CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.8283593

Available online at: http://www.iajps.com *Review Article*

REVIEW OF LIPOSPHERE CONTAINING CHLORTHALIDON SUSPENSION FOR ORAL DELIVERY

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Abstract:
The present investigation of this work "To Design and Development of Liposphere Containing Chlorthalidon Suspension for Oral Delivery" were developed and leads to liposphere, present work explain the mechanism of Liposphere release from Suspension In this work particles were prepared by using Cetyl alcohol consisting of Cetostearyl alcohol Xanthum gum, which can be act as a suspending agents. Melt dispersion method based on Though number of micro encapsulation technique have been employed to produce polymeric multiparticulate system, The morphological characterization of the optimized liposphere were examined by scanning electron microscope with suitable magnification
Keywords: Liposphere, Chlorthalidon, Phospholipids

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Please cite this article in press Vaibhav Kishor Patil et al, ***Review Of Liposphere Containing Chlorthalidon Suspension For Oral Delivery****, Indo Am. J. P. Sci, 2023; 10 (08).*

1. INTRODUCTION:

Pharmaceutical research is recently geared towards the development of new delivery systems for the existing drugs. These novel delivery systems improve the bioavailability of the drug(s) and at the same time minimize their toxic effects. The oral delivery of lipophilic drugs presents significant challenges to pharmaceutical scientists due to their inherent low aqueous solubility, which generally lead to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality. The advances in combinatorial chemistry have lead to tremendous increase in sparingly soluble drugs and currently 40 to 70% of the new pharmacologically active chemical entities which exhibits poor aqueous solubility. Many formulation approaches are presently being employed in tackling the formulation challenges posed by drugs belonging to the bio - pharmaceutical classification system (BCS) class (II) and (IV), either by pre-dissolving the compound in a suitable solvent and subsequently filling the formulation into capsules or by formulating as solid solution using water soluble polymers. These approaches however, can probably resolve the issues related to initial dissolution of drug molecules in aqueous environment within the gastrointestinal tract (GIT) to a certain extent. However, major limitations like drug precipitation during dispersion of formulation in the GIT or drug crystallization in the polymer matrix may be unresolved. These problems have been effectively resolved by the use of lipid based drug delivery systems (DDS).Drug delivery systems (DDS) are capable of designing to increase the bioavailability of drugs, control drug delivery and maintain the drug intact, transport to the site of action while avoiding the non-diseased host tissues. Briefly, in a suitable dosage and mode of administration, using the smallest dose to achieve the best therapeutic effect is the research objective of DDS. Colloidal drug delivery systems (CDDS) have been developed which play an important role for the effective transportation of loaded drug to the target site. The proven safety and efficacy of lipid-based carriers make them potential alternative drug carrier materials to polymers as well as attractive candidates for preparing lipid-based formulations. These formulations allow hydrophilic and/or hydrophobic drugs to be incorporated which provide protection of incorporated active compounds against degradation as well as offer the possibility of improved bioavailability, controlled drug release and drug targeting.

1.1. COLLOIDAL DRUG CARRIER (CDC)

Many drugs are characterized by poor solubility in aqueous media and thus cause formulation problems with regard to parenteral administration. Besides, the use of co-solvents, drug complications and solubilization in surfactant micelles, incorporation into colloidal carrier systems represents an alternative way to render poorly water soluble drugs. Furthermore incorporation of drugs in particulate carriers provide a possibility to manipulate drug release, if controlled or sustained release (SR) is desired. During the last few decades, several approaches have been investigated to develop sub micron-sized drug delivery system. Colloidal drug carrier is a unique entity essentially required for the successful transport of loaded drug. It sequesters, transports and retains the active drug to deliver it at its site of action. Targeting of drug to its specific site of action improves the access of optimum amount of drug with reduction of drug and improvement in the therapeutic index. The highly selective strategy lowers systemic side effects to a greater extent. An ideal colloidal drug carrier should posses the ability to navigate anatomical barrier which selectively recognizes the target cell through surface ligand. The drug: ligand complex must be stable in the biological milieu. The nature of carrier must be biodegradable with non toxicity. This novel colloidal drug delivery systems offer various advantages over conventional delivery system such as minimization of drug degradation and drug loss, increased drug bioavailability, increase in the fraction of drug accumulation in the target area, prevention of harmful toxic effects, versatility and flexibility in handling drug with better patient compliance. Based on the carrier material, the conventional vehicles used as drug carriers can generally be divided in to two groups, polymeric and lipidic systems.

1.1.1. Polymeric carrier system (PCS)

Polymeric nanoparticles are amorphous colloidal particles of non- biodegradable synthetic polymer or biodegradable macro molecular materials of synthetic, semi synthetic and natural polymer. The methods for the preparation of polymeric nanoparticles such as emulsion polymerization and solvent evaporation techniques often involve the use of toxicologically harmful excipients and additives. For example organic solvents, cancerogenic monomers and reactive cross linking agents, the complete removal of which from the product is hardly possible from a technical point of view8. Moreover, the carrier material itself can act as a potential toxicological risk. Apart from polymer accumulation on repeated administration owing to slow biodegradation, toxic metabolite may be formed

during the biotransformation of polymeric carriers; for example, formaldehyde as a metabolite of poly cyanoacrylate.

