CHAPTER

4

Clinical considerations on micro- and nanodrug delivery systems

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1. Introduction

Over the past few years, an unrivaled increase in research innovations in the area of nanotechnology in medicine, more specifically in drug delivery, has been evidenced. Micro- and nanoparticles in drug delivery are in the size range of 10 nm−1000 μm and comprise at the minimum two components, namely active pharmaceutical ingredients (APIs) and inert excipients, though the nanoparticle formulation of only APIs is also achievable. These micro- and nanoparticles are often associated with special functions such as treatment, prevention, and/or diagnosis of diseases. These are also termed smartdrugs or theranostics [1].

One of the major challenges in the treatment of various diseases is the delivery of APIs at target site. Drug delivery through traditional systems (such as emulsions, suspensions, and solutions) is thought to be less effective, having poor biodistribution of drugs and the absence of selectivity. These systems possess limitations such as high dose, relatively lower bioavailability, high first-pass metabolism, and fluctuations of drug levels in plasma [2]. These constraints and drawbacks of traditional drug delivery systems can easily be overcome by controlling the delivery of APIs by incorporating them into micro- or nanoparticles. These encompass microemulsions, nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipidic carriers (NLCs), polymer lipid hybrids or complexes (PLH), nanocapsules, metallic nanoparticles, polymeric microparticles, polymeric nanoparticles, liposomes, transfersomes, ethosomes, and niosomes. While incorporating drugs into these micro- and nanoparticles, targeted delivery is achieved in a controlled manner and unwanted side effects can easily be avoided. Despite these benefits, micro- and nanoparticles also increase bioavailability, prevent fast degradation as well as clearance of drugs from the body, and increase the concentration of drugs at the target sites, thereby lowering doses. As a result, maximum therapeutic effect and minimum toxic effects can be achieved [3]. So, due to these reasons, nowadays, researchers are

https://doi.org/10.1016/B978-0-12-817870-6.00004-3

mainly focusing their research on the development of micro- and nanoparticle-based drug delivery systems.

After achieving promising results in preclinical studies, these drug delivery systems are subjected to clinical trials, which are regulated by the US Food and Drug Administration (US FDA). Clinical trials are systematic studies and are considered to be the best medical approach that works for specific illnesses and/or groups of people. Clinical trials generate blue ribbon data that are important for healthcare. Thus these clinical studies follow rigid scientific guidelines that assure patients and also help in achieving trustworthy results of clinical trials. Clinical trials are the final stage of an interminable and thoughtful research and development methodology or strategy [4].

This chapter offers an overview of clinical trials and an understanding of various types of micro- and nanodrug delivery systems and their applications. The authors have summarized the current status of various products based on the aforementioned drug delivery systems at different phases of clinical trials. Regulatory concerns regarding nanotechnology-derived products have also been discussed, albeit in brief.

2. Outline of drug development

The US FDA has been describing and managing the prevailing pathway to the development of drugs and their approval. The agency places heavy importance primarily on safety and then on efficacy. The main purpose of clinical trials is to evaluate safety and maximum tolerated dose of drug, pharmacokinetics, and pharmacodynamic behavior of drug in humans, and also drug–drug interactions. When investigational drugs show promising results in preclinical studies, investigational new drug applications are submitted to the US FDA by drug sponsors or sponsor investigators. These applications give detailed information regarding the qualifications of investigators, data on preclinical studies of drugs, and appeals to federal statutes to transport unapproved drugs nationwide. Once approval is granted, drugs are subjected to phase I–III clinical trials. If after these phases, drugs are found to be safe and effective in the designed population, drug sponsors or sponsor investigators can file a new drug application to the US FDA. Then, the US FDA with the involvement and recommendation of an external panel/committee thoroughly analyzes the results of phases I–III and decides whether to grant an indication for drugs to be marketed. After passing the phase III trial, drugs reach the phase IV trial where again safety and efficacy in the designed population are observed. The four phases of clinical trials are explained here in brief (Fig. 4.1). Phase I trials are also known as "dose-escalation" and "human pharmacology" studies. These trials are performed in smaller numbers of healthy and/or diseased human beings. Phase II trials are also known as "therapeutic exploratory" trials. These are performed in a small number of humans having the specific disease of interest to evaluate the safety, pharmacokinetics, and pharmacodynamics of investigational drugs. These phase II trials also include studies related to optimization of dose, dosing frequency, and route of administration that are crucial for the preparation of phase III trials. When drugs pass the phase I and II trials, they enter into phase III trials. The phase III trial is also known as a "therapeutic confirmatory," "pivotal," or "comparative efficacy" trial. This phase III trial is done in diverse target patients (not more than 300–3000 people) to confirm efficacy and to evaluate common adverse reaction incidences. Once the US FDA approves a drug, then phase IV clinical trials are done. Phase IV clinical trials are also known as "postmarketing" or "therapeutic use" studies. These phase IV trials are done on FDA-approved drugs to evaluate rare adverse reactions, cost effectiveness, and drug effectiveness in particular diseases and populations. Therefore phase IV trials are often regarded as observational studies [4].

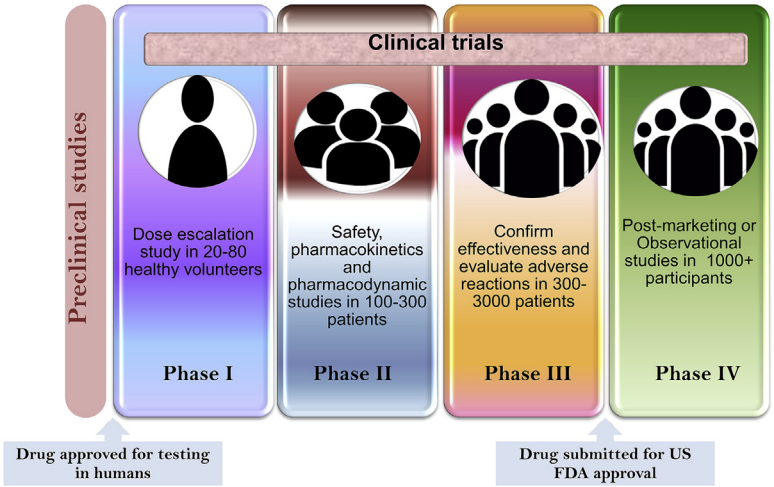

FIGURE 4.1 Different phases of clinical trials.

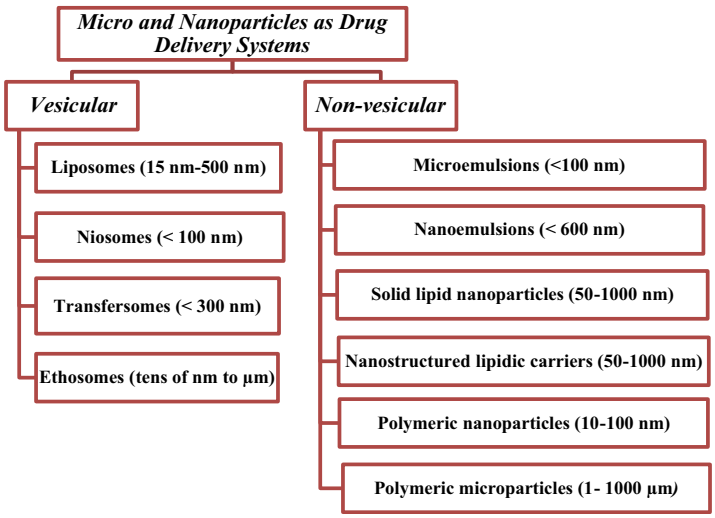

FIGURE 4.2 Vesicular and nonvesicular systems in drug delivery.

3. Micro- and nanoparticles in drug delivery

Micro- and nanoparticles in drug delivery are broadly classified into two categories, namely vesicular and nonvesicular drug delivery systems (Fig. 4.2). Vesicular drug delivery systems include liposomes, transfersomes, ethosomes, and niosomes. Nonvesicular drug delivery systems include microemulsions, nanoemulsions, SLNs, NLCs, polymeric nanoparticles, and polymeric microparticles.

