Exploitation of lipid-polymeric matrices at nanoscale for drug delivery applications

Débora Sgorla, Élcio J. Bunhak, Osvaldo A. Cavalcanti, Pedro Fonte & Bruno Sarmento

Taylor & Francis
Taylor & Francis Group

REVIEW

Exploitation of lipid-polymeric matrices at nanoscale for drug delivery applications

Débora Sgorla[a], Élcio J. Bunhak[a], Osvaldo A. Cavalcanti[b], Pedro Fonte[c,d] and Bruno Sarmento [ID][a,d,e,f]

[a]Centro de Ciências Médicas e Farmacêuticas, Universidade Estadual do Oeste do Paraná, Cascavel, Brasil; [b]Departamento de Farmacologia e Terapêutica, Universidade Estadual de Maringá, Maringá, Brasil; [c]UCIBIO, REQUIMTE, Department of Chemical Sciences - Applied Chemistry Lab, Faculty of Pharmacy, University of Porto, Porto, Portugal; [d]CESPU, Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde and Instituto Universitário de Ciências da Saúde, Gandra-PRD, Portugal; [e]i3S, Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal; [f]INEB − Instituto de Engenharia Biomédica, Universidade do Porto, Porto, Portugal

ABSTRACT

Introduction: Progress in drug delivery and a better quality of life for patients, relies on the development of new and suitable drug carrier systems, with unequivocal therapeutic benefits, low systemic toxicity and reduced side effects. Lipid-polymeric nanoparticles have been explored to produce nanocarriers due to their features and applications such as high drug entrapment, physical-chemical stability and controlled release properties.

Areas covered: In this review, we describe several hybrid nanoparticles obtained from mixing a polymer with a lipid matrix. This association can potentiate the efficacy of drug delivery systems, due to the enhancement of encapsulation efficiency and loading capacity, tailoring the drug release according to the therapeutic purpose, and improving the drug uptake by targeting it to specific receptors. Contrary to lipid nanoparticles, these hybrid nanoparticles can decrease the initial burst release and promote a more sustained and localized release of the drug.

Expert Opinion: Lipid-polymeric nanoparticles are versatile vehicles for drug delivery by different administration routes in the treatment of multiple diseases. Different solid lipids, polymers, surfactants and techniques for producing these carriers have been investigated, revealing the importance of their composition to achieve optimal characteristics to drug delivery.

1. Introduction

The development of suitable drug carrier systems is a constant demand to ensure progress in drug therapy, mainly because a lot of bioactive molecules still possess intrinsic drawbacks related with therapy failure such as poor solubility and permeability, rapid elimination from the body, and high drug toxicity.[1,2] In this context, nanotechnology has been revolutionizing the development of new therapies. The nanoscale drug delivery development is providing tools to allow drug uptake through physiological barriers, raising their bioavailability and decreasing their toxicity and side effects.

In the 1990s, solid lipid nanoparticles (SLN) were introduced with the purpose of gathering the advantages of other colloidal carriers such as polymeric nanoparticles, nanoemulsions, and liposomes [3–5] but avoiding some of their disadvantages.[6] The mean particle diameter is frequently in the range of 50–1000 nm and they are composed of lipids in solid state at room and body temperature.[6–8] The lipids employed to produce SLN are physiologically well tolerated, with reduced risk of acute and chronic toxicity.[1,9] Additionally, SLN may also control and/or target drug release, improve the stability of drugs enhancing its bioavailability, and ease scale up for industrial production.[8] Because of all these features, SLN have attracted increasing attention during recent years and have been extensively investigated to encapsulate anticancer drugs,[10] to incorporate or adsorb proteins and peptides,[11] and also used in gene delivery. [12] Moreover, SLN have been used in different administration routes, such as parenteral,[13,14] oral,[15,16] ocular,[17] pulmonary,[18] dermal,[6,19] and rectal.[20] Although SLN present many advantages, some limitations have also been reported, such as low drug loading capacity, high water content of the dispersions that may expulse the active compounds during storage, polymorphic transitions, and lipid crystallinity.[1,13] To overcome these disadvantages, a new generation of lipid nanoparticles comprised by nanostructured lipid carriers (NLC) and lipid–drug conjugates (LDC) have been developed by introducing modifications to SLNs.

NLC are produced by mixing different blends of solid with liquid lipids (oils), preferably in a ratio from 70:30 to 99:1, lowering the melting point of mixtures comparatively to the solid lipid alone. The natural consequence for the lipid matrix is an increase in the drug loading capacity due to a less-ordered matrix, resulting in more spaces available for drugs in the nanoparticles core, reducing the potential expulsion of the active compound during storage.[6,18,19] The LCD were developed as a different approach to improve the loading capacity of hydrophilic active compounds, so the lipophilicity of hydrophilic drugs may be increased by its conjugation with lipids and can either be prepared by salt formation or by covalent linking.[7,14,21]

Recently, a new approach to enhance the features of lipid-based nanoparticles has been based in the modification of the lipid matrix with polymers, creating a lipid-polymeric matrix entrapping drugs. Such platforms are fully described in this review. The physical association between polymers and lipids in the same particle is able to enhance the encapsulation efficiency and loading capacity of drugs, taking advantage of polymer moieties to target specific cell receptors, and decrease the initial burst release usually associated with SLN. These hybrid particles are good alternatives to decrease systemic toxicity and number of administrations, consequently reducing side effects and improving treatment adherence by patients.

The purpose of this review is to fully describe the recent findings of the use of lipid-polymeric nanoparticles. Thus, it is important to understand how the polymers can improve the features of lipid matrices, which polymers have been studied so far and how they are embedded in the matrix to load drugs, whereas they are hydrophilic or lipophilic, and also the different diseases that can potentially be treated by these carriers.