1.1.2. Lipid based carrier systems (LBCS)

In order to avoid potential toxicological problems associated with polymeric nanoparticles, a great deal of interest focuses on lipid based carrier system. Lipid carriers include liposomes, lipoproteins and lipid oil-in-water emulsions. The vehicle for lipid carriers is composed of physiological lipids such as phospholipids, cholesterol, cholesterol ester and triglycerides. Owing to the biological origin of carrier materials, the toxicological risk is much lower than that of polymeric particles.

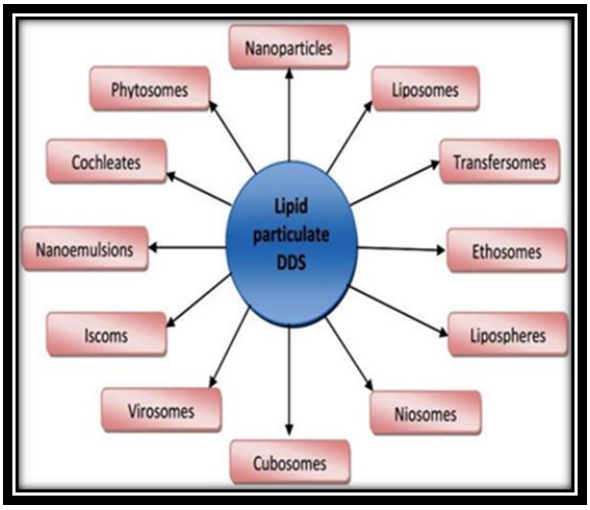

Fig. 1: Types of lipid carrier delivery system

The following are positive features of potentially used solid lipid particles as drug carrier systems: they offer the possibility of controlled drug release and drug targeting. They provide protection of incorporated active compounds against degradation. Their solid mixture is composed of physiological and well-tolerated lipids. They allow for hydrophilic and/or hydrophobic drugs to be incorporated10.The drug solubility and miscibility in melted lipid, chemical and physical structure of lipid materials and their polymorphic states determine the loading capacity of drug in the lipid particles 11,10,12. The amount of drug encapsulated can vary from 1% to 5% for hydrophilic compounds and 80% for lipophilic compounds 13,14. Solid microparticles in dispersions are usually obtained by using a melt dispersion method or a solvent evaporation method.The degradation of carrier lipid is assumed to determine the drug release, which in that case could be controlled to a certain extent by the choice of matrix constituents. Moreover, the presence of a static interface might facilitate a surface modification of the carrier particles after solidification of the lipid matrix; for e.g., by subsequent absorption of nonionic surfactants. The latter might be of the relevance to reduce carrier uptake by the reticulo endothelial system, which is known to relate to surface properties. Surface modification is, therefore, one approach to drug targeting using colloidal carriers. The need for safe, therapeutically effective and patient-compliant drug delivery systems continuously leads researchers to design novel tools and strategies. The main concept in such modified delivery technology is that any pharmaceutical dosage form should be designed to provide therapeutic levels of drug to the site of action and maintain them throughout the treatment18. These goals may be achieved by modifying the rate and/or time and/or site of drug release in comparison with conventional formulations. Such modifications in release of active substances provide a reduction in toxic effects or for some other therapeutic purpose. Negatively charged particles can be rapidly opsonized and massively cleared by fixed macrophages of the reticulo endothelial system (RES) in the blood stream. Many existing drug candidates have poor solubility in biological fluids which results in low and highly variable bioavailability and a high food dependency after oral administration. Intravenous injection of this kind of drug is not possible because of its poor solubility. Hence, colloidal delivery system (CDS) has gained much attention to deliver the drugs in the body with enhancement of oral bioavailability, decrease in variability and food dependency, drug targeting to specific tissues and life cycle management.

1.1.2.1 Advantages of lipid based delivery systems

- Lipid based delivery systems disperse, solubilize and maintain solubility of drug in GI fluids.
- Bioavailability of most of the lipophilic drugs is altered in the presence of lipid content in food. Lipid carriers mimic such lipid food and thus reduce the food effect on bioavailability of drugs and render flexibility to dosage regimen.
- Transfer drug into bile-salt mixed micelle and promote lymphatic uptake of carrier drug particles.
- Influence gut wall permeability.
- Normalize and/or modify pharmacokinetic parameters.

1.2. LIPOSPHERES:

Lipid micro particles, often called as lipospheres (LS), have been proposed as a new type of lipid based encapsulation system for drug delivery of bioactive compounds. LS consists of solid microparticles with a mean diameter usually with the size range between 0.2 to 500 µm, composed of a solid hydrophobic fat matrix where bioactive compounds are dissolved and dispersed and surrounded by a layer of phospholipids

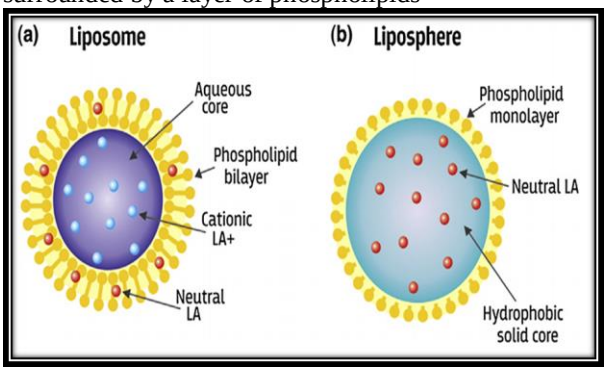

Fig.2 Structure of Liposome and Schematic Liposphere

1.2.1. Lipids

Lipid excipients provide attractive alternatives over their traditional counter parts, as they have the ability to solubilize hydrophobic drugs within the dosage form matrix. This leads to the improved absorption case of or l drug delivery, which is primarily mediated by the reduction in the barriers of poor aqueous solubility and slow drug dissolution in the gastrointestinal (GI) fluids

