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ADVANCES IN LIPOSPHERE TECHNOLOGY FOR THE DELIVERY OF BCS CLASS II DRUGS: A REVIEW

Osama Uddin*, Dr. Satkar Prasad
Bhabha University, Bhopal (M.P.)

Abstract:
Lipospheres have emerged as promising drug delivery systems for Biopharmaceutical Classification System (BCS) Class II drugs, characterized by low solubility and high permeability. This review explores the formulation strategies, physicochemical properties, and pharmacokinetic advantages of lipospheres in enhancing the bioavailability and therapeutic efficacy of BCS Class II compounds. The lipid-based nature of lipospheres allows for improved drug solubilization, stability, and controlled release profiles, addressing the challenges associated with these poorly water-soluble drugs. Additionally, the impact of lipid composition, particle size, and surface modifications on drug encapsulation efficiency and release kinetics are discussed. Furthermore, recent advancements in liposphere technology, including hybrid and targeted delivery systems, are highlighted to underscore their potential in optimizing the delivery of BCS Class II drugs. This comprehensive review provides insights into the current state of lipospheres as versatile carriers for enhancing the oral delivery of poorly soluble drugs, thereby fostering new opportunities in pharmaceutical development and therapeutic applications.

Keywords: *Lipospheres, BCS Class II drugs, drug delivery systems, bioavailability, solubility enhancement, lipid-based carriers, controlled release, drug encapsulation, pharmacokinetics, poorly soluble drugs.*

Corresponding author:
Osama Uddin*,
Bhabha University, Bhopal (M.P.)

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INTRODUCTION:

Lipids are usually used to enhance drug absorption and permeability, thus there rising usage in formulating lipid nanoparticles, nanostructured lipid carriers and lipospheres (Dixit *et al*., 2017). Moreover, the presence of these lipids protects the loaded drugs from chemical and enzymatical degradation, making them quite advantageous for oral drug delivery systems (Motawee *et al*., 2023). Different methods have been used to create oral drug delivery systems that improve the water-insoluble medication's absorption efficiency by improving its dissolving profile. Various techniques such as solid dispersion, drug micronization, lyophilization, microencapsulation, and incorporation of the drug solution or liquid drug into soft gelatin capsules have been employed to improve the dissolving properties of water-insoluble pharmaceuticals. These include lipospheres, which were first described as a particulate dispersion of solid spherical particles between 0.2 and 100µm in diameter consisting of solid hydrophobic fat core, such as triglycerides or fatty acid derivatives, stabilized by monolayer of phospholipids. Lipospheres are among the most promising particulate drug delivery systems for improving the dissolution rate of water insoluble drugs (Rathor *et al*., 2018).

Lansoprazole is a proton pump inhibitor (PPI) which inactivates the final step in the gastric acid secretion pathway in gastric parietal cells in a dose-dependent manner. Bioavailability is 85% after the first dose – the highest among PPIs and acid inhibition is swift, resulting in rapid relief of symptoms. Lansoprazole also exhibits antibacterial activity against Helicobacter pylori in vitro (Hassan *et al*., 2000; Swan *et al*., 1999). Seventeen years of clinical experience worldwide have shown lansoprazole to be an effective and well-tolerated treatment option in the management of acid-related disorders, including gastric and duodenal ulcers and gastroesophageal reflux disease, and the treatment or prevention of gastroduodenal lesions induced by NSAIDs (Muhrer *et al*., 2006). Lansoprazole is also effective in combination with different regimens for *H. pylori* eradication and is included in the first-line PPI-based options for this purpose. Lansoprazole comes under the BCS II classification drug which has poor aqueous solubility & bioavailability (Balakrishna *et al*., 2017).

Biopharmaceutics Classification System (BCS)

Biopharmaceutics Classification System is important for determining the bioavailability of the drugs. The bioavailability issue can be due to insufficient solubility of permeability. Most compounds face the solubility problems (Mehta *et al*., 2014).

Classification of BCS Class Drugs

The Biopharmaceutics Classification System (BCS) is a scientific method that analyses pharmaceutical substances based on their capacity to dissolve in water and pass through the intestinal lining (Singh *et al*., 2022). The BCS categorises the chemicals that are utilised in the production of pharmaceuticals into one of four groups.

