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Effective carriers of therapeutic drugs

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EVEN the most effective of medicines may not be easily administered and absorbed by the human body. Hence, active therapeutic substances need to be carried in an inactive substance or an excipient which can efficiently carry it to the target site in effective concentrations or make the active palatable or dispensible.

Traditional excipients include buffer salts like citrates, phosphates; sweetening agents like sucrose, glucose, glycerol; viscosity-enhancing agents like cellulose derivatives, non-ionic and ionic polymers like alginates; antioxidants like butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA); preservatives like benzoic acid, sorbic acid and their salts. All these serve to bind and provide bulk to the dosage form, to facilitate or control drug release from the excipient matrix, and to facilitate product manufacturing on high-speed, automated, production equipment.

In pharmaceutical solutions, both the therapeutic agent and the excipients are legally required to be present in solution over the shelf-life of the formulated product. As a result, pharmaceutical solutions are termed homogeneous. A major challenge to the pharmaceutical scientist is the attainment of homogeneity in the formulation, due to the limited aqueous solubility of the therapeutic agent.

Lipid excipients provide an attractive alternative over their traditional counterparts as they have the ability to solubilise hydrophobic drugs within the dosage form matrix. This leads to improved absorption in case of oral drug delivery, which is primarily mediated by a reduction in the barriers of poor aqueous solubility and slow drug dissolution rate in the gastrointestinal (GI) fluids. Some of these excipients also have desirable self-emulsifying properties, readily forming fine dispersions of lipid solubilised drug in the aqueous contents of the GI tract and creating optimal conditions for absorption.

Lecithin is used as a synonym for Phosphatidylcholine (PC) which is one of the major fractions of Phospholipids extracted and purified from egg yolk or soyabean. Purified Lecithin is commercially available (Lipova-E120 & Leciva-S70). Lecithin can be totally biodegraded and metabolised since it is an integral part of biological molecules. It has been given GRAS or Generally Regarded As Safe status by FDA.

Lecithins in parenteral drug delivery

Lecithins as membrane lipids make an ideal emulsifier for parenteral use as compared to its synthetic alternatives like polysorbates which need to be metabolised by the human body. Depending on its intended use, lecithin is purified to different degrees. Minor components of lecithin include phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI) etc. Soya lecithins contain more PA and PI than egg lecithin. The higher PI content in soya lecithin probably was responsible for certain adverse reactions seen with parenteral use of soya lecithins. The commercially used egg yolk lecithin, designed for parenteral use, is enriched in PC. Today egg lecithin has become the standard lecithin type for parenteral use.

> Lecithins as membrane lipids make an ideal emulsifier for parenteral use as compared to its synthetic alternatives

Improving oral bioavailability of drug with Lecithin

The absorption of a given drug depends on the balance of its solubility in the aqueous environment of the gastrointestinal lumen and its capability to diffuse across the lipophilic apical membrane of enterocytes. Generally, drugs have to be dissolved in order to attain sufficient bioavailability. The solubility of a given drug directly depends on its solid-state properties, e.g. particle size, crystalline or amorphous state, wettability, etc. A primary requirement of a lipid-based formulation is its ability to retain a poorly soluble substance in a solubilised state and to enhance solute-solvent interactions also after mixing with endogenous solubilisers, such as bile acids or phospholipids produced naturally in the body or after intra-luminal processing prior to absorption.

Lecithins may improve the oral bioavailability of poorly water-soluble drugs by number of possible mechanisms. They can increase effective drug solubility in the GI tract and blood vessels by stimulating the secretion of bile salts and endogenous biliary lipids such as phospholipid and cholesterol, forming intestinal mixed micelles, and then increases the solubilisation capacity of the GI tract. Moreover, as a result of the intercalation of administered phospholipids into these bile salt structures, either directly or by secondary digestion, micelle structures swell up and lead to a further increase in solubilisation capacity. Lecithins can also increase the gastric retention time, resulting in slow delivery to the absorption site and increased time available for the absorption.

A good example is an oral formulation of the immunosuppressant Rapamycin, Sirolimus (Rapamune Wyeth Pharmaceuticals), used to prevent rejection of kidney transplants. It is formulated with standardised Phosphatidylcholine concentrate with at least 50% soyabean phosphatidylcholine (Leciva-S50), as solubiliser of the highly lipophilic drug. A previous study investigated the impact of two different formulations of Sirolimus on blood levels and the development of arthritis induced in rats. On the one hand, Sirolimus was formulated as a suspension with polysorbate 80, and, on the other hand, as a highly water diluted emulsion containing 50%PC (soya lecithin) and 1% polysorbate 80. In all, the orally administered doses (0.5 mg/kg, 1.5 mg/kg and 4.5

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Lipid-based delivery has attracted attention

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mg/kg), the blood levels of the active ingredient were higher with the vehicle containing phosphatidylcholine. These higher blood levels correlated positively with the therapeutic effect on arthritic symptoms in the animals. With the soya lecithin formulation, approximately one sixth of the dose proved sufficient to inhibit the arthritis, demonstrating that the application of phosphatidylcholine improves the absorption, effectiveness, and therapeutic index of the active ingredient, while simultaneously enabling the administration of a lower dosage and reducing medication costs' side effects.

