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LIPOSPHERES: A NOVEL APPROACH FOR DRUG DELIVERY

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ABSTRACT

Lipospheres (LS) were utilized for the conveyance of numerous sorts of medications by different courses of organization. Lipid based conveyance frameworks like strong lipid nanoparticles, lipospheres are being created as substitutes for "polymer based conveyance frameworks" because of the expanding danger related concerns of monomers on intracellular handling of polymers and alluring advantages offered by lipids as bearers. Strong, water-insoluble lipospheres including a strong hydrophobic center, having a layer of a phospholipid inserted on the surface of the center that contain an API, antigen, immunization and bug control are revealed for utilization in a creature. The bioactive compound is broken down or scattered in the strong lipid network of the inner center. Lipospheres have a few points of interest over other conveyance frameworks, for example, better physical soundness, minimal effort of fixings, simplicity of readiness and scale-up, high dispersibility in a watery medium, high entanglement of hydrophobic medications, controlled molecule size, and amplified arrival of captured medication after organization, from a couple of hours to a few days. This survey article concentrates on redesigned data on a few parts of lipospheres, including readiness systems, sanitization, stockpiling and in vitro assessment strategies. Lipospheres have different applications, for example, controlled medication discharge, enhance physical soundness furthermore in protein and peptide and immunization conveyance.

KEY WORDS

Lipospheres, Lipid Dispersion System and Bioavailability.

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INTRODUCTION

Lipospheres were firstly reported by Domb and Maniar as scattering of strong circular particles of molecule size between 0.2-500 µm in breadth. [1-8]Lipospheres comprise of strong lipophilic fat center like triglycerides or unsaturated fat subordinates. The medication introduce either in broke down or medication scattered in strong fat framework, balanced out by monolayer of phospholipids. [1,3]Phospholipid particles embeded in

their surface which is potential entrance enhancer[5]. Egg and soyabean phosphatidylcholine which contains unsaturated fats may be in charge of upgraded vulnerability. [2,5]They likewise raise the smoothness of stratum corneum to high degree. Lecithin has high proclivity for epidermal tissue and shows skin hydration. Being biodegradable and made out of characteristic body constituents topically regulated phospholipids are for the most part considered as protected[5]. Liposphere detailing is a fluid miniaturized scale scattering of strong water insoluble round smaller scale particles of molecule size somewhere around 0.01 and 100 μm in diameter. [1-8]Truth is told, to date, more than 40% of new concoction elements are lipophilic and display poor water solubility. [6]Development of such ineffectively water solvent mixes towards clinically accessible medications introduces an awesome test confronting the pharmaceutical scientists. [2]Lipospheres are promising method to beat these obstructions in the advancement of suitable medication conveyance frameworks (DDS). Because of a few confinements with polymeric conveyance frameworks, broad endeavors are being made to create exchange carriers. [6-19]Lipids particularly, are presently being concentrated on generally because of their alluring properties in particular physicochemical assorted qualities, biocompatibility, biodegradability, capacity to expand the oral bioavailability of inadequately water solvent medication moieties, along these lines making them perfect competitors as bearers for risky drugs. [7]The understanding that the in vivo destiny of the medication is directed by the medication itself, as well as by the method of organization and the transporter framework which ought to empower an ideal medication discharge profile as indicated by the treatment prerequisites which is pivotal for such development. [6,19]Lipospheres have been proposed as lipid-based embodiment framework for lipophilic bioactive compounds[2]. Lipospheres like strong lipid nanoparticles are transporters of decision for topically connected medications in light of the fact that their lipid parts have a sanction status or are excipients utilized as a part of economically accessible topical restorative or pharmaceutical arrangements. The little size of the lipid particles guarantees close contact to the stratum conium and can build the measure of the medication entering into the mucosa or skin. Because of their strong lipid grid, controlled discharge from these bearers is conceivable which is imperative to supply the medication over a delayed stretch of time and to decrease systemic ingestion, expanded medication soundness can be accomplished lastly lipospheres have a film framing capacity prompting occlusive properties[21]. Numerous current medication applicants are ineffectively solvent in natural liquid coming about low and very variable bioavailability. I.V infusion of such medications is unrealistic on account of lipophilicity. Colloidal medication conveyance (CDS) conveys the medication in body with enhanced oral bioavailability, diminished variability, medication focusing with decreased general poisonous quality. It is normal that advancement of CDS is expanded as an aftereffect of obliged medication wellbeing and expanded number of ineffectively solvent mixes[2].