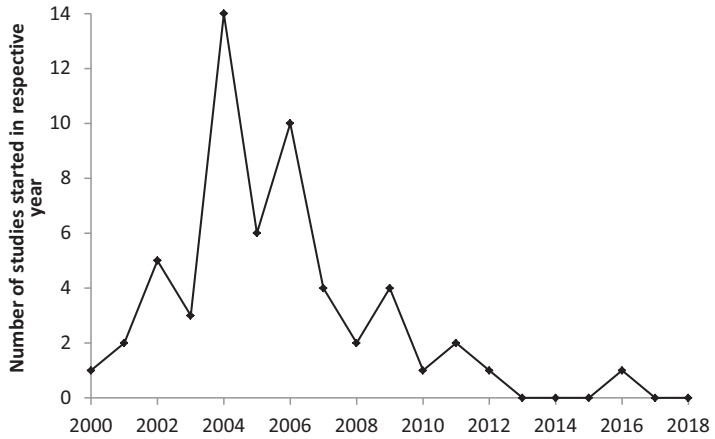

FIGURE 4.3 Trend of clinical trial studies started in 2000–18 for microemulsion.

3.1 Nonvesicular drug delivery systems

3.1.1 Microemulsions

Microemulsions have been extensively explored as drug delivery systems; these (globule size <100 nm) are a clear, thermodynamically stable, isotropic mixture of oil and water, which is stabilized by an interfacial film of surfactant and cosurfactant molecules. These systems have gained attention in drug delivery due to their thermodynamic stability and ease of preparation. Microemulsions are broadly classified into water-in-oil (w/o) microemulsions, oil-in-water (o/w) microemulsions, and bicontinuous microemulsions. The important pharmaceutical application of w/o microemulsions is the oral administration of hydrophilic drugs having low bioavailability. The o/w microemulsions have been explored as systems for oral, transdermal, and pulmonary delivery of lipophilic drugs. Bicontinuous microemulsions have been generally suggested as a drug delivery system for topical and oral routes of administration. Due to their good adhesive and wetting properties, these are used as drug delivery systems for topical applications. In the oral delivery route, these systems prevent acidic degradation of drugs (in the stomach). Some examples of the marketed formulations of microemulsions are Neoral, Norvir, Fortovase, Lipire, Convule, Vesanoid, etc. [5]. A total of 56 microemulsion-based products is undergoing clinical trials (www.clinicaltrials.gov). Fig. 4.3 shows the trend of number of clinical trials started in the period 2000–18. The maximum number of studies was found to be 56 in 2004. Seven studies have been terminated, two studies have status "unknown," and 47 studies have been completed, i.e., these were clinical trial phases that may be phase I, phase II, phase III, or phase IV. Table 4.1 summarizes studies that have completed phase IV clinical trials.

3.1.2 Nanoemulsions

These are analogous to microemulsions in terms of composition, i.e., oil, water, surfactant, and possibly a cosurfactant. Nanoemulsions have globule size <600 nm. The major difference between these two systems lies in their stability. Nanoemulsions are thermodynamically unstable, whereas microemulsions are stable. There are also three types: o/w nanoemulsion, w/o nanoemulsion, and bicontinuous nanoemulsion [6]. Table 4.2 lists the different formulations containing nanoemulsions as drug delivery systems that are going to clinical trials [7].

TABLE 4.1 Microemulsion-based products that have completed phase IV clinical trials.

Year of start	Title of study	Health condition	Drug/Formulation	ClinicalTrials.gov identifier
2002	Cyclosporine A C-2h monitoring versus tacrolimus C-0h monitoring in de novo liver transplant recipients	Liver transplant	Cyclosporine A, tacrolimus, basiliximab, methylprednisolone, prednisone	NCT00149994
2003	Evaluation of cyclosporine microemulsion and tacrolimus on the rate of new onset diabetes mellitus in kidney transplantation recipients	Kidney transplant	Cyclosporine	NCT00171496
2004	Everolimus versus mycophenolate mofetil in combination with reduced dose cyclosporine microemulsion in maintenance heart transplant recipients	Heart transplantation	Everolimus	NCT00170859
2004	Efficacy and safety of cyclosporine microemulsion given once a day in adult stable liver transplant recipients	Liver transplant	Cyclosporine microemulsion	NCT00171509
2004	Efficacy and safety of cyclosporine microemulsion in diabetic adult stable liver transplant recipients	Liver transplant	Cyclosporine microemulsion	NCT00171743
2004	Conversion from tacrolimus to cyclosporine microemulsion in liver transplant patients with new onset diabetes after the 3rd month post-transplant	Maintenance liver transplant patients with new-onset diabetes	Cyclosporine −cyclosporine microemulsion	NCT00171717
2004	Nordic study in cardiac and lung transplantation: outcome in relation to cyclosporine microemulsion C2 levels	Heart and lung transplant	Cyclosporine	NCT00154193
2004	Study of enteric-coated mycophenolate sodium (EC-MPS) with cyclosporine microemulsion and steroids in pediatric de novo renal transplant patients	Kidney transplantation	EC-MPS, cyclosporine	NCT00154206
2004	Study to evaluate the combination of enteric-coated mycophenolate sodium (EC-MPS), basiliximab, and C2-monitored cyclosporine in de novo renal transplant recipients at potential high risk of delayed graft function (DGF)	Renal transplantation	EC-MPS	NCT00154232
2004	A one-year, open label study to investigate the safety and the effect of enteric-coated mycophenolate sodium (EC-MPS) in combination with cyclosporine microemulsion in de novo kidney transplant recipients	Kidney transplantation	EC-MPS	NCT00154245

(*Continued*)

TABLE 4.1 Microemulsion-based products that have completed phase IV clinical trials.—cont'd

Year of start	Title of study	Health condition	Drug/Formulation	ClinicalTrials.gov identifier
2004	Efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS) in de novo kidney transplant recipients	De novo kidney transplant recipients	EC-MPS	NCT00312143
2004	Study comparing cyclosporine dose reduction versus cyclosporine elimination in kidney transplant recipients taking sirolimus	Kidney failure, graft versus host disease	Cyclosporine	NCT00195468
2005	Everolimus in combination with cyclosporine microemulsion in de novo renal transplant recipients	Kidney transplantation	Everolimus	NCT00170885
2005	Efficacy and safety of everolimus with enteric-coated mycophenolate sodium (EC-MPS) in a cyclosporine microemulsion-free regimen compared to standard therapy in de novo renal transplant patients	Renal transplantation	Everolimus, cyclosporine, EC-MPS, corticosteroids	NCT00154310
2005	Efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS) in renal transplant patients	Kidney transplantation	EC-MPS	NCT00239083
2006	Efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS) in a cyclosporine microemulsion-based regimen in de novo living donor kidney transplant recipients	Kidney transplant	Cyclosporine	NCT00537862
2006	A study to evaluate the efficiency of intravenously administered cyclosporine in de novo liver transplant recipients	Liver transplantation	Cyclosporine (Sandimmun i.v.), Cyclosporine (Sandimmun Optoral)	NCT00332462
2006	SOCRATES: Steroid or cyclosporine removal after transplantation using everolimus	Renal-transplanted recipients	Everolimus (RAD001), cyclosporine (calcineurin inhibitor, methylprednisone/prednisone, mycophenolate sodium)	NCT00371826
2006	Evaluation of the therapeutic benefit of an initial intensified dosing regimen of mycophenolate sodium versus a standard regimen in renal transplant patients	Kidney transplantation	Enteric-coated mycophenolate sodium (Myfortic), cyclosporine (Neoral), prednisone	NCT00419926
2011	Efficacy and tolerability of a topical microemulsion in patients with allergic rhinitis due to sensitization to pollen	Allergic rhinitis	Lipidic microemulsion, saline	NCT01478425

i.v., Intravenous.
Data from www.clinicaltrials.gov.

