Review Article

Lipid Nano- and Microparticles: An Overview of Patent-Related Research

Luigi Battaglia and Elena Ugazio

Università degli Studi di Torino-Dipartimento di Scienza e Tecnologia del Farmaco, via Pietro Giuria 9, Turin, Italy

Correspondence should be addressed to Luigi Battaglia; luigi.battaglia@unito.it

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The traits of lipid biocompatibility and versatility have led to many nano- and microparticulate lipid formulations being engineered, over the last two decades, in the form of spheres and capsules, using solid and liquid lipids as the matrices. This review describes the main types of lipid nano- and microparticles, as well as their preparation methods, administration routes, and main fields of application. It will also provide a synthetic overview of the main patents that have been filed. Patenting activity in the lipid nanoparticle field has been ongoing for 25 years and has been driven by the boom in the use of nanotechnology as an innovative tool for disease treatment and potential commercial interest in a fully biocompatible vehicle. Initially, activity was mainly focused on technological aspects, and later focus shifted more to usage and composition. An increasing number of patents are also being filed by Emerging Countries. However, the most important limitation here is the low number of marketed products, which is mainly caused by regulatory restrictions and economic reasons.

1. Introduction

Lipid nano- and microparticles show many advantages over polymeric nanoparticles and have seen widespread use in the delivery of drugs and actives. They show better biocompatibility than do polymeric nanoparticles as they are made of lipids that are similar to their physiological counterparts [1].

In particular, lipid nanoparticles are a versatile delivery tool. Besides liposomes and niosomes, which are vesicular nanostructures that are made up of phospholipids and amphipathic lipids, respectively, and have a long and safe history of use, the last two decades have seen many nanoparticulate formulations being engineered using solid and liquid lipids as matrixes. Kinetic stability and rigid morphology are major advantages that lipid nanoparticles have over vesicular lipid colloidal systems (liposomes, niosomes, etc.). Lipid-based nanoparticles overcome the limitations of other widespread pharmaceutical and cosmetic carriers, the emulsions, because they improve the stability and the loading capacity and prevent the drug/active molecule expulsion during storage. However, nanoemulsion systems can be regarded as a template for nanoparticle generation. Analogously, lipid nanoparticles are frequently prepared from microemulsions, which are thermodynamically stable systems [2]. Nanoparticles can be divided into two main families: nanospheres, which have a homogeneous structure across the particle, and nanocapsules, which exhibit a typical core-shell structure. The most important types of lipid nanoparticles are shown in Figure 1.

1.1. SLN. Solid lipid nanoparticles (SLN) are the best-known type of nanospheres. SLN are made up of solid lipids with a photon correlation spectroscopy mean diameter of approximately between 50 and 1000 nm [1]. General ingredients include solid lipid(s), surfactant(s), and water. The term lipid is used here in a broad sense and includes triglycerides (e.g., tristearin), partial glycerides, fatty acids (e.g., stearic acid), steroids (e.g., cholesterol), and waxes (e.g., cetyl palmitate). All classes of surfactants (with respect to charge and molecular weight) have been used to stabilize lipid dispersions [3]. SLN were developed in the early 1990s and have long been considered promising drug carrier systems, as they are physico-chemically stable and can be easily produced on a
large industrial scale, while raw material and production costs are relatively low [1]. SLN production is based mainly, but not solely, on solidified nanoemulsion technologies. High-pressure homogenization (HPH), high shear homogenization, and ultrasonication are used in nanoemulsion preparation [4, 5].

1.2. NLC. Nanostructured lipid carriers (NLC) are lipid nanoparticles that are characterized by a solid lipid core that consists of a mixture of solid and liquid lipid. While the resulting lipid particle matrix shows melting point depression compared to the original solid lipid, the matrix is still solid at body temperature. Different types of NLC are obtained, imperfect, amorphous, and multiple-type, depending on the method of production and lipid blend composition (Figure 1). “In the imperfect type, lipid crystallization is altered by small amounts of oils. In the amorphous type, the lipid matrix is solid, but not crystalline (amorphous state) - this can be achieved by mixing particular lipids, for example hydroxyoctacosanyl hydroxystearate and isopropyl myristate. In the multiple type, the solid lipid matrix contains tiny oil compartments. This type is obtained by mixing a solid lipid with a higher amount of oil. The basic idea is that, by giving a certain nanostructure to the lipid matrix, the active compound payload is increased and the expulsion of entrapped compounds during storage is avoided” [6]. NLC can be produced by HPH, and the process can be modified to yield lipid particle dispersions with solid contents that range from 30 to 80% [7].

1.3. LDC. Lipid-drug conjugate (LDC) nanoparticles were developed to overcome the low drug loading capacities of SLN and NLC for hydrophilic drugs (Figure 1). “In a typical process, an insoluble drug-lipid conjugate bulk is prepared either via salt formation (e.g., with a fatty acid), or via covalent linking (e.g., esters or ethers). The obtained LDC is then processed to create a nanoparticle formulation, using HPH with the assistance of an aqueous surfactant solution” [6, 8].

1.4. LNC. Lipid nanocapsules (LNC) are the best-known patented form of lipid core shell nanostructures. They are composed of an external shell, formed of solid lipids and emulsifying agents, and an oily core (Figure 1) [2]. Unlike multiple-type NLC, which are made up of a solid lipid matrix containing numerous oily compartments, into which drugs tend to partition, LNC possess a sole drug-containing oily core, which is surrounded by a thin solid coating (core shell structure).

Moving now to lipid microparticles, the best-known types are solid lipid microparticles (SLM).

1.5. SLM. “SLM have an equivalent composition to SLN, but with a larger particle size (>1000 nm), meaning that their application domains and administration routes may be different” [6, 9]. In fact, despite their considerable potential
as drug carrier systems, SLM have yet to see significant use, compared to SLN. The main restriction to their use in parenteral drug delivery is the fact that they are not suitable for i.v. administration because of size limits. However, their use in pulmonary drug delivery is promising.

1.6. Patent Overview. A summary of the main types of lipid particles that are the subject of patent applications is shown in Table 1. Besides the abovementioned types of nanoparticle, patents concerning polymer lipid hybrid nanoparticles (PLN) were also included. PLN consist of a mixed lipid and polymer matrix, in which the polymer is introduced either to improve nanoparticle characteristics or to facilitate drug incorporation. Furthermore, patents concerning functionalized and variable-shape nanoparticulate systems are also listed.

2. Preparation Methods

2.1. Lipid Nanoparticle Preparation Methods

(a) Hot Homogenization. HPH has repeatedly proven itself to be a simple solvent-free technique since the 1950s. It is well established for the large-scale production of O/W parenteral emulsions and is available to the pharmaceutical industry. It has recently been used in the production of SLN, NLC, and LDC and is the main method for these nanoparticles. However, it involves some critical process parameters, such as high temperatures and pressures (cavitation forces), that may cause significant thermodynamic and mechanic stress to the resulting product. For this reason, and in order to overcome patented methods, alternative and easy handling preparation methods have seen extensive investigation [4, 6, 23].

