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Polymer-lipid hybrid systems used as carriers for insulin delivery

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Abstract

The polymer-lipid systems successfully have been applied for loading and controlled release of insulin. These hybrid systems used the advantages of both components: enhancing of muchoadesivity and lipophilicity, respectively. Even that few polymers, but a large number of lipids were combined by different methods it is still an open field to obtain pharmaceutical formulations suitable for insulin delivery, especially by oral route. Considering that the researchers are continuously interested to find and test new materials for insulin delivery, the lipid systems (liposomes, nanoparticles, microparticles) based on natural (chitosan, lectin, ε-poly-*L*-lysine) or synthetic (poly(lactide-*co*-glycolide), poly(allylamine)) polymers were reviewed in this paper.

Key words: Insulin carriers; Natural polymers; Synthetic polymers; Lipids

Insulin (Ins) is a therapeutic macromolecule intensively used to improve the life of diabetics. Structurally, it is a protein with polyampholyte behavior. Above its isoelectric point (pH 5.3) is negatively charged, capable to interact with many types of positively charged molecules (low molecular weight compounds or macromolecules).

Beside the conventional parenteral administration of insulin, there are other more investigated routes: intense vascularized nasal/pulmonary, ocular, and oral mucosa. The therapists appeal to these alternative routes to avoid the patient stress and to control the drug bioavailability. In case of the oral administration of the therapeutic insulin some limitations must be overcome: the drug degradation in the stomach, the inactivation and proteolytic digestion of insulin in lumen, and the poor permeability through intestinal epithelium due to the high dimensions of the hydrophilic macromolecule. In this regards, the researchers are working to find new strategies in order to design efficient therapeutic systems for insulin loading: vesicles, nanoparticles and microparticles. As biologically inert and biocompatible systems, the liposomes represent simplified models of the biological membranes, composed of natural or synthetic amphiphilic phospholipid layers. On the other hand, the solid lipid particles are colloidal systems prepared from surfactant-stabilized lipids, capable to keep their solid state at room and body temperatures.

For a long time, many studies explored the insulin carriers bearing only bioadhesive polymers like microcrystaline cellulose, [1] carboxyl dextran,[2] chitosan[3] or trymethyl chitosan[4] and ε-poly-*L*-lysine.[5] No one polymer was able to provide protection against all enzymes from gastrointestinal tract (pepsin, trypsin, chymotrypsin and carboxypeptidases). The protection capability depends on the polymer architecture and the optimum pH of enzyme.

Other innovative carriers based only on lipids, intended for oral or pulmonary delivery of insulin, have been designed: phosphatidilicoline/cholesterol/dicetylphosphate (7:2:1 molar ratio) for liposomes,[6] stearic acid-octarginine/soybean phospholipids (9:1 w/w) for solid lipid nanoparticles (SLNPs),[7] stearic acid/palmitic acid (1:1 w/w) with soybean phosphatidylcholine and sodium cholate for mixed reverse micelles[8] or for SLNs,[9] cetyl palmitate to prepare SLNs,[10] egg yolk phosphatidilicoline/cholesterol (7:3 molar ratio) for liposomes,[11] bile salts for liposomes,[12–14] 1,2-distearoyl-sn-glycero-3-phosphatidyl ethanolamine conjugated with biotin for incorporation in liposomes membranes,[15] and lecithin for phospholipids contained vesicles.[16]

Recently, a new trend has developed to prepare carriers for the oral administration of insulin. The *hybrid carriers* bearing polymeric and lipid components brings together the advantages of both. The polymeric component has double role: protector against the enzymatic attack and enhancer of the drug permeability through the epithelial membranes. Due to its hydrophlicity, insulin is likely to cross the intestinal mucosa too quickly. To enhance its lipophylicity, the drug was complexed or entrapped with/in lipid components in different formulations. To achieve a drug loading into polymer, different methods are used: physical entrapment or solubilization, polyionic complexation, and chemical conjugation.[17]

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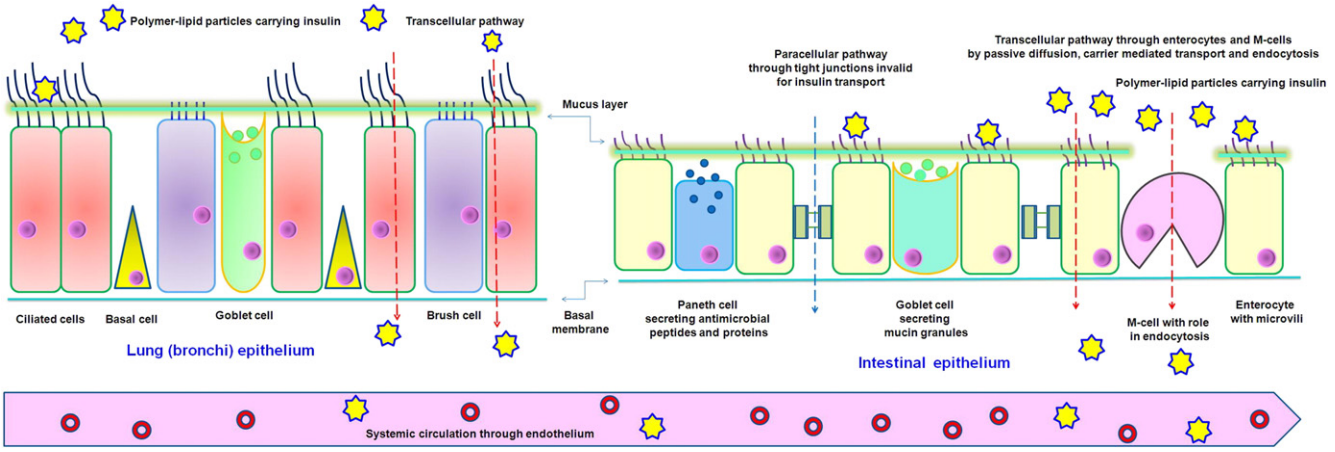

