable 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.[36] 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.[40] 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.

Stability studies

Many studies have 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 phosphotidylcholine. 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.[41]

Table 1: List of drugs incorporated in to lipospheres by various techniques.

Drug	Lipid composition	Method of Preparation	Ref.
Cyclosporin	Triglyceride	w/o/w emulsion	[42]
Glipizide	Paraffin wax and Stearic acid	Melt dispersion	[43]
Pioglitazone hydrochloride	Compritol® 888 ATO	Melt dispersion	[44]
Metformin hydrochloride	Phospholipon® 90H	Melt-emulsification	[45]
Ofloxacin	Cetyl alcohol	Melt dispersion	[56]
Aceclofenac	Glyceryl stearate, stearic acid and stearyl alcohol	Melt and Solvent evaporation	[47]
Ibuprofen	Phospholipon® 90H	Hot emulsification	[48]
Ceftriaxone sodium	Phospholipon® 90H in Softisan® 154	Melt-emulsification	[49]
Vinpocetine	Cetyl alcohol, stearic acid	Emulsion method	[50]
Clotrimazole	Stearic triglyceride	Melt-dispersion	[51]
Nebivolol	T-20	Solvent evaporation	[52]
Ercanidipine hydrochloride	cetostearyl alcohol	Melt dispersion	[53]
Indomethacin	Capra hircus and Phospholipon® 90G	Melt emulsification	[54]

Current & Future developments

Anticancer drugs-carrying lipospheres (MRX-552) were developed recently and evaluated as a new ultrasound contrast agent for chemotherapeutic drug delivery. Acoustically active lipospheres represent a new class of acoustically active drug delivery vehicles. The high incorporation of drug is due to an increase in their lipophilicity as a result of the formation of ion-pairs with monoalkyl phosphate esters current research in the field of lipospheres based drug delivery. Future studies will assess efficacy of AALs for ultrasound mediated drug delivery. Liposphere delivery of local anesthetic drugs may be well suited for site-specific pharmacotherapy of neural tissue to produce SLAB in the upcoming future. Dose-dependent effects in duration of action which may include lipophilic tissue storage are major challenges for the upcoming research.

CONCLUSIONS

Lipospheres are a novel carrier system for most of the lipophilic or poor water insoluble drugs for enhancement of drug absorption and bioavailability due to their low cost of ingredients, high entrapment of hydrophobic drugs, controlled particle size and extended release of entrapped drug. Lipospheres can easily carry all the formulation ingredients due to

better physical stability, ease of preparation and scale up and better aqueous dispersibility. Improved adsorption and penetration properties of lipospheres have the potential for better oral, parenteral and topical drug delivery systems. This approach is very useful in treating chronic CNS ailments like Alzheimer and neurodegenerative disorders. The lipospheres are viable for commercial scale production of life saving drugs and cosmetics.

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