Types of Lipospheres[1]

Based on matrix composition lipospheres are classified as -

Classical Lipospheres

These comprises lipid based matrix and mostly neutral lipid used in their penetration of lipophilic core e.g. Tri Caprin, Tri Lauren, Stearic acid, Hydrogenated vegetable oil, Tri Stearin, Ethyl Stearate.

Polymer Lipospheres

These comprises matrices made from biodegradable polymer e.g. poly lactic acid (PLA), poly caprolactone (PCL), poly lactic-co-glycolide (PLGA). Lipospheres of polymeric matrix have been investigated to achieve longer release periods and considered as efficient tool for controlled delivery. This suffers from major draback including potential toxicology.

Advantages[1-22]

Lipospheres has preferred over other drug delivery system such as

- Better physical stability.

- Low cost of its components.
- Ease of preparation.
- High degree of dispersibility in aqueous medium loading of lipophilic drug.
- Extended release of loaded drug.
- High entrapment of hydrophobic drug.
- Reduced mobility of entrapped drug.

The main advantage of lipospheres is that it offers better biocompatibility and being physiological substance.

They are comparatively polymers but offers high degree of variability due to different degree of esterification and chain lengths or even mixtures of lipid components.

Lipospheres can be administered by various routes such as oral, I.V, I.M and topical route.

Disadvantages[1-22]

Lipospheres suffers from following disadvantage such as

- Low drug loading capacity of lipophilic proteins.
- Variable kinetics.
- Drug degradation due to high pressure.
- Insufficient stability.

Different lipid modifications and colloidal species coexist that may cause different solubility and melting point of active and auxillary species.

FORMULATION OF LIPOSPHERES

The formulation of lipospheres utilizes naturally occurring biodegradable lipid components. The hydrophobic core of lipospheres is composed of lipids, especially triglycerides and the surrounding phospholipid layer to provide the lipospheres their surface activity. Lipids, emulsifiers and stabilizers used in lipospheres are shown in table No.[1-7]. Some biodegradable polymers can be used to form surrounding layer of lipospheres for enhanced stability e.g. low molecular weight poly (lactic acid), Poly (caprolactone). The phospholipids are used to form the surrounding layer It gives emphasis on phospholipid including pure egg phosphatidylcholine (PCE), soya bean phosphatidylcholine (PCS), phosphatidyl ethanolamine (PE), and dimyristoyl phosphatidylglycerol (DMPG), food grade lecithin (96% acetone insoluble)[2.]

METHOD OF PREPARATION

Melt Dispersion Technique[15-17]

The blend of lipospheres containing lipids, phospholipids, cholesterol is readied with and without lipophilic medication. The blend is softened at 700˚ C and after that emulsified into hot outer fluid stage at 700˚ C containing suitable surfactant. The emulsion is then mixed by utilizing stirrer furnished with exchange impellers and keeps up temperature 700˚ C. Quickly cool the emulsion at 200˚C by putting plan into ice shower with persistent tumult to yield uniform scattering of lipospheres. The acquired lipospheres is then washed with water and disconnected by filtration through a paper channel.

Solvent Evaporation Technique[15-17]

This is procedure is different option for the melt scattering strategy. The principle target is minimizing the introduction to high temperature of thermo labile mixes, for example, nucleic acids, proteins and so on. This procedure is in view of the vanishing of natural dissolvable in which lipids are broken up and permitting the detailing of strong microparticles. The lipidic framework is broken up in natural dissolvable, for example, ethyl acetic acid derivation and kept up the temperature 500˚ C and after that emulsified with outside watery stage containing surfactant. The subsequent oil in water emulsion is mixed for 6 to 8 hours till complete vanishing of dissolvable and secluded by filtration.