2. Hybrid lipid-polymeric nanoparticles

2.1. Types of lipid-polymeric nanoparticles

Polymers can be located in nanoparticles in four different manners: (1) surrounding the solid lipid core, (2) complexed with the drug, (3) dispersed at the solid lipid matrix, or (4) in a polymeric core (Figure 1). For example, when zidovudine, a model hydrophilic active, was encapsulated in a lipid-polymeric nanoparticle, the pemulen polymer created a layer around Cutina® HR matrix. In this delivery system, the lipid in which the drug would is dispersed needs to be polar, because zidovudine is hydrophilic, so the hydroxyl groups in Cutina® HR may render a partial hydrophilic environment accommodating the drug within the solid matrix. The pemulen polymer, which is an amphipathic macromolecule due to both its hydrophilic (poly acrylic acid blocks) and lipophilic region (methacrylate unit) may help to reduce the interfacial tension between the lipid and the external water phase, facilitating zidovudine encapsulation.[22] Additionally, pemulen can create a diffusion barrier that could control the drug release.[23]

The ionic complexation between anionic polymers and cationic drugs may increase its loading into lipid-polymeric nanoparticles, improving drugs bioavailability. Examples of this are the assembly of nanocarriers containing dextran sulfate for delivery of doxorubicin/verapamil or quinidine/verapamil [24] and sodium alginate-polymyxin B sulfate complex entrapped
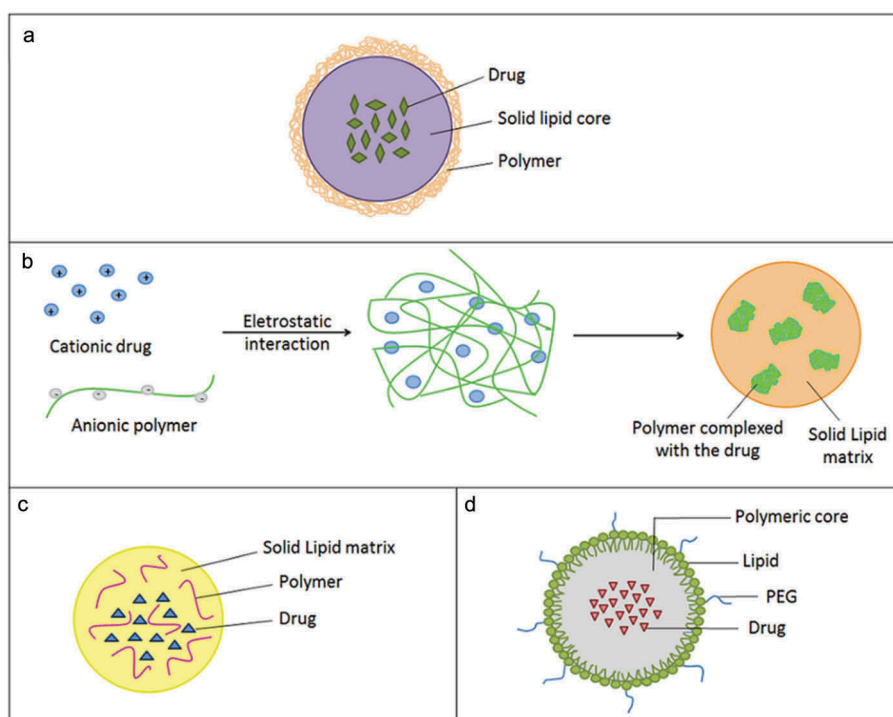

Figure 1. Different types of hybrid lipid-polymeric nanoparticles considering the localization of the polymer. (a) surrounding the solid lipid core, (b) complexed with the drug, (c) dispersed at the solid lipid matrix or (d) forming a polymeric core.

into SLN.[25] The latter revealed to be less toxic than free polymyxin, and enhanced the minimal inhibitory concentration against the evaluated strains. In addition to ionic complexation between dextran sulfate and doxorubicin, Ramasamy et al. developed a carrier in which the solid lipid core containing the complex was coated with two layers of polymers to further improve nanoparticles delivery features.[26] The first layer was composed of chitosan interacting with hyaluronic acid (HA) by electrostatic interaction, with shorter HA chains diffusing between the longer chitosan polymer chains. The HA may be useful to control the release kinetics of drugs and act as targeting moiety, ensuring a constant exposure at the tumor site, and thus present a low systemic cytotoxicity and enhance the therapeutic effect of doxorubicin.

Another strategy is by incorporating curcumin into lipid-polymeric nanoparticles composed by stearic acid as solid lipid, poly-hydroxyethyl methacrylate (PHEMA) as polymer and Pluronic F68 as emulsifier. These nanoparticles allowed a high drug loading, and the conjoint effort to encapsulate curcumin appeared to be promising due to the potential of long-term systemic circulation.[27] Besides, in some papers, the poly(lactic-co-glycolic acid) (PLGA) was very important to form the primary w/o emulsion during SLNs preparation, when its content was increased the stability of the emulsion was improved and it also enhanced encapsulation efficiency and loading capacity of the drug.[28–30]

A different strategy may use the polymer to create the nanoparticle core, surrounded by the lipid which is conjugated with polyethylene glycol (PEG) chains allowing a longer half-life in blood circulation. These nanoparticles tend to accumulate into the cytoplasm of cells and the drug release may occur by progressive hydrolysis of the polymeric matrix in the lysosomal environment.[31–33]

Most of lipid-polymeric nanoparticles present a controlled or sustained release with a reduced burst release. Abbaspour et al. explained that the burst release can be related with hydrophilic drugs accumulated at the o/w interface and in the outer shell during nanoparticles preparation; on other hand, when the drug is in the lipid core, a more prolonged release would be achieved.[34] Therefore, the polymer incorporation (ionic complexed with the drug or dispersed at the lipid matrix) can facilitate drug partitioning in the lipid phase, increasing the amount of drug entrapped within the lipid matrix and result in a slower drug release. Polymer surrounding the solid lipid core can offer a barrier for diffusion of incorporated drug and at the same way result in an enhanced sustained slow-release profile.

Still talking about stability in some researches were studied the store stability of the lipid-polymeric nanoparticles, some of them assessed it for 1 or 2 weeks others for 1–6 months or even 1 year (in different temperature conditions). In all tests, there were no significant changes in hybrid nanoparticle features such as particle size, zeta potential, or percent drug encapsulation, demonstrating their stability over the different conditions. For example, Ridolfi et al. evaluated their lipid-polymeric nanoparticles during 1 year at 4°C protected from the light.[35] The results indicate a high physical stability, explained by their high zeta (55.9 ± 3.1 at time zero and after 1 year 63.7 ± 2.7 mV). In general, particles could be dispersed stably when absolute value of zeta potential was above 30 mV due to the electric repulsion between particles.