(b) Microemulsion Templates. SLN can be produced from microemulsion templates. Gasco et al. [24] were the first researchers to use a microemulsion template for SLN preparation; “lipids are heated above their melting point and an aqueous phase, containing surfactants and co-surfactants, is added under stirring at the same temperature to form a clear O/W microemulsion” [6]. Multiple W/O/W can be prepared as well. The microemulsion is then diluted in cool water (2-10°C), in order to precipitate the nanoparticles.

A few years ago, another microemulsion-based method was developed for the production of stable SLN [25]. The authors started from an O/W microemulsion, which consisted of an emulsifying wax as the lipid phase and a polymeric surfactant solution as the aqueous phase, which was kept at a temperature of 37-55°C, according to the melting point of the emulsifying wax. SLN were obtained by cooling the undiluted O/W microemulsion at room temperature while stirring. “An advantage of this invention is that SLN can be rapidly, reproducibly and cost effectively formulated at mild operating temperatures from the microemulsion precursor in a one-step process and contained in a single manufacturing vessel, vial or container” [6].

(c) Solvent-Based Methods. Solvent-based methods have been proposed as a means to encapsulate molecules that present stability and bioavailability issues in various types of lipid nanoparticles, regardless of the limiting aspects of solvent toxicology issues. “One of the main advantages of solvent-based methods is mild operating temperature, which can be useful for the encapsulation of thermosensitive drugs” [6]. Solvent displacement is the simplest of these methods. It is based on dissolving the lipid in a water-miscible organic solvent (e.g., ethanol, acetone, and isopropanol) and injecting this solution into water, using a syringe needle, under stirring. Alternative solvent-based methods start with an emulsion precursor; O/W or W/O/W emulsions can be prepared using either a volatile or partially water-miscible organic solvent, which dissolves the lipid. Nanoparticles are formed when the solvent is removed either by evaporation (solvent evaporation method) or by water dilution (solvent diffusion method) [4, 22, 23].

(d) Coacervation Method. A new solvent-free method (named coacervation) for the preparation of fatty acid SLN has recently been developed. This technique allows, even thermosensitive, drugs to be incorporated without using very complex equipment or dangerous solvents. It is therefore a cheap method for laboratory and industrial applications [26]. “It is based on the slow interaction that occurs between a micellar solution of a fatty acid sodium salt and an acid solution (coacervating solution) in the presence of a proper amphiphilic polymeric stabilizing agent” [6]. Fatty acid nanoparticles can be precipitated by lowering the pH.

(e) Supercritical Fluid Technology. Supercritical fluid (SCF) technology has attracted increasing levels of interest, in recent years, for the benefits that it provides as a nanoparticle production method. The SCF condition is obtained above a substance’s critical pressure and temperature, wherein its solubility in the fluid can be modulated by relatively small changes in pressure. Carbon dioxide is the most widely used
SCF due to its low critical point, of 31°C and 74 bar, its safety and low cost. Two main SCF-based methods have been developed for SLN production: the SCF extraction of emulsions (SFEE) and gas-assisted melting atomization (GAMA).

In SFEE, lipid nanosuspensions are obtained through the SCF extraction of the organic solvent from O/W emulsions [27]. Solvent extraction into supercritical CO₂ leads to the precipitation of lipid/drug material, which is dissolved as composite particles. One of the advantages of this technique is the high solvent extraction efficiency of supercritical CO₂, compared to conventional methods, which allows the solvent to be quickly and completely removed and a more uniform particle size distribution to be achieved (Figure 2).

In the GAMA method, “lipids are melted in a thermostated mixing chamber (CM), where they are melted and kept in contact with supercritical CO₂” [6]. Then, a valve is opened at the bottom of the CM, where the lipid-saturated mixture is forced through a nozzle. The rapid depressurization of the mixture creates a high degree of supersaturation and leads to the precipitation microparticles, which are gathered by a collection system and dispersed in water via vortexting and ultrasound treatment to give the nanosuspensions (Figure 3) [28]. This method is solvent-free, making it advantageous for industrial processes.

(f) Microwave Assistance. Microwaves can assist in forming the microemulsion template used for nanoparticle preparation [31] and in the direct production of nanoparticles [32]. In this second case, using a microwave reactor is simple, quick, cheap, and sustainable. This technology facilitates the one-pot production of the particles, in one or two steps and in a closed system. Furthermore, it does not use organic solvents or large volumes of water.

(g) Dual Asymmetric Centrifuge. Lipid nanoparticles can be prepared in a dual asymmetric centrifuge (DAC) [33]. DAC differs from conventional centrifugation as the sample is also rotated around its own vertical axis. While conventional centrifugation constantly pushes the sample material outwards, this additional rotation constantly forces the sample material towards the centre of the centrifuge. This unique combination of two contra-rotating movements results in shear forces and, thus, in efficient homogenization.

(h) Membrane Contactor. Another method for producing SLN, one which makes use of a membrane contactor, has been developed [34]. A functioning module has been produced. It includes a ceramic membrane (0.1, 0.2, or 0.45 μm pore size) “that separates the aqueous phase, which is allowed to circulate tangentially to the membrane surface, and the lipid phase” [6]. The lipid phase is melted in a pressurized vessel and forced through a tube towards the membrane pores placed in the module, leading to small droplet formation, which are detached from membrane pores by tangential water flow. SLN are formed after the obtained water dispersion is cooled (Figure 4). The proposed method permits the continuous preparation of large volumes and is therefore claimed to be highly suitable for industrial scale-up.

(i) Phase Inversion Temperature. The phase inversion temperature (PIT) method is usually employed for the preparation of nanoemulsions. The PIT concept exploits the specific ability of some polyethoxylated surfactants to change their affinities for water and oil as a function of temperature. “The use of such a surfactant type leads to an emulsion inversion from an O/W macroemulsion to a W/O emulsion when the temperature is increased above the PIT” [6]. An O/W nanoemulsion is then formed when the temperature decreases below the PIT. The PIT method has been employed for LNC preparation, too, with an internal liquid or semi-liquid oil core and an external lipid layer that is solid at room temperature [2]. It has recently been adapted for SLN preparation, too. The aqueous phase, containing NaCl, and the oil phase, made up of solid lipids and nonionic surfactants, are separately heated at ~90°C (above the PIT). “The aqueous phase is then added dropwise, at constant temperature and under agitation, to the oil phase, in order to obtain a W/O emulsion. The mixture is then cooled to room temperature under slow and continuous stirring. The turbid mixture becomes clear at the PIT, and, below the PIT, an
O/W nanoemulsion is formed, which turns into SLN below the lipid melting point” [6, 36].

2.2. Lipid Microparticle Preparation Methods. SLM can be obtained in suspension or in a solid powdered state, depending on the technique used [37].