TABLE 4.2 Nanoemulsions undergoing different phases of clinical trials.

Drug	Route of administration	Health condition	Clinical trial phase	ClinicalTrials.gov identifier
5-Aminolevulinic acid	Topical	Lentigo maligna	IV	NCT02685592
5-Aminolevulinic acid	Topical	Basal cell carcinomas	II, III	NCT02367547
Diclofenac	Topical	Knee osteoarthritis	II	NCT00484120
NB-001	Topical	Recurrent herpes labialis	III	NCT01695187
BF-200ALA (Ameluz)	Topical	Actinic keratosis	III	NCT02799069
Testosterone derivative	Transdermal	Menopause, women libido	II	NCT02445716
Cyclosporine	Ophthalmic	Dry eye syndrome	III	NCT02461719
Brimonidine tartrate	Ophthalmic	Dry eye disease	III	NCT03785340
Brimonidine tartrate	Ophthalmic	Ocular graft versus host disease	III	NCT03591874
Curcumin	Oral	Atypical ductal breast hyperplasia	Not applicable[a]	NCT01975363
Curcumin	Oral	Breast cancer, joint pain	Not applicable[a]	NCT03865992
CoQ10	Oral	Ataxia oculomotor apraxia 1	III	NCT02333305
14C-Cholesteryloleate and 3H-cholesterol-labeled low density lipoprotein-like nanoemulsion	I.V.	Diabetic dyslipidemia	Completed	NCT01010035
Propofol	I.V.	Leukemia	II, III	NCT01326078
Methotrexate	I.V.	Left ventricular remodeling	II, III	NCT03516903

I.V., Intravenous.
[a] *Not applicable is used to describe trials without Food and Drug Administration-defined phases (as explained on www.clinicaltrials.gov).*

3.1.3 SLNs

SLNs consist of a solid matrix that is composed of biocompatible and biodegradable lipids that are solid at both room and body temperatures, with a mean particle size range between 50 and 1000 nm [8,9]. SLNs are able to accommodate hydrophilic vis-à-vis hydrophobic therapeutic agents. These were first introduced in 1991 to overcome the problems associated with historic drug delivery systems [10]. SLNs are endowed with advantages of the aforesaid systems, including physiologically acceptability and release of the drug from the lipid matrix in a controlled manner and at the target site. Some of the advantages of SLNs are greater physical stability, improved drug stability, immunity of incorporated therapeutic agents against chemical, oxidative, light, and moisture degradation, high drug payload, minimal adverse effects of encapsulated drug moiety,

circumvention of organic solvents, absence of a carrier's biotoxicity, less danger of acute and chronic toxicity, better controlled release because of the reduced mobility of the drug in a solid lipid, avoidance of coagulum during storage, ease of sterilization, and cost-effective large-scale production [9,11,12]. SLNs also possess disadvantages such as lipid crystallization/particle growth, uncertain gelation tendency, and unforeseen dynamics of polymeric conversions. SLNs have pervasively been utilized to deliver numerous therapeutic agents through oral, dermal, ocular, pulmonary, rectal, and parenteral routes of drug administration. Most of the SLN-based products that are marketed as well as those at the preclinical stage belonging to cosmeceutical and pharmaceutical fields are summarized in Table 4.3 [13–15]. To date, only one study has reported completion of clinical trial phase I, i.e., "Clinical assessment of oxiconazole nitrate solid lipid nanoparticles loaded gel" (www.clinicaltrials.gov).

3.1.4 NLCs

These are a new generation of lipid nanoparticles, an aqueous colloidal dispersion consisting of a mixture of very different lipid molecules, i.e., solid lipid is blended with liquid lipid (oils) [16]. The resulting matrix shows many imperfections in crystal lattices and leaves enough space to accommodate drug molecules [17]. NLCs overcome the limitations associated with SLNs, namely limited drug-loading capacity, risk of gelation, and drug expulsion during storage caused by lipid polymorphism [18,19]. Recently, these have been recognized as promising drug

TABLE 4.3 Solid lipid nanoparticle-based pharmaceutical and cosmeceutical products at different stages of development.

Field	Product name	Route of administration	Development stage	Manufacturer/Marketed by
Pharmaceutical	Cipro	Oral	Marketed	Bayer Healthcare Pharmaceuticals Inc.
	Mucosolvan Retard	Oral	Marketed	Boehringer
	CyCol	Oral	Preclinical	Pharmatec (Sigmoid Pharma)
	TransoPlex	Parenteral	Preclinical	Pharmasol
	Ocusolin	Ocular	Preclinical	Alpha RX
	Zysolin	Pulmonary, parenteral	Preclinical	Alpha RX
	Vansolin	Parenteral	Preclinical	Alpha RX
	Rifamsolin	Oral	Preclinical	Alpha RX
Cosmeceutical	Allure body cream	Dermal	Marketed	Chanel
	Allure Parfum bottle	–	Marketed	Chanel
	Allure Eau Parfum spray	–	Marketed	Chanel
	Soosion facial lifting cream SLN technology	Dermal	Marketed	Soosion
	Phyto NLC Active Cell Repair	Dermal	Marketed	Sireh Emas
	Nanobase	Dermal	Marketed	Yamanouchi

TABLE 4.4 Various marketed products of nanostructured lipidic carriers.

Field	Product name	Manufacturer name/Marketed by
Nutraceutical (oral delivery)	FloraGlo	Kemin Industries
Cosmeceutical (Dermal delivery)	IOPE Line	AmorePacific
	NLC deep effect eye serum	Beate Johnen
	NLC deep effect repair cream	Beate Johnen
	NLC deep effect reconstruction cream	Beate Johnen
	NanoLipid Restore CLR	Chemisches Laboratorium (Dr. Richter)
	NanoLipid Q10 CLR	Chemisches Laboratorium (Dr. Richter)
	NanoLipid Basic CLR	Chemisches Laboratorium (Dr. Richter)
	NanoLipid Repair CLR	Chemisches Laboratorium (Dr. Richter)
	Olivenol Anti Falten Pflegekonzentrat	Dr. Theiss/Medipharma Cosmetics
	Olivenol Augenpflegebalsam	Dr. Theiss/Medipharma Cosmetics
	Surmer Crème Legere Nano-Protection	Isabelle Lancray
	Surmer Crème Riche Nano-Restructurante	Isabelle Lancray
	Surmer Elixir du Beaute Nano-Vitalisant	Isabelle Lancray
	Surmer Masque Crème Nano-Hydratant	Isabelle Lancray
	Surmer Crème Contour Des Yeux Nano-Remodelante	Isabelle Lancray
	Regenerations Crème Intensiv Ampoules	Scholl
	Swiss Cellular White Illuminating Eye Essence	La Prairie
	Cutanova-Cream Nanorepair Q10	Dr. Rimpler
	Intensive Serum Nanorepair Q10	Dr. Rimpler
	Cutanova Cream Nanovital Q10	Dr. Rimpler

carrier systems for topical application because of their unique properties. NLCs have been found to deliver drugs through oral, topical, and parenteral routes of administration [2]. Table 4.4 lists NLC-based marketed products [14,15].