Pokharkar et al. evaluated the store stability of the hybrid nanoparticles in three different temperatures, at 4°C, 25°C/60% RH, and 40°C/75% RH and also achieved good results.[23] At the end of 6 months, the sizes were 240 ± 2.1, 248 ± 3.42, and 251 ± 4.2 nm and the encapsulation efficiency were calculated to be 82.19 ± 2.1%, 80.73 ± 3.7%, and 78.91 ± 2.19%, for it temperature, respectively. Furthermore, the zeta potential also remained within −40.16 ± 2.53 and −43.16 ± 3.13 mV at all the three temperature conditions.

Moreover, all lipid-polymeric nanoparticles had a semispherical to spherical morphology and the average particle size ranged from 50 to 900 nm, its submicron-sized particles and also the solid state of physiological lipid-based carriers favor the pharmaceutical and biopharmaceutical applications of lipid-polymeric nanoparticles.

Gao et al. developed microspheres for colon-specific drug delivery and achieved a pH-dependent controlled drug release.[36,37] The 10-hydroxycamptothecin (HCPT)-loaded lipid-polymeric microspheres uptake at the upper gastrointestinal tract were decreased and increased in the colon tissue. It is confirmed in the pharmacokinetics studies that compared the results between hybrid microspheres and enteric ones. After oral administration, the enteric microspheres released HPCT in the ileum or the ileocecal region, resulting in higher drug concentration for systemic absorption before reaching the colon. On the other hand, due to slow and incomplete release of HCPT from lipid-polymeric microspheres in the terminal ileum, the peak time of drug absorption was delayed to 6 h (by contrast 2 h to enteric microspheres), being easily retained by the mucosa when they reach the colon, and decreasing the possible systemic bioavailability.

In vitro tests showed that insulin entrapped into nanoparticles prepared with stearic acid–octaarginine (SA-R8), passed through a Caco-2 monolayer more efficiently than unloaded insulin.[38] Moreover, insulin-loaded lipid-polymeric nanoparticles promoted the internalization of insulin in these cells 8 times higher than insulin-loaded SLN. Figure 2 shows the glucose response profiles after subcutaneous or duodenal administration to streptozocin-diabetic rats and it was in agreement with aforementioned studies that these hybrid nanoparticles is a useful tool for delivering macromolecules across cell membranes. According to the authors, lipid-polymeric nanoparticles achieved good hypoglycemic effects with a maximum blood glucose lowering of 29.7% at 1.5 h, better than insulin-loaded SLN that was 73.2% at 2 h.

Another carrier, lipid-polymeric nanoparticles prepared with wheat germ agglutinin-*N*-glutaryl-phosphatidylethanolamine conjugate (WGA) also enhanced the intestinal uptake of insulin.[39] These nanoparticles protected insulin from degradation by digestive enzymes in *in vitro* tests, and *in vivo* they exhibited enhanced hypoglycemic effect after oral administration. This system presented an insulin relative bioavailability of 7.11% in comparison to subcutaneous insulin and to insulin-loaded SLNs with only 4.99%. These results occurred because the lipid-polymeric nanoparticles improved the intestinal uptake of insulin, decreasing the blood glucose level.
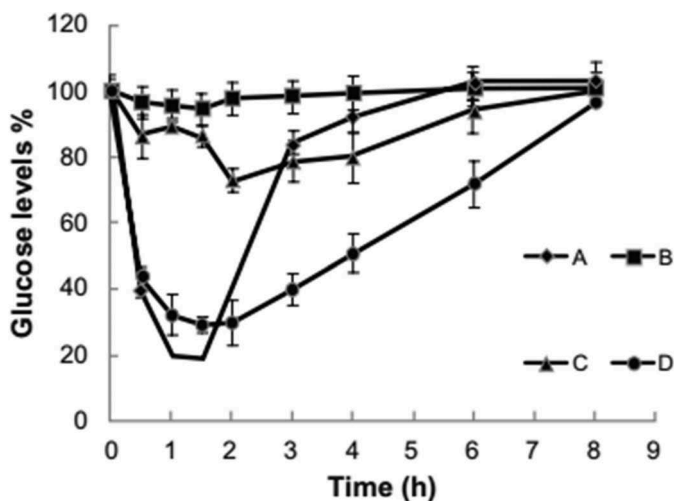
Figure 2. Glucose response profiles at blood circulation after subcutaneous or duodenal administration into diabetic-rats. (A) subcutaneous administration of insulin (2 IU/Kg); (B) insulin standard solution (25 IU/Kg); (C) duodenum administration of Ins-SLNs (25 IU/Kg); (D) SA-R8.Ins-SLNs (25 IU/Kg). Adapted with permission from [38].

2.2. Effect of polymer–lipid–drug interactions

Lipid-polymeric nanoparticles can be administered by different routes, so it is important to understand how the polymers can interfere on cell–lipid matrix interaction or like the lipid–polymer conjunct acts on cellular level.

The nasal route was chosen to analyze the delivery of tenofovir disoproxil fumarate (TDF) entrapped into hybrid nanoparticles in a gel.[23] The drug permeation through nasal mucosa was enhanced by action of lauric acid that can increase the fluidity of membrane phospholipids, and pemulen polymer can open the tight junctions increasing the paracellular pathway transport. Histopathology studies after nanoparticles permeation showed no significant effect in the mucosa structure.

Chitosan is known by its bioadhesive properties, so when this polysaccharide is used for topical delivery of a drug it is possible increase the retention of the drug at the site of action because its positive charges adhere to negative-charged skin. Besides, chitosan antimicrobial activity could be added to certain drugs. In their study, Ridolfi et al. assessed the *in vitro* cytotoxicity of the lipid-polymeric nanoparticles loaded with tretinoin in keratinocytes because these ones are the predominant resident cells in the epidermis and observed absence of cytotoxicity.[35] Moreover, a better antibacterial activity against *Proprionibacterium acnes* and *Staphylococcus aureus* were achieved with the hybrid nanoparticles. It was necessary for a low lipid-polymeric nanoparticles concentration to inhibit the growth of these bacteria compared to tretinoin-loaded SLN.

The administration of HCPT and insulin were assessed by oral route. For the first, the polymer (Eudragit S100) employed an important role to deliver the drug to the site of action.[37] On the other hand, the polymers used in the fabrication of nanocarriers for insulin delivery were responsible for protect the active from enzymatic degradation and enhanced its uptake and hypoglycemic effect.[38,39] So, in both cases, polymers were used to protect the drugs from harsh environment of the upper gastrointestinal tract.