1.2.2 Phospholipids

As the main components of cellular membrane, phospholipids have excellent biocompatibility. In addition, phospholipids are renowned for their Amphiphilic Structures. The amphiphilicity confers phospholipids with self-assembly, emulsifying and wetting characteristics. When introduced into aqueous milieu, phospholipids self-assembly generate different super molecular structures which are dependent on their specific properties and conditions. Phospholipids have good emulsifying property which can stabilize the emulsions. In addition, phospholipids as surface-active wetting agents can coat the surface of crystals to enhance the hydrophilicity of hydrophobic drugs. The above properties are successfully employed in the DDS design. Phospholipids are molecules in which hydrophilic head group and hydrophobic acyl chains are linked to the alcohol. The variation in head groups, aliphatic chains and alcohols leads to the existence of a wide variety of phospholipids. In addition, the different sources of phospholipids also enhance the species of phospholipids. Various phospholipids such as soybean phosphatidylcholine, egg phosphotidyl choline or synthetic phosphatidylcholine, as well as hydrogenated phosphatidylcholine, are commonly used in different types of formulations. Phospholipids become intriguing as they can offer various options. However, the diverse species of phospholipids make the selection of an appropriate phospholipid to achieve the therapeutic purpose become a crucial problem in the design of DDS, so as to summarize the structures, main sources, properties of phospholipids which can give a guideline in the design of DDS. Phospholipids are widely distributed in animals, plants and the main sources of them include vegetable oils (e.g. soybean, cotton seed, corn, sunflower and rapeseed) and animal tissues (e.g. egg yolk and bovine brain). In terms of production, egg yolk and soybean are the most important sources for phospholipids 26 However, soybean and egg yolk have differences in the contents and species of phospholipids, mainly which include: 1) Egg yolk lecithin contains a higher amount of Phosphatidyl choline (PC); 2) Phospholipids in egg yolk exist long chain polyunsaturated fatty acids of n-6 and n-3 series, primarily arachidonic acid (AA) and docosahexanoic acid (DHA), which are absent in soybean lecithins; 3) Animal lecithins have characteristic of the presence of SM 27; 4) The saturation level of egg yolk lecithins is higher than that of soybean lecithins . So their oxidative stability is better than that of soybean lecithins; 5) For egg yolk phospholipids, saturated fatty acid is usually at sn-1 position and unsaturated fatty acid is at sn-2 while for soybean lecithin, sn- 1 and sn-2 position will be both unsaturated fatty acids. For e.g., dilinoleoyl phosphatidylcholine (DLPC) is the main component of soybean phosphatidylcholine (SPC)30. The cost of isolation of phospholipids from natural sources is always lower than that obtained by synthetic or semisynthetic methods. For natural phospholipids, the more pure they are, the higher the price is. S can protect the drug from hydrolysis, as well as improve drug bioavailability31. Physical stability of lipid dosage forms like polymorphic phase transitions of drug and lipid based drug delivery systems like solid lipid nanoparticles (a technology owned by Skye Pharma)32,33 and lipospheres are now being studied widely. Solid lipid micro particles are microsized lipid carriers in which lipidic core contain the drug in dissolved or dispersed state. These systems were designed to substitute polymeric carriers due to the inherent toxicity. Researchers are facing challenges to develop and improve the bioavailability of poorly water soluble

drugs towards clinical application. Novel technology has shown great potential for improving the effectiveness and efficiency of delivery of neutraceuticals and bioactive compounds.

Researchers are looking at the application of lipid in drug delivery from a different fact. Much of the researchers are now focusing on using lipids as novel carriers for drug moieties. Obviously research bench works have become replete with lipid drug delivery system just as manufacturers are becoming more enthusiastic in both translational research and commercialization of lipid dosage form. This is because of their ability to effectively overcome physical and biological carrier related to poor aqueous solubility, stability and membrane permeability, drug efflux and availability. The new drug molecules greater than 40% are lipophilic in nature and showing poor water solubility. Lipid based drug delivery system like liposphere and solid lipid nanoparticles (SLN) are being developed due to increasing toxicity related concerns of monomers after intra cellular processing of polymers and attractive benefits offered by lipid as carrier. Lipid systems such as emulsions, micellar solutions, solid lipid micro particles, structured lipid carriers, self-emulsifying lipid formulation, solid dispersion, dry emulsions, solid liquid compacts and drug lipid conjugates are available to drug formulators. In recent developments a number of lipid based systems like liposphere, liposome, niosomes, ethosomes, transferosomes were to solve the problem of insolubility, instability , rapid degradation and which are widely used in specialized areas like protein delivery, gene delivery targeting to brain, tumor targeting etc. Among these solid lipid micro particle or liposphere seems to hold great promise as regards stability and low pay load.