3.1.5 *Polymeric nanoparticles*

Polymeric nanoparticles are structures made up of polymers (synthetic or natural) having diameters in the range of 10−100 nm. These systems enhance the dissolution rate and absorption of the drug in the gastrointestinal tract (GIT) because of their small particle size, thereby increasing drug bioavailability. These systems protect the entrapped drug from the external environment. Also, controlled drug release from the system is achieved [20]. Polymeric nanoparticles are classified as biodegradable (e.g., poly-(L-lactide) and polyglycolide) and nonbiodegradable (e.g., polyurethane) depending upon their in vivo performance. These systems are being used to deliver drugs through oral, parenteral, topical, and ophthalmic routes of administration. The main application of

polymeric nanoparticles is targeted delivery of anticancer drugs to specific sites by increasing the therapeutic effect and reducing the toxic effect of the anticancer drug [3,21]. The FDA-approved products of polymeric nanoparticles are Adagen/pegademase bovine, Copaxone/Glatopa, Cimzia/certolizumab pegol, Eligard, Macugen/pegaptanib, Mircera/methoxy polyethylene glycol-epoetin beta, Neulasta/pegfilgrastim, Pegasys, PegIntron, Somavert/pegvisomant, Renagel (sevelamer hydrochloride)/Renagel (sevelamer carbonate), Oncaspar/pegaspargase, Krystexxa/pegloticase, Plegridy, and ADYNOVATE [22]. Polymeric nanoparticles in clinical trials are summarized in Table 4.5.

3.1.6 Polymeric microparticles

One type of polymeric microparticle is polymeric microspheres. These are small globular particles in the size range of 1−1000 μm. Polymeric microspheres are considered excellent vehicles for controlled drug delivery because of their different properties such as biocompatibility and biodegradability, capacity to encapsulate different types of drugs, enhancement of the bioavailability of drugs, and sustained release attributes [20,23]. Polymeric microspheres are most commonly used to deliver drugs through a parenteral route in a controlled manner from days to weeks to months [24]. The FDA-approved controlled release parenteral formulations based on microspheres available in

TABLE 4.5 Polymeric nanoparticles undergoing clinical trials.

S. No.	Title of study	Health condition	Drug/Formulation	Clinical trial phase	ClinicalTrials.gov Identifier	Status
1	A trial to determine the maximum tolerated dose and evaluate the safety and pharmacokinetics of docetaxel-PNP, polymeric nanoparticle formulation of docetaxel in subjects with advanced solid malignancies	Advanced solid malignancies	Docetaxel-PNP	I	NCT01103791	Completed
2	Targeted polymeric nanoparticles loaded with cetuximab and decorated with somatostatin analogue to colon cancer	– Colon cancer – Colorectal cancer	Cetuximab nanoparticles, oral approved anticancer drug	I	NCT03774680	Recruiting
3	Pharmacokinetic study of docetaxel-PNP and taxotere to treat patient with advanced solid cancer	Solid tumor	Docetaxel-PNP, taxotere	I	NCT02274610	Completed
4	A randomized controlled trial comparing urea loaded nanoparticles to placebo: a new concept for cataract management	Drug action increased	Urea-loaded nanoparticle eye drops, balance salt solution eye drops	II	NCT03001466	Completed
5	Assessment of pain and antibacterial activity of chitosan versus sodium hypochlorite as irrigant in infected canal	Postoperative pain	Chitosan nanoparticles, Sodium hypochlorite	II, III	NCT03719261	Not yet recruiting
6	Clinical study of antibacterial nanoparticles incorporated in composite restorations	Oral health	Alkylated polyethylenimine nanoparticles antibacterial evaluation	–	NCT00299598	Completed

the market are Nutropin Depot, Lupron Depot, Zoladex, Santostatin LAR Depot, Trelstar LA, Resperidal Consta, Vitrol, and Bydureon [23,25]. In total, 356 products based on microspheres are under different phases of clinical trials (www.clinicaltrials.gov). Out of 373 studies, 35 have been terminated, 19 have a status "Not yet recruiting," 28 have a status "Unknown," 16 have been withdrawn by the respective sponsors/investigators, two have been suspended due to inadequate number of subjects, 76 have a status "Recruiting," six have a status "Enrolling by invitation," 36 have a status "Active, not recruiting," and 151 have completed their clinical phase trials, which can be phase I, phase II, phase III, or phase IV. The studies that have completed their phase IV trials are summarized in Table 4.6.

3.2 Vesicular drug delivery systems

3.2.1 *Liposomes*

Liposomes are spherical vesicles that possess diverse size ranges from 15 nm to certain μm, having an aqueous core enclosed by hydrophobic lipid bilayers. Liposomes are made up of natural phospholipids (e.g., lecithins) and most often steroids (e.g., cholesterol) that impart stability of the phospholipid bilayers when exposed to biological fluids. Depending upon their lamellarity and size, liposomes are classified into three types: multilamellar vesicles having sizes more than 0.5 μm, large unilamellar vesicles having sizes more than 100 nm, and small unilamellar vesicles having sizes in the range of 20−100 nm [3,26]. The main advantage of liposomes is that they can deliver both hydrophilic drugs (via trapping in the aqueous core) and hydrophobic drugs (via absorption into the lipidic bilayers). Despite this, liposomes are biodegradable and biocompatible in nature because of the presence of phospholipids, which are listed as generally recognized as safe. Liposomes are used to deliver various hydrophilic and hydrophobic drugs through oral and topical routes of administration. They incorporate hydrophobic drugs into their lipidic bilayer, thereby increasing the dissolution behavior of the drugs. Furthermore, liposomes protect the drugs from the GIT environment leading to enhanced bioavailability of the drugs [20]. The FDA-approved products of liposomes are DaunoXome, DepoCyt©, Marqibo, Onivyde, AmBisome, DepoDur, Visudyne, Doxil/Caelyx, Abelcet, and Curosurf/poractant alfa [22]. A total of 689 liposomal products are undergoing different stages of clinical trials (www.clinicaltrials.gov). Currently, 29 studies have a status "Not yet recruiting," while 114 studies have a status "Recruiting." Four studies have a status "Enrolling by invitation," whereas 39 studies have a status "Active, not recruiting." Five studies have been suspended and 80 studies were found to be terminated. Twenty-nine studies have been withdrawn by the sponsors or investigators, and 69 studies have status "Unknown." Three hundred and nineteen studies have completed their clinical phase trials, which can be phase I, phase II, phase III, or phase IV. Those studies that have completed their phase IV trials are summarized in Table 4.7.

3.2.2 *Transfersomes*

These are also known as elastic or ultraflexible liposomes made up of numerous phospholipid bilayers along with an auxiliary component, i.e., edge activator (such as sodium cholate, sodium deoxycholate, Spans, and Tweens), which provides elasticity to the vesicles that further helps deep penetration into the skin. These have particle sizes less than 300 nm, and have 5−8 times more elasticity than liposomes. This unique property helps the transfersomes to penetrate deeply into the skin via crossing the subcutaneous layer of the skin. Therefore transfersomes are mainly utilized to deliver the therapeutic agents through dermal and transdermal routes [20,27]. A list of tranfersomes undergoing clinical trials are summarized in Table 4.8 (www.clinicaltrials.gov).

TABLE 4.6 Microsphere-based products that have completed phase IV clinical trials.