(a) Melt Dispersion. The melt dispersion technique is employed for SLM formulation. SLM can be obtained from either O/W or multiple W/O/W emulsions, depending on the chemical nature of the drug. In the case of the O/W precursor, the lipophilic drug is dissolved into the melted lipids, which are emulsified with a hot surfactant solution in water using a high shear mixer. Lipid microparticles are then solidified by cooling at room temperature [38]. In the case of the W/O/W precursor, a primary W/O emulsion is formed by dissolving the drug in the water phase; this is then placed into contact with an external aqueous phase at the same temperature. The resulting W/O/W multiple emulsion is then cooled to room temperature to obtain the microparticles [39].

(b) Cryogenic Micronization. “In cryogenic micronization, lipid matrices that are either obtained via melt dispersion (the drug is mixed with a melted lipid) or solvent stripping (drug and lipid are dissolved into a solvent mixture under stirring)” [6], stored at −80°C, and then micronized in a customized apparatus under the effect of liquid nitrogen. This technique can only be used for the production of microparticles of 5-5000 μm in diameter [40].

(c) Spray-Drying. The spray-drying of lipid particles is performed using an organic solvent solution as the feed. This solution is evaporated to a dried particulate form in a one-step process [41].

(d) Electrospay. The electrostatic atomizer in the electrospay technique includes a nozzle that is connected to a high-voltage power supply and supplied with the liquid to be atomized. The lipid solution, which is in an organic solvent, is contained in a syringe, and a metal capillary is connected to a high-voltage power supply and functions as an electrode. A metal foil collector is placed opposite the capillary and functions as a counter electrode. Solid lipid particles can be formed by evaporating the solvent from the droplets that are produced by the electrical field [42].

(e) Spray-Congealing. “In the spray-congealing method, lipids are heated to a temperature above their melting point”
A. (lipid phase), B (aqueous phase), M (porous membrane), 1 (pressurized vessel containing the lipid phase), 11 (thermostated bath), 12 (thermostat), 2 (nitrogen bottle), 3 (manometer), 4 (vessel containing the aqueous phase), 41 (thermostated bath), 42 (thermostat), 5 (stirrer), 6 (pump), 7 (tangential flow filtration unit), and 8-9 (manometer) [35].

2.3. Patent Overview. An overview of the most important technological patents that concern the abovementioned preparation methods, both for lipid nano- and microparticles, is shown in Table 2.

3. Administration Routes

Dermal administration is an area of great potential for lipid nano- and microparticles, and its short time-to-market makes it especially promising for use in cosmetic formulations. The distinct advantages of the cutaneous drug delivery of lipid particles are the ability to protect chemically labile ingredients against chemical decomposition, the ability to modulate drug release, and the ability to form adhesive lipid films on the skin, providing a possible occlusive effect [64].

Their particle size and therapeutic objectives mean that lipid nano- and microparticles can be used for all parenteral applications: from intra-articular to intramuscular, subcutaneous, and intravenous administration [65]. Because of their small size, lipid nanoparticles can be injected intravenously and used to target drugs to specific organs. However, they are cleared from circulation by the liver and spleen, as is the case with all intravenously injected colloidal particulates. “Stealth” lipid nanoparticles that are able to avoid the reticuloendothelial system (RES) can be obtained by coating their surface with polyethylene glycol (PEG).

Lipid nano- and microparticles can be orally administered in the form of aqueous dispersions or, alternatively, after transformation into a solid dosage form, such as tablets, pellets, capsules, or powders in cachets. Aqueous particulate dispersions can be used as a granulation fluid for the production of tablets. Alternatively, they can be transformed into a powder (e.g., by spray-drying or freeze-drying) and added to a tableting powder mixture or used to fill hard gelatin capsules. Lower production costs mean that spray-drying may be the preferred method for transferring lipid particulate dispersions into powders [1]. If administered via the oral route, lipid nano- and microparticles can help drug solubilization in the gastrointestinal tract (GIT). In fact, they can retain a poorly soluble substance in a solubilized state and enhance solute-solvent interactions, especially after being mixed with endogenous solubilizers, such as bile acids or phospholipids. Moreover, their protective effect, coupled with their sustained and/or controlled release properties, prevents drugs (macromolecules in particular) from undergoing premature degradation and improves their stability in the GIT [66]. Furthermore, nanosized particles can be taken up by the M cells of Peyer’s patches, which in turn enables the carrier system to bypass first-pass effect metabolism and undergo lymphatic absorption. The reduction of side effects (i.e., the stomach toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs)) and taste masking are also two relevant goals for the oral administration of lipid particles [67].

The pulmonary application of lipid microparticles is also promising as they show good aerosolization properties and excellent stability when nebulized as a liquid formulation. SLM that are obtained in the solid form (i.e., by spray-drying) are suitable for this application method thanks to their aerodynamic size. Proper lipid particle design should avoid them being deposited in the bronchial regions. In fact, whereas rapid bronchial clearance may lead to drug concentrations below therapeutic levels, the retention of lipid particles in the lungs contributes to prolonged drug release. Higher drug bioavailability and longer therapeutic effects can thus be achieved, resulting in reduced dosage and prolonged dosing intervals. Lipid particles may therefore be able to offer a broad range of benefits in the local treatment of severe airway diseases, as well as for systemic drug delivery. In addition, the pulmonary administration of lipid matrices has been demonstrated to present low toxicological potential in several studies. However, no investigations into the long-term effects of repeated pulmonary administration have been performed [68].

Lipid nanoparticles can improve the therapeutic efficiency, compliance, and safety of ocular drugs, administered via several different routes, to both the anterior and posterior segments of the eye. They are suitable for topical administration because of their ability to increase corneal residence time and thus overcome corneal barriers. Moreover, despite
effective drug delivery to the posterior segment of the eye being challenging and alternative routes of administration (periocular and intravitreal) generally being required, lipid nanoparticle formulations that are optimized for the retina should aim at controlling drug release and reducing administration frequency [69].

3.1. Patent Overview. Several usage patents on specific administration routes for lipid particles have been filed: a summary is shown in Table 3.

| Preparation method          | Patent number       | Lipid particle type | Size range | Ref. |
|-----------------------------|---------------------|---------------------|------------|------|
| HPH                         | WO0103670           | SLN, NLC, and LDC   | 50-1000 nm | [44] |
|                            | WO2015148483        | SLN                 | <240 nm    | [45] |
| Solvent evaporation         | WO2008013785        | SLN                 | <150 nm    | [46] |
| Solvent displacement        | CN20101012202       | SLN, NLC            | 50-300 nm  | [47] |
|                            | US5529236           | SLN                 | 20-100 nm  | [48] |
| Microemulsion templates     | US7153525           | SLN                 | 50-300 nm  | [49] |
|                            | IN127/DEL/2012      | SLN                 | 200-1000 nm| [50] |
| Coacervation                | WO2008149215        | SLN                 | 20-90 nm   | [51] |
| SFEE                        | WO2008004862        | SLN                 | <240 nm    | [52] |
| GAMA                        | WO2007028421        | SLN, SLM            | 0.2-20 μm  | [53] |
| Microwave assisted          | WO201810690         | SLN, NLC            | 60-300 nm  | [54] |
| DAC                         | EP1838286           | SLN                 | 15-200 nm  | [55] |
| Membrane contactor          | WO2007000531        | SLN                 | 100-200 nm | [56] |
| Temperature phase inversion | WO2009004214        | SLN                 | 30-100 nm  | [57] |
|                            | WO2011036234        | LNC                 | 50-2000 nm | [58] |
| Melt dispersion             | WO201233344         | SLM                 | 1-250 μm   | [59] |
|                            | WO200705065         | SLM                 | 1-500 μm   | [60] |
| Cryogenic micronization     | US2004091522        | SLM                 | 0.3-10 μm  | [61] |
| Spray-drying                | WO2008066367        | SLN, SLM            | Nearly 1 μm| [62] |
|                            | WO0185137           | SLM                 | 50-2000 μm | [63] |
| Electrospray                | ITTO2008A000475     | SLN, SLM            | 50-2000 μm | [64] |

