Polymer–Lipid Pharmaceutical Nanocarriers

Subjects: Nanoscience & Nanotechnology

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Some issues in pharmaceutical therapies such as instability, poor membrane permeability, and bi-oavailability of drugs can be solved by the design of suitable delivery systems based on the com-bination of two pillar classes of ingredients: polymers and lipids. At the same time, modern tech-nologies are required to overcome production limitations (low productivity, high energy con-sumption, expensive setup, long process times) to pass at the industrial level.

polymers lipids hybrid nanoparticles nanotechnologies production technologies drug delivery

1. Introduction

Nanoparticle (NP) technology represents a revolutionary drug delivery platform that enhances the conveyance of active molecules to maximize their therapeutic index and to minimize undesirable side-effects, improving the treatment of several diseases [1][2]. In a scenario characterized by the rapid pharmaceutical development of new drug products such as gene silencing molecules based on RNA interference, recombinant proteins/peptides, and other promising biotech-therapeutics, NP engineering stands as an advanced strategy that, projected towards the continuous optimization of carrier material; size; and physical, chemical and structural properties, allows us to overcome issues of instability, biocompatibility, poor membrane permeability, and bioavailability of drugs, improving their pharmacokinetics and pharmacodynamics.

The biomimetic behavior of the lipid materials and the mechanical advantages linked to the polymeric materials are the strengths of the latest generation nanocarrier systems. The latter are characterized by the combination of several kinds of natural/synthetic lipids and polymers [3], showing different properties (i.e., architectures, size, external charge, response to external stimuli) and being suitable for encapsulating a multitude of active molecules that cannot be delivered effectively through conventional routes and could not even be efficiently encapsulated in a carrier system entirely composed of lipid or polymeric materials. Biocompatibility is a topic of spirited discussion and relevance.

Indeed, each with its own peculiarities, these lipid polymeric nanoparticles (LPNs), including polymer-modified liposomes [4][5], polymeric micelles [6], surface-modified solid lipid nanoparticles (SMSLNs) [7] lipid–polymer hybrid nanoparticles (LPHNs) [8], and other combinations of polymer and lipid building blocks, allow for the overcoming of the non-negligible limitations of “pure nanoparticles” totally composed of lipids (i.e., liposomes) or polymers,

offering countless advantages in various fields of applications such as biomedical, pharmaceutical, and nutraceutical spheres. The interest of the scientific community in these hybrid systems has increased tremendously over the last decade, as attested by the number of papers published in last 10 years, with more than 670 products focused on the concept of lipid polymer hybrid nanostructures (see Figure 1).

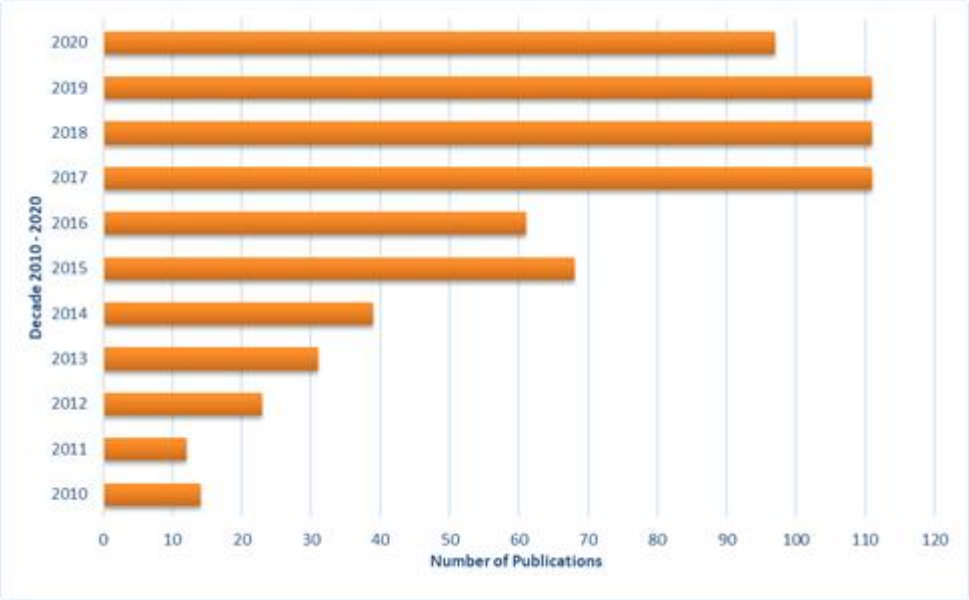

Figure 1. Number of publications from the years 2010 to 2020 (source: Web of Science Core Collection, query search: "lipid polymer hybrid nanoparticles", last accessed 27 December 2020).