Multiple Microemulsion[6-16]

In this strategy arrangement of peptide is scattered in stearic corrosive melt at 700˚ C taking after by scattering of this essential emulsion into fluid arrangement of egg, lecithin, butaric corrosive and taurodeoxycholate sodium salt at 700˚C. Fast cooling of various emulsion shaped strong lipospheres with 90% ensnarement of peptides. Support discharge is accounted for by numerous emulsion methods with incorporation of lipophilic counter particle to frame lipophilic salt of peptide. Polymeric lipospheres have additionally been

accounted for by twofold emulsification for epitome of antigen.

Sonication Method[8]

In this method drug is mixed with lipid in scintillation vial precoated with phospholipid. The vial is heated till lipid melts and then vortexed for 2 minutes to ensure proper mixing of ingredients. A 10mililitre of hot buffer solution is added in this mixture and sonication for 10 minutes with intermittent cooling until it reaches to room temperature.

Rotoevaporation Method[8]

On this system lipid arrangement with medication is readied in round base cup (RBF) containing 100 grams of glass dots (3 mm in measurement) blended altogether till clear arrangement is dissipated utilizing rotoevaporator under lessened weight at room temperature. A meager film is framed on surface of RBF and glass beds. Raise the temperature up to 400˚ C until complete dissipation of natural dissolvable. Known amount of 0.9% saline arrangement is added to RBF and substance are blended to 30 minutes at room temperature and afterward temperature is brought down to 100˚C by setting in ice shower and blending proceeded for 30 minutes until lipospheres are framed.

Micro fluidizer Method[8]

Lipospheres can be prepared by using micro fluidizer which is equipped with two separate entry ports. From one entry port a homogenous melted solution or suspension of drug and carrier is pumped and from second entry port an aqueous port aqueous buffer is pumped. The liquids are mixed in the instrument at high temperature. Where the carrier is melted and rapidly cooled to form lipospheres. The temperature of micro fluidizer can also be changed at any stage of processing to manipulate the particle size and distribution.

Solvent Extraction Method[17]

This method is based on dissolution of triglyceride (e.g. tripalmitin) and cationic lipid inorganic solvent and an addition of an aqueous polyvinyl alcohol (PVA) solution (0.5% w/w) is used as extraction fluid. The solution and extraction fluid are pumped in static micro channel mixer leading to production of oil in water emulsion. The mixture leads to production of fine lamellae in which subsequently disintegrate into droplets, allowing the formation of lipid microspheres in extraction medium.

Polymeric Lipospheres[8]

Polymeric biodegradable lipospheres can also be prepared by solvent or melt processes. The difference between polymeric lipospheres and standard lipospheres formulation is the composition of internal core of the particle. Standard lipospheres consist of lipophilic fat core that is composed of neutral fats like tri stearin while in polymeric lipospheres biodegradable polymers such as poly lactide (PLD). Both types of lipospheres are thought to be stabilized by one layer of phospholipid molecules embedded in their surface.

Sterilization of lipospheres[6,8]

Sterile liposphere formulation are prepared by sterile filtration of dispersion in hot stage during preparation using 0.2 μm filter at temperature that is 5^0 C above the melting point of liposphere composition. Heat sterilization using a standard autoclave cycle is reliable procedure. However, it might decomposes the formulation γ-sterilization of liposphere formulation did not affect their physical properties. γ- irradiation sterilization of liposphere formulations on the other hand, did not affect their physical properties.

Storage[2-18]

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

FACTORS AFFECTING QUALITY OF LIPOSPHERES:

Morphology Related Durg Loading[7]

At maximum drug lipid ratio (1:1) insufficient coating of drug by lipid forms aggregate during cooling phase which results in irregular, fluffy and fragile particles.

Type of Lipid

Polar (glyceryl monostearate, glyceryl monoleate) and apolar (tristearin, tripalmitin or tribehenin)

lipids combinations gave lipospheres satisfactory in respect of size, shape and recovery.

Type of Impeller

Lipospheres could not be formulated using 2-blade rotor and resulted in the formation of elliptical particles. Different impellers used are rotor (2-blade, 3-blade) type, helicoidal rotor (4-blade) type, double truncated cone rotor.