The parenteral route is the most common to administrate anticancer drugs and polymers influence the drug release kinetics, prolonging its half-life in blood circulation by decreasing unnecessary interactions between plasma proteins and nanoparticles. Lipid-polymeric nanoparticles formulated by Palange et al. were constituted by a polymeric core that was responsible for drug release through progressive hydrolyses in the lysosomal environment. On the other hand, the PEG chains and lipid layer, which formed a surface coating, would provide a long circulation half-life.[31]

3. Applications of lipid-polymeric nanoparticles on drug delivery

Both synthetic and natural polymers are used to produce new drug delivery systems, and Table 1 summarizes the composition of several modified lipid-polymeric nanoparticles. The table also describes the drugs that were incorporated into hybrid nanoparticles and shows that these systems can encapsulate different actives from several therapeutic classes.

Eudragit S100 is a synthetic polymer used to produce lipid-polymeric microspheres for colon-specific drug delivery with a pH-dependent drug release.[36,37] Consequently, a lower systemic toxicity and a more efficient therapy probably may be achieved with this particles, because the lipid (Compritol 888 ATO) and polymer (Eudragit S100) have a synergetic action for delivery of the drug to the site of action. This synergism occurs due to the polymer and lipid arrangement, allowing the release of the drug on to the colon because the solid lipid prevents the rapid or premature swelling of the polymer and thus helping to control the drug release. Therefore, the polymer forms a film on both internal and external surfaces of the lipid matrix, allowing the pH sensitive drug release and the lipid matrix can restrict the swelling property of Eudragit, decreasing the early drug release caused by the polymer swelling. The polymeric coating is formed during the freeze-drying process due to an earlier solidification of lipid than the polymer; Compritol 888 ATO might solidify immediately after being sprayed, even before immersion in liquid nitrogen, while Eudragit S100 did not solidify until it enters the liquid nitrogen; so, most of the polymer might condense on the surface of the solidified lipid during the process. The model drug of these studies was HCPT, a semisynthetic analog of camptothecin, an insoluble drug which had the systemic absorption greatly reduced after administration of these carriers, because the system could develop a sustained-release, decreasing drug release in the upper gastrointestinal tract and target selectively the diseased tissue in the colon.

Dextran sulfate is an anionic polysaccharide and natural polymer used to form complexes with cationic drugs, to improve the drug-loading efficiency in SLN or lipid-polymeric nanoparticles.[25,26,34,40] This polymer commonly used with a molecular weight of 5 kDa forms electrostatic interactions with drugs influencing its sustained release because the strong ionic interactions form a hydrophobic complex prolonging its retention in the lipid matrix, which is represented by Figure 1(b). The complexation of dextran sulfate with drugs may be affected by

Table 1. Lipids and polymers used to produce drug-loaded hybrid lipid-polymeric nanoparticles.

Lipid	Polymer	Encapsulated drug	Matrix arrangement	References
Compritol 888 ATO	Eudragit S100	Hydroxycamptothecin	Polymer complexed with the drug into lipid matrix	[36,37]
Stearic acid	Dextran sulfate	Doxorubicin, verapamil hydrochloride, and quinidine sulfate Clindamycin phosphate	Polymer complexed with the drug into lipid matrix	[24,34]
Stearic acid	Sodium alginate	Clindamycin phosphate	Polymer complexed with the drug into lipid matrix	[34]
Stearic acid	Poly-hydroxyethyl methacrylate	Curcumin	Lipid polymeric matrix	[27]
Cutina® HR	Pemulen™	Zidovudine	Polymer surrounding the lipid core	[22]
Dodecanoic acid	Dextran sulfate	Verapamil hydrochloride	Polymer complexed with the drug into lipid matrix	[40]
Myristyl myristate	Chitosan	Tretinoin	Polymer surrounding the lipid core	[35]
Cetyl alcohol	Sodium alginate	Polymyxin B sulfate	Polymer complexed with the drug into lipid matrix	[25]
Stearic acid	PEG	VB	Lipid polymeric matrix	[41]
Hydrogenated castor oil	PLGA	Insulin plasmid DNA	Lipid polymeric matrix	[28–30]
Stearic acid	Soybean oil polymer	Doxorubicin	Polymer complexed with the drug into lipid matrix	[42]
Monostearin	Chitosan	Doxorubicin	Polymer surrounding the lipid core	[43]
Monostearin	Conjugate of PEG–stearic acid	Paclitaxel	Lipid polymeric matrix	[44]
Stearic acid + soybean phospholipids	Conjugate stearic acid–octaarginine	Insulin	Polymer surrounding the lipid core	[38]
Stearic acid + lecithin	WGA conjugate	Insulin	Polymer surrounding the lipid core	[39]
Lauric acid	Pemulen™	Tenofovir disoproxil fumarate	Polymer surrounding the lipid core	[23]
Compritol 888 ATO	Dextran sulfate, chitosan, and HA	Doxorubicin	Polymer complexed with the drug into lipid matrix and this one surrounded by polymers	[26]
Stearic acid + soya lecithin + soybean oil	HA	5-fluorouracil and cisplatin	Polymer surrounding the lipid core	[45]
Hydrogenated soy phosphatidylcholine and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000 (DSPE-PEG2000)	PCL	Erlotinib	Lipid surrounding the polymeric core	[33]
DPPC and DSPE-PEG2000	PLGA	Curcumin	Lipid surrounding the polymeric core	[31]
Lecithin and DSPE-PEG2000	PLGA	ICG	Lipid surrounding the polymeric core	[32]

PEG: Polyethylene glycol; PLGA: poly(lactic-co-glycolic acid); DPPC: 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; VB: vinorelbine bitartrate; PCL: polycaprolactone; ICG: indocyanine green; WGA: wheat germ agglutinin-N-glutaryl-phosphatidylethanolamine; HA: hyaluronic acid.

the degree of substitution, chain length, and branching density of the anionic polymer. Moreover, the interactions of the complex with the solid lipid matrix may influence the drug release profile, which occurs mainly by ion exchange and diffusion.