Year of start	Title of study	Health condition	Drug/Formulation	ClinicalTrials.gov identifier
2004	A study of stress echocardiography in post-menopausal women at risk for coronary disease	– Coronary artery disease – Heart disease	Perflutren lipid microsphere injectable suspension	NCT00162370
2004	Determining the effects of risperdal consta in patients with psychotic disorders and incomplete adherence	– Schizophrenia – Schizoaffective disorder	Depot risperidone microsphere (consta)	NCT00215579
2005	A study to evaluate symptomatic remission in schizophrenia with long acting risperidone microspheres	Schizophrenia	Risperidone	NCT00216528
2005	An efficacy and safety study of long-term risperidone microspheres in participants with schizophrenia	– Schizophrenia – Schizoaffective disorder	Risperidone long-acting injectable	NCT00269919
2006	A prospective study comparing Contour SE microspheres to Embosphere microspheres for treating symptomatic uterine fibroids with uterine fibroid embolization (UFE)	– Leiomyoma – Uterine fibroids – Uterine neoplasms – Menorrhagia – Leiomyomatosis	Contour SE microspheres, Embosphere microspheres	NCT00628901
2006	DMP115 in patients with an ejection fraction between 25%-40% to evaluate the use of contrast echocardiography to assess heart function	Ventricular ejection fraction	DEFINITY vial for (perflutren lipid microspheres) injectable suspension	NCT00401687
2006	Preventing relapse in schizophrenia: oral antipsychotics compared to injectables: evaluating efficacy	– Schizophrenia – Schizoaffective disorder	Risperidone microspheres, risperidone	NCT00330863
2007	Long-term safety of minocycline in patients with gum disease	Periodontitis	Minocycline HCl microspheres	NCT00668746
2007	An efficacy and safety study of risperidone long-acting microspheres in participants with schizophrenia, schizophreniform or schizoaffective disorders	– Schizophrenia – Schizophreniform disorder – Schizoaffective disorder	Risperidone	NCT01855074
2007	An efficacy and safety study of long-acting risperidone in participants with schizophrenia or schizoaffective disorders who are receiving psychiatric home care treatment	– Schizophrenia – Schizoaffective disorders	Risperidone	NCT00526877
2008	Traditional (Traditional Chemoembolization) TACE versus microsphere TACE	Carcinoma, hepatocellular	Doxorubicin	NCT00936689
2008	A prospective, phase IV, surveillance registry study to evaluate the safety of DEFINITY ® in clinical practice	Cardiovascular disease	DEFINITY ®	NCT00625365
2008	A prospective surveillance trial to evaluate the safety of optison in clinical practice	Echocardiography	Perflutren protein-Type A microspheres injectable suspension, United States Pharmacopeia	NCT00730964

TABLE 4.6 Microsphere-based products that have completed phase IV clinical trials.—cont'd

Year of start	Title of study	Health condition	Drug/Formulation	ClinicalTrials.gov identifier
2009	Evaluate effect of optison on pulmonary artery systolic pressure (PASP) and Pulmonary Vascular Resistance (PVR)	Pulmonary hypertension	Optison (perflutren protein-Type A microspheres injectable suspension), dextrose	NCT00878878
2009	Proof of Concept study to investigate the recurrence of acne post isotretinoin	Acne	Tretinoin microsphere 0.04% gel, Vehicle gel	NCT00939133
2009	A study of commercial DEFINITY ® to monitor the effects of the heart's pulmonary artery pressure	Pulmonary heart disease	DEFINITY ®	NCT00918866
2009	A study of different use regimens using two acne treatments	Acne vulgaris	Benzoyl peroxide wash, tretinoin gel	NCT00907257
2010	Locally delivered doxycycline adjunct to nonsurgical periodontal therapy	Periodontal disease	Doxycycline	NCT02487186
2012	Split-face tolerability comparison between adapalene-benzoyl peroxide gel versus tretinoin gel	Acne vulgaris	Epiduo gel, Retin-A Micro microsphere 0.1%	NCT01522456
2012	Local minocycline to reduce future inflammation and bone loss in periodontal maintenance patients	Moderate to advanced chronic periodontitis	Locally applied minocycline HCl (1 mg)	NCT01647282
2012	Pre-release VIVITROL for opioid dependent inmates	Substance-related disorders	Naltrexone for extended release injectable suspension	NCT01563718
2013	Efficacy of belatacept in reducing DSA	Kidney transplantation	Belatacept	NCT02078193
2013	Efficacy of optison echo contrast to detect thrombus in left atrial appendage	Atrial fibrillation	Optison echocardiography contrast agent	NCT01721447
2016	Real time myocardial perfusion echocardiography for coronary allograft vasculopathy	Cardiac allograft vasculopathy	Perflutren lipid microsphere	NCT02880137

3.2.3 *Ethosomes*

Ethosomes are ethanol (20%–45%)-containing soft vesicles. These are the vesicles made up of phospholipids, water, and ethanol. The presence of ethanol makes the lipidic bilayer more flexible, thereby enhancing skin permeability. The particle size of ethosomes varies from a few tens of nm to μm [20,28]. These are considered as potential drug carriers for dermal and transdermal drug delivery. To date only one study has been found that has reached in the fourth phase of clinical trials, i.e., "Formulation and clinical evaluation of liposomal and ethosomal preparations of anthralin in psoriasis" (www.clinicaltrials.gov).

TABLE 4.7 Liposome-based products that have completed phase IV clinical trials.

Year of start	Title of study	Health condition	Drug/Formulation	ClinicalTrials.gov identifier
2001	DepoCyt therapy in patients with neoplastic meningitis from lymphoma or a solid tumor	Meningeal neoplasms	Intrathecal (injected into the spinal fluid) DepoCyt, intrathecal methotrexate, intrathecal cytarabine (also known as ara-C)	NCT00029523
2002	Maintenance treatment with liposomal doxorubicin (Caelyx) in metastatic breast cancer patients	Breast neoplasms	Pegylated liposomal doxorubicin (Caelyx)	NCT00128778
2003	Randomized control trial of a topical anaesthetic to evaluate pain and anxiety during venipuncture	− Pain − Anxiety	Lidocaine	NCT00676364
2004	A study to evaluate efficacy and tolerance of Caelyx in patients with epithelial ovarian cancer. (Study P04072)	Ovarian neoplasms	Doxorubicin hydrochloride	NCT00727961
2006	Antifungal locks to treat fungal-related central line infections	Central line fungal infections	Amphotericin B (AmBisome)	NCT00936910
2007	CRITIC—Treatment of candidemia and invasive candidiasis	− Candidemia − Invasive candidiasis	AmBisome	NCT00670657
2008	Pharmacokinetics study of liposomal paclitaxel in humans	Cancer	Paclitaxel	NCT00606515
2008	The effect of liposomal lidocaine on perceived pain in children during percutaneous interosseous pin removal in the outpatient setting	Pain	Lidocaine, placebo	NCT01542125
2011	Adult patients undergoing open colectomy MA402S23B303 (IMPROVE-open)	Bowel obstruction	IV morphine sulfate, Exparel (bupivacaine)	NCT01507246
2011	Anidulafungin versus amphotericin B safety in high risk hepatic transplant recipients	− Liver disease − Fungal infection	Anidulafungin, Liposomal amphotericin B	NCT01303549
2011	Endovenous versus liposomal iron in CKD	− Iron deficiency anemia − Chronic kidney disease	Gluconate iron, Active Comparator: endovenous iron	NCT01864161
2012	Efficacy of liposomal bupivacaine versus 0.25% bupivacaine for laparoscopic urologic surgery	Pain, postoperative	Bupivacaine, Liposomal bupivacaine	NCT02222129
2012	A health economic trial in adult patients undergoing ileostomy reversal MA402S23B501 (IMPROVE-IR)	Retraction of colostomy	Group 1 standard of care, Group 2 Exparel	NCT01509638