Figure 1. Schematic diagram of the mechanisms for penetration of insulin carrying particles through pulmonary and intestinal epithelials.

Often, the performances of investigated systems were tested and confirmed *in vivo* and *in vitro* experiments using *e.g.* the Caco-2/HT29 cell monolayer model (to test the mucoadhesive properties of polymers),[18,19] the fluorescently labeled insulin (to reveal the effectiveness of nanocarriers to promote the intestinal absorption of drug) or the streptozotocin induced diabetic rats (to test the hypoglycemic effect of novel molecules).

The aim of this review is to update the literature results about insulin carriers, specifically about of those that unify the advantages of the polymers and the lipids. There are a lot of lipids, but a restricted number of polymers used to design *polymer-lipid hybrid carriers of insulin*. Usually, the investigated lipids simulate the components of cellular membranes, and polymers are biocompatible materials.

Polymer-lipid hybrid carriers for insulin delivery

To avoid repeated injections of insulin solution over a day, the researchers explored another way to delivery this drug in a more efficient and unstressed protocol meaning by oral or inhalator carriers. In case of oral pathway distribution, they have to exceed inconvenience of gastric pH. In this regard, they discovered that the hybrid systems that contain lipid component will protect insulin from inactivation until the drug reaches the intestinal system. Here, in a favorable pH medium, the absorption of the drug is assured by the extensive vascularized zone of the intestine. It seems that the nasal mucosa, also an extensive vascularized zone, represents an efficient pathway for the insulin containing hybrid systems based on lipid. The basic mechanisms for the insulin penetration supposed the adhesion of the polymer-lipid hybrid systems carrying insulin to the respiratory or intestinal epithelial mucus layer (produced by Goblet cells), and the infiltration of them through transcellular pathways (passive diffusion through enterocytes or ciliated cells due to an enhanced lipophylicity of hybrid systems; endocytosis in M-cells) until to the systemic circulation. Like other large proteins, the therapeutic insulin in not able to penetrate through paracellular pathway, being restricted by the tight junctions (1–5 nm) (Figure 1).

Relatively recent studied hybrid systems composed by polymers and lipids could be classified function of the type of the polymer component: natural or synthetic ones. Until nowadays, only a reduce number of polymers were tested to form polymer-lipid hybrid systems able to load and controlled release of insulin: chitosan, lectin, ε-poly-*L*-lysine), poly(lactide-*co*-glycolide) and poly(allylamine) (Figure 2).

These polymers are used in their original form or could be chemically modified to introduce useful functional groups which will ensure nonspecific interactions with the other partners of the pharmaceutical formulation. All updated information regarding the main characteristics of the polymer-lipid hybrid systems designed as carriers for insulin were summarized in Table 1 and completed with each one performance.

Natural polymer-based carriers

Chitosan

Being a biocompatible, biodegradable, nontoxic, hydrophilic and inexpensive material, **chitosan** was intensively used to design pharmaceutical carriers, mainly for insulin. This biopolymer, obtained from the partial deacetylation of chitin, is a polysaccharide structurally composed by a linear chain containing randomly distributed β-(1–4)-linked D-glucosamine and *N*-acetyl-D-glucosamine units.

As enhancer in pharmaceutical formulations intended for oral administration, chitosan was implemented in design of insulin delivery systems, too. Usually, it covered and protected the preformed liposomes or nanoparticles. This polymer has the capacity to bind various fatty acids and form complexes which were stable in the acidic environment of the stomach.[20] In addition, the mucoadhesiveness of chitosan-coated liposomes/solid lipid particles helped in delaying these systems in the intestinal tract and thus to increase the absorption of insulin.

The multilamellar liposomes consisting of dipalmitoylphosphatidylcholine (DPPC) and dicetyl phosphate (DCP) (DPPC: DCP = 8:2 in molar ratio) were coated with chitosan (CS). After the oral administration of insulin loaded and CS-coated liposomes to rats, the blood glucose level significantly decreased, and it was maintained in this limit for more than 12 h, suggesting that the