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Review Article

LIOSPHERES DRUG DELIVERY SYSTEM OF ANTIDIABETIC DRUGS: A REVIEW

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Abstract:

Diabetes is a long-term metabolic disease caused by insufficient insulin that is characterized by elevated blood sugar, changed metabolism of fats, proteins, and carbohydrates, and a higher risk of cardiovascular problems. Anti-diabetic medications are a great fit for liposphere drug delivery systems because to their drawbacks, which include inconsistent bioavailability, substantial first pass metabolism, and more frequent administration. Compared to emulsions, liposomes, and microspheres, the lipospheres carrier system offers a number of benefits, including improved physical stability, reduced ingredient costs, ease of preparation and scaling up, high dispersability in an aqueous medium, high entrapment of hydrophobic drugs, controlled particle size, and extended release of entrapped drug. This review article provides a thorough understanding of diabetes, including its causes, classifications, and current treatment options. It further expands on the topic by discussing lipospheres as innovative drug delivery systems and their historical implications for the administration of anti-diabetic medications.

Keywords: Liposphere, Diabetes, Novel drug delivery system, Antidiabetic drugs

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INTRODUCTION:

People with diabetes mellitus are afflicted with this frequent and highly prevalent disease in both industrialized and developing nations. This disease is thought to afflict 25% of the global population. Anomalies in the metabolism of carbohydrates lead to low blood insulin levels or insulin-sensitive target organs, which is what causes diabetes mellitus (Maitiet *al.*, 2004). Even though oral hypoglycemic medications have made significant progress in treating diabetes, there is still a need for additional medications due to the drawbacks of the synthetic ones now on the market. Herbal medications possessing antidiabetic characteristics have not been developed into modern pharmaceuticals for commercial use, although being highly valued in conventional medical systems (Wadkaret *al.*, 2008). Greek is where the phrases "Diabetes" and "Mellitus" originate. "Diabetes" implies "a siphon or passer through," while "Mellitus" is a synonym for "sweet." It is thought that the Greeks gave it this name because diabetic patients' inflated urine production attracted flies and bees (Patlak, 2002).

Diabetes mellitus (DM) is a grave, long-lasting, and intricate disease marked by elevated blood sugar levels caused by insufficient insulin produced by pancreatic β -cells. This occurs when the body is unable to effectively produce either or both of these hormones (World Health Organization, 2016).

Classification

There are three primary forms of DM

Insulin dependant diabetes mellitus (IDDM): Insulin must be administered daily to treat type I diabetes, sometimes referred to as insulin dependent diabetes, which is characterized by insufficient insulin synthesis. This occurs as a result of the pancreatic β cells' autoimmune destruction caused by cellular mediation (Jun and Yoon, 2002).

Non-insulin dependant diabetes mellitus (NIDDM): Type-II diabetes, sometimes referred to as non-insulin dependent diabetes, is brought on by the body's inefficient use of insulin. Type-II diabetes is frequently caused by a number of risk factors, including advancing age, genetics, obesity, poor food, insufficient physical exercise, and hypertension (Newman *et al.*, 1987). Another type of diabetes is called gestational diabetes, and it is primarily caused by glucose intolerance and begins during pregnancy. Although this is a transient ailment, it may carry a long-term risk of diabetes (Bellamy *et al.*, 2009).

Gestational Diabetes Mellitus: A kind of diabetes mellitus that is not immediately apparent that is detected in the second or third trimester of pregnancy is called gestational diabetes mellitus (GDM). Pregnancy-related GDM is a temporary condition

that increases the long-term risk of type II diabetes (Piero, 2015).

Diagnosis of Diabetes Mellitus

It is never appropriate to diagnose diabetes in a patient who exhibits no symptoms based on a single abnormal blood glucose reading. If diabetes is diagnosed, the doctor must be certain that the diagnosis is confirmed because the patient will have serious, permanent repercussions. Urine sugar, blood sugar, glucose tolerance test, renal glucose threshold, reduced glucose tolerance, increased glucose tolerance, renal glycosuria, extended glucose tolerance curve, cortisone-stressed glucose tolerance test, intravenous glucose tolerance test, and oral glucose tolerance test are among the methods used to diagnose diabetes mellitus (Mohan and Pradeepa, 2009).