Under formulation point of view, one key point about the use of lipids and polymers to design and to realize nano-delivery systems is the biocompatibility of the starting ingredients. Biocompatibility is defined as the "*ability of a biomaterial to perform its desired functions … without eliciting any undesirable effect …*" [9]. The biocompatibility should be tested by in vivo experiments, which, however, are costly and have ethical issues. Therefore, several in vitro methods have been defined and used, mainly cytotoxicity and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays, to assess the cell metabolic activity [9]. For commonly used polymers and lipids, the biocompatibility is well studied and well known (readers can refer to recent reviews, for polymers [10], as well as for lipids [11]). Lipids (and in particular the membrane-forming phospholipids) are inherently well tolerated, since they are the natural constituent of living cell membranes. Among them, the cationic phospholipids, which are the ideal candidates to build delivery systems for negatively charged molecules (nucleic acid-based drugs, for example, such as mRNA and short interfering RNA (siRNA)), may pose biocompatibility issues. Therefore, for cationic lipids and cationic liposomes, the biocompatibility is often the starting point for the research, even before to test their usability [12][13].

Under the production point of view, the advancements in design of performant LPN blended delivery systems require a continuous improvement of the production strategies that can be easily adopted at an industrial level to effectively translate the potential of these smart particles from the laboratory to the market. To date, the greatest limitation in the production of these sophisticated systems lies precisely in the use of conventional techniques that

do not reflect industrial needs. Indeed, traditional batch techniques, operating on small volumes and requiring long preparation times, without offering a control over the final carriers features, must be urgently replaced by versatile and economic methodologies, which, working in continuous, can allow for rapid and massive production.

This work is focused on products and production technologies, at the nanoscale, involving lipid and polymeric materials. It is structured in two sections. In the first section, features of representative polymeric and lipid nanoparticles are briefly introduced. Then, examples of blended nanometric carriers obtained by lipid–polymeric technologies are presented in terms of structural and functional main features. In the second section, the problem related to the use of “ancient” techniques to produce the increasingly sophisticated “new generation” delivery systems is emphasized by highlighting the advantages and disadvantages of the conventional and latest used methodologies.

2. Polymeric, Lipid, and Hybrid Nanostructures

Polymeric nanoparticles (PNs) are biodegradable delivery systems with several interesting properties that strictly depend on the type of matter they are made up of [14]. They can be composed of natural (i.e., chitosan, hyaluronic acid, starch, dextran, alginate, albumin, and heparin), semi-synthetic (i.e., poly(methacrylic acid) and polysorbate 80-grafted starch), or synthetic polymers (i.e., PLGA, PLA, PCL, PEG, PHEMA, PHPMA, PVA, PNIPAm, amphiphilic polymer, polystyrene, PAA, PEI, and PBAE—see Table 1 for the full names) and can assume different architectures such as solid nanoparticles, core–shell structures, polymeric micelles, and polyplexes [15][16][17][18]. The notable advantages of PNs lie in their great stability (higher than that possessed by lipid particles), which guarantees a sustained drug delivery, and in their stimuli-responsive properties (such as temperature, pH, redox, ionic strength), which allow for the obtaining of a precise control over the intracellular release of the active molecule [19]. However, due to the poor biocompatibility and the low affinity to the cell membrane, PNs present a low cell interaction, resulting in a poor drug delivery efficiency. To overcome these specific lacks, polymeric nanoparticles have recently been used as a “bearing structure” for a revolutionary class of biomimetic delivery systems. In particular, we applied the idea to use cell membranes for coating nanoparticles in an attempt to mimic the ability of cells to interface and interact with physiological environments [20]. This approach falls inside the development of biomimetic nanotechnologies based on the “camouflaging” methods. The biomimetic NPs not only retain the physicochemical features of the synthetic vehicles but also inherit the cell membranes’ intrinsic functionalities [21][22]. As examples, erythrocytes (red blood cell (RBC) membrane-camouflaged nanocarriers (RBC-MCNs)) are used in studies for tunable paclitaxel (PTX) release kinetics from biocompatible isotactic and atactic polylactide (PLA) polymeric vesicles [23] and 5-fluorouracil (5-FU) delivery from by chitosan-coated poly(lactide-co-glycolic acid) nanoparticles [24].