4. Therapeutic and/or Technological Aims

Lipid nano- and microparticles have been proposed for drug and active delivery with several therapeutic and/or technological aims [4, 118, 119]; the most relevant are described below.

4.1. Cancer Therapy. The rationale of using lipid nanoparticles for anticancer drug delivery is based on a number of physiological mechanisms. A tumor is often associated with defective, leaky vasculatization that results from poorly regulated angiogenesis. Submicron-sized particulate matter may thus preferentially extravasate into the tumor and be retained there, because of the so-called enhanced permeability and retention (EPR) effect. EPR-effect-based passive tumor targeting can be achieved using properly designed lipid nanoparticles, which can avoid opsonization by the complement and consequent elimination by the RES. “Long-circulating” lipid nanoparticles are designed to have reduced particle sizes and hydrophilic surfaces (they are coated with hydrophilic polymers) for this very reason [120]. Moreover, surface-engineered lipid nanoparticles can be used for active targeting to increase cancer cell-selective cytotoxicity. This can be done by exploiting differences in the surface antigens and receptors of cancer and healthy cells [96]. Finally, multidrug resistance (MDR) is an important limitation of anticancer drug therapy. MDR is mainly associated with P-glycoprotein (P-gp), which acts as an efflux pump from the cell for many drugs (anticancer agents, antibiotics, etc.). Lipid nanoparticles can help to overcome the MDR phenomenon, probably because they carry encapsulated drugs into cancer cells via endocytosis, thereby bypassing the P-gp drug efflux mechanism [120].

4.2. Overcoming the Blood-Brain Barrier. Lipid nanoparticles have frequently been proposed as vehicles that can overcome the blood-brain barrier (BBB). The BBB acts as a physical barrier and regulates the passage of selected molecules between the bloodstream and the brain. In particular, the tight junctions between the endothelial cells mean that the passive diffusion of solutes through the paracellular pathway is very limited. Lipid nanoparticles can be useful in the brain uptake process at various levels, as they can (i) stabilize drugs against chemical degradation in biological fluids, (ii) increase permanence in the bloodstream and

Table 2: Most important patents that concern the preparation methods for lipid nano- and microparticles.
| Administration route | Patent number | Lipid particle type | Aim | Ref. |
|----------------------|---------------|---------------------|-----|------|
| Dermal               | WO2010051918 | SLN, SLM            | Codelivery of metal nanoparticles and SLN/SLM in dermal formulations | [70] |
|                      | WO2010112749 | SLN                 | Dermal composition for minoxidil delivery | [71] |
|                      | WO0103652    | SLN                 | Increase in UV filter efficacy and stability through nanoparticulate delivery | [72] |
|                      | WO2008041116 | SLN                 | Transdermal delivery of drugs with short half-lives and/or high activity | [73] |
|                      | WO2004098555 | SLN                 | Targeted release of fragrances and aromas | [74] |
|                      | US20100104522| NLC                 | Skin delivery of omega-3 fatty acid for antiaging and moisturizing purposes | [75] |
|                      | WO2009111852 | SLN                 | Formulation of retinoids in the form of ion pairs with lipophilic amines, suitable for skin delivery | [76] |
|                      | US20130034612| LNC                 | Avermectin delivery for acne rosacea treatment | [77] |
|                      | WO2014077712 | SLN                 | Roxithromycin topical delivery to stop hair loss or for acne treatment | [78] |
|                      | WO2017143421 | SLN                 | Cosmetic composition aimed at the sustained release of substances that repel insects | [79] |
|                      | BR1020140173161| SLN                | A method to obtain trans-resveratrol- (RES-) loaded SLN and their use in the antitumor therapy of melanoma | [80] |
|                      | IN611/MUM/2011| SLN                | Terbinaine-loaded SLN incorporated into a gel with enhanced skin deposition and improved antifungal activity | [81] |
|                      | IN149/CHE/2014| SLN                | Improved treatment of psoriasis | [82] |
|                      | IN3658/MUM/2014| SLN            | Mupirocin SLN incorporated into a Carbopol-based gel to enhance efficacy in skin infection treatment | [83] |
|                      | IN201711046022| SLN            | SLN used as a carrier in the development of transdermal patches for diltiazem permeation | [84] |
|                      | IN428/DEL/2010| SLN            | Topical antioxidants loaded in SLN as therapeutics to combat photoageing | [85] |
|                      | IN1394/DEL/2011| SLN            | Gel loaded with vitamin D analogues and corticosteroids entrapped in SLN to treat psoriasis | [86] |
|                      | IN26/KOL/2014| SLN               | Acyclovir-loaded SLN to avoid systemic drug penetration through the skin | [87] |
|                      | WO2012127037 | NLC               | Vitamin D and corticosteroid coloaded into NLC in order to increase drug accumulation in the skin | [88] |
| Parenteral           | WO2009102121 | SLN               | Cacao butter nanoparticles that are suitable for the parenteral administration of drugs | [89] |
|                      | US2011082214 | SLN               | Preparation of tablets from SLN suspensions | [90] |
|                      | EA200900215  | SLN               | Treatment of tuberculosis and diseases mediated by Helicobacter pylori via the peroral administration of SLN loaded with rifabutin and rifampicin | [91] |
|                      | WO2014140268 | SLN               | Delivery of food grade actives in SLN (antimicrobial, antioxidant, polyphenols, vitamins, etc.) | [92, 93] |
|                      | CN201510071840| SLN               | Increase in docetaxel oral bioavailability via the use of freeze-dried quaternary ammonium salt chitosan-modified SLN | [94] |
|                      | KR20150093510| SLN              | Formulation of docetaxel in SLN for oral delivery | [95] |
|                      | WO2015039199 | SLN, LNC, and nanoemulsions | Improvement of the dissolution profile of benznidazole with increased bioavailability | [96] |
| Oral                 | CN200910192553| SLN               | Increase in the oral uptake of lappaconitine-loaded SLN, prepared using HPH | [97] |
|                      | CN200910034968| SLN               | Increase in Tripterygium glycoside dissolvability, improving oral bioavailability | [98] |
|                      | CN200910027782| SLN               | Solving the problems of the low solubility, low dissolution rate, and low bioavailability of finasteride | [99] |
|                      | CN201410531574| SLN               | Increased bioavailability of asiatic acid | [100] |
thus indirectly favor translocation to the brain, and (iii)
directly trigger endothelial cells, thus inducing endocytosis,
which may also be receptor-mediated via an active target-
ing mechanism. Although plain lipid nanoparticles have
been used as vehicles to overcome the BBB, research is cur-
rently evolving towards targeted lipid nanoparticles, which
improve interaction selectivity between nanoparticles and
endothelial cells [121].