- **Advantages of liposphere**
  - Liposphere exhibit enhanced physical stability due to avoidance of coalescence.
  - High dispersability in an aqueous medium.
  - Low cost of ingredient.
  - Ease of preparation and scale up.
  - High entrapment of hydrophobic drugs.
  - Controlled particle size.
  - Extended release of entrapped drug after a single injection.
  - Static interface facilitates surface modification of carrier particles after of the lipid matrix.

- **Dis-advantages of Lipospheres**
  - Different lipid modifications and colloidal species coexist that may cause differences in solubility and melting point of active and auxillary species.
  - Low drug loading capacity for hydrophilic proteins.
  - Variable kinetics of distribution processes.
  - High-pressure induced drug degradation.
  - Insufficient stability data
  - Toxic effects of organic residues after the production of polymers, Lack of large industrial scale production

Lipospheres are more effectively dispersed than most suspension based systems and the substances to be delivered do not have to be soluble in the vehicle since it can be dispersed in the solid medium. The release rate of the drug from the liposphere is dependent in part upon the composition of ore as well as the outer phospholipid layer and can be altered by varying the composition appropriately. The liposphere based carrier system has several advantages over other delivery system including emulsions, liposomes and microspheres such as good physical stability, low cost of ingredients, ease of preparation and scale up, high entrapment yield for hydrophobic drugs and controlled particle size nd extended release of entrapped drug LS Showed the reduced mobility of incorporated drug molecules responsible for reduction of drug leakage, circumvention of instabilities due to interaction between drug molecules and emulsifier film and extended release of entrapped drug.

Lipospheres have been widely used for controlled delivery of various classes of drug like vasodilators, antiplatalets, local anesthetics, antibiotics and anticancer agents. They have also been used successful as carrier for vaccines and adjuvants. Lipids can be used as they are well tolerated by the body which promotes solubilization of poorly water soluble drugs, high drug loadings, protection of drug against chemicals and biological degradation related to administration of route and also controlled release.

Liposphere in micrometer size range seems to be more stable. The particle sizes and distributions were found to be similar to the original formulation after 30 days41 and for one formulation Domb and Maniar observed no signs of aggregation for 10 months stored at 4°C. The extended release of drugs from micro particulate liposphere formulations has been demonstrated by in-vitro release studies. Drug release was observed over several days, although there is an initial burst of drugs related to the first few hours 41, indicating that parts of the drug are not incorporated in the particle core but are associated with the carrier surface; for e-g. In the lecithin layer, from where the drug is fast released. The in-vitro data on sustained release could be substantiated by in-vivo studies and the sustained delivery of local anesthetics, anti-inflammatory agents, insect repellents and antibiotics

was observed in different animal models by monitoring the therapeutic effects over times after liposphere administration.

1.3. TECHNIQUES WIDELY EMPLOYED IN PREPARATION OF LIPOSPHERE

1.3.1. Solvent evaporation method

In this method, lipid is dissolved in an organic solvent. Commonly used organic solvents include ethyl acetate, ethanol, acetone or dichloromethane. This lipid phase is emulsified into aqueous phase containing emulsifier. Organic solvent is evaporated by stirring the oil in water emulsion for 6-8h under ambient conditions. Discrete lipospheres can be collected by filtration through paper filter after the water rises to the surface. Examples of the drugs formulated as lipospheres by this method include Paclitaxel, Thymocartin, bovine serum albumin and Triptorelin.

1.3.2. Co-solvent solvent evaporation method

The co-solvent - solvent evaporation method employ chloroform and N-methyl pyrolidine to create a clear solution. Although low yield and large particle size is obtained, it is altered by variation in the solvent used. Lipospheres made up of polar and non-polar lipids using synthetic stabilizers instead of phospholipids are the deviations from the definition of liposphere repeated by Domb in his patent. Although their work is not related to protein delivery but they tried it with hydrophilic drug and reported around 50 % entrapment by double emulsification method.

1.3.3 Sonication method

In this technique, the drug is mixed with lipid in a scintillation vial which is precoated with phospholipids. The vial is heated until the lipid melt, and then vortexed for 2 min to ensure proper mixing of the ingredients. A 10 ml of hot buffer solution is added into the above mixture and sonicated for 10 min with intermittent cooling until it reaches to the room temperature.

1.3.4. Roto evaporation method

In this technique, lipid solution with drug is prepared in a round bottom flask containing 100 grams beads (3mm in diameter) mixed thoroughly till a clear solution is obtained. Then, the solvent is evaporated by using rotoevaporizer under reduced pressure at room temperature and a thin film is formed around the round bottom flask and the glass beads. The temperature is raised up to 40ºC until the complete evaporation of the organic solvent. A Known amount of 0.9 % saline is added to the round bottom flask and the contents are mixed for 30 min at room temperature and then the temperature is lowered to 10ºC by placing in ice bath and mixing is continued for another 30 min until lipospheres are formed.

1.3.5. Polymeric lipospheres

Polymeric biodegradable lipospheres can also be prepared by solvent or melt processes. The difference between lipospheres and the standard lipospheres formulation is the composition of the internal core of the particles. Standard liposphere consit 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 is substituted by one layer of phospholipid molecules embedded in their surface.

