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Review

A review on phospholipids and their main applications in drug delivery systems

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ABSTRACT

Phospholipids have the characteristics of excellent biocompatibility and a especial amphiphilicity. These unique properties make phospholipids most appropriate to be employed as important pharmaceutical excipients and they have a very wide range of applications in drug delivery systems. The aim of this review is to summarize phospholipids and some of their related applications in drug delivery systems, and highlight the relationship between the properties and applications, and the effect of the species of phospholipids on the efficiency of drug delivery. We refer to some relevant literatures, starting from the structures, main sources and properties of phospholipids to introduce their applications in drug delivery systems. The present article focuses on introducing five types of carriers based on phospholipids, including liposomes, intravenous lipid emulsions, micelles, drug-phospholipids complexes and cochleates.

1. Introduction

Therapeutic agents such as proteins/peptides, nucleic acids, anticarcinogens, and other drugs have the drawbacks of low bioavailability, rapid clearance, and high toxicity. Therefore, there is a great demand to develop delivery methods and carriers, which will bring a more efficient delivery for therapeutics.

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.

As 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 generates different supermolecular structures which are dependent on their specific properties and conditions. For example,

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phospholipids have a propensity to form liposomes, which can be employed as the drug carriers [1]. Phospholipids have good emulsifying property which can stabilize the emulsions [2]. In addition, phospholipids as surface-active wetting agents which can coat on the surface of crystals to enhance the hydrophility of hydrophobic drugs [3]. The above properties are successfully employed in the DDS design.

Phospholipids based DDS have been found promising for better and effective delivery of drugs and providing much appropriate systematic drug delivery. In recent years, a variety of phospholipid-related formulations, such as Doxil® [4], Cleviprex® [5], Valium® [6] and Silybin Phytosome™ [7], have been used in clinic, and achieving good results.

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 phosphatidylcholine, 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 species diversity of phospholipids make how to select an appropriate phospholipid to achieve the therapeutic purpose become a crucial problem in the design of DDS, so we summarized the structures, main sources, properties of phospholipids which can give a guideline in the design of DDS. In addition, we set liposomes, intravenous lipid emulsions, PC/bile salt mixed micelles, phospholipid micelles, drug-phospholipid complexes, cochleates as examples to introduce the main applications associated with phospholipids and further explain how to make a choice among the phospholipids in drug delivery.

2. Phospholipids

Phospholipids are lipids containing phosphorus, a polar potion and non-polar potion in their structures.

2.1. *The structures of phospholipids*

According to the alcohols contained in the phospholipids, they can be divided into glycerophospholipids and sphingomyelins.

2.1.1. *Glycerophospholipids*

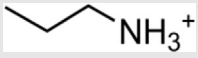
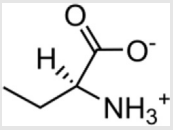
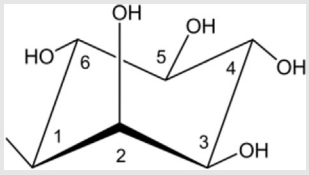
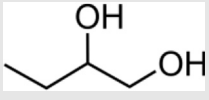
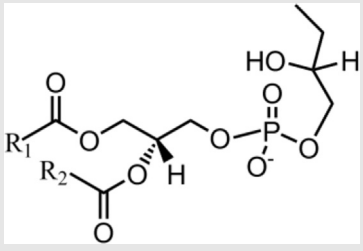
Glycerophospholipids which are the main phospholipids in eukaryotic cells, refer to the phospholipids in which glycerol is the backbone. All naturally occurring glycerophospholipids possess α-structure and L-configuration [8].

The chemical structures of glycerophospholipids can be classified by the head group, the length and the saturation of hydrophobic side chains, the type of bonding between the aliphatic moieties and glycerol backbone, and the number of aliphatic chains. Variation in the head group leads to different glycerophospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylinositol (PI), phosphatidylglycerol (PG) cardiolipin (CL) (Table 1). The length of the apolar moieties leads to different glycerophospholipids, e.g. dipalmitoyl, dimyristoyl, distearoyl PC. The saturation of aliphatic groups characterizes different glycerophospholipids, such as dioleoyl, distearoyl PC. The type of bonding (ester or ether) between aliphatic chains and glycerol determines different glycerophospholipids, such as plasmalogen [9]. The number of aliphatic chains is different, for example, lysophospholipids have only one acyl group at the glycerol backbone [10] (Fig. 1).

2.1.2. *Sphingomyelins*

In 1884, Thudicum first described sphingomyelins (SMs), but it was not until 1927 that Pick and Bielschowsky proved their structures to be N-acylsphingosine-1-phosphatidylcholine

Table 1 – Commonly used phospholipids [11].

Phospholipid	X	Net charge in pH 7
PC		0
PE		0
PS		−1
PA		−1
PI		−1
PG		−1
CL		−2