Sodium alginate, another biocompatible natural polymer is obtained from brown algae, and its molecular weight is within 150–170 Da. It has been employed in improving lipophilicity of cationic drugs by complexation and in specific for antibiotics such as clindamycin and polymyxin B, two drugs widely used to treat certain types of infectious diseases. The formation of the complex is extremely important to increase the drug loading capacity and encapsulation efficiency of hydrophilic drugs in lipid-based nanoparticles.[25,34] The encapsulation of the complex into lipid nanoparticles is usually performed by high-pressure homogenization. In an antibiotic susceptibility test, Severino et al. demonstrated that the sodium alginate/polymyxin complex (ratio 1:1) loaded into lipid nanoparticles increased the solubility of the drug in the bacterial membrane, enhancing the total inhibition of bacterial growth.[25]

HA, a biodegradable and biocompatible polysaccharide, has aroused interest for several biomedical applications.[45–48] Han et al. demonstrated that HA with a molecular weight of 1000 kDa was unable to open the junctions between epithelial cells, suggesting that it may present a good long-term safety.[46] Moreover, the affinity of HA for CD44 receptors overexpressed in many tumor cells, makes this natural polymer a potent ligand for targeting of cancer drug delivery. [26,45,47] Previously, Ramasamy et al. produced hybrid nanoparticles for delayed release of doxorubicin.[26] The drug was complexed with dextran sulfate and entrapped into a lipid matrix coated with two layers of polymers, first with low molecular weight chitosan and externally coated with HA 3 kDa. The carboxyl groups of HA ionically interact with the amine groups of chitosan, and this layer may control the degradation of the lipid matrix, and minimize protein adsorption and opsonization in bloodstream, prolonging the plasmatic nanoparticle half-life. After administration of a single intravenous dose (10 mg/kg) of each of the nanoarchitectures into rats, free drug was quickly cleared from the circulation (within 6 h) compared to hybrid nanoparticles that maintained the therapeutic drug levels during all the study period (Figure 3). Moreover, pharmacokinetic studies revealed doxorubicin-loaded lipid-polymeric nanoparticles presented the maximum retention time, six times that of the free drug, and 1.5 times that of the DOX loaded SLNs.

In another study, Qu et al. developed a cisplatin-loaded NLC coated with HA. The carriers were administered to BALB/c nude mice, and demonstrated to be effective to inhibit gastric tumors. The authors hypothesized that the lower systemic toxicity of the coated nanoparticles compared to free cisplatin and uncoated carriers, probably occurred due to the presence of HA and its affinity to specific receptors. [45] Both cisplatin and 5-fluoracil (5-FU) are indicated for gastric cancer chemotherapy; however, they exhibit some drawbacks such as nephrotoxicity in the case of cisplatin, and mucositis, nausea, and emesis in the case of 5-FU. These drawbacks may be avoided by their encapsulation into the developed carrier.
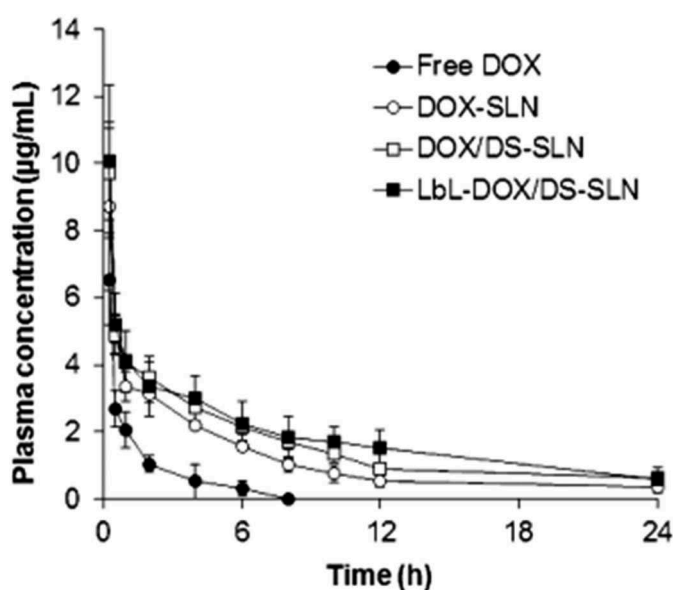

Figure 3. Plasma concentration-time profiles of different nanosystems after intravenous administration into rats. Adapted with permission from [26].

Curcumin, a hydrophobic natural compound extracted from *Curcuma longa*, has demonstrated anticancer properties, but it can suffer degradation at alkaline pH and has poor oral bioavailability. To overcome these problems and promote a sustained release, curcumin was encapsulated in hybrid nanoparticles prepared with stearic acid and PHEMA, a hydrophilic polymer obtained from HEMA (2-hydroxyethyl methacrylate). [27] These lipid-polymeric nanoparticles may be promising nanocarriers due to their potential of long-term systemic circulation, arising from the combination of the PHEMA and stearic acid prepared with the use of copolymer nonionic surfactants (Pluronic F-68) as emulsifiers. This drug delivery system demonstrated to be an effective and potential alternative method to conventional treatments for tumor treatment in MCF-7 cell line.

Pemulen™ is a commercial polymeric emulsifier with high molecular weight (about 500 kDa), composed of cross-linked copolymers of acrylic acid and a hydrophobic portion. It is able to form a gel network around the drug-loaded lipid core (prepared with Cutina® HR or lauric acid), so the concentration of the polymer is the major factor in stabilizing lipid-polymeric nanoparticles dispersions containing hydrophilic actives. [22,23] Pemulen may form a barrier that can help to encapsulate drugs and control its release from the nanoparticle matrix. Pokharkar et al.. described the formation of a strong H-bonding between the amino (–NH$_2$) group of the drug and the carboxyl (–COOH) group of the polymer.[23] This drug was TDF, a nucleotide reverse transcriptase inhibitor that acts against the human immunodeficiency virus (HIV), but it is a poor oral bioavailability molecule. To overcome this issue, as previously mentioned, it was created a lipid-polymeric nanoparticle for its administration by nasal route using lauric acid associated with Pemulen.