1.3.6. Micro emulsion

In this method, drug is added to the melted lipid and aqueous phase is prepared by adding surfactant like Tween 80 into water maintained at the same temperature as for the lipid phase. This is followed by the addition of co-surfactants like butyl alcohol to the aqueous phase. The aqueous phase containing surfactant and co-surfactant is added to lipid phase kept under stirring and rapid cooling of the above mixture results in the formation of discrete lipid particles. Flurbiprofen lipospheres were prepared by this method. Presence of tween 80 at 2% butyl alcohol at 2 ml and water at 50 ml was found to give discrete lipospheres of superior quality.

1.3.7. Multiple emulsions

In this method, drug solution (aqueous phase) is added to melted lipid. The primary emulsion is added into aqueous solution containing emulsifier kept at the same temperature as primary emulsion. The multiple emulsions formed are subjected to rapid cooling to form lipospheres. About 90% entrapment efficiency of D-Trp-6- LHRH peptide from stearic acid-egg lecithin based lipospheres prepared by this technique. Drugs like thymopentin, cyclosporine and peptides like papain were investigated for liposphere formulations by this method.

1.3.8. Melt dispersion technique

In this method drug is dissolved or dispersed in the melted lipidic phase. Aqueous phase is composed of water or suitable buffer which is heated to the same temperature as lipid phase. The aqueous phase is kept under stirring during which emulsifier is added. To the aqueous phase containing emulsifier, lipid phase containing drug is added drop by drop while maintaining the temperature and stirring speed. After this “hot emulsification phase” the temperature of the mixture is rapidly brought down to room temperature or below room temperature by adding ice cold water

or ice under continuous stirring. This cold resolidification results in the formation of discrete lipospheres which can be filtered. Melatonin lipospheres of melt method for topical applications was proved to be effective compared to that of gels and lotions. Several drugs like bupivacaine, glypizide50,aceclofenac, retinyl acetate, progesterone, sodium cromoglycate, diclofenac, Carbamazepine, c14-diazepam, proteins like somatostatin, thymocartin, casein, bovine serum albumin, R32NS1 malarial antigen55, tripalmitin based lipospheres for lab-on -chip applications have been prepared by melt dispersion methods. Lipids carrying antigens exert their adjuvant effect to immunogenicity of antigens and the effect was found to decrease in the following order for the lipids studied: ethyl stearate> olive oil> tristearin> tricaprin> corn oil> stearic acid. Also inclusion of negatively charged lipids like dimyristoyl phosphotidyl glycerol in the lipid core was found to improve the antibody response to encapsulated malaria antigen. The advantage in the melt method is that no organic solvents are needed.

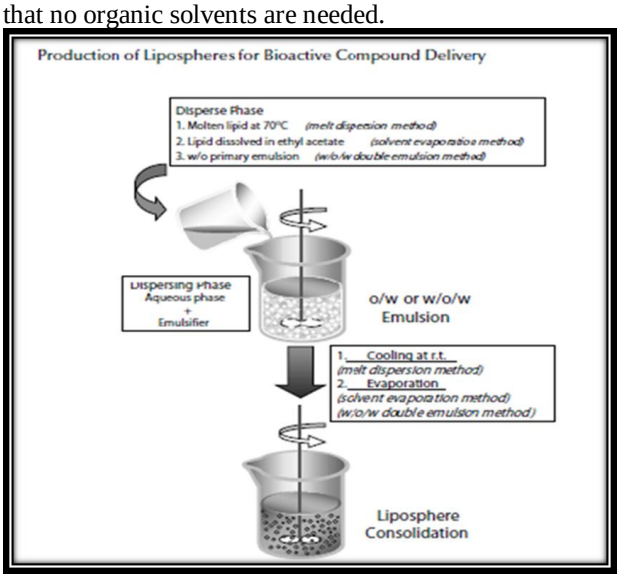

Fig 3: Preparation of liposphere by melt dispersion

1.4. CHARACTERIZATION OF LIPOSPHERE

1.4.1 Measurement of Particle size and Zetapotential

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. The morphology of lipospheres was characterized by transmission electron microscopy where interaction of the electrons with lipid surface produces the images and SEM where electronic transitions with particle surface produce the images. Field Emission SEM (FESEM) can be effective in case of particles that were not recognized by SEM where sample preparation may damage the particle morphology. Cryogenic FESEM, where liquid nitrogen was used to freeze the liquid dispersion, produced microscopic images in the frozen state. The above methods were of two dimensional analyses of the particles and three-dimensional profiles which include structural, mechanical, functional and topographical information of lipospheres were given by atomic field microscopy.

Zeta potential measurements allow predictions about the storage stability of colloidal dispersion. It is clearly the surface properties of colloidal systems are critical in determining their drug carrier potential, since they will control their interactions with plasma proteins. Zeta potential measurements will give information about overall surface affected by changes in this environment (e.g. pH, presence of counter-ions, adsorption of proteins). Charge shielding by PEG or other hydrophilic groups can be used to predict the effectiveness of the barrier function against opsonisation in-vivo. Zeta potential can also be used to determine the type of interaction between the active substance and the carrier: i.e. whether the drug is encapsulated within the body of the particle or simple adsorbed on the surface. This is important because adsorbed drug may not be protected from enzymatic degradation, or may be released very rapidly after administration58.

1.4.2. X-ray diffraction (powder X-ray diffraction) and differential scanning calorimetry (DSC)

The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus permitting the degree of crystallinity to be assessed. Another method that is a little different from its implementation with bulk materials, DSC can be used to determine the nature and speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies.