Entrapment Efficiency Related[7]

Type of Lipid

Entrapment in lipospheres is promoted by lipophilicity of API. Long chain triglycerides (tristearin and triarachidin) are generally more hydrophobic than short chain triglycerides like tricaprin and trilaurin. Long chain triglycerides increases the gastrointestinal residence of API compared to medium and short chain fatty acids thus increases the bioavailability. Lipid excipients reduce the activity of P-glycoprotein and MDR (multi drug resistant) associated protein by down regulating the protein expression and increase in cell membrane permeability in addition to lymphatic uptake.

Amount of Phospholipid

Triglyceride: phospholipid at a 1:0.5 to 1: 0.25 w/w revealed that 70-90% of phospholipid polar heads were accessible on liposphere surface thus enhancing the entrapment of drug.

Method of preparation

Melt dispersion technique was found to be superior than solvent evaporation in terms of entrapment efficiency as melt method increases drug incorporation core where as in solvent evaporation promotes drug incorporation in coat.

DRUG RELEASE RELATED[7]

DRUG RELEASE INFLUENCED BY FOLLOWING FACTORS

Release Pattern

The release pattern of tetracaine, etomidate and prednisolone entrapped in lipid particles. Tetracaine and etomidate lipospheres have shown explode release and prednisolone lipospheres gave sustained release.

Particle size

Smaller particles have greater surface area exposed to dissolution medium and higher diffusion coefficient. If the drug resides in the outer shell diffusion distance becomes shorter resulting in fast (burst) release.

Type of lipid

Hydroxyl groups of stearic alcohols promote matrix hydration by providing a hydrophilic pathway for water molecules to solubilize the drug and increase in dissolution than the fatty acids like stearic acid.

Stabilizer

Polaxomer 407 releases lipospheres in biphasic pattern (burst release followed by slow release) whereas gelatin releases drug in sigmoid release pattern.

EVALUATION

Particle Size

It is a standout amongst the most imperative assessment parameter for liposphere definition as it altogether influences the material properties. It is critical for their collaboration with natural environment. Molecule measuring results are in this way urgent parameter in the improvement and advancement of readiness procedure and also in the assessment of scattering steadiness. Molecule size is controlled by photon connection spectroscopy, laser light dissipating method.

Particle Morphology and Ultra structure of dispersion

Because of little molecule size of this framework, electronic tiny methods have been especially utilized to portray general measurements (structure and shape) of strong lipid molecule. Transmission electron microscopy (TEM) can give significant information on molecule size, shape and structure and in addition vicinity of diverse sorts of colloidal structures inside of scattering. TEM gives 2D pictures while 3D imaging is under scrutiny. Examining electron microscopy (SEM) is utilized for morphological examination of lipospheres including shape and surface structure regarding change with contact with discharge media. Optical microscopy is valuable in location of stage isolated crystalline bioactive mixes.

Micro particulate Contaminant

Particularly trace amounts of microparticles may be difficult to detect in light scattering techniques. The Coutler-Counter method has been used to detect absolute number of particles in the micrometer range. For dispersion of lipid nanoparticles this method has also been applied for particle size determination of solid lipid microparticles.

Zeta Potential

Colloidal particles possess surface charge because of ionized groups or of an ion adsorption from the dispersion medium. These surface charges and the strength and extension of electric field of the surrounding medium play important role repulsion of lipospheres and their stability against aggregation. Surface charge also has an impact on *in-vivo* behavior of colloidal carriers. Zeta potential measurements were done to access different compositions with respect to electrolyte and pH stability.

Crystallinity and Polymorphism

Characterizing crystallinity and polymorphism of lipospheres X-Ray diffraction (XRD) and Differential scanning calorimetry (DSC) are utilized. DSC is convenient method which confirms solid lipid particles by detecting melting transition. XRD is used to analyse microparticles with respect to influence of composition and preparation procedure on resulting polymorphic form.

Entrapment efficiency

The total amount of drug loaded into liposphere can be determined by, first extracting free drug (uncapsulated) into suitable buffer then encapsulated drug is then determined by dissolution of drug loaded microparticles in Triton solution or in a solvent which can dissolve the Microparticles.