Class I drugs – High solubility, High permeability. Examples: Metoprolol , Propranolol (Wu and Benet, 2005)

Class II drugs – Low solubility, High permeability. Examples: Nifedipine, naproxen (Blagden *et al*., 2007; He *et al*., 2010a)

Class III drugs – High solubility, Low permeability. Examples: Cimitidine, Metformin

Class IV drugs - Low solubility, Low permeability. Examples: Taxol, Clorthiazole (Onoue *et al*., 2010b)

(a) CLASS II: Class II moieties are categorized as low solubility and high permeability candidates. These molecules exhibit high absorption but low dissolution; therefore, the rate-limiting step of bioavailability for such drugs is dissolution. A slight increase in dissolution produces a significant increase in its bioavailability (Lobenberg and Amidon, 2000). Thus, dissolution plays a vital role in enhancing the bioavailability of chemical entities. BCS class II drugs have potential for biowaiver extension because of the limitation of oral absorption by in vivo dissolution. Because of numerous in vivo processes involved (Oberle and Amidon, 1987) as well as the limitation of intestinal absorption of Class II drugs by their solubility. Oral route for administration.Drug absorb rapidly.Drug dissolve slowly. Bioavailability is controlled by dosage form and rate of release of the drug substance (Yu, 1999).

e. g: Lansoprazole

Solubility Enhancement of BCS Class II Drugs

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Various techniques are available to improve the solubility of poorly soluble drugs. These techniques can be categorized in three basic approaches such as - Traditional Techniques, Newer and Novel Techniques or Solid Dispersion Technique (Singh *et al*., 2013).

(a) Traditional techniques

Traditional techniques includes - Use of co-solvents, Hydrotropy (Ahuja *et al*., 2007), Micronization (Chaumeil, 1998), Change in dielectric constant of

solvent (Babu *et al*., 2010), Amorphous forms, Chemical modification of drug, Use of surfactants (Bakatselou *et al*., 1991), Inclusion complex or clathrates (Challa *et al*., 2005) and Alteration of pH of solvent (Talari *et al*., 2009) etc.

(b) Newer and novel techniques

Newer and novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs are Size reduction technologies (Bertucco *et al*., 2001; 25), Nanoparticle Technology, Nanocrystal Technology, Nanosuspension, Cryogenic Technology, Supercritical Technology, Lipid based delivery system and Self Dispersing Lipid Formulation (SDLF) (Chowdary and Madhavi, 2005) etc.

Lipospheres

Lipospheres were first reported as a particulate dispersion of solid spherical particles between 0.2-100 µm in diameter consisting of solid hydrophobic fat core such as triglycerides or fatty acids derivatives, stabilized by monolayer of phospholipids (Mangenheim *et al*., 1993).

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. Lipospheres are single unit system with respect to their uniform drug dispersion, maintain the uniform absorption of drug at gastrointestinal tract and more advantages than multiple unit drug delivery systems like Nanoparticles microparticles, microemulsions, and liposomes. The amount of drug encapsulated can vary up to 95% for Lipophilic as well as for hydrophilic drugs and because they are made from physiological or physiologically related materials, they are well tolerated in living systems (Manogna and Sagar, 2019).

Advantages

Lipospheres have versatile advantages over other delivery systems, such as: Liposphere exhibit enhanced physical stability due to avoidance of coalescence, High dispersability in an aqueous medium, Low cost of ingredients, Ease of preparation and scale up, High entrapment of hydrophobic drugs, Controlled particle size, 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 after a single injection (Satheeshbabu and Gowthamarajan, 2011).

Disadvantages

Different lipid modifications and colloidal species coexist that may cause differences in solubility and melting point of active and auxiliary species. Low drug loading capacity for hydrophilic compounds.Variable kinetics of distribution processes. High-pressure induced drug degradation.Insufficient stability data (Amselem *et al*., 1994; Salome and Ikechukwu, 2012).

Formulation of lipospheres

The formulation of lipospheres approach utilizes naturally occurring biodegradable lipid constituents. The internal hydrophobic core of lipospheres is composed of lipids, especially triglycerides, while the surface activity of liposphere is provided by the surrounding phospholipid layer. The neutral fats, stabilizers are additionally used in the preparation of the hydrophobic cores of the lipospheres (Sirisha *et al*., 2020).