1.5. EVALUATION OF LIPOSPHERE 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. 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 dispersion61. 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. Ultrafiltration and microdialysis were considered as the most reliable techniques for EE quantification, while result obtained by ultracentrifugation, the fastest and easiest technique, but not always accurate63. 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/lipids 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

1.5.1 APPLICATIONS OF LIPOSPHERES

a) Oral route

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

b) Transdermal route

Properties of lipospheres like film forming ability and occlusive properties; controlled release from solid lipid matrix resulting in prolonged release 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.

In recent years, scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence time and unpredictable gastric emptying time. The most important parameters affecting gastric emptying and hence the gastric retention time of oral dosage forms include:

- Density, size and shape of the device.
- Concomitant ingestion of food and its nature, caloric content and frequency of intake.

1.6. LIPOSPHERE FOR ORAL DELIVERY

Oral lipid-based drug delivery systems have proved their immense potential in ameliorating the poor and inconsistent gastrointestinal absorption of poorly soluble drugs. Of late, an alarmingly high spurt of various literature instances and marketed products of such lipid based formulations has been witnessed across the global pharma world. The concept of lipidic systems, therefore, has become immensely vital, both at industrial and academic levels. Controlled or sustained release formulations have become very popular over conventional multi- dose therapy because of their uniform therapeutic efficacy, lesser or no side effects and better patient compliance. The development of oral controlled-release dosage forms have attracted much attention in recent years. Oral delivery of nearly one-half of the drug compounds gets thwarted owing to their high lipophilicity and consequently poor aqueous solubility. Oral bioavailability of such drugs, being a function of their aqueous solubility and dissolution, tends to exhibit low magnitude and high intra and inter-subject variability. Though many drug carrier system, such as microspheres and liposomes have been used for controlled or sustained drug delivery, they suffer from poor loading capacity for lipophilic drugs. Hence, lipid microspheres are assumed to be the better choice. These are solid, water insoluble, microparticles having the size between 0.2 -500 µm in diameter composed of a solid hydrophobic core having a layer of a phospholipid embedded on the surface of the core69,70. The hydrophobic core is made up of solid triglycerides, fatty acid ester or bioerodible polymers containing the drug. On the other hand, the addition of phospholipids made the formulation more stable with little particle size change even during storage in solution at room temperature. The phospholipids provide the necessary means of dispersing the lipospheres in a pharmaceutically acceptable vehicle. The advantages offered by the liposphere delivery system include ease of manufacture, low production cost of components, high stability of the drug formulation and ease of controlling drug release rate by simply manipulating the ratio of triglycerides to phospholipid. Liposphere formulations are effective in delivering various drugs and biological agents including: local anesthetics, antibiotics, vaccines and anticancer agents with a prolonged activity of up to four to five days (Domb Abraham J European patent). Multiple unit system offers the advantage

that they distribute more uniformly in the gastro intestinal tract resulting in more uniform drug absorption, low possibility of dose dumping and reduced local irritation, when compared to single – unit dosage form on chronic dosing. Over the last years, a number of poorly soluble drugs have steadily increased. Estimates state that 40% of the drugs in the pipelines have solubility problems . Progress in high throughput screening methods leads to invent of greater amount of newly discovered drugs that have poor water solubility. Other literature states that about 60% of all drugs coming directly from synthesis are nowadays poorly soluble. Poor solubility in water correlates with poor bioavailability. If there is no way to improve drug solubility it will not be absorbed from the gastrointestinal tract into the bloodstream and reach the site of action. There are many ways to solubilize certain poorly soluble drugs, but this method is limited to drugs with certain properties regarding to their chemistry (eg, solubility in certain organic media) or for example to their molecular size or conformation (eg, molecules to be incorporated into the cyclodextrin (CD) ring structure). Apart from that, the usage of surfactants or cosolvents is also possible, but sometimes leads to increased side effects and other disadvantages (eg, organic solvent residues). The micronization of drug powders to sizes between 10 and 100 µm increased the surface area and thus the dissolution velocity is increased.

1.7. DRY SUSPENSION

Dry suspension is defined as an intimate mixture of dry, finely divided drug with excipients, which, upon the addition of suitable vehicle, yields a suspension. Reconstitutable suspension is reconstituted at the time of use and thus can be used as liquid formulation which avoids swallowing problem. Moreover, stability of products for tropical countries is a great challenge, as these products are exposed to elevated temperatures (up to 40°C) and relative humidity (up to 90%) especially during transport and storage. Oral suspension is preferred to many patients because of the ease of swallowing and the flexibility in the administration. It is particularly advantageous for children, the elderly and infants, in the meantime, the unpleasant taste of the bitter medicinal agents can be overcome by administrating as undissolved particles. Dry powders for suspension are more desired due to their stability and convenience80. The prepared suspensions were evaluated for flow properties, rheological and sedimentation behaviour. Reconstitutable oral suspension shows adequate chemical stability of the drug during shelf life, avoids the physical stability problems. Most of the drugs administered as granules for oral suspension under pediatric therapy are Antibiotics, which when administered orally as any other dosage form have a bitter taste making it unpleasant for Children to consume the medication. These are the dry mixture that requires the addition of water at the time of dispensing which reduce the weight of the final product because the aqueous vehicle is absent and consequently the transportation expenses may be reduced85. The dry mixure for oral suspension is prepared commercially to contain the drug, colorants, flavors, sweeteners, stabilizing agents, suspending agents and preserving agents that may be needed to enhance the stability of the formulation. After reconstitution, these systems have a short but acceptable life if stored at refrigerator temperatures86,87. The prepared suspensions were evaluated for flow properties, rheological and sedimentation behavior.