APPLICATIONS

Controlled drug release

Prolonged drug release of lipophilic drugs can be facilitated by lipospheres. Gibaly et al identified that prolonged activity of allopurinol can be achieved by lipospheres and also avoids hepatotoxicity. They reported lipophilic emulsifier played main role to encapsulate drug and also increases controlled release profile of allopurinol from wax matrix[9]. Gohel *et al.* formulated controlled release liposphere based dosage form of diclofenac sodium to reduce damage to gastro-intestinal mucosa and reduce dosing frequency[11].

Improved physical stability

Maha Nasr *et al.* reported lipospheres containing acelofenac intended for topical delivery, the lipospheres proves as a highly stable and is superior anti-inflammatory activity compared to marketed product. [5]Toongsuwan *et al.* prepared bupivacaine lipospheres by hot emulsification method and cold re solidification method and formed lipospheres were physically stable for more than one year at ambient temperature[23].

Improved photo stability

Rosanna Tursilli *et al.* prepared lipospheres in which melatonin was encapsulated into lipid microspheres improve photo stability of melatonin. Moreover biocompatibility and sustained release characteristics of lipospheres shows additional advantages[10].

Enhancement of drug release

Shivakumar *et al.,* reported melt dispersion as ideal for encapsulating fat soluble drugs. Lipospheres prepared by using stearic acid have enhanced drug release than produced with paraffin wax only[25-26].

Rectal delivery

Malgorzata *et al.,* demonstrated diazepam incorporated in lipospheres prepared by high pressure homogenization of melted Witepsol dispersed in aqueous lecithin for rectal delivery for infants and children[27].

Protein and peptide

Lipospheres have good physical stability and dispersibility with the ease of freeze drying and reconstitution further provides interface necessary for solubilization and proper orientation as potential carrier for protein drugs[14-29.]

Vaccine delivery

Lipospheres employs fat-lipid environment to serve as carrier to protect antigen to serve as “depot” and to provide surface interface for solubilization[30-32].

VARIOUS PATENTS ON LIPOSPHERE

Bassett, Richard Simon *et al,* LIPOSPHERES FOR CONTROLLED DELIVERY OF SUBSTANCE studied this invention is in the area of controlled delivery systems for substances, including pharmaceuticals, vaccines and insect control agents. Many dispersion systems are currently in use as, or being explored for use as, carriers of substances, particularly biologically active compounds. These systems are designed to protect the substance from the environment during delivery and to provide a controlled release of the substance to a targeted area. In some cases, the goal is to target specific 10 sites in the body using the dispersion. In other cases, the goal is to prepare a drug carrier system that acts as a reservoir at the site of injection. Dispersed systems for delivery are also important in the non-pharmaceutical area, for example, for use in controlled release of substances for insect control and agricultural applications.

Abraham J. Domb, Manoj' Maniar, liposphere delivery systems for local anesthetics, studied a local anesthetic micro suspension system which includes lipospheres, that are solid, water-insoluble microparticles that have a layer of a phospholipid embedded on their surface. The core of the liposphere is a solid anesthetic such as lidocaine or marcaine or an anesthetic dispersed in an inert solid vehicle such as a wax. Anesthetic lipospheres provide a controlled delivery of local anesthetics to achieve extended, effective relief from pain by slowly releasing the anesthetic from the solid hydrophobic core. This is highly preferred over the situation in which an aqueous solution of local anesthetic must be frequently administered because it is quickly systemically absorbed.

Abraham J. Domb, Baltimore, liposphere carriers of vaccines studied solid, Water-Insoluble lipospheres including solid hydrophobic core. Having a layer of a phospholipid embedded on the surface of the core, that contains an antigen which is disclosed for use in immunizing an animal. The antigen (or "immunogen"), alone or in combination with a carrier, can form the core, be attached to or within the phospholipid, or both. Lipospheres containing antigens are prepared by two general procedures either melt preparation or Solvent preparation. The resulting lipospheres have several advantages over other delivery systems, including emulsions, vesicles and liposomes, including stability, low cost of reagents, ease of manufacture, high dispersibility in an aqueous medium, a release rate for the entrapped substance that is controlled the coating and the carrier.