4.3. Gene Therapy. Lipid nanoparticles can be successfully
used as nonviral vectors for gene therapy. Gene therapy is
achieved by introducing genetic material (plasmid DNA,
pDNA) into target cells, in order to induce protein expression,
or, alternatively, by using either antisense oligonucleotides
(ASO) or small interfering RNA (siRNA) as transcription
and/or translation inhibitors to silence defective genes.
Naked nucleic acids are easily digested by enzymes in biolog-
ical fluids. Moreover, cell internalization does not happen
spontaneously because both nucleic acids and cell mem-
branes have negatively charged surfaces, resulting in nonef-
fective therapeutic responses. Even if viral vectors are the
most effective carriers, nonviral vectors are safer, have lower
costs, are more reproducible, and do not present a DNA size
limit. The use of lipid nanoparticles as nonviral vectors in
gene therapy entails the use of positively charged lipids that
can electrostatically bind nucleic acids. This is bene
fi
cial for
transfection because condensation facilitates nucleic acid
mobility, protecting them from environmental enzymes,
while the cationic character of the vectors allows for interac-
tion with the negatively charged cell surfaces [122].

4.4. Protein and Peptide Delivery. Lipid nano-
and micro-
particles are widely employed for protein delivery. The
therapeutic use of peptides and proteins is restricted by
their high molecular weight, hydrophilic character, and lim-
ited chemical stability, which lead to low bioavailability,
poor transfer across biological membranes, and low stabil-
ity in the bloodstream. Most peptides and proteins available
are delivered via injection, but their short half-life means
that repeated doses, which are expensive, painful, and
poorly tolerated by patients, are required. Recent years have
seen significant effort being directed towards needle-free

| Table 3: Continued. |
|---------------------|
| Administration route | Patent number | Lipid particle type | Aim | Ref. |
| NLC | Agglutinin-modified and glutaraldehyde cross-linked NLC for the oral delivery of insoluble compounds | [101] |
| IN430/DEL/2004 | SLN | Antitubercular drug (rifampicin, isoniazid, and pyrazinamide) association for oral delivery | [102] |
| IN3139/DEL/2005 | SLN | Improved bioavailability of drugs via gut lymphatic system absorption | [103] |
| IN3310/DEL/2012 | SLN | Cocoa butter SLN loaded with tenofovir with controlled release | [104] |
| IN3356/DEL/2012 | SLN | Improved bioavailability of rifampicin and limited drug degradation and interaction with isoniazid in the acidic environment of the stomach | [105] |
| IN3509/DEL/2012 | SLN | Azathioprine-loaded SLN with prolonged release with the aim of colon delivery | [106] |
| IN264/DEL/2013 | SLN | Lercanidipine enhanced oral bioavailability and prolonged release of action | [107] |
| IN1365/MUM/2014 | SLN | Sustained release of glipizide | [108] |
| IN3299/MUM/2010 | SLN | Treatment of fungal infections and leishmaniasis with amphotericin B-loaded SLN | [109] |
| IN2194/CHE/2010 | SLN | Improved oral bioavailability of olanzapine | [110] |
| IN2960/DEL/2014 | SLN | SLN loaded with the extract of the aerial portion of Ficus benjamina are incorporated into floating tablets | [111] |
| Pulmonary | WO2009050217 | SLM | Spray-dried powder for dry inhalers with enhanced flow and dispersal properties | [112] |
| WO2004039351 | SLN | Suitable eye drop composition for the treatment of ocular diseases | [113] |
| WO2012085318 | SLN | Treatment of ocular diseases using nucleic acid-complexed SLN | [114] |
| WO201605976 | SLN | Silibinin-loaded mucoadhesive SLN, NLC, and calixarenes, with sustained drug release, for the treatment of ocular neurodegenerative diseases | [115] |
| Ocular | IN2339/DEL/2014 | SLN | Statin-loaded SLN for topical application and the treatment of age-related macular degeneration, glaucoma, and other ocular inflammatory diseases | [116] |
| CN201610005904 | NLC | NLC - intraocular lens system, which is loaded with anti-inflammatory drugs and antibiotics, in order to prevent or treat cataract surgery complications | [117] |
alternatives to the administration of these biomacromolecules that mainly, but not exclusively, make use of the oral route. However, buccal, nasal, pulmonary, and transdermal administration routes have also been investigated [98]. Lipid nano- and microparticles may be useful in peptide and protein delivery due to the stabilizing and absorption promoting effect of lipids. Moreover, particulate carriers have been sought as vehicles for protein antigens for some time. Extensive work has been carried out in the area of vaccine formulation using lipid particles, since most peptide or protein antigens are ineffective for mucosal immunization due to proteolytic degradation at mucosal sites [123].

4.5. Antioxidant and Vitamin Delivery. Lipid nano- and microparticles have great potential for efficiently protecting antioxidants and vitamins against degradation (they are often light- and oxygen-sensitive). Furthermore, they can improve skin penetration. The use of lipid particles as dermal delivery systems may therefore be regarded as a convenient strategy with which to enhance the topical effectiveness of antioxidants. Some skin care products that contain antioxidant-loaded lipid nanoparticles have already been marketed [124]. Furthermore, antioxidants are frequently characterized by low bioavailability following oral administration. Their entrapment within lipid nanoparticles can help to increase intestinal uptake and thus improve their pharmacokinetics [125].

4.6. Diagnostics Delivery. Important preclinical studies have recently been carried out in the diagnostic field using lipid nanoparticles that are set up for positive contrast magnetic resonance imaging (MRI). These systems include MnCl2, gadolinium(III) diethyltriaminepentaacetic acid (Gd-DTPA), and the manganese(II) equivalent (Mn-DTPA). Near infrared (NIR) dyes have also been conjugated to lipid nanoparticles, such as Alexa Fluor™ 488. However, a new concept is currently gaining attention in cancer therapy: the conjugation of therapeutic agents and diagnostic tools in the same multimodal theranostic nanoparticle [126].

4.7. Patent Overview. Table 4 provides a summary of the most important patents that concern the usage and composition of lipid nano- and microparticles that are dedicated to specific therapeutic or technological aims.

5. Market Concerns

The last few decades have seen a gradual and significant increase in the number of registered patents that concern lipid nano- and microparticles. On the other hand, it is worth noting that most formulations that have been marketed belong to the cosmetic field. Only three lipid-nanoparticle-based oral formulations are currently marketed, but one of them is licensed as a “nutraceutical” product (Table 5). However, while it can be estimated that more than 500 cosmetic products that contain NLC are present worldwide, they are hard to count as NLC are often not listed as NLC products on the International Nomenclature of Cosmetic Ingredients (INCI) list [182].