Treatment of Diabetes Mellitus

Eliminating the triggering factor and administering frequent high doses of insulin constitute the treatment. Once the condition is under control, the insulin requirement returns to normal. The goals of managing diabetes mellitus are to: prevent or delay the progression of the short- and long-term risks of the disease; give the patient the information, inspiration, and resources they need to take charge of their own informed care; and restore the diabetic's disturbed metabolism as close to normal as is safe and comfortable (Singh *et al.*, 2016).

Medications**Insulin**

There are numerous ways to give insulin. The most popular techniques consist of (Wilcox, 2005):

- **Insulin pump:** This provides consistent, little amounts of insulin all day long.
- **Needle and syringe:** An injection of insulin is administered by drawing fluid from a container. The stomach is the most efficient site for injections, however the upper arm, buttocks, or thigh can also be used. It takes multiple doses for some people to get their blood sugar levels back to normal. For some, one injection may be all they need.
- **Insulin pen:** While some insulin pens are discarded, others have a slot for an interchangeable insulin cartridge. They resemble pens with a needle in place of a nib, although they are more expensive than needles. They are also simpler to use.
- **Inhaler:** Certain forms of insulin are available as powder that can be inhaled using an inhaler device. The blood can absorb inhaled insulin more quickly than other forms. It is only

appropriate for adults with type 1 or type 2 diabetes, though.

- **Jet injector:** Using this technique, a tiny, high-pressure spray is injected into the skin in place of a needle.
- **Injection port:** This has a little tube that is inserted just under the skin by the insulin recipient. After that, they would fit a replacement port every few days and inject insulin into the port using a pen, needle, and syringe. An injection port can be used as a substitute for daily skin punctures. Those with type 2 diabetes may also benefit from other drugs that lower blood sugar, such as (Maruthur *et al.*, 2016):
- **Alpha-glucosidase inhibitors:** Following a meal, the conversion of starches into glucose is slowed down by acarbose and miglitol, which also reduces the rise in blood sugar.
- **Bile acid sequestrants (BASs):** Since they don't enter the bloodstream, these are safe for those who also have liver problems and lower blood sugar and cholesterol.
- **DPP-4 inhibitors:** Saxagliptin, linagliptin (Tradjenta), and alogliptin all aid in enhancing the blood's ability to bind glucose without lowering blood sugar levels.
- **Meglitinides:** Although these may result in low blood sugar, nateglinide and repaglinide increase the release of insulin.
- **SGLT2 inhibitors:** By preventing the kidneys from reabsorbing glucose, canagliflozin and dapagliflozin (Farxiga) help remove carbohydrates from the body through the urine.
- **Sulfonylureas:** The pancreas releases insulin when glipizide, chlorpropamide, and glimepiride are administered.
- **Thiazolidinediones, or TZDs:** Actos (pioglitazone) slows down the liver's synthesis of glucose while enhancing the effects of insulin in muscle and fat.
- **GLP-1 agonists:** A few medications that can aid in weight loss are dulaglutide (Trulicity), exenatide (Byetta), liraglutide (Victoza), lixisenatide, and semaglutide (Ozempic).

Less common treatments

Bariatric surgery

Also referred to as weight loss surgery, this may assist individuals with type 2 diabetes and obesity in returning to their desired blood sugar levels (Dixon *et al.*, 2012).

Artificial pancreas

The hybrid closed-loop device, an artificial pancreas that measures blood sugar levels every five minutes

and automatically delivers the proper dosages of insulin and glucagon, substitutes glucose monitoring and insulin injections (Albisser *et al.*, 1974).

Pancreatic islet transplantation

Insulin is produced by cell clusters called islets. When a person has type 1 diabetes, their immune system targets these cells (Marfil *et al.*, 2022).

Lipospheres drug delivery system

Lipid nanoparticles have the potential to enhance therapeutic profiles as compared to free drug because they can shield loaded medicines from enzymatic and chemical degradation and release drug molecules into blood gradually from the lipid matrix.

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).

Improved drug stability, the potential for regulated drug release, controlled particle size, and high drug loading are advantages of the liposphere drug delivery method (Ganesan and Allimalarkodi, 2015).