Table 1. Full name of polymers cited in the text.

Abbreviation	Full Name

PLGA	poly(lactic-co-glycolic acid)
PLA	poly(lactic acid)
PCL	polycaprolactone
PEG	polyethylene glycol
PHEMA	poly hydroxyethyl methacrylate
PHPMA	poly(2-hydroxypropyl methacrylate)
PVA	polyvinyl alcohol
PNIPAm	poly(N-isopropylacrylamide)
PAA	poly(amidoamine)
PEI	polyethyleneimine
PBAE	poly-(β-amino ester)

Lipid nanoparticles (LNs) are safe and effective carriers made from natural or synthetic lipids, among which the ones generally most used are fatty acids (i.e., palmitic, myristic, and stearic acids), glycerides (i.e., glyceryl monostearate and caprate), steroids (i.e., cholesterol (Chol)), phospholipids (i.e., PC, DPPC, DSPE, DMPC, DOPE, DOPC, POPC, HSPC, PE, and lecithin—see Table 2 for the full names), and other lipids such as 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) and 1,2-dipalmitoyl-3-trimethylammonium-propane (DPTAP) [25].

Table 2. Full name of lipids cited in the text.

Abbreviation	Full Name

Chol	cholesterol
PC	soybean phosphatidylcholine
DPPC	1,2-dipalmitoyl-sn-glycero-3-phosphocholine
DSPE	1,2-distearoyl-sn-glycero-3-phosphoethanolamine
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
DMPC	1,2-dimyristoleoyl-sn-glycero-3-ethylphosphocholine
DOPE	1,2-dioleoyl-sn-glycero-3-phosphoethanolamine
DOPC	1,2-dioleoyl-sn-glycero-3-phosphocholine
POPC	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine
HSPC	hydrogenated soy phosphatidylcholine
PE	phosphor-ethanolamine
DOTAP	1,2-dioleoyl-3-trimethylammonium propane
DPTAP	1,2-dipalmitoyl-3-trimethylammonium-propane

In particular, LNs can assume disparate structures and can be classified into solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NCLs), lipid nanocapsules (LNCs), micelles, and liposomes [26]. LNs are highly appreciated for their extraordinary biocompatibility, higher than that of polymeric particles, which allows for a prompt cellular uptake of the therapeutic substances. However, lipid particles show relevant limitations given their poor drug loading capacity, which is often restricted by the solubility of drug in the lipid melt, the rapid drug loss due

to the structure of the lipid matrix, its expulsion during storage, the tendency to aggregate, as well as a high instability in biological fluids [27][28]. An emblematic example is represented by liposomes that, although reflecting the main features of an ideal drug delivery system [29] and being in great demand for their large affinity for plasma membrane due to their remarkable biomimetic properties, are characterized by several issues related to the rapid degradation by the reticuloendothelial system (RES), the difficulty to achieve a sustained drug delivery for long periods of time, and the tendency to aggregate with serum proteins (typical of cationic liposomes).

In light of the above, in recent years, an attempt has been made to merge the advantages of polymeric and lipid materials in a single smart carrier system by suitable technique and through a careful selection of biocompatible polymer–lipid combinations, which guarantee a high affinity with biological membranes, allow a controlled drug release over a prolonged period of time, and provide the possibility to co-encapsulate therapeutics with different properties [30][31] (conceptualization schemed in Figure 2).