The efforts of researchers from all around the world are increasing, as demonstrated by the amount of research published in recent years. This increase is due to the potential industrial applications of lipid nano- and microparticles and the fact that they can boast of solvent-free and easily scaled-up preparation methods, the use of biocompatible materials, etc. These data highlight a general trend in the patenting activity of lipid particles; in the 1990s, the scientific community, especially in Europe, showed increased interest in innovative preparation techniques for lipid nanoparticles, while, from the beginning of the new millennium, patenting activity shifted mainly towards drug delivery applications, and researchers from Emerging Countries became progressively more involved. Some small and medium industries (SMEs) and spin-off companies that dedicate their core business to lipid nanoparticles have also arisen: Italian Nanovector Srl, Russian Nanosystem Ltd., German PharmaSol GmbH, Spanish Lipotec SA, Indian Transgene Biotek Ltd., and Korean AmorePacific Corp are some examples [189, 190]. In fact, SMEs can be seen to be the main driving force for innovation in this field, even more so than large companies [182].

However, there is a large gap between the number of literature articles and patents despite the increasing interest in lipid carriers [189, 190]. Furthermore, an evaluation of the status of existing patents reveals that only a few have reached the granted status, while the remainder are still classified as applications. This is even more evident when we compare filed patents and marketed products.

There are a number of reasons why many patented works in this area remain at an initial stage and are not translated into industrial products; regulatory concerns can play a key role. Thus, despite the huge amount of research carried out on the use of lipid nanoparticles for dermal administration [191], regulatory aspects mean that all marketed products for dermal administration are licensed as cosmetics (Table 5); in fact, cosmetic products are easier to process in terms of time and economic investment as they do not require clinical evaluation.

In fact, the exponential development of nanotechnology in recent years has raised not only high hopes but also a number of safety, ethical, and, consequently, regulatory questions that can significantly hamper the marketing process [192]. From a regulatory point of view, lipid nanoparticles undergo the general regulatory concerns of nanomaterials.

Harmonizing the definition of nanomaterials, as used by researchers, producers, and regulators, is a stringent necessity. According to the European Commission Recommendation on the definition of a nanomaterial (2011/696/EU), 100 nm is the demarcating upper limit as it refers to the size around which the properties of materials can change significantly from conventional equivalents. Lipid nanoparticle sizes tend to exceed 100 nm, but particles that are greater than 100 nm, in the submicron size range, can still offer “nano-related properties” due to higher superficial energy, despite having a lower capacity to penetrate through membranes and skin [193].

Classification may depend on scientific discipline and on the impact of nanomaterials on the human organism,
Table 4: Most important patents that concern the specific therapeutic/technological aims of lipid nano- and microparticles.

| Therapeutic/technological aim | Patent number | Lipid particle type | Drug/active delivered | Brief description | Ref. |
|-------------------------------|---------------|---------------------|-----------------------|------------------|------|
| Cancer therapy                | FR2935270     | SLM                 | Temozolomide          | Galenic form of SLM formulated with temozolomide in a lipid matrix | [127] |
|                               | WO2006128888  | SLN                 | Cholesteryl butyrate, propionate | SLN, made up of cholesteryl butyrate and propionate as a lipid matrix, are used for the prevention and treatment of inflammatory pathologies | [128] |
|                               | US6685960     | SLN                 |                      | SLN, made up of cholesteryl butyrate and propionate as a lipid matrix, are used for tumor treatment | [129] |
|                               | WO2005092298  | SLN                 | Platinum compounds   | The loading of platinum derived compounds in SLN is obtained using a warm microemulsion method | [130] |
|                               | WO2004071498  | LNC                 |                      | LNC are stabilized by surfactants that can act as P-glycoprotein inhibitors and reduce tumor drug resistance | [131] |
|                               | CN200910065523| SLN                 | Cucurbitacin         | A cucurbitacin-loaded SLN preparation method is disclosed, in which the formulation maintains its stability | [132] |
|                               | CN201110022618| PLN                 | Adriamycin           | The loading of adriamycin into SLN is achieved via complexation with polyanion sodium alginate, leading to a sustained release formulation | [133] |
|                               | CN200810041865| SLN                 | Docetaxel            | Long-circulating docetaxel-loaded SLN are formulated | [134] |
|                               | WO2014206093  | SLN                 | Chinese herbal compound | The loading of Chinese herbal antitumor compounds into SLN significantly improves their bioavailability, reducing dosage and increasing therapeutic effects | [135] |
|                               | IN421/DEL/2008| SLN                 | Paclitaxel           | Controlled delivery | [136] |
|                               | US2010247619  | NLC                 | Riluzole             | Medicinal formulations are prepared to treat amyotrophic lateral sclerosis and multiple sclerosis | [137] |
|                               | US6514519     | SLN                 | Octadecyl-2-methyl-sn-glycero-3-phosphorylcholine (edelfosin) | SLN are loaded with edelfosin, which is suitable for the treatment of brain tumors and can also be administered orally | [138] |
|                               | WO99920256    | SLN                 |                      | BBB targeting of SLN is obtained via either specific protein linkages or absorption onto the SLN surface | [139] |
|                               | WO2011019954  | SLN                 |                      | SLN delivery to the brain is achieved via the perilymphatic fluid of the inner ear, through the cochlear aqueduct | [140] |
|                               | WO99927918    | SLN                 |                      | Small-sized SLN, obtained from warm microemulsions, can cross the BBB | [141] |
| Brain delivery                | US20100129431 | SLN                 | Idebenone            | Injectable nanoparticles that are loaded with idebenone can protect from neuronal damage and improve recovery after brain trauma | [142] |
|                               | CN201610002634| SLN                 | Aripiprazole         | Aripiprazole-loaded SLN for injection have high bioavailability, low toxic and side effects, and controlled-release targeting properties | [143] |
|                               | CN201610262638| SLN                 | Antidepressant composition | A mixture of curcumin, folic acid, lecithin, and HU-211 is loaded into SLN, with increased bioavailability | [144] |
|                               | IN201621034343| SLN                 | Tapentadol           | *In situ* gel composition of loaded SLN for nose-to-brain delivery | [145] |
|                               | IN1251/MUM/2012| NLC               | Ubidecarenone        | Treatment of neurodegenerative disorders | [146] |
|                               | IN2009/MUM/2012| SLN                 | Granisetron          | SLN-cyclodextrin complex for nose-to-brain delivery | [147] |
|                               | IN3451/DEL/2012| SLN                 | Carbidopa            | Bionanoparticles and SLN to target the brain via administration through the ear cavity | [148] |
| Therapeutic/technological aim | Patent number | Lipid particle type | Drug/active delivered | Brief description | Ref. |
|------------------------------|---------------|--------------------|----------------------|------------------|------|
| Gene therapy                 | WO2011015701  | SLN                | p-DNA                | A solid lipophile siRNA cargo can be obtained using cationic SLN, a dextrin, and a sugar | [154] |
|                              | WO2017015552  | SLN                | siRNA                | A vaccine formulation is obtained by coating SLN with a nucleic acid that encodes for an immunogenic peptide, in the presence of a cholera toxin, used as an adjuvant | [155] |
|                              | WO20040530056 | SLN                | p-DNA                | In order to achieve transfection, p-DNA is complexed with SLN that is functionalized with a cationic lipid or peptide, a nonionic surfactant, and a polysaccharide | [153] |
|                              | IN201611003140| SLN                | p-DNA, siRNA         | Two-step process to entrap pDNA and siRNA within the lipid matrix of SLN | [156] |
| Protein and peptide delivery | WO9956733     | SLN                | Cyclosporine         | When cyclosporine is loaded into SLN, a better pharmacokinetic profile, compared to commercial formulations, is obtained after oral administration | [157] |
|                              | CN201610203074| SLN                | Sirolimus            | Sirolimus-loaded SLN are employed as a nonirritant topical formulation for the treatment of multiple immune and inflammatory skin diseases (atopic dermatitis, eczema, dermatitis, lichen planus, psoriasis, vitiligo, rosacea, and sarcoidosis) | [158] |
|                              | WO2015007398  | SLN                | Antibody             | Antibodies are loaded into SLN through hydrophobic ion pairing | [159] |
|                              | WO2009080164  | SLM                | Growth hormone       | Lipid-coated microparticles that are loaded with growth hormone are obtained by spray-drying, without denaturing the protein | [161] |
|                              | WO2010017965  | SLM                | Growth hormone       | Lipid-coated microparticles that are loaded with growth hormone are obtained by spray-drying and spray congealing, without denaturing the protein | [162] |
|                              | WO0071077     | SLN                | Antigen for vaccine  | Aminoalkyl glucosaminide phosphate is employed as a vaccine adjuvant in antigen-complexed cationic SLN | [165] |
|                              | WO0071154     | SLN                | Antigen for vaccine  | Antigen-loaded spray-dried SLM are functionalized with a ligand that is specific for antigen-presenting cells, inducing immune responses | [166] |
|                              | CN20100522545 | SLN                | Catalase             | A two-step emulsion process from a multiple W/O/W emulsion is used to load catalase into SLN, greatly increasing the stability of the enzyme and prolonging its effective activity duration | [167] |
|                              | WO200164254   | SLM                | Various therapeutic peptides | Lectin-functionalized PLN are loaded with therapeutic peptides in order to increase oral uptake and/or immunization | [168] |
but also on environmental exposure. In particular, European Regulation on cosmetic products (CE n.1223/2009) associate the concept of nanomaterial insolubility and persistence to dimensional limits (100 nm) [194], whereas the efficacy and/or safety assessment of nanomaterials in medicinal products is still based on case-by-case evaluation because of the complexity of these systems. The European Medicines Agency (EMA) issued a reflection paper on nanotechnology-based medicinal products for human use, in 2006, which also included an official definition of nanomedicine, as being up to a size of ca. 100 nm [195]. However, nanotechnology-based products that have been investigated for pharmaceutical applications have broader size ranges than the proposed definition, inducing the EMA to also include all “structures” with sizes of less than 1000 nm that are designed to have specific properties [196] and can improve site-specific drug delivery and significantly alter toxicological profiles. Regulatory agencies therefore require manufacturers to perform accurate preauthorization studies to assess the quality, safety, and efficacy profiles of a new drug product [197, 198].