Table No.1: Lipids in Lipospheres[7]

S.No	Ingredient	Class	Examples
1	Lipid	Triglycerides	Witepsol W35, Witepsol H35, Compitrol 888 ATO (Glyceryl behenate), Dynasan 112, Precirol (Glyceryl palmito stearate), tricaprin, trilaurin, tripalmitin, Tristearin, trimyristin.
		Monosaturated fatty acids	Cis forms of monosubstituted fatty acids have lower melting point than triglycerides hence used as mixture with higher saturated fatty esters.
		Partially hydrogenated vegetable oils	Soyabean oil, coconut oil, cotton seed oil.
		Oils	Olive oil, wheat gram oil, evenin primrose oil, arachis oil, safflower oil, corn oil, rice bran oil.
		Waxes	Bees wax, spermaceti, cetyl palmitate, arachidyl oleate, carnuba wax, cetyl alcohol, cholesteryl butyrate

Table No.2: Emulsifier in Lipospheres[7]

S.No	Ingredient	Class	Examples
1	Emulsifier	Phospholipids	Pure-egg phosphatidylglycerol, phosphatidyl ethanolamine, dimyristoyl phosphatidyl glycerol, soyabean phosphatidylcholine
		Surfactant	Tween 80, butyl alcohol

Table No.3: Stabilizers in Lipospheres[7]

S.No	Ingredient	Examples
1	Stabilizer	Gelatin 200 bloom, pectin, carrageenan K, polyvinyl alcohol, polyoxyethylene sorbitan trioleate, Pluronic PE 8100, lauryl sarcosine

CONCLUSION

Findings of this investigation suggest that liposphere can be considered a promising delivery system. In this we studied liposphere in detail including their different types, methods of preparation, different factors affecting liposphere, formulation of liposphere, various evaluation factors and their application in detail. Also it includes some patents available on liposphere.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Alladi S, Kothakota S. Lipospheres: A versatile drug delivery system, *Inventi Impact: NDDS,* 4, 2012, 237-42.
2. Sateesh G B, N Gowthamarajan K. Manufacturing techniques if lipospheres, *Overview, Int J Pharm Sci,* 3(4), 2011, 17-21.
3. Lognathan, Veerappan, Shivaprasada Reddy. Formulation Development and Evaluation of Flurbiprofen Lipospheres, *International Journal for the Advancement of Science and Arts,* 1(1), 2010, 90-95.
4. Surajit Das, Anumita Chaudhari. Recent advances in lipid nanoparticle formulation with solid matrix, for oral delivery, *AAPS Pharm Sci Tech,* 12(1), 2011, 62-76.
5. Maha Nasr, *et al.* Lipospheres as a carrier for topical delivery for Acelofenac, Preparation, Characterization, and *In Vivo* Evaluation, *AAPS Pharm Sci Tech,* 9(1), 2008, 154-62.
6. Anna Elgart *et al.* Lipospheres and pro-nano lipospheres for delivery, of poorly water soluble compounds, *Chemistry and Physics of Lipids,* 165, 2012, 438-53.
7. Leeladhar Prajapati *et al.* Lipospheres: Recent Advances in Various Drug Delivery System, *International Journal of Pharmacy and Technology,* 5(1), 2013, 2446-64.
8. Domb Abraham J, Maniar Manoj. Lipospheres for Controlled Delivery of Substances, *European Patent,* EP0502119.
9. El-Gibaly I, Abdel-Ghaffar S K. Effect of hexacosanol on characteristics of novel sustained-release allopurinol solid lipospheres (SLS), factorial design application and product evaluation, *International Journal of Pharmaceutics,* 294, 2005, 33-51.
10. Rosanna Tursilli, *et al.* Enhancement of melatonin, photo stability by encapsulation in lipospheres, *Journal of pharmaceutical and biomedical analysis,* 40, 2006, 910-14.
11. Cavalli R, Morel S, Gasco M R, Chetoni M F. Saettone "Preparation and evaluation *in vitro* of colloidal lipospheres containing pilocarpine as ion pair" *International Journal of Pharmaceutics,* 117, 1995, 243-246.
12. Santo Scalia, Rosanna Tursilli, Nicoletta Sala, Valentina Iannuccelli. "Encapsulation in lipospheres of the complex between butyl methoxy dibenzoylmethane and hydroxypropyl-_-cyclodextrin", *International Journal of Pharmaceutics,* 320, 2006, 79-85.
13. Valentina Iannuccelli, Nicoletta Sala, Rosanna Tursilli, Gilberto Coppi. *Santo Scalia* Influence of liposphere preparation on butyl methoxy dibenzoylmethane photo stability European, *Journal of Pharmaceutics and Biopharmaceutics,* 63, 2006, 140-145.
14. Manju Rawat, Swarnlata Saraf. "Lipospheres, Emerging carriers in delivery of proteins and