Chitosan is a polysaccharide with biodegradable, biocompatible, and bioadhesive properties, since this positively charged polymer may adhere to negative charged epithelia

and mucous membranes. It can be employed in many pharmaceutical applications, such as oral administration of insulin, [48] ocular drug delivery,[49] and more specifically to the cornea [50] and may also exhibit antibacterial activity.[51] Chitosan has been used in combination with SLN for topical treatment of acne, forming a coating on nanocarriers surface. [35] In this system, the polysaccharide with a molar mass of 296.6 kDa and deacetylation degree of 82.83 ± 3.63% increased the retention of tretinoin at the application site enhancing the antibacterial activity and thus increasing the therapeutic efficacy. Chitosan derivatives may also be associated with SLN for antitumor drugs release.[26,43] Chitosan oligosaccharide with a molecular weight of 450 kDa, and was adsorbed onto the negative charge surface of SLN through electrostatic interaction, which can control the release rate of drugs. The coating of SLN with chitosan oligosaccharide could reduce the burst release of the drug comparatively to SLN without polymer.[43]

PEG is a polymer commonly used in pharmaceutical products and as a food additive. The modification of nanocarriers with PEG is useful to inhibit their cellular uptake by mononuclear phagocyte system increasing the plasma half-life of nanoparticles. PEGylated SLN have been applied in the development of anticancer drug such as paclitaxel and vinorelbine bitartrate (VB)-loaded nanocarriers, and a good biocompatibility of nanoparticles was observed, the phagocytosis during blood circulation decreased, and the uptake of nanoparticles by cancer cells improved.[41,44]

Similar to other anticancer drugs, paclitaxel is effective against many solid tumors, but its application is limited by poor its hydrophilicity. Therefore, paclitaxel may be encapsulated into lipid-polymeric nanoparticles to improve its cytotoxicity.[44] Another drug, VB, a semi-synthetic vinca alkaloid, has excellent hydrophilicity but it can be degraded at high temperatures; so, to entrap this drug, it is necessary to use a technique without heat exposure, such as cold homogenization technique.[41]

PLGA is a biocompatible and biodegradable polymer approved by the FDA – Food and Drug Administration.[28–30] PLGA is an amphiphilic molecule because they are composed of lactic acid (hydrophobic) and glycolic acid (hydrophilic), and may be used to load hydrophilic peptides and proteins or plasmid DNA into SLN. It has been used in a wide range of molecular weight within 5–143 kDa, and may play an important role to overcome the difficulties of encapsulating hydrophilic proteins or DNA into SLN, and then improve its therapeutic potential. In addition, PLGA-based lipid-polymeric nanoparticles associated with PEG can even originate a longer blood half-life.[31,32] The degradation of nanocarriers in acid pH (5.0) such as in cell lysosomal environment avoids drug loss in places with different pH such as during circulation (pH 7.4) and also maximizes the dose delivered to the target cells.[31] The drug tested in this study was curcumin and due to anti-inflammatory activity it was used to modulate the expression of proteins involved in tumor cell proliferation, adhesion, and migration decreasing the metastatic process. Then, when encapsulated in lipid-polymeric nanoparticles, the drug was active in two different targets both circulating breast cancer cells (MDA-MB-231) and inflamed endothelial cells.

A soybean-oil-based anionic polymer was obtained from epoxidized soybean oil and used to produce a new lipid-polymeric nanoparticle system for anticancer drug delivery. [42] To form hydrolyzed polymer, the epoxidized soybean oil was polymerized by boric trifluoride diethyl etherate, and then hydrolyzed with sodium hydroxide. After the manufacturing process, the weight average molecular weight of the polymer was determined by gel permeation chromatography and found to be about 4.9 kDa. The complex of doxorubicin and soybean-oil-based anionic polymer was loaded into SLN of stearic acid, and an enhanced efficacy against multidrug-resistant breast cancer cells was observed.

Another widely used biodegradable polymer in drug delivery is polycaprolactone, which may be used to deliver low molecular weight drugs such as erlotinib.[33] This drug is used to treat non-small-cell lung cancer by inhibiting tyrosine kinase of epidermal growth factor receptor. Its encapsulation into lipid-polymeric nanoparticles may overcome adverse effects after oral administration. The developed carrier exhibited a biphasic release profile, being the diffusion of the predominant mechanism of drug release and it was observed a significant reduction of cell viability of A549 cells after 72 h, compared to an erlotinib solution. Furthermore, it was observed an accumulation of nanoparticles into cytoplasm of cells.

A tricarbocyanine dye, indocyanine green (ICG) loaded into hybrid nanoparticles was used to evaluate its biodistribution and accumulation in tumors.[32] These nanoparticles enhanced ICG stability and their size influenced endocytosis and tumor accumulation, and they were tolerable and safe *in vivo* tests, being good tools for cancer imaging for diagnostic and photothermal therapy.

Nanotechnology applied to the delivery of insulin has been deeply debriefed to avoid the uncomfortable administrations in conventional treatment of diabetes. Insulin presents high hydrophilicity that difficult its incorporation in lipid cores, faces degradation in acid pH and has poor oral bioavailability.[28,30,38,39] Obviously, its oral administration with acceptable bioavailability, would bring an enormous contribution to diabetes treatment, improving patient compliance. Two different strategies to modify SLN and promote the oral administration of insulin were developed,[38,39] one using WGA and the other using stearic acid–octaarginine. Both modified SLN-induced insulin uptake after oral administration, and *in vitro* tests revealed that these systems were able to protect insulin from degradation by digestive enzymes and showed an enhanced hypoglycemic effect.

4. Conclusion

In a general way, the results demonstrated a good potential of the lipid-polymeric nanoparticles until now. Their features such as morphology, size, superficial charge, and stability were positive, indicating a possible successful final performance of the drug delivery system to pharmaceutical and biopharmaceutical applications. A lot of different drugs both hydrophilic as hydrophobic were loaded into hybrid nanoparticles with high encapsulation efficiency due to the association between solid lipids and polymers that favor the drug

partitioning in the lipid phase and also improve the release profile, resulting in a controlled drug release. Furthermore, these nanoparticles have been performed for various administration routes to become their access more specific to the site of action.

5. Expert opinion

SLN have attracted great attention since their development in the early 1990s, since they showed good biocompatibility, being well tolerated by the human body. Despite being a considered safe carrier for drug delivery, SLN present some disadvantages such as low drug loading capacity and premature release of the drug. To overcome these drawbacks, new types of lipid nanoparticles have been developed, such as NLC, LDC, and lipid-polymeric nanoparticles. The latter are produced using different strategies to facilitate the incorporation of drugs and into lipid-polymeric matrices. In drug delivery, it is extremely important to obtain high encapsulation efficiency and loading capacity of drugs ensuring its therapeutic efficacy. The lipid-polymeric nanoparticles developed so far have shown high drug encapsulation efficiency and loading capacity, and good *in vivo* performance. Additionally, these hybrid nanoparticles have the potential to load both hydrophilic and lipophilic drugs and target their delivery to specific tissues or organs.