1.7.1 Disadvantages of liquid oral suspensions

- It is a bulk formulation so there are chances of inaccuracy in single dosing.
- Drug dose depends on various physical factors of the dosage form such as temperature of storage, sedimentation rate of the formulation, liquid flow properties like viscosity, pourability, redispersion, flocculation and content uniformity.
- Stability of the liquid suspension largely depends on the temperature of storage.
- Caking occurs upon storage

1.7.2 Advantages of dry granules for oral suspension.

- There is an accurate single dosing as the dose is packed in single dose sachets.
- Drug dose is comparatively independent of physical factors like temperature, sedimentation rate and liquid flow properties.
- Packaging of the powder mixture is done in sachets making the formulation easy to carry.
- Enhanced convenience of single dosage regimen.
- Colored, flavoured, sweetened formulation is advantageous for administration to the pediatric population.
- Stable on storage and when reconstituted with an ingestible liquid for administration, the corresponding liquid suspension is stable for the duration for which the therapy is required.

1.8. EXCIPIENTS USED

The criteria for selecting excipients are based both on suitability for reconstitution and on the physical type of powder mixture desired. A common method of reducing the number of excipients is to use an excipient that performs more than one function. Eg. Sucrose can be used as a diluent, sweetener and suspending agent. All excipients should disperse rapidly on reconstitution. This criterion eliminates several suspending agents. Many preservatives are also not suitable.

1.8.1. Suspending agents

Suspending agents should be easily dispersed by vigorous hand shaking during reconstitution. These rules out several common suspending agents because many require hydration, elevated temperatures or high shear mixing for adequate dispersion. Suspending agents that are recommended for use are Acacia, Carboxy methyl cellulose sodium, Iota carrageenan, Microcrystalline cellulose with carboxy methyl cellulose sodium, Povidone, Propylene glycol alginate, Silicon dioxide, Sodium starch glycolate, Tragacanth, Xanthan gum. The combination of microcrystalline cellulose and sodium carboxy methyl cellulose is a common suspending agent. Total concentrations of the combination greater than 1% in the reconstituted product can result in thixotropic gels. This agent and sodium carboxy methyl cellulose alone are anionic; they are incompatible with many cationic excipients.

The natural gums are usually anionic and include exudates of tree and extract from seaweed. Acacia and tragacanth have been used as suspending agents for many years. The carrageenan and alginate suspending agents are seaweed extracts. The alginates produce highly viscous solutions and the iota-carrageenans produce thixotropic dispersions. A disadvantage of these natural products is batch variation in color, viscosity, gel strength and hydration rate. Xanthan gum is a common suspending agent in suspensions for reconstitution. Since it is produced by microbial fermentation, there is good batch-to-batch uniformity and few microbial problems. It's solution viscosity is practically independent of pH and temperature.

1.8.2. Sweeteners

The sweetener is a significant component of suspensions for reconstitution. Drugs frequently have a bitter taste and suspending agents, particularly clays, may have a bland taste. Sweeteners can mask the unfavourable taste and enhance patient is acceptance in the pediatric population that uses this. An increased viscosity as a result of the sweetener, aids suspension of the drug particles. The sweeteners used are Sucrose, Mannitol, Aspartame, Sodium saccharin, Dextrose. Sucrose can perform both functions of sweetener and suspending agent and can serve as a diluent in the dry mixture. Aspartame has fair acid stability but poor heat stability. Saccharin may become restricted by the Food and Drug Administration because of its carcinogenic potential86.

1.8.3. Wetting agents

Polysorbate 80 is a common wetting agent. It is nonionic and is chemically compatible with both cationic and anionic excipients and drugs. It is used in concentrations lesser than or equal to 0.1%. Another common wetting agent is Sodium lauryl sulphate

1.8.4. Other excipients

The other excipients include buffers, preservatives, flavors and colors. Flocculating agents are not commonly used in suspensions for reconstitution because these products are usually redispersed frequently enough to prevent caking86.

Preservatives are required in most suspensions because the suspending agents and sweetener are often good growth media for microorganisms. The choice of preservatives is limited because most of these ingredients require extended time periods for dissolution at room temperatures. Eg sorbic acid. Sucrose in sufficient concentrations (60%w/w) can aid in the prevention of microbial growth. Other common preservatives used are Sodium benzoate and Sodium propionate. Flavors enhance patient acceptability of product. Both natural and artificial flavors are used. Additional flavors used include raspberry, pineapple etc. In some cases, refrigeration after reconstitution is required for the stability of the flavoring agent rather than for the stability of the drug. Colorants are intended to provide a more aesthetic appearance to the final suspension. As relatively large cations or anions, these agents may be chemically incompatible with other ingredients. For example FD and C Red No.3 a disodium salt, is anionic and would be incompatible with a cationic wetting agent.

1.9. PREPARATION OF DRY MIXTURE

1.9.1 Powder blends

Powder blends sometimes called powder mixtures are prepared by mixing the excipients of the dry mixture in powder form. Excipients present in small quantities may require a two stage mixing operation. Such excipients can be mixed with a portion of a major excipient to aid in their dispersion. For example, milled sucrose provides a large surface area for the adsorption of the small quantities of flavor

oils. The second stage comprises the mixing of the remaining excipients. The selection of the appropriate mixer involves several considerations, the most significant of which is that the mixer should rapidly and reliably produce a homogenous mixture.