Lipospheres

When Abraham J. Domb originally presented lipospheres, they were designed to include an antigen that was utilized in animal vaccines (Domb, 1994). Triglycerides, the hydrophobic lipid core that makes them up, can dissolve or stay solid at body temperature but are solid at normal temperature. A layer of embedded phospholipid molecules stabilizes the lipospheres' outer surface and has the potential to either entrap the medication or enhance its coat (Elgart *et al.*, 2012; Dudala *et al.*, 2014). Their particle sizes vary from 0.01 to 100 µm, and the medicine is dissolved or disseminated within their internal core. One lipid-based drug delivery method that effectively satisfies regulatory requirements is lipospheres. This is due to their high dispersibility in

aqueous media, ease of preparation and scaling up, and exceptional capacity to entrap hydrophobic drugs, thereby improving the permeability and

solubility properties of class II and IV drug candidates in particular (Ganesan and Allimalarkodi, 2015; Kumar *et al.*, 2021).

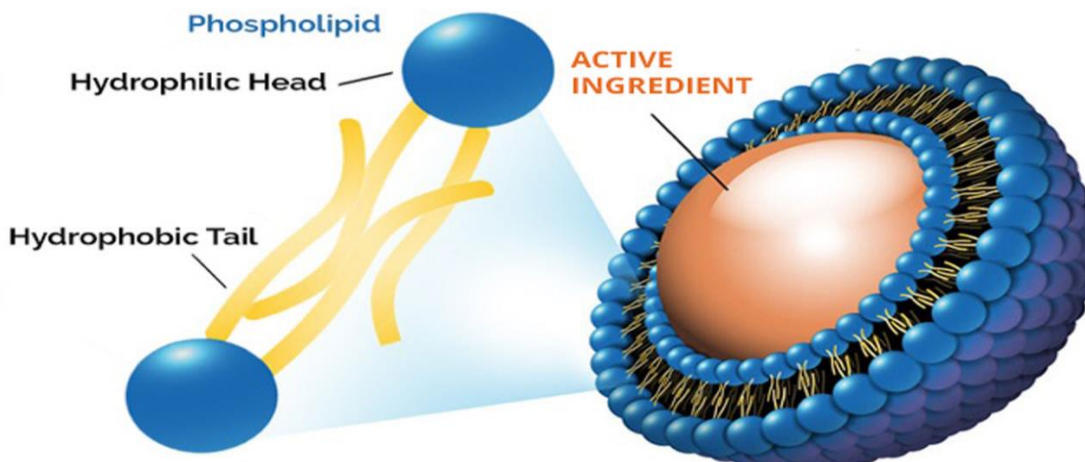


Figure 1: Structure of a lipospheres

Method for preparation of Lipospheres

Melt dispersion technique: Both with and without a lipophilic model medication, the lipidic physical combination comprising lipid, phospholipids, cholesterol, etc., is created. After melting the physical combination at 70°C, it is emulsified into a hot, external aqueous phase that is kept at that temperature and contains the appropriate surfactant. The emulsion is kept at 70°C and mechanically agitated using a stirrer fitted with alternating impellers. The emulsion formulation is then quickly cooled to roughly 20°C by submerging it in an ice bath while maintaining agitation to produce a homogeneous dispersion of LS. Following a water wash, the resulting LS is separated by passing it through a paper filter (Nastruzzi, 2004).

Solvent evaporation method: This technique is an alternative to the melt dispersion technique and it is considered with the objective of possibly minimizing the exposure to high temperatures of thermo labile compounds, such as proteins and nucleic acids. This technique is based on the evaporation of organic solvent in which lipids are dissolved and allowing the formation of solid microparticles. Specifically, the lipidic matrix is dissolved in an organic solvent (ethyl acetate) at a temperature of roughly 50–60°C. An external aqueous phase containing the surfactant agent is then added to the mixture to emulsify it. The resultant oil-in-water emulsion is swirled for six to eight hours, or until the solvent has completely evaporated. After being retrieved by filtering via filter paper, the LS are dried and preserved (Morels *et al.*, 1994).

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).

Sonication method: Using this method, the medication is combined with lipid in a scintillation vial that has already been phospholipid-coated. To make sure the materials are well mixed, the vial is heated until the lipid melts and then vortexed for two minutes. The combination above is combined with 10 milliliters of hot buffer solution, which is sonicated for 10 minutes while being periodically cooled until it reaches room temperature (Rawat and Saraf, 2008).

Co-solvent solvent evaporation method: While a transparent solution is produced using this co-solvent - solvent evaporation process that uses chloroform and N-methyl pyrrolidone, a low yield and large particle size are obtained, which can be changed by varying the solvent employed. Lipospheres composed of polar and non-polar lipids that deviate from the concept of a liposphere as stated by Domb in his

patent by employing synthetic stabilizers in place of phospholipids. Even though their research had nothing to do with protein delivery, they did experiment with a hydrophilic medication and found that the double emulsification method could entrap about 50% of the drug (Cortesi, 1999).