2012	A health economic trial in adult patients undergoing ileostomy reversal MA402S23B504	Retraction of colostomy	IV morphine sulfate or sponsor-approved equivalent, Exparel	NCT01509807
2012	TAP-patients with robotic assisted lap prostatectomy (TAP)	– Postsurgical pain – Analgesia – Prostatectomy	Exparel	NCT01582477
2012	Study of Exparel in patients undergoing breast augmentation	– Mammoplasty – Postoperative pain	Instillation-Exparel, infiltration-Exparel	NCT01582490
2012	Pain control in bariatric patients: Exparel (R) vs. the On-Q(R) pain ball	Obesity	Exparel, On-Q pain ball	NCT02142829
2012	Exparel infiltrated into the TAP for postoperative analgesia in unilateral abdominal hernia repair (702)	Hernia	Exparel	NCT01801124
2013	TAP block with liposomal bupivacaine versus bupivacaine in robotic hysterectomy	Acute pain	Bupivacaine, Liposomal bupivacaine	NCT02289079
2013	The effect of Exparel on post operative pain and narcotic use after colon surgery	– Postoperative pain – Colon cancer – Diverticulitis	Bupivacaine Bupivacaine liposome injection	NCT02052557
2013	PAIN—Postoperative Analgesia INvestigation	Postoperative pain	Exparel, bupivacaine hydrochloride, patient-controlled analgesia (PCA)	NCT02111746
2013	Subcostal TAP block with liposomal bupivacaine versus bupivacaine in donor nephrectomy patients: a prospective study	Acute pain	Liposomal bupivacaine, bupivacaine	NCT02287623
2013	Comparing post-op narcotic usage in patients receiving periarticular Exparel versus standard periarticular joint inj	– Arthroplasty – Knee replacement	Bupivacaine (liposome injectable suspension), Standard preparation	NCT02682498
2014	Efficacy of interscalene brachial plexus block with liposomal bupivacaine for arthroscopic shoulder surgery	– Shoulder pain – Rotator cuff tear	Bupivacaine, bupivacaine 0.25%	NCT01977352
2014	Trial liposomal bupivacaine following retropubic suburethral sling for stress urinary incontinence	Urinary incontinence, stress	Bupivacaine, placebo	NCT02296099
2014	Liposomal bupivacaine in total shoulder arthroplasty	Pain	Bupivacaine, ropivacaine	NCT02570022
2014	Liposomal bupivacaine for post operative pain after knee replacement surgery	Postoperative pain	Liposomal bupivacaine, bupivacaine HCl	NCT02274870

Continued

TABLE 4.7 Liposome-based products that have completed phase IV clinical trials.—cont'd

Year of start	Title of study	Health condition	Drug/Formulation	ClinicalTrials.gov identifier
2014	Liposomal bupivacaine (Exparel) for postoperative pain control for open and laparoscopic abdominal hernia repair	Pain	Bupivacaine, ketorolac	NCT02128646
2014	Liposomal bupivacaine for pain control following anterior cruciate ligament reconstruction	Anterior cruciate ligament rupture	Bupivacaine	NCT02189317
2014	Pharmacokinetic evaluation of Exparel in adults undergoing tonsillectomy	Pain	Exparel	NCT02199574
2014	Foot and ankle clinic application for liposomal related anesthetic	– Ankle arthrodesis – Hindfoot arthrodesis – Tibitalocalceal arthrodesis	Bupivacaine	NCT02586077
2014	TAP block with plain bupivacaine versus wound infiltration with Exparel for postoperative pain management	Postoperative pain	Plain bupivacaine, Liposomal bupivacaine	NCT02074709
2014	Exparel infiltration in anterior cruciate ligament reconstruction	Pain	Bupivacaine, ropivacaine	NCT02606448
2014	Peripheral nerve blocks versus periarticular local anesthetic injection for total knee arthroplasty (TKA)	Total knee arthroplasty	Peripheral nerve blocks with bupivacaine, intraarticular injection with ropivacaine, intraarticular injection with liposomal bupivacaine	NCT02223364
2014	Total hip arthroplasty (THA) lumbar plexus verses periarticular	Total hip arthroplasty	PNB bupivacaine, PAI ropivacaine, PAI liposomal bupivacaine, epinephrine, ketorolac	NCT02242201
2014	Safety and effectiveness of short-course AmBisome in the treatment of PKDL in Bangladesh	Post-kala-azar dermal leishmaniasis	AmBisome	NCT03311607
2015	Liposomal bupivacaine in simultaneous bilateral total knee arthroplasty	– Arthroplasty – Replacement – Knee pain	Bupivacaine	NCT02349542
2015	Improvement of pain following robotic sacrocolpopexy and rectocele repair for pelvic organ prolapse	Pelvic organ prolapse	Bupivacaine, placebo	NCT02449915
2015	Randomized trial of wound infiltration with extended-release bupivacaine before laparoscopic or robotic hysterectomy	– Postoperative pain, surgical procedure	Bupivacaine	NCT02352922

2015	Exparel for Pain After Tonsillectomy	– Tonsillectomy – Tonsillitis – Postoperative pain	Bupivacaine	NCT02444533
2015	Exparel for postoperative pain management in shoulder surgery	Fracture of shoulder and upper arm	Bupivacaine	NCT02472314
2015	The use of liposomated iron after bariatric surgery in patients that are receiving parentheral therapy with iron (BARIFER)	– Liposomated iron – Roux-en-Y gastric bypass – Parenteral iron therapy	Fisiogen ferro forte, Venofer	NCT02390921
2016	A clinical trial of two periarticular multimodal drug injections in total hip arthroplasty	Total hip arthroplasty	Bupivacaine, ropivacaine, clonidine, ketorolac, epinephrine	NCT02543801
2016	Hip arthroscopy pain control randomized control trial (RCT)	– Hip pain chronic – Anesthesia – Bupivacaine	Bupivacaine, liposomal bupivacaine	NCT02947178
2016	Adductor canal block versus periarticular bupivacaine injection in total knee arthroplasty	Osteoarthritis	Bupivacaine	NCT02777749
2016	TAP vs surgical infiltration of local anaesthetic in laparoscopic and robotic hysterectomy	Acute pain	Bupivacaine	NCT02519023
2017	Liposomal bupivacaine after arthroscopic rotator cuff repair	Rotator cuff tear	Bupivacaine	NCT03149887
2017	Liposomal bupivacaine versus standard bupivacaine in the adductor canal for total knee arthroplasty	Pain	Bupivacaine	NCT03182933
2017	Mixture of liposomal bupivacaine for TAP block for open hysterectomy	Hysterectomy	Bupivacaine	NCT03250507
2017	FLIPS: Ferfer liposomal iron performance study (FLIPS)	Iron deficiency anemia	Iron supplement	NCT03112187
2017	Randomized controlled trial for Exparel hip fracture	Hip fracture	Exparel	NCT03289858
2018	Liposomal amphotericin B (AmBisome) pharmacokinetics given as a single intravenous dose to obese patients (ASPEN)	Morbid obesity	Amphotericin B	NCT02320604

TABLE 4.8 Transfersomes undergoing different phases of clinical trials.

S. No.	Title of study	Health condition	Drug/ Formulation	Clinical trial phase	ClinicalTrials.gov identifier	Status
1	Ketoprofen in transfersome compared to oral celecoxib and placebo for pain associated with osteoarthritis of the knee	Osteoarthritis, knee	Ketoprofen	II	NCT00317733	Completed
2	Study of epicutaneously applied ketoprofen transfersome gel with or without combination with oral celecoxib for the treatment of muscle pain induced by eccentric exercise	Musculoskeletal pain	Celecoxib, ketoprofen	I	NCT01020279	Completed
3	TDT 067 onychomycosis study	Onychomycosis	TDT067, placebo, Transfersomes	III	NCT01145807	Unknown
4	Study of safety and efficacy of Diractin for the treatment of osteoarthritis (OA) of the knee	Osteoarthritis of the knee	Ketoprofen, placebo	III	NCT00722852	Completed
5	Safety and efficacy of two dosages of Diractin ® in osteoarthritis (OA)	Osteoarthritis of the knee	Ketoprofen, placebo, Celecoxib	III	NCT00716547	Completed

3.2.4 Niosomes

These are particular colloidal systems formed by nonionic surfactants, able to self-assemble to form closed bilayer structures. Morphologically, these are similar to liposomes but differ in chemical composition. They are also known as "nonionic liposomes." These have the potential to offer benefits in comparison to liposomes such as low cost, greater chemical and physical stability, extended shelf life, and wider formulation versatility [29]. These are of three types depending on their size: small unilamellar vesicles (0.025−0.05 μm), multilamellar vesicles (>0.05 μm), and large unilamellar vesicles (>0.10 μm). These are also considered as promising drug carriers for parenteral, peroral, dermal, and transdermal delivery of drugs [30]. Niosomal preparations that have reached clinical trial studies are enlisted in Table 4.9 (www.clinicaltrials.gov).

4. Applications of micro- and nanoparticles

Micro- and nanoparticles have many applications in drug delivery. The following are some of the major applications.