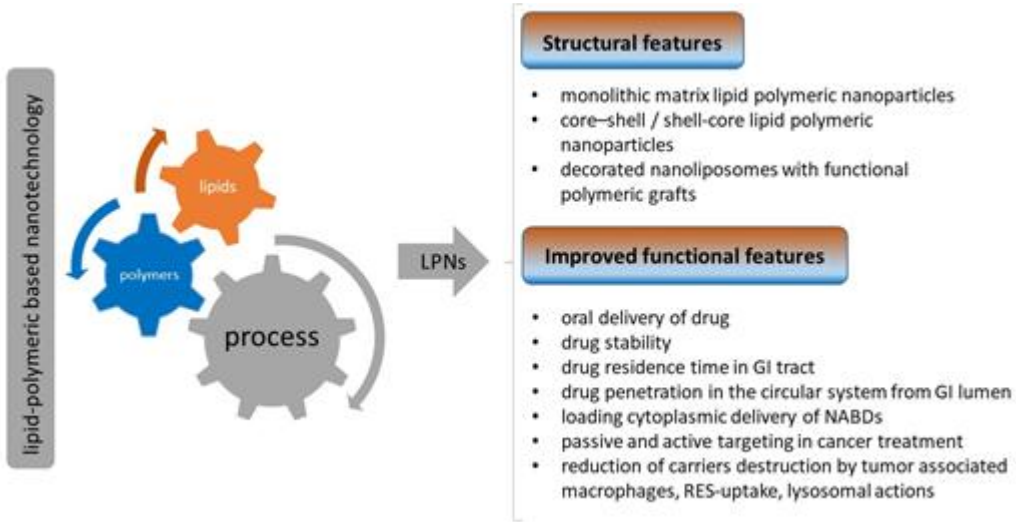

Figure 2. Schematic representation of structures and potential improvements of functional features of lipid–polymeric nanoparticles for pharmaceutical purposes.

Among these new blended particles, the most explored and appreciated are the lipid–polymer hybrid nanoparticles (LPHNs) and the liposomes covered with polymers, especially chitosan, carriers capable of loading and transporting a wide range of functional molecules from anticancer to vitamins, peptides, proteins, gene material (see also in following paragraphs), metallic inclusions, cells, and other therapeutics [32] (in Table 3 are several examples of LPHNs loaded with different active ingredients and produced by different preparation methods).

The lipid–polymeric-based technology can concern the modification of single lipids (i.e., polyethyleneimine (PEI) stearate, poly(lactic-co-glycolic acid) (PLGA) lipid, polyethylene glycol (PEG) lipid) or of entire lipid/polymeric particles with the consequent production of hybrid systems that, according to their architecture and manufacturing process, can be classified into monolithic matrix lipid polymeric nanoparticles, in which a lipid phase contains an homogeneously dispersed polymeric drug complex (or otherwise a polymeric core covered by a lipid shell); core–shell lipid polymeric nanoparticles, characterized by a polymeric core surrounded by a lipid shell (or otherwise a

lipid core covered by a polymer shell); and liposomes, whose surface is decorated with polymeric materials [32][33][34] (a simplified schematic representation in Figure 3).

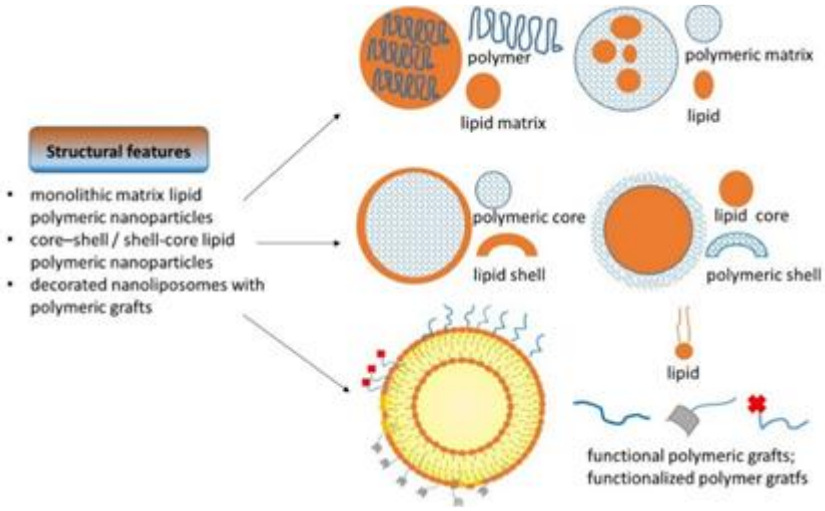

Figure 3. Simplified schematic representation of structural features of lipid–polymeric nanoparticles.

Release properties and payload entity of LPHNs are based on features of the used ingredients and on architecture of the final delivery structure. Mechanisms of release such as erosion and diffusion, and actions such as membrane fusion, endocytosis, and passive and active targeting are also inducible and tunable by suitable formulations that can also confer the capability to respond to external physical stimuli (stress, electricity, light irradiation) or to internal chemical or biochemical triggers (pH, metabolites, antigens, or enzyme presences) [35].