Lipid-polymeric nanoparticles may be produced with different solid lipids and polymers of synthetic or natural origin, but their combination must be carefully regarded to avoid undesirable interactions with each other and with the drug, negatively affecting the carrier features. When the composition of hybrid nanoparticles is properly regarded, they can load a wide array of drugs to be administered through different routes and according to the therapeutic target. The polymers of hybrid nanoparticles may play important roles in prolonging nanoparticles half-life in the bloodstream, protecting the drug stability, creating a diffusion barrier that can control the release kinetics of drugs and also act as targeting moiety for specific drug delivery.

The hybrid nanoparticles have been mainly used in cancer therapy due to their ability for target drug delivery, increasing the therapy efficacy and reducing potential side effects and toxicity; or even used to deliver proteins such as insulin for oral administration due to the ability of carriers to protect proteins from enzymatic degradation and increase the intestinal uptake. These abilities of nanoparticles have the potential to drastically improve the quality of life of patients. Besides the positive results obtained so far, further work is needed to deeply understand the interactions of hybrid nanoparticles with cells, revealing potential toxicity issues and showing their safe application. Additionally, the interactions between polymers, lipids, and drugs within the nanoparticles need to be clearly debriefed to assure the drug stability and the mechanisms of drug release and targeting.

The ongoing developments of lipid-polymeric nanoparticles have proposed these carriers as good candidates to deliver a wide array of drugs and reach the market in the future. Therefore, the quality of life of patients may be drastically improved and severe pathological conditions may be treated by these promising carriers.

ORCID

Bruno Sarmento 🔵 http://orcid.org/0000-0001-5763-7553

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest.

1. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001;47:165–196.
   • **A comprehensive review paper over SLN for drug delivery purposes. Despite published 15 years ago, it is still an updated and reference paper.**
2. Charcosset C, El-Harati A, Fessi H. Preparation of solid lipid nanoparticles using a membrane contactor. J Control Release. 2005;108:112–120.
3. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. Eur J Pharm Biopharm. 2000;50:161–177.
   •• **The first relevant paper revising the state of the art of SLN for drug delivery applications.**
4. Hou D, Xie C, Huang K, et al. The production and characteristics of solid lipid nanoparticles (SLNs). Biomaterials. 2003;24:1781–1785.
5. Uner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomedicine. 2007;2:289–300.
6. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev. 2002;54:S131–S55.
7. Battaglia L, Gallarate M. Lipid nanoparticles: state of the art, new preparation methods and challenges in drug delivery. Expert Opin Drug Deliv. 2012;9:497–508.
   •• **Paper of an overview about general lipid nanoparticles, including their physicochemical properties and pharmacological applications.**
8. Ekambaram P, Abdul Hasan Sathali AKP. Solid lipid nanoparticles: a review. Scientific Rev Chem Communications. 2012;2(1):80–102.
9. Saupe A, Rades T. Solid lipid nanoparticles. In: Mozafari MR, editor. Nanocarrier technologies: frontiers of nanotherapy. Dordrecht: Springer; 2006. p. 41–50.
10. Wong HL, Bendayan R, Rauth AM, et al. Chemotherapy with anticancer drugs encapsulated in solid lipid nanoparticles. Adv Drug Deliv Rev. 2007;59:491–504.
11. Almeida AJ, Souto E. Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Adv Drug Deliv Rev. 2007;59:478–490.
12. Bondi ML, Craparo EF. Solid lipid nanoparticles for applications in gene therapy: a review of the state of the art. Expert Opin Drug Deliv. 2010;7:7–18.
13. Wissing SA, Kayser O, Müller RH. Solid lipid nanoparticles for parenteral drug delivery. Adv Drug Deliv Rev. 2004;56:1257–1272.
14. Joshi MD, Müller RH. Lipid nanoparticles for parenteral delivery of actives. Eur J Pharm Biopharm. 2009;71:161–172.