4.1 Cancer therapy

The current therapy used for the treatment of cancer patients possesses severe side effects due to nonspecific action of chemotherapeutics agents, thereby affecting the whole body. Cancer is a complex biological episode where cancerous cells divide and multiply very quickly in a short period of time. The prevailing chemotherapy is mainly aimed at the devastation of swiftly dividing cells. As a result, other normally proliferating cells of the body are also destroyed leading to serious side effects. So, these nanoparticles help

TABLE 4.9 Niosomal products undergoing different phases of clinical trials.

S. No.	Title of study	Health condition	Drug/Formulation	Clinical trial phase	ClinicalTrials.gov identifier	Status
1	Pharmacokinetics of melatonin niosomes oral gel in healthy volunteers	Pharmacokinetics of melatonin	Melatonin	I, II	NCT02845778	Unknown
2	*In vivo* investigation of novel nano-vesicles of salbutamol sulphate	– Drug effect – Pulmonary disease	Salbutamol sulfate, Niosomes	I	NCT03059017	Completed
3	Niosomal propolis as oral mucoadhesive film: in vitro, ex vivo and in vivo investigations	– Drug effect – Drug effect prolonged	Niosomal PPE oromucoadhesive film, Oromucoadhesive film	I	NCT03615820	Completed

to achieve targeted drug delivery at a specific tumor site or tumor cells bypassing the normal cells of the body. Many nanosystems have been tested to achieve targeted drug delivery in cancer patients [31]. For example, polymeric nanoparticles, microspheres, and liposomes are currently being tested for the delivery of chemotherapeutic agents. The polymeric nanoparticles containing docetaxel and cetuximab are under different phases of clinical trials. A microsphere containing doxorubicin for the treatment of hepatocellular carcinoma has completed clinical trial phase IV. Liposomes containing paclitaxel, doxorubicin, and bupivacaine have already completed phase IV of clinical trials.

4.2 Nanoparticles as diagnostic agents

The application of nanoparticles in diagnostic testing has been extensively explored in academics. Current technology in diagnostic testing mainly uses fluorescent markers, which pose many challenges such as vanishing of fluorescence with single use, problem in the matching of color, and prohibitive use of dyes caused by the bleeding effect. So, these problems can easily be eradicated by the use of fluorescent nanoparticles. Currently, theranostic particles (also known as smartdrugs) have gained a lot of attention due to their use in the treatment of diseases along with their diagnoses. Examples of theranostic particles include micelles and vesicles. So, this combination drug and imaging agent helps to monitor the pathway, targeted delivery of the nanoparticles, and drug action [31].

4.3 Treatment of acquired immunodeficiency syndrome

Human immunodeficiency virus (HIV) infection when not treated on time leads to a serious disease, i.e., acquired immunodeficiency syndrome. Previously, its treatment was harsh and included 30–40 tablets a day. But with the advancement in therapeutics, the number of tablets has been reduced to only a few per day. Efforts have been made by numerous researchers to make this therapy more effective by developing polymeric nanoparticles for the delivery of antiretroviral drugs. Depending on the stage of the HIV cycle, antiretroviral drugs are accordingly categorized. Usually, a combination of three or more drugs is used, called highly effective antiretroviral therapy to inhibit the progression of HIV and the development of resistance [31]. Currently, nanotechnology is playing a crucial role in the delivery of antiretroviral drugs and also improving patient

compliance. One of the major sites of HIV infection is the lymphoid tissues. Many reports have shown that antiretroviral drug-loaded nanoparticles were effective in targeting macrophages and monocytes during in vitro studies [32,33]. For example, Destache and coworkers developed three drug (i.e., ritonavir, lopinavir, efavirenz)-loaded nanoparticles using poly(lactic-*co*-glycolic acid), which provided sustained drug delivery for 28 days (4 weeks), and the free drug was eliminated from the body within 2 days (48 h) [34]. Another main site of HIV infection is the central nervous system leading to a severe HIV-associated neurocognitive disorder [35]. Numerous reports have shown the successful delivery of antiretroviral drugs via nanoparticles to the brain because nanoparticles easily cross the blood–brain barrier by phagocytosis/endocytosis [36,37].

4.4 Delivery of nutraceuticals

Nutraceuticals are the products derived from food and have additional health benefits in addition to their standard nutritional value. These are usually taken with allopathic medicines to add auxiliary health benefits and to minimize the risks associated with numerous chronic diseases. The oral bioavailability and efficacy of nutraceuticals are largely affected by factors that are the same as other drugs, namely aqueous solubility, food–matrix interactions, degradation or metabolism, and permeability of the epithelium. Mainly, nutraceuticals are lipophilic in nature such as vitamins A, D, E, and K (fat-soluble vitamins), lipids, and phytochemicals. Nanoparticle formulations have been targeted to improve the dissolution of nutraceuticals by increasing aqueous solubility [38–40].

Nutraceuticals are found to have many activities such as antiinflammatory, anticancer, antioxidant, neuroprotective, antiobesity, and antiangiogenic activity. Some examples of nutraceuticals are curcumin, omega-3-fatty acids, and resveratrol. Curcumin (i.e., diferuloylmethane) has very low oral bioavailability due to its low solubility in water. Numerous efforts have been made by researchers to improve its bioavailability by incorporating curcumin into different nanocarriers like polymeric nanoparticles, liposomes, and phospholipid vesicles [41–43]. Omega-3-fatty acids are mainly consumed as dietary supplements due to their cardioprotective and inflammatory activity. But these are highly prone to oxidation that results in unpleasant odor and taste. To overcome this problem and enhance the stability of omega-3-fatty acids, nanoemulsion formulation was developed in European Patent EP2563164A1 [44]. Resveratrol is a natural polyphenol, largely found in berries (blueberries, raspberries, etc.) and grapes. It has many activities such as antiinflammatory, cardioprotective, anticancer, and antioxidant activity. It also has low water solubility and oral bioavailability. To overcome these, many resveratrol-loaded nanocarriers have been developed such as polymeric nanoparticles, liposomes, nanoemulsions, etc. [31]. Table 4.10 summarizes nutraceutical (i.e., curcumin and omega-3-fatty acid)-loaded nanocarriers undergoing different phases of clinical trials.

5. Regulatory aspects of nanotechnology-based products

Over the last few decades, an exponential rise in nanotechnology-based products relating to cosmeceutical, nutraceutical, and pharmaceutical fields in the market has been seen. But most of the marketed products based on SLNs, NLCs, liposomes, niosomes, and nanoemulsions belong to the cosmeceutical field [14,15], and only a few belong to the pharmaceutical and nutraceutical fields.

SLN- and NLC-based marketed cosmeceutical products are listed in Tables 4.3 and 4.4, respectively. Examples of liposome-based marketed cosmeceutical products are Capture

TABLE 4.10 Nutraceutical-loaded nanocarriers undergoing clinical trials.

S. No.	Title of study	Delivery system	Nutraceutical	Clinical trial phase	ClinicalTrials.gov identifier	Status
1	Comparison of curcumin bioavailability	Liposome	Curcumin	Not applicable[a]	NCT03530436	Completed
2	Pilot study of curcumin for women with obesity and high risk for breast cancer	Nanoemulsion	Curcumin	Not applicable[a]	NCT01975363	Active, not recruiting
3	Curcumin in reducing joint pain in breast cancer survivors with aromatase-inhibitor induced joint disease	Nanoemulsion	Curcumin	Not applicable[a]	NCT03865992	Recruiting
4	Topical omega-3 fatty acids (REMOGEN ® OMEGA) in the treatment of dry eye (REMOTOP)	Microemulsion	Omega-3 fatty acids	Not applicable[a]	NCT02908282	Completed

[a] *Not applicable is used to describe trials without Food and Drug Administration-defined phases (as explained on www.clinicaltrials.gov).*

Totale, Dermosome, Decorte Moisture Liposome Face Cream, Decorte Moisture Liposome Eye Cream, Natural Progesterone Liposomal Skin Cream, C-Vit Liposomal Serum, Advanced Night Repair Protective Recovery Complex, Fillderma Lips Lip Volumizer, Lumessence Eye Cream, Russel Organics Liposome Concentrate, Clinicians Complex Liposome Face and Neck Lotion, and Kerstin Florian Rehydrating Liposome Day Crème.