Thus, despite the scientific community and private pharmaceutical companies making considerable effort to develop new nanoscale drug products, the approval rate for novel nanomedicine products has not exceeded 10%, mainly because of safety and efficacy profile failures during preclinical and clinical studies [199]. Other nanosystems, such as lipid nanoparticles, therefore become increasingly interesting as they offer different advantages: undoubted matrix biocompatibility, solvent-free preparation methods, and, in some cases, no need for high temperatures. In particular, the presence of solvents may represent a shortcoming for an
| Manufacturer | Trademark | Lipid particles type | Drug/active | Administration route | Field of application | Reached development stage | Ref. |
|--------------|-----------|----------------------|-------------|----------------------|-----------------------|---------------------------|-----|
| Alpha RX     | Ocusolin  | SLN                  | Gentamicin  | Ocular               | Pharma                | Preclinical               | [183]|
|              | Zysolin   | SLN                  | Tobramicin  | Pulmonary, parenteral| Pharma                | Preclinical               | [183]|
|              | Vansolin  | SLN                  | Vancomycin  | Parenteral           | Pharma                | Preclinical               | [183, 184]|
| AmorePacific | IOPE Line | NLC                  | Ubidecarenone, omega-3 and omega-6 unsaturated fatty acids | Dermal | Cosmetic | Marketed | [124]|
| Bayer HealthCare Pharmaceuticals Inc. | Cipro | SLN | Ciprofloxacin | Oral | Pharma | Marketed | [185, 186]|
| Beate Johnen | NLC deep effect eye serum | NLC | Ubidecarenone, highly active oligosaccharides | Dermal | Cosmetic | Marketed | [124]|
|              | NLC deep effect repair cream | NLC | Ubidecarenone, TiO₂, and highly active oligosaccharides | Dermal | Cosmetic | Marketed | [124]|
|              | NLC deep effect reconstruction cream | NLC | Ubidecarenone, acetyl hexapetide-8, highly active oligosaccharides in polysaccharide matrix, and micronized plant collagen | Dermal | Cosmetic | Marketed | [124]|
| Boehringer   | Mucosolvan Retard | SLN | Ambroxol | Oral | Pharma | Marketed | [184]|
| Chemisches Laboratorium (Dr. Richter) | NanoLipid Restore CLR | NLC | Black currant seed oil | Dermal | Cosmetic | Marketed | [124, 183]|
|              | NanoLipid Q10 CLR | NLC | Ubidecarenone and black currant seed oil | Dermal | Cosmetic | Marketed | [124]|
|              | NanoLipid Basic CLR | NLC | — | Dermal | Cosmetic | Marketed | [124]|
|              | NanoLipid Repair CLR | NLC | Black currant seed oil and manuka oil | Dermal | Cosmetic | Marketed | [124]|
| Dr. Rimpler  | Cutanova Cream Nanorepair Q10 | NLC | Ubidecarenone, polypeptide, Hibiscus extract, ginger extract, and ketosugar | Dermal | Cosmetic | Marketed | [124]|
|              | Intensive Serum Nanorepair Q10 | NLC | Ubidecarenone, polypeptide, Acmella oleracea extract | Dermal | Cosmetic | Marketed | [124]|
|              | Cutanova Cream Nanovital Q10 | NLC | Ubidecarenone, TiO₂, polypeptide, ursolic acid, oleanolic acid, and sunflower seed extract | Dermal | Cosmetic | Marketed | [124]|
| Dr. Theiss   | Olivenöl Anti Falten Pflegekonzentrat | NLC | Olea europaea oil, panthenol, Acacia senegal, tocopheryl acetate | Dermal | Cosmetic | Marketed | [124]|
|              | Olivenöl Augenpflegebalsam | NLC | Olea europaea oil, Prunus amygdalus Dulcis oil, hydrolyzed milk protein, tocopheryl acetate, Rhodiola rosea root extract, and caffeine | Dermal | Cosmetic | Marketed | [124]|

**Table 5: Most important marketed and close-to-market products that contain lipid nano- and microparticles.**

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industrial process, as solvents can affect the stability of active compounds, their removal may be expensive, and they may induce toxicological (residues) and environmental problems.