Lecithin formulation types

Oral drug delivery systems

1. Liposomes

Liposomes are aqueous compartments enclosed by lipid bilayer membranes. The liposome, first introduced by Bangham et al, in the 1960s, was successfully developed as lipid-based drug delivery vehicle. Liposomes can be prepared from lecithins by a simple thin film hydration method. Water-soluble drugs can be trapped inside the aqueous compartment of liposomes. However, water-insoluble ones can be incorporated into the bilayer membrane. Liposomes have been designed to reduce side effects of incorporated drugs and to enhance the therapeutic efficacy. Liposome structure can be adjusted to control release of the drug. Also, the surface of the liposome can be modified with polyethyleneglycol (PEG) to increase the residence time in the bloodstream and decrease recognition by the immune system. Such a modification also slows down the clearance of the liposome from the system.

2. Solid Lipid Nanoparticles (SLN)

SLNs are colloidal drug delivery systems composed of solid lipids which are stabilised with an emulsifying layer in an aqueous dispersion. Colloidal size varies between 50 and 1,000 nm. They offer several advantages, such as the avoidance of organic solvents and the possibility to produce high concentrated suspensions and they allow fast and effective manufacturing processes up to large-scale production. SLNs can protect encapsulated peptides /proteins against enzymatic degradation in the gastrointestinal mucosa. Furthermore, the carrier itself can be taken up to a certain extent by epithelial cells or the lymphoid tissues in Peyer's patches.

SLNs based on soybean phosphatidylcholine were selected as carrier systems for Insulin by Zhang et al. In vitro studies showed these carrier systems to deliver insulin with greater protection from enzymatic decomposition. Praziquantel (marketed under different trade names such as Biltricide (Bayer Vital GmbH) and Cesol (Merck KGaA), an antihelmintic drug was administered to rats in SLNs comprised of soyabean lecithin as one of the components. The encapsulation efficiency for such SLNs was 80%.

> Drug emulsions are normally formulated to be isotonic, and the amount of dissolved components can be minimised because the drug is in the lipid phase

Transdermal drug delivery systems

Transferosomes

Despite all the efforts devoted by several researchers, it was impossible to formulate a liposomal compound that permits the systemical release of an active principle, mainly because the dimension of the liposomes does not allow them to penetrate the stratum corneum.

Transferosomes are special type of liposomes, consisting of phosphatidylcholine and an edge activator. The concept of transferosomes was introduced in 1992 by Cevc and coworkers. These vesicular transferosomes are several orders of magnitude more elastic than the standard liposomes and thus well suited for the skin penetration. From the composition point of view, a transferosome is a self-adaptable and optimised mixed lipid aggregate. Transferosomes are vesicles composed by phospholipids as the main ingredient (soya phosphatidylcholine: Leciva-S70, egg Phosphatidylcholine: Lipova-E120, dipalmityl phosphatidylcholine, etc.), 10-25% surfactants for providing flexibility like sodium cholate, 3-10% alcohol as a solvent (ethanol, methanol) and hydrating medium consisting of saline phosphate buffer (pH 6.5-7).

Parenteral drug delivery systems

Fat emulsions

Intravenously administered oil in water emulsions containing triglycerides as the dispersed phase and egg lecithin as the preferred emulsifier are common in intensive care medicine.

Parenteral fat emulsions can be used as potential carriers for poorly water-soluble drugs. Drug emulsions are normally formulated to be isotonic, and the amount of dissolved components can be minimised because the drug is in the lipid phase. A good example of the system is the intravenous anaesthetic propofol (Diprivan) which has been considered as one of the most successful fat emulsions applied to drug delivery systems so far. It comprised of soyabean oil in which Propofol can readily dissolve, egg lecithin as an emulsifier and glycerol which maintained it isotonic to blood. The pain on injection was reduced since the concentration of Propofol to be administered decreased.

A decrease in toxicity, together with an increase in the therapeutic window, is another potential advantage. Different combinations of emulsifiers like egg lecithin

(Lipova-E120), egg lecithin plus soya lecithin and soya lecithin alone have been used in preparation of fat emulsions.