LPHNs find their application in various fields. First, they have been applied in the pharmaceutical field, improving the oral delivery of drugs, increasing their stability; prolonging their residence time in the gastrointestinal (GI) tract; increasing their penetration in the circular system from GI lumen [30]; and improving the systemic delivery of several active molecules, i.e., increasing the loading and ameliorating the cytoplasmic delivery of nucleic acid-based drugs (NABDs) [36]. LPHNs play a crucial role in the field of cancer treatment for the delivery of cytotoxic drugs (i.e., hormonal therapy, gene targeted therapy, immunotherapy) by improving the passive and active targeting of the loaded drug, and overcoming the limitations related to the therapeutics off-target accumulation, carrier destruction by tumor-associated macrophages, RES uptake, and the lysosomal degradation of nanocarriers [37].

Table 3. Examples of lipid–polymeric hybrid nanoparticles loaded with different active ingredients and by different preparation methods.

LPHN Composition/*Active Ingredient*/Preparative Method	Application	Reference
Lipid, lipoid S75-chitosan, low molecular weight (monolithic nanostructures)/*cisplatin*/ionic gelation (ethanolic solution dropped	cancer therapies	Khan et al., 2019 [38]

in chitosan acidulate solution with cisplatin)		
Nanoparticles with PLGA core layered by lecithin lipid PEG modified with iRGD peptides/*isoliquiritingenin*/modified single-step nanoprecipitation	breast tumor therapy	Gao et al., 2017 [39]
· Poly(lactide-co-glycolic acid) layered by chitosan, erythrocyte membrane*/*fluorouracil*/double emulsion (w/o/w) method (5-FU aqueous solution in PLGA-dichloromethane and, finally, dropped into an aqueous phase) *NEs were added by incubation into 5-FU polymeric nanoparticle suspension · 1,2-Dipalmitoyl-snglycero-3-phosphocholine, cholesterol, erythrocyte membrane/*fluorouracil*/ /thin film hydration method—liposomes; liposomes incubated in chitosan acidulate solution then membrane extrusion methods—chitosomes, i.e., liposomes with chitosan coating *NEs were added by incubation into 5-FU nanochitosome suspension	liver cancer therapies	AlQahtani et al., 2021 [24]
Ionizable lipid L319, distearoylphosphatidylcholine, cholesterol, and 1,2-dimyristoyl-rac-glycero-3-methoxy-PEG (nanoliposomes PEGylated)/*siRNA*/spontaneous vesicle formations method by pumping ethanolic solution with lipids and citrate buffer solution with siRNA within a chromatography tubing	vaccine therapy against SARS-CoV-2	Polack et al., 2020 [40] Walsh et al., 2020 [41] Maier et al., 2013 [42] Pardi et al., 2015 [43]
1,2-Distearoyl-sn-glycero-3-phosphoethanolamine—PEG, gelucire, PLA, (fructose-tethered phospholipid coated lipophilic polymeric core)/*beta carotene and methotrexate*/modified single-step nanoprecipitation method	breast cancer therapy	Jain et al. 2017 [44]

L-α-Phosphatidylcholine, cholesterol, chitosan (nanoliposomes coated by chitosan)/*indomethacin*/simil-microfluidic method	cancer therapies	Dalmoro et al., 2018 [45]
L-α-Phosphatidylcholine, cholesterol, chitosan (nanoliposomes coated by chitosan)/*D3, K2 vitamins*/simil-microfluidic method	food supplements	Dalmoro et al., 2019 [46]
PLA, soya lecithin, stearylamine (lipid shell, polymer core with antimicrobic)/*norfloxacin*/emulsification solvent evaporation method	antimicrobial therapies	Dave et al., 2017 [47]
PLGA, soybean lecithin, and PEG *(*polymer core-encapsulating gold crystals, lipid monolayer surrounding, outer lipid PEG)*/gold nanocrystals/*nanopreciptitation method	bioimaging purposes	Mukherjee et al., 2019 [48]

Examples of Application

Recent literature providing promising approaches are discussed in the following section. In Table 3, examples of lipid–polymeric hybrid nanoparticles (composition and field of application) are shortly summarized.

In 2019, Khan and collaborators produced and tested cisplatin-loaded lipid–chitosan hybrid nanoparticles, demonstrating a supported controlled delivery of the drug with enhanced mean residence time and half-life in rabbits, suggesting the promising application of these new LPHNs for the controlled delivery of cisplatin in cancer therapy.