Lipid stabilizers

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

Factors Influencing Quality Attributes of Lipospheres:

1. Morphology of lipospheres

a) Drug loading
b) Type of lipid
c) Type of impeller

2. Entrapment efficiency

a) Type of lipid
b) Amount of Phospholipid:
c) Effect of method of preparation:

3. Drug release

a) Release pattern
b) Effect of particlesize
c) Type of lipid.
d) Effect of stabilizer (Wattamwar *et al*., 2014)

Lipospheres are prepared by various techniques includes:-

Melt dispersion technique: In this method, the lipid or lipid mixture is melted and maintained at a temperature slightly above the melting point of the lipid, in which the drug is dispersed. This mixture is emulsified with an external aqueous phase containing

a suitable surfactant and phospholipids and it's maintained at a temperature nearly or slightly higher than the lipid phase. The formed emulsion is continuously agitated with a mechanical stirrer, then the formulation is immediately cooled by submerging it in an ice bath with continuous agitation to produce a uniform dispersion of lipospheres (Natarajan *et al*., 2013; Yalavarthi *et al*., 2014).

Solvent evaporation technique: In this technique, co-solvent exists to enhance the solvability about lipoid and lipophilic drugs to get a fully homogenous lipospheres solution. Choice of solvents and co-solvents was the consequence of miscibility everywhere influences the output. Examples of co-solvents are dichloromethane, Ethyl ethanoate, Propanone, Flavin, tetra hydro furane and aceto nitrile (Anzar *et al*., 2020).

Multiple microemulsion: The uniform size about 300 nm with 90% EE was reported with multiple microemulsion method. In this approach, the hydrophilic drugs were dissolved in an aqueous phase, and this solution was added to the lipid phase to yield primary emulsion at high temperatures. Then, the solution was added to the oil phase containing hydrophobic emulsifier to yield uniform size lipospheres (Morel *et al*., 1994).

Sonication method: In this technique, the drug is mixed with lipid in a scintillation vial which is pre-coated with phospholipids. The vial is heated until the lipid melts, and then vortexes for 2min to ensure proper mixing of the ingredients. A 10 ml of hot buffer solution is added into the above mixture and sonicated for 10min with intermittent cooling until it reaches to the room temperature (Rawat and Saraf, 2008).

Roto evaporation method: Using this method, a lipid solution containing the medication is made in a round-bottom flask along with 100 grams of glass beads (3 mm in diameter), which are well mixed to produce a transparent solution. The solvent is then removed using a roto evaporator set to low pressure at ambient temperature, forming a thin coating surrounding the glass beads and round-bottom flask. Increase the temperature to 40°C to allow the organic solvent to completely evaporate. After adding a known quantity of 0.9% saline, the vessel's contents are mixed for 30 minutes at room temperature. Next, the temperature is dropped to 10°C by placing it in an ice bath, and mixing is done for an additional 30 minutes, or until lipospheres develop (Ahirwar *et al*., 2023).

Microfluidizer method: Another method for creating lipospheres is to use a microfluidizer with two distinct entrance ports. A uniform melting solution or suspension of the drug and carrier is pushed from one entrance point, while an aqueous buffer is pumped from the second entry port. The liquids are combined in the device at a high temperature, melting the carrier and quickly cooling it down to create the lipospheres. At any point during the liposphere processing, the temperature of the microfluidizer can be adjusted to control the distribution and size of the particles (Domb *et al*., 2005).

Solvent extraction method: The solvent extraction method is based on the dissolution of the triglyceride (i.e., tripalmitin) and the cationic lipid in the organic solvent (i.e., dichloromethane), and on the addition of an aqueous polyvinyl alcohol (PVA) solution (0.5% w/w) used as extraction fluid. The solution and the extraction fluid are pumped into a static microchannel mixer, leading to the production of an O/W emulsion. The mixing leads to the production of fine lamellae, which subsequently disintegrate into droplets, allowing the formation of lipid microspheres dispersed in the extraction aqueous medium (Nastruzzi, 2004).

Polymeric lipospheres: Polymeric biodegradable lipospheres can also be prepared by solvent or melt processes. The difference between polymeric lipospheres and the standard liposphere formulations is the composition of the internal core of the particles. Standard lipospheres, as those previously described, consist of a solid hydrophobic fat core that is composed of neutral fats like tristearin, while in the polymeric lipospheres, biodegradable polymers such as polylactide (PLD) or PCL substitute the triglycerides. Both types of lipospheres are thought to be stabilized by one layer of phospholipid molecules embedded in their surface (Morel *et al*., 1996).

Evaluation parameters of Lipospheres

Microscopic Evaluation: Photomicroscopic experiments (DMWB1-123 MOTIC MICROSCOPE) were used to determine the particle size of several batches of lipospheres. A microscope was used to examine 100 randomly chosen particles for analysis. The average particle size of every formulation was found (Leeladhar, 2013).