Conclusion

As a new and evolving discipline, lipid-based drug delivery has attracted considerable attention from academia to industry. The availability of a wide variety of pharmaceutical grade lipid excipients like lecithin from egg yolk and soyabean has

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Modern R&D facility with skilled scientists

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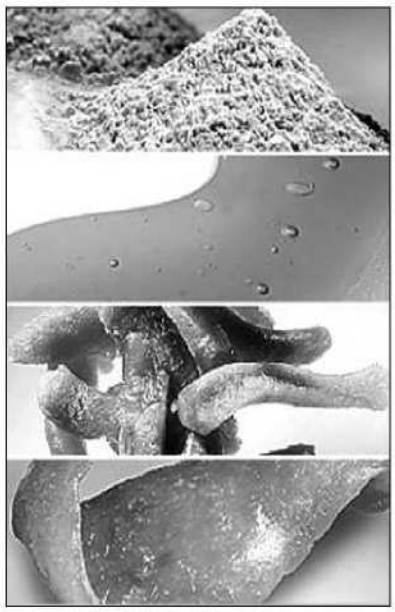
coincided with a recent advance in encapsulation technology. This advance, along with the fact that almost half of all new chemical entities fit the category of 'poorly water-soluble' has created a window of opportunity for the rapid introduction of Lecithin-based drug formulations into the marketplace.

VAV Life Sciences Pvt. Ltd, an India-based company, announces its entry into research and development of lipid drug delivery systems. Headquartered in Mumbai, VAV is entering discovery and development of potential lipid- based technologies for various pharmaceutical, biotechnology and nutritional applications. The company provides contract research services for clients interested in liposome-based technologies in their product development and invites project proposals for development of phospholipids-based delivery systems. From a modest beginning in 2003, VAV has been growing steadily offering its products and services globally and has several reputed companies as customers. Besides we also offer to



develop and manufacture customised products to commercial scale. VAV has set up a new, modern Research & Development facility with skilled and experienced scientists performing development work for its project partners in the field of Lipids.

VAV specialises in the purification of phospholipids from Lecithin for the development and production of Lipid drug delivery systems. We offer a wide range of Soya & Egg Phospholipids fractions.

Leciva-S35 (Soya Phosphatidylcholine 35%)

Used in: Oral Pharmaceuticals and topical preparations.

Leciva-S50 (Soya Phosphatidylcholine 50%)

Used in: Oral pharmaceuticals and intramuscular injectables.

Leciva-S70 (Soya Phosphatidylcholine 70%)

Used in: Injectable formulations.

Lipova-E120 (Egg Phosphatidylcholine 80%)

Used in: Parenteral Fat/Lipid emulsions such as Propofol, Omega 3 etc. in Pharmaceutical industry, preparation of Liposomes in Pharmaceutical industry, Lipid micelles for Oncology, Neurology & Metabolic drugs.

(The author is MD, VAV Life Sciences)

Quality of formulation depends on quality of API

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any of the conditions of the registration certificate, the agency after giving them an opportunity to showcause why such order should not be passed, can issue suspension and cancellation of registration certificate. If the manufacturers wish to appeal, they should appeal to the Central Government within 30 days of the receipt of such order.

Requirements for import licence application
Application

An application for licence to import drugs can be made in Form 8 by providing the details of the API to be imported, copy of registration certificate obtained from regulatory agency and copy of wholesale licence or copy of manufacturing licence with undertaking in Form 9 signed by manufacturer or his authorised agent in India. Fee for import licence is Rs 1,000 per drug.

Import licence

An import licence will be issued in Form 8 to the importer which is valid for three years and the importer can import the said API without any quantity restriction. A photocopy of the said licence shall be displayed in a prominent place of the premises. Each batch of drug imported into India shall be accompanied by detailed batch test report and batch release certificate duly signed by the manufacturer. If the authority wishes, it can subject the said imported API for examination. The licensee would be responsible for the business activity of the manufacturer in India and if there were any changes in the constitution of the firm, the current import licence would be valid for maximum three months from the date that change took place, unless a fresh import licence was obtained from the agency.

Conclusion

The quality of the formulation really depends on the quality of API and the manufacturing premises where API are manufactured. Of late, since lots of companies have been importing APIs from the overseas market, the regulator - Drugs Controller General of India has started inspecting overseas API manufacturing sites. This is really a shot in the arm for Indian pharma manufacturers who can now showcase their quality of imported APIs that had been successfully inspected and approved by the Indian regulatory agency.

(The author works in a large pharma company based in Hyderabad. The views expressed in the article are his own)