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.

Evaluation of liposphere

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.

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.

Entrapment efficiency: Equation 1 can be used to compute the entrapment efficiency, which is defined as the quantity of drug entrapped in the lipid-based particles compared to the total amount of drug added. In other words, it is the percentage of drug included in the particles vs the percentage of drug still in the dispersion medium. With increasing drug concentration, the EE rises. Additionally, the polymer concentration affects the EE. This was demonstrated by the EE of gentamycin, which was dependent on PEG. As a result, the amount of PEG in the

succeeding microencapsulation grew gradually (Gander *et al.*, 1996).

Entrapment efficiency (EE %) = mass of drug in lipospheres / initial weight of 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:

$$LC = \frac{W_a - W_s}{W_a - W_s + W_l} \times 100$$

Where W_s is the quantity of API found in the supernatant following the separation of the lipid and aqueous phase, W_a is the weight of API added to the formulation, and W_l 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).

Applications of lipospheres

Parenteral route: Lipospheres have been utilized for the parenteral administration of antibiotics such as ofloxacin, norfloxacin, chloramphenicol palmitate, and oxytetracycline, as well as antifungal agents like nystatin and amphotericin B for the parenteral administration of adjuvants and vaccines (Rainer *et al.*, 2000).

Transdermal route: Lipospheres are appealing candidates for topical delivery because of their abilities to form films, their occlusive qualities, their controlled release from solid lipid matrix, which delays systemic absorption of drugs and prolongs their release, and their ability to stabilize drugs that are subject to extensive hepatic metabolism.

Nasal drug delivery: Antigenic compounds can be delivered to the nose in an appropriate manner with the help of lipid nanocarriers. Thus, the development of an enhanced vaccine nanocarrier presents a viable approach to nasal mucosal immunization.

Oral delivery: Aerosol lipospheres are being produced using a variety of therapeutic categories, including antibiotics, anti-inflammatory chemicals, vasodilators, anticancer medicines, proteins, and peptides (Larsson, 1989).

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

Name of drugs	Excipients used	Methods of preparation	References
Pioglitazone hydrochloride	Cetylalcohol, poloxamer, polysorbate and sorbitanmonooleate	Solvent injection technique	Rafieet <i>al.</i> , (2023)
Saxagliptin	potassium dihydrogen phosphate, Behenic acid, potassium bromide	Hot Emulsion Congealing Technique	Rasulet <i>al.</i> , (2021)
Glibenclamide	Phospholipon 90G, solidified reverse micellar solutions	Hot melt homogenization	Nnamaniet <i>al.</i> , (2022)
Metformin	glycerol monooleate oil , ethano, hydrochloric acid	Double emulsion-solvent evaporation method.	Masoomzadeh and Maghsood, (2022)
Pioglitazone	Labrasol, Span 80 and Tween 80	Nano-emulsion template technique	Ilyaset <i>al.</i> , (2022)
Rosiglitazone maleate	Glycerylmonostearate, lecithin E-80	Cold homogenization technique	Dangiet <i>al.</i> , (2011)

CONCLUSION:

Lipospheres are crystal lipid particles made up of lipids that are usually chosen based on physiochemical characteristics and stability. Because lipid carriers naturally increase the bioavailability of lipophilic medicines with low solubility, they have a bright future ahead of them. A coating of phospholipids is embedded on the surface of the solid hydrophobic core that makes up lipospheres, which are solid, water-insoluble nano- and microparticles. Even though phospholipids are easily degraded, the formulation can remain hard and stable by using stabilizers and lipid. It is possible to synthesize the powerful and sensitive medication as a liposphere to improve stability at low dosages. The most popular routes are ideal for administering liposphere compositions. A variety of biological and pharmacological substances, such as local anesthetics, antibiotics, vaccinations, and anticancer treatments with sustained activity lasting up to five days, can be effectively delivered by liposphere formulation. We were able to create lipospheres whose size and shape were determined by the experimental parameters used through the use of melt dispersion, solvent evaporation, and micro emulsion techniques. Due to their mucoadhesive qualities, biodegradability, and lack of need for removal during the treatment period, lipid-based microspheres seem to be the best options for delivering antibacterial drugs. The lipospheres are useful for producing cosmetics and medications on a large commercial basis.

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