In 2021, AlQahtani and collaborators, in order to contrast liver cancer, developed a membrane using hybrid NPs coated with nanoerythrocytes (NEs) with the aim of prolonging the 5-FU delivery circulation time. Several formulations of hybrid biomimetic nanocarriers have been used for in vitro and in vivo tests: NE-decorated, 5-FU-loaded, chitosan-coated poly(lactide-co-glycolic acid) nanoparticles (5-FU-C-NPs-NEs); chitosomes—chitosan in combination with liposomes made by 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and cholesterol as lipids—(5-FU-C-LPsNEs); and 5-FU-NEs (nanostructures without NEs were also prepared as control). The achieved results revealed that 5-FU-C-NPs-NEs showed the most desirable characteristics in terms of sustained release profile, drug load efficiency, and retention of erythrocyte membrane properties .

In the work of Gao and collaborators (2017), in order to improve the therapeutic outcome of isoliquiritigenin, the authors developed a natural anti-breast cancer dietary compound characterized by low bioavailability, a tumor-targeting lipid–polymer hybrid nanoparticle system composed of a polymeric PLGA core coated with a layer of lecithin lipids, and an additional PEG film modified by the iRGD (9-amino acid cyclic) peptides. The in vitro and in

vivo studies' outcome showed that the developed nanoparticles did not have damaging effects on normal tissue, and increased the cell-uptake efficiency and improved the targeting ability with an accumulation in breast tumors.

It is well known that the recent vaccine therapy against SARS-COV-2 (severe acute respiratory syndrome - coronavirus -2), as reported in Polak and collaborators (2020) and Walsh and collaborators (2020), is based on mRNA molecule delivered by LNs [40,41]. The vaccine, commercially known as Comirnaty, is based on a LN technology that has been pointed out in recent years. It is based on a combination of four components: an ionizable lipid designed for the purpose of increasing bioavailability by a tailored biodegradation (cleavage), a PEGylated molecule to modulate the half-life of the formulation, and the common components of liposomes (phosphatidylcholine and cholesterol). The approach is the most promising for the delivery of drugs that are based on RNA molecules, particularly for vaccines [49], which are, currently, a highly topical issue.

The targeting potential of new fructose-tethered lipid-polymeric hybrid nanoparticles (F-BC-MTX-LPHNPs) co-loaded with beta carotene (BC) and methotrexate (MTX), for intravenous administration, was also investigated by Jain et al. (2017), showing the ability of these systems to selectively convey the chemotherapeutic agent to the breast cancers, with an improvement of MTX-induced hepatic and renal toxicity due to the co-delivery of BC. Finally, in a recent work of Dalmoro and collaborators (2018), chitosan–lipid hybrid delivery systems for indomethacin dosage, to be used for the oral-controlled release of the drug, were produced, showing a gastro-retentive behavior in simulated gastric and intestinal fluids.

It should be noted that, in addition to the oral and systemic traditional pathways, LPNs can be administered by alternative routes such as ocular, pulmonary, rectal, nasal, buccal, sublingual, and transdermal routes, expanding their fields of application and patient compliance [50][51][52]. By way of example, buccal adhesive drug delivery systems, exploiting polymers as the adhesive component (i.e., chitosan and polyacrylates), have been studied for the production of water-soluble bioadhesive formulations, with a strong affinity for mucosal membranes [53]. In that regard, in a work of Dalmoro and coworkers (2019), polymer–lipid hybrid nanoparticles, encapsulating vitamin D3 and vitamin K2, with improved features in terms of stability, loading, and mucoadhesiveness, were produced for potential nutraceutical and pharmaceutical applications. The work, which concerns the production of liposomes coated with chitosan, is deepened in the next section in terms of the innovativeness of the production technique presented.

In the dermatological field, LPNs are highly appreciated for the treatment of several topical infections caused by bacteria, fungi, surgery, and accidental injury or abrasion [54]. In a work of Dave and coworkers (2017), PLA and soya lecithin-based lipid–polymer hybrid nanoparticles were prepared for the topical and site targeting delivery of norfloxacin and tested for their antimicrobial properties against *Staphylococcus aureus* and *Pseudomonas aeruginosa,* showing their high potential for usage as a topical antibiotic drug carriers.

Moreover, with the growing interest in health/enriched/functional foods, polymer–lipid hybrid systems are also highly desirable in nutraceuticals and food supplement fields to exceed the restrictions of poor water solubility, low bioavailability, bad taste and aroma, pH sensitivity, and easy degradation of a wide number of active molecules [55].

Finally, LPNs also find application in the bioimaging field as delivery systems for contrast agents (diagnostic tools) [56].

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