Yield of Liposphere: To find the yield of lipospheres formulated per batch, the produced lipospheres were filtered out of the medium, dried, and weighed.

Determination of Drug Content: After dissolving 10 mg of the loaded liposphere exactly in 10 ml of phosphate buffer (pH7.4), the mixture was sonicated for 15 minutes. The buffer (pH 7.4) was used to dilute the obtained sample to volume (100 ml). After that, the mixture was filtered and subjected to a 288 nm wave length UV spectroscopic analysis. At the same wave length, unloaded lipospheres yielded negligible absorption values. Every sample was examined three times (Dudala *et al*., 2014).

Entrapment efficiency: Amount of drug loaded into lipospheres can be determined by first extracting the free drug (unencapsulated) by centrifugation into a suitable buffer. The encapsulated drug is then determined by dissolution-extraction of drug loaded Microparticles in Triton solution or in a solvent which can dissolve the Microparticles.Percentage (%) of the drug entrapped can be calculated using the formula (Gander *et al*., 1996):

Entrapment Efficiency Percentage = Entrapped drug/Total drug *100

Loading capacity (LC): LC indicates the proportion between the weight of the lipids overall and the API that is trapped. It is ascertained in this manner:

$$LC = Wa - Ws / Wa - Ws + Wl \times 100$$

Where Ws is the quantity of API found in the supernatant following the separation of the lipid and aqueous phase,Wa is the weight of API added to the formulation, and Wl is the weight of lipid added to the formulation (Attama *et al*., 2009).

Differential Scanning Calorimetry (DSC): By analyzing the thermograms that are produced from the readings on a differential scanning calorimeter, the compatibility of the drug excipient can be investigated. Nitrogen gas is used to maintain an inert atmospheric state during the measurements. Every precisely weighed sample (about 3-5 mg) is put inside a sealed aluminum pan and heated from 40 to 240 degrees Celsius at a rate of 10 degrees Celsius per minute. As a guide, an empty aluminum pan is utilized (Pouton, 2006).

Application of lipospheres

The use of lipid nanocarriers provides a suitable way for the nasal delivery of antigenic molecules. In this sense, the design of optimized vaccine nanocarriers offers a promising way for nasal mucosal vaccination. SLNs offer the opportunity of controlled drug release and the possibility to incorporate poorly soluble drugs. The application of lipids as vehicle for the delivery of drugs has revolutionarized drug delivery with some old drugs with very serious side effects being safe for use. Some anti-inflammatory drugs for example, indomethacin, have shown that indomethacin lipid formulations could be used with minimal gastro-intestinal irritation. Lipospheres also serves as a gene vector carrier SLN can be used in the gene vector formulation. There are several recent reports of SLN carrying genetic/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 into SLN gene vector (Nancy *et al*., 2017).

Table 1: List of BCS Class II drugs incorporated in to lipospheres by various techniques

S. No.	Name of drugs	Excipients used	Methods of preparation	References
1	Pioglitazone hydrochloride	Phospholipon 90G, Poloxamer 188 as surfactants	Melt dispersion (homogenization) technique	(Bhosale *et al*., 2016)
2	Ibuprofen	Phospholipon 90G, Beeswax	Hot homogenization technique	(Momoh *et al*., 2015)
3	Saxagliptin	Potassium dihydrogen phosphate, Behenic acid, potassium bromide	Hot emulsion congealing technique	(Rasul *et al*., 2021)
4	Glimepiride	Poloxamer 188, PVA and P 90G	Melt dispersion technique	(Galgatte *et al*., 2015)
5	Celecoxib	Ethyl oleate, Phospholipon 80H	Melt dispersion technique	(Patil *et al*., 2020)

CONCLUSION:

Lipospheres represent a highly effective and versatile drug delivery system, particularly suited for BCS Class II drugs, which are plagued by poor aqueous solubility but possess good permeability. By leveraging lipid-based formulations, lipospheres enhance the solubility, stability, and bioavailability of these drugs, addressing one of the primary challenges in their oral delivery. The ability to control drug release, protect the active pharmaceutical ingredient (API) from degradation, and target specific tissues or organs further increases their therapeutic potential. Recent advancements in liposphere technology, including surface modifications and hybrid systems, offer promising solutions for more tailored and efficient drug delivery. As research in this field continues to evolve, lipospheres may become an integral part of next-generation drug delivery strategies for improving the pharmacological performance of BCS Class II drugs, ultimately enhancing patient outcomes and treatment efficacy.

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