- **Advantages**
- Least capital equipment and energy.
- Least likely to have chemical and physical stability problems because no heat or solvents are used.
- Low moisture content can be achieved in dry mixture.

- **Disadvantages**
- Prone to homogeneity problems. Two most important properties for the mixing of these powders are Particle size and Powder flow.
- Loss of the active ingredient during mixing.

1.9.2. Combination product

Powdered and granulated excipients can be combined to overcome some disadvantages of granulated products. Less energy and equipment for granulation may be required if the majority of the diluents can be added after granulation. Also heat sensitive excipients such as flavors can be added after drying of the granulation to avoid exposure to elevated temperatures. The general method is first to granulate some of the excipients, then blend the remaining excipients with the dried granules before filling the container. The presence of the diluents helps to improve flow and reduces both segregation and dust formation.

- **Disadvantages**
- Risk of non-uniformity
- Particle sizes of various fractions should be carefully controlled.

1.10. EVALUATION OF ORAL RECONSTITU TABLE SYSTEM

1.10.1. Flow properties

Flow properties such as angle of repose, bulk density, tap density and porosity of powder mixture, granulations and combination product should be carried out.

1.10.2. Rheological behavior

The rheological behavior of the reconstituted suspensions is determined using Brookefield viscometer (Model – RVT).

1.10.3. Sedimentation behavior

a) Redispersibility: The redispersibility is determined by studying the number of strokes to redisperse the formed sediment at the end of 7 days of storage of the formulations (not more than 100 strokes = Redispersibility).

1.10.4. Sedimentation Volume Ratio (SVR)

Sedimentation volume of a suspension is expressed by the ratio of the equilibrium volume of the sediment, Vu, to the total volume, Vo of the suspension.i.e. F=Vu/VoThe value of F normally lies between 0 to 1 for any pharmaceutical suspension. The value of F provides a qualitative knowledge about the physical stability of the suspension.

1.10.5. Drug content

The required weight of drug mixture is taken and extracted with 100ml solvent and solution is filtered through nylon filter membrane. 0.1ml of the solution is further diluted to 10ml with solvent and absorbance of the solution is read on UV Spectroscopy. The drug concentration is extrapolated from the calibration curve in solvent.

1.10.6. In vitro drug release

The In vitro dissolution studies were carried out using USP apparatus Type II at 100 rpm. The dissolution medium consisted of 900 ml distilled water maintained at 37ºC ± 0.5ºC. The drug release at different time intervals was measured for two hours using UV spectrophotometer.

1.10.7. Particle size

The oral reconstitutable suspensions is evaluated, the average particle size of the formulation is examinely using standard microscopic method and average and standard deviations of 100 particles are estimated.

1.10.8. Viscosity

The rheological behavior of the suspension is determined by using Brookfield viscometer (Model - LVDI).

1.10.9. Stability study

The reconstitutable suspension is stored in air tight amber coloured glass bottles for 36 days at 45°C and then reconstituted with distilled water to make up the volume to 60 ml with gentle shaking. The reconstituted suspension is stored at 4°C, 25°C and 45°C for 15 days. The reconstituted suspensions stored at various temperatures are evaluated after reconstitution and after 7th and 15th day of reconstitution.

1.10.10. pH values

The pH of suspensions was measured with the aid of a pH meter

2. SUMMARY AND CONCLUSION:

The hydrophilic and lipophilic drugs can be delivered successfully into deep and peripheral tissues such as cerebrospinal fluid and central nervous system by encapsulating them with crystalline lipids as lipospheres. They explained that the sensitive and potent drugs can be formulated as lipospheres to enhance stability and therapeutic efficacy at low doses and emphasized that the liposphere formulations are well suitable for administering as oral, topical and intravenous in order to enable therapeutics to reach deep/peripheral tissues such as cerebrospinal fluid and central nervous system. They discussed about the preliminary screening factors to determine the liposphere formation such as dimensions with morphological scenario, stability and storage issues etc. The marked differentials in enhancing solubility and permeability characteristics of BCS Class II and IV drug candidates by liposphere delivery systems with an evident of in-vivo outcomes were emphasized

Oral reconstituted suspension was formulated by using a suitable suspending agent. A suspending agent is needed in the dry suspension system in the case of reconstitution upon dilution and agitation with a specified quantity of vehicle, dispersed particle have a tendency to settle to the bottom of the container because they have a greater density than that of the dispersion medium. According to the Stock's law an increase of the viscosity of the dispersion medium can decrease the rate of particle sedimentation. By adding suspending agent to the dry suspension we can expect a slower rate descent of the particles when the dry powders of suspension are reconstituted. Xanthan gum was used as a suspending agent and stabilizer in dispersing medium due to its acceptable toxicological and safety properties for food and pharmaceutical application. It imports its high viscosity at low concentration with thixo tropic flow characteristic which increases with increasing concentration..

3. ACKNOWLEDGEMENT

The authors are thankful to the Principal, Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Maharashtra, India. Necessary facilities for work.

4. CONFLICTS OF INTEREST:

Authors have no conflicts of interest to declare.

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