15. Luo Y, Teng Z, Li Y, et al. Solid lipid nanoparticles for oral drug delivery: chitosan coating improves stability, controlled delivery, mucoadhesion and cellular uptake. Carbohydr Polym. 2015;122:221–229.
   • **Recent paper regarding SLN and polymers for oral delivery applications.**
16. Sarmento B, Martins S, Ferreira D, et al. Oral insulin delivery by means of solid lipid nanoparticles. Int J Nanomedicine. 2007;2:743–749.
17. Seyfoddin A, Shaw J, Al-Kassas R. Solid lipid nanoparticles for ocular drug delivery. Drug Deliv. 2010;17:467–489.
18. Weber S, Zimmer A, Pardeike J. Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) for pulmonary application: A review of the state of the art. Eur J Pharm Biopharm. 2014;86:7–22.
19. Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm. 2009;366:170–184.
20. Din FU, Mustapha O, Kim DW, et al. Novel dual-reverse thermosensitive solid lipid nanoparticle-loaded hydrogel for rectal administration of flurbiprofen with improved bioavailability and reduced initial burst effect. Eur J Pharm Biopharm. 2015;94:64–72.
21. Muchow M, Maincent P, Muller RH. Lipid nanoparticles with a solid matrix (SLN, NLC, LDC) for oral drug delivery. Drug Dev Ind Pharm. 2008;34:1394–1405.
22. Kumbhar D, Pokharkar B. Physicochemical investigations on an engineered lipid–polymer hybrid nanoparticle containing a model hydrophilic active, zidovudine. Colloids Surf A: Physicochem Eng Aspects. 2013;436:714–725.
23. Pokharkar B, Jolly R, Kumbhar D. Engineering of a hybrid polymer–lipid nanocarrier for the nasal delivery of tenofovir disoproxil fumarate: physicochemical, molecular, microstructural, and stability evaluation. Eur J Pharm Sci. 2015;71:99–111.
24. Wong HL, Bendayan R, Rauth AM, et al. Development of solid lipid nanoparticles containing ionically complexed chemotherapeutic drugs and chemosensitizers. J Pharm Sci. 2004;93:1993–2008.
25. Severino P, Chaud MV, Shimojo A, et al. Sodium alginate-cross-linked polymyxin B sulphate-loaded solid lipid nanoparticles: Antibiotic resistance tests and HaCat and NIH/3T3 cell viability studies. Colloids Surf B: Biointerfaces. 2015;129:191–197.
   • **Paper describing a mixing procedure to produce lipid nanoparticles entrapping polymers, and its effect on stability of lipid matrix and interaction with cells.**
26. Ramasamy T, Tran TH, Choi JY, et al. Layer-by-layer coated lipid–polymer hybrid nanoparticles designed for use in anticancer drug delivery. Carbohydr Polym. 2014;102:653–661.
   • **Paper describing a layer-by-layer procedure to produce lipid nanoparticles entrapping polymers, and its effect on stability of lipid matrix.**
27. Kumar D, Mahesh A, Mahadevan S, et al. Synthesis and characterization of curcumin loaded polymer/lipid based nanoparticles and evaluation of their antitumor effects on MCF-7 cells. Biochimica et Biophysica Acta (BBA) – General Subjects. 2014;1840:1913–1922.
28. Wang L, Xie S, Zhu Y, et al. Effects of poly (lactic-co-glycolic acid) as a co-emulsifier on the preparation and hypoglycaemic activity of insulin-loaded solid lipid nanoparticles. IET Nanobiotechnol. 2009;3:103–108.
29. Zhu L, Xie S, Dong Z, et al. Effects of poly(lactic-co-glycolic acid) on preparation and characteristics of plasmid DNA-loaded solid lipid nanoparticles. IET Nanobiotechnol. 2011;5:79–85.
30. Xie S, Wang S, Zhao B, et al. Effect of PLGA as a polymeric emulsifier on preparation of hydrophilic protein-loaded solid lipid nanoparticles. Colloids Surf B: Biointerfaces. 2008;67:199–204.
31. Palange L, Di Mascolo D, Carallo C, et al. Lipid–polymer nanoparticles encapsulating curcumin for modulating the vascular deposition of breast cancer cells. Nanomed: Nanotechnol Biol Med. 2014;10:e991–e1002.
32. Zhao P, Zheng M, Yue C, et al. Improving drug accumulation and photothermal efficacy in tumor depending on size of ICG loaded lipid-polymer nanoparticles. Biomaterials. 2014;35:6037–6046.
33. Mandal B, Mittal NK, Balabathula P, et al. Development and in vitro evaluation of core–shell type lipid–polymer hybrid nanoparticles for the delivery of erlotinib in non-small cell lung cancer. Eur J Pharm Sci. 2016;81:162–171.
34. Abbaspour M, Makhmalzadeh BS, Arastoo Z, et al. Effect of anionic polymers on drug loading and release from clindamycin phosphate solid lipid nanoparticles. Trop J Pharm Res. 2013;12:477–482.
35. Ridolfi M, Marcato D, Justo Z, et al. Chitosan-solid lipid nanoparticles as carriers for topical delivery of tretinoin. Colloids Surf B: Biointerfaces. 2012;93:36–40.
36. Gao Y, Zhu C, Zhang X, et al. Lipid-polymer composite microspheres for colon-specific drug delivery prepared using an ultrasonic spray freeze-drying technique. J Microencapsul. 2011;28:549–556.
37. Gan L, Gao Y, Zhu C-L, et al. Novel pH-sensitive lipid-polymer composite microspheres of 10-hydroxycamptothecin exhibiting colon-specific biodistribution and reduced systemic absorption. J Pharm Sci. 2013;102:1752–1759.
38. Zhang Z-H, Zhang Y-L, Zhou J-P, et al. Solid lipid nanoparticles modified with stearic acid–octaarginine for oral administration of insulin. Int J Nanomedicine. 2012;7:3333–3339.
39. Zhang N, Ping Q, Huang G, et al. Lectin-modified solid lipid nanoparticles as carriers for oral administration of insulin. Int J Pharm. 2006;327:153–159.
40. Li Y, Wong HL, Shuhendler AJ, et al. Molecular interactions, internal structure and drug release kinetics of rationally developed polymer–lipid hybrid nanoparticles. J Control Release. 2008;128:60–70.
41. Wan F, You J, Sun Y, et al. Studies on PEG-modified SLNs loading vinorelbine bitartrate (I): preparation and evaluation in vitro. Int J Pharm. 2008;359:104–110.
42. Wong L, Rauth A, Bendayan R, et al. A new polymer-lipid hybrid nanoparticle system increases cytotoxicity of doxorubicin against multidrug-resistant human breast cancer cells. Pharm Res. 2006;23:1574–1585.
   • **Paper describing a simultaneous procedure to set up lipid-polymeric nanoparticles and their effect on targeting of a drug against cells.**
43. Ying Y, Cui D, Yu L, et al. Solid lipid nanoparticles modified with chitosan oligosaccharides for the controlled release of doxorubicin. Carbohydr Polym. 2011;84:1357–1364.
44. Yuan H, Miao J, Du Z, et al. Cellular uptake of solid lipid nanoparticles and cytotoxicity of encapsulated paclitaxel in A549 cancer cells. Int J Pharm. 2008;348:137–145.
45. Qu C-Y, Zhou M, Chen Y-W, et al. Engineering of lipid prodrug-based, hyaluronic acid-decorated nanostructured lipid carriers platform for 5-fluorouracil and cisplatin combination gastric cancer therapy. Int J Nanomedicine. 2015;10:3911–3920.
   •• **Paper describing a hybrid structure coated with a polymer to of lipid nanoparticles entrapping polymers, and its effect on the stability of the lipid matrix.**
46. Han L, Zhao Y, Yin L, et al. Insulin-loaded ph-sensitive hyaluronic acid nanoparticles enhance transcellular delivery. AAPS PharmSciTech. 2012;13:836–845.
47. Jin Y-J, Ubonvan T, Kim -D-D. Hyaluronic acid in drug delivery systems. J Pharm Investig. 2010;40:33–43.
48. Mukhopadhyay P, Chakraborty S, Bhattacharya S, et al. pH-sensitive chitosan/alginate core-shell nanoparticles for efficient and safe oral insulin delivery. Int J Biol Macromol. 2015;72:640–648.
49. Nagarwal C, Kumar R, Pandit K. Chitosan coated sodium alginate–chitosan nanoparticles loaded with 5-FU for ocular delivery: In vitro characterization and in vivo study in rabbit eye. Eur J Pharm Sci. 2012;47:678–685.
50. Tsai Y, Woung C, Yen C, et al. Thermosensitive chitosan-based hydrogels for sustained release of ferulic acid on corneal wound healing. Carbohydr Polym. 2016;135:308–315.
51. Chang H, Lin V, Wu J, et al. pH Effects on solubility, zeta potential, and correlation between antibacterial activity and molecular weight of chitosan. Carbohydr Polym. 2015;134:74–81.