peptides" *International Journal of Pharmaceutical Sciences and Nanotechnology*, 1, 2008, 207-214.
15. Cortesi R, Esposito E, Luca G, Nastruzzi C. Production of lipospheres as carrier for bioactive compounds, *Biomaterials*, 23, 2002, 2283-2294.
16. Elisabetta E, Rita C, Nastruzzi C. Production of lipospheres for bioactive compound delivery, In: Claudio Nastruzzi, lipospheres in targets and delivery, Approaches, Methods and Applications, *CRC press, London*, 2, 2005, 23-40.
17. Claudio Nastruzzi, editor. Lipospheres in drug targets and delivery Approaches, Methods and Applications, *New York: Washington*, 2005.
18. Simon Benita. Microencapsulation methods and industrial application, In: Abraham J. Domb, Editors, Lipospheres for controlled delivery of substance, 2, 297-315.
19. Mehnert W, Mader K. Solid lipid nanoparticles: production, characterization and applications, *Adv. Drug Delivery, Rev.* 47, 2001, 165196.
20. Valjakka-Koskela R, Kirjavainen M, Monkkonen J, Urtti A and Kiesvaara J. Enhancement of percutaneous absorption of naproxen by phospholipids, *Int. J. Pharm*, 175, 1998, 225-230.
21. Escribano E, Calpena A C, Queralt J, Obach R and Domenech J. Assessment of diclofenac permeation with different formulations, anti-inflammatory study of a selected formula, *Eur. J. Pharm Sci*, 19, 2003, 203-210.
22. Reithmeire H, Hermann J, Gopferich A. Development and characterization of lipid microparticles as drug carrier for somastatin, *Int J. Pharm*, 218, 2001, 133-143.
23. Toongsuwan S, Chiuli L, Erickson B K. Chang HC Formulation and characterization of bupivacaine lipospheres, *International Journal of Pharm*, 280, 2004, 57-65.
24. Gohel M C, Amin A. Development and evaluation of diclofenac sodium, *International Journal of Pharm Sci*, 3(3), 1997, 1-8.
25. Patel J K, Patel R P, Amin A F, Patel M. Formulation and evaluation of glipizide microspheres, *AAPS Pharm Sci Tech*, 6, 2005, 49-55.
26. Chowdary K P R, Rao Y S. Design and *in vitro* and in vivo evaluation of mucoadhesive microcapsules of glipizide for oral controlled release, *AAPS Pharm Sci, Tech*, 4, 2003, 1-6.
27. Malgorzata S, Stainslaw J, Monika Gajewska, Miroslawa K. Investigation of diazepam lipospheres based on Witepsol and lecithin intended for oral or rectal delivery, *Acta Poloniae Pharmaceutica- Drug Research*, 57(1), 2000, 61-64.
28. Bekerman T, Golenser J, Domb A. Cyclosporin nano particulate lipospheres for oral administration, 93(5), 2004, 1264-1270.
29. Swapnlata T, Saraf S, Deependra S, Manju R. Lipid carriers, A versatile delivery vehicle for proteins and peptides, *Yakugaku Zasshi*, 128(2), 2008, 269-280.
30. Abraham J. Domb, Aviva Ezra, Boaz Mizrahi. Lipospheres for vaccine delivery, In Claudio Nastruzzi, Lipospheres in drug targets and delivery, Apparatus, Methods and Applications, *CRC press, London*, 5, 2005, 87-100.
31. Mukherjee S, Ray S, Thakur R S. Solid lipid nanoparticles, A modern formulation approach in drug delivery system, *Indian Journal Pharm Sci*, 71(4), 2002, 349-358.
32. Domb, Abraham J. Liposphere carriers of vaccines US Patent, 5340588.

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