There is a certain typical time frame between the invention of a system and its introduction to the market. From the invention of liposomes in 1965, it took about 20 years for them to reach the cosmetic market (“Capture” launched by Dior in 1986) and 25 years for the first pharmaceutical product (Alveofact by Dr. Karl Thomae GmbH Germany). Based on this, and taking 1992 as year of the invention of SLN, one could have expected the first pharmaceutical products to arrive around 2016-2020. However, only two lipid nanoparticle-based pharmaceutical products have been marketed to date. Moreover, after the financial crisis of 2008, companies have rethought their investment and product development policies and have become more conservative. This may have influenced the clinical testing of lipid nanoparticulate systems [182].

6. Conclusions

Research into lipid nano- and microparticles has been performed for nearly 25 years. Patenting activity has grown, and, at the same time, the use of nanotechnology as an innovative tool to treat diseases has boomed, while potential commercial interest in bio compatible materials and solvent-free preparation techniques has increased as well. In fact, microemulsion templates were the first technique

| Manufacturer          | Trademark                  | Lipid particles type | Drug/active                                                                 | Administration route | Field of application | Reached development stage | Ref. |
|-----------------------|----------------------------|----------------------|-----------------------------------------------------------------------------|----------------------|-----------------------|--------------------------|------|
| Isabelle Lancray      | Surmer Crème Legère        | NLC                  | Kukui nut oil, Monoi Tiare Tahiti®, pseudopeptide, coconut milk, and wild indigo | Dermal               | Cosmetic              | Marketed                 | [124]|
|                       | Nano-Protection            |                      |                                                                             |                       |                       |                          |      |
|                       | Surmer Crème Riche         | NLC                  | Kukui nut oil, Monoi Tiare Tahiti®, pseudopeptide, coconut milk, wild indigo, and tamanol | Dermal               | Cosmetic              | Marketed                 | [124]|
|                       | Nano-Restructurante        |                      |                                                                             |                       |                       |                          |      |
|                       | Surmer Elixir du Beauté     | NLC                  | Kukui nut oil, Monoi Tiare Tahiti®, pseudopeptide, coconut milk, and wild indigo | Dermal               | Cosmetic              | Marketed                 | [124]|
|                       | Nano-Vitalisant            |                      |                                                                             |                       |                       |                          |      |
|                       | Surmer Masque Crème        | NLC                  | Kukui nut oil, Monoi Tiare Tahiti®, pseudopeptide, coconut milk, wild indigo, and tamanol | Dermal               | Cosmetic              | Marketed                 | [124]|
|                       | Nano-Hydratant             |                      | Kukui nut oil, pseudopeptide, hydrolyzed wheat protein, Ximenia americana seed oil, and tamanol | Dermal               | Cosmetic              | Marketed                 | [124]|
|                       | Surmer Crème Contour Des Yeux | NLC                  |                                                                             |                       |                       |                          |      |
|                       | Nano-Remodelante           |                      |                                                                             |                       |                       |                          |      |
| Isabelle Lancray      | Kemin Industries FloraGlo  | NLC                  | Lutein                                                                      | Oral                 | Food                  | Marketed                 | [187]|
|                       |                            |                      | Glycoproteins, Panax ginseng root extract, Equisetum arvense extract, Camellia sinensis leaf extract, and Viola tricolor extract |                       |                       |                          |      |
|                       | La Prairie Swiss Cellular White | NLC                  |                                                                             | Dermal               | Cosmetic              | Marketed                 | [124]|
| Pharmasol TransoPlex | Pharmatec CyCol            | SLN                  | Macadamia ternifolia seed oil, avocado oil, urea, and blackcurrant seed oil | Dermal               | Cosmetic              | Marketed                 | [183, 188]|
| Pharmasol (Sigmoid Pharma) | Regenerations Creme Intensiv | NLC                  |                                                                             |                       |                       |                          |      |
| Scholl                | Yamanouchi Nanobase        | SLN                  |                                                                             | Dermal               | Cosmetic              | Marketed                 | [183]|

Table 5: Continued.
that was patented, by Gasco et al. in 1993, for lipid nanoparticle preparation. Since then, an increasing number of patents were filed, up to 2010. Great importance should be given to the patents filed by Müller and Lucks in 1996. They are a milestone in lipid nanoparticle research as they adapted HPH, which is a well-established industrial technique that is currently employed for nanoemulsion preparation, for use in SLN, NLC, and LDC production. Since then, several technological patents on alternative preparation techniques have been filed to overcome the limitations of existing methods.

Furthermore, an increasing number of composition and usage patents have been filed, especially since 2000. This can probably be correlated to the discovery of new practical pharmacological and technological fields in which lipid nanoparticle technologies can be successfully used. In fact, a significant number of dermal drug delivery patents have been filed that demonstrate a range of advantages offered by these delivery systems, including chemical stabilization and the increased skin penetration/permeation of drugs. This latter aspect is mainly due to the lipid occlusion effect on skin. However, a significant number of oral drug delivery patents are currently being filed. This is probably because the oral route is the most widespread and acceptable for therapy, and Biopharmaceutics Classification System (BCS) class IV drugs suffer from several bioavailability issues. Moreover, some drug delivery challenges can be considered opportunities for lipid nanoparticles. Firstly, lipid nanoparticles are seen to be an interesting means of overcoming the BBB because of their lipid composition and ease of functionalization. Secondly, a number of mechanisms that are linked to lipid nanoparticle use can benefit cancer therapy. Some of the most intriguing approaches in these fields have been the subject of patents. Finally, a considerable number of patents have focused on macromolecule delivery; nucleic acids and proteins are the future of pharmacological therapy, and both present comparable issues with stability, poor bioavailability, and high molecular weight, which hamper their use in current therapies and can also be a technological drawback for lipid nano- and microparticle loading.

Most marketed lipid nano- and microparticle-based products are currently licensed as cosmetics, while the development of pharmaceutical drug delivery systems, especially for oral and parenteral use, is still mostly, with some exceptions, at the clinical or even preclinical stage. The main obstacle to reaching the market in the pharmacological field seems to be the regulatory aspect: expensive clinical studies are required, and these costs should be justified by significant clinical results and advantages over commercial formulations and high reproducibility, as well as the total safety of all the materials and formulations employed. Although Europe and USA are the leading countries in terms of patent applications, it is worth noting that there has been an increase in the patenting activity of Emerging Countries in recent years.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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