Niosome-based marketed cosmeceutical products are Niosome+, Niosome+ Perfected Age Treatment, Mayu Niosome Base Cream, Anti-Age Response Cream, Identik Masque Floral Repair, Identik Shampooing Floral Repair, and Eusu Niosome Makam Pom Whitening Facial Cream.

Some of the examples of marketed cosmeceutical products based on nanoemulsions are Korres Red Vine Hair Sun Protection, Nanocream, Vital Nanoemulsion A-VC, Bepanthol-Protect Facial Cream Ultra, Coco Mademoiselle Fresh Moisture Mist, Precision-Solution Destressante Solution, Coni Hyaluronic Acid and Nanoemulsion Intensive Hydration Toner, Phyto-Endorphin Hand Cream, Nanovital Vitanics Crystal Moisture Cream, and Vitacos Vita-Herb Nona-Vital Skin Toner [14].

In the pharmaceutical field, extensive exploration in nanotechnology-based drug delivery systems has been attempted to overcome the significant challenges associated with conventional drug delivery systems. The major challenges include precise medicine, reduction in toxicity, and achieving required clinical needs. The evolution of these contemporary nanomedicines has shown globally a marked effect in the healthcare system. The main advantages of nanotechnology-based drug delivery systems are to deliver drugs at the target site in the body and a specific interaction of the drugs within the cells and tissues because of their nanoscaled size with large surface area. A large number of strategies can be adopted by using these nanotechnology-based drug delivery systems. For example, a number of manufacturing methods and materials can be used to overcome the problems associated with the stability of the formulation and also for targeted delivery of molecules to the specific site. The nanoscaled size of drug delivery systems also helps them to penetrate through the physiological barriers, thereby releasing the drug at the targeted site. Moreover, these systems also have a great ability to entrap a large amount of hydrophilic as well as hydrophobic drugs and to protect them from harsh environments. Also, at low therapeutic doses, high therapeutic effects can be achieved and side effects can be avoided by specific delivery of the drug [45].

Besides all of these advantages and strategies, the specific properties of nanomedicines (like physicochemical, biological, and physiological) have raised serious challenges for pharmaceutical industries as well the regulatory agencies. Although a large number of approved nanomedicines are available in the market, there is a lack of general protocols for characterization of these nanomedicines at preclinical developmental stage, which hinders their potential in clinical trials. For the evaluation of safety as well as toxicity and compatibility of nanomedicines, strategies for the evaluation of conventional medicinal products are frequently being used for nanomedicines. Until now, no global regulatory trends have been defined despite multiple efforts being done by various regulatory agencies. There is a strong need for cooperation between different regulatory agencies globally [45].

The main obstacle in the regulation of nanomedicine is related to their specific characteristics. The clinical use of these nanotechnology-based medicines fully relies upon the thorough evaluation, characterization, and understanding of their important properties because their properties can be easily changed via slight alteration in raw materials as well as slight modification in manufacturing process. Although these changes result in slight alterations in the structure, the biological properties and biodistribution patterns are highly affected. Moreover, there is a need to develop robust methods and quality control assays for the effective monitoring and characterization of physicochemical properties (e.g., size and its variability, morphology, and charge) of nanomedicines. Also, their performance in terms of drug release, protein binding, metabolism, and cellular uptake needs to be assessed. So, these methods help to understand the effect of modifications and alterations in the physicochemical properties of nanomedicines on their biological properties, therapeutic effect, and biocompatibility [45].

Nanomedicines have the tendency to be adsorbed into the plasma proteins and to combine with immune cells based upon their size and physicochemical properties. Therefore the crucial parameters that must be studied for safety evaluation and quality of nanomedicines in preclinical studies are discussed here in brief. The first parameter is the characterization of physicochemical properties that includes morphology, crystallinity, surface charge, deformability/rigidity, mean size, distribution, and aggregation of particle size, and their chemical and molecular structure to assess the intermediate product quality of the nanomedicine. Also, control of critical points of production need to be studied to assess the product quality of the nanomedicine. Second, contamination tests, including microbial contamination, endotoxin levels, and viral/mycoplasma levels, must be performed for evaluation of the quality and safety of nanomedicines. Third, immunology tests such as cytokine production, macrophage uptake, cytotoxicity of natural killer cells, complement activation, plasma protein binding, leukocyte proliferation, and in vivo immune response need to be performed for the assessment of immunogenicity (immunosuppression/immunostimulation). Moreover, biocompatibility studies are also required that include the assessment of platelet aggregation, coagulation time, and hemolysis. Lastly, in vivo toxicity studies (mainly toxicity to immune cells) and biodistribution studies (i.e., pharmacodynamics, pharmacokinetics, metabolism, and clearance) must be performed to assess the safety as well as toxicity of the nanomedicines. Furthermore, dosage regimen, therapeutic index, route of drug administration, and targeted disease are taken into consideration to assess toxicity during the development stage [45].

Another problem related to the development of nanomedicines and their clinical translation is their "manufacturing process," i.e., at production facilities and at scale-up stages, because of

the variety of properties of new materials. Therefore identification of critical points and their control during the manufacturing process are important [45].

In spite of all these difficulties, a substantial amount of nanotechnology-based pharmaceutical products is available in the market approved by the FDA and European Medicines Agency (EMA). Most of the marketed products are based on liposomes for the treatment of tumor diseases (examples are given under Section 3.2.1) [45]. Only two SLNs-based marketed products are found, i.e., "Cipro" and "Mucosolvan Retard" for oral administration [15].

Currently, to develop global regulatory approaches through the International Conference on Harmonization on nanomedicines, numerous initiatives are being taken by regulatory bodies and industries from the United States, Europe, and Japan. Despite this, different perspectives are prevailing regarding numerous procedures by the US FDA and EMA. Several harmonized approaches and sensitive assays are required aimed at aspects that certainly influence the in vivo safety and efficacy of nanocarriers. But the main hurdle associated with the implementation of a sensitive assay is its inability to detect nanocarriers at low concentrations and differentiate them from their aggregates and metabolized forms. To overcome this, alternate techniques such as fluorescence or cell imaging methods have been investigated. Another problem in regulating nanomedicines is to furnish the nature of data before and during the product life stage, thereby requiring in vivo and clinical studies. Currently, a working group has been designed by the EMA to harmonize the development of leading nanomedicines and minimize the impact of the main barriers that exist in the development process. This working group made many determinations regarding the quality, safety, and efficacy of nanomedicines along with the preparation of documents, specifically "orientation documents," which cover the important aspects to be taken into account by applicants during the development of nanomedicines. Also, the regulatory agencies from different countries such as the EMA, the US FDA, and the Pharmaceuticals and Medical Devices Agency/Ministry of Health, Labor, and Welfare (PDMA/MHLW) have worked in sync to accomplish universal perspectives in the development of nanomedicines. On the other hand, pharmaceutical companies have also made efforts in the "proof-of-concept" and clinical development of these nanomedicines. Collectively, these efforts will help to achieve procedures for the identification of safety and efficacy of nanomedicines.

In addition, pharmacoeconomic studies are also important before commercializing any nanomedicine to assess their social and economic values in comparison to existing treatments. For this, crucial indices such as the rise in quality-adjusted life expectancy years and/or expenses related to succeeding hospitalizations in the future shall be taken into account in the development of nanomedicines.

Although various initiatives have been taken by the different regulatory bodies collectively, few nanotechnology-based drug delivery systems enter the market. This may be due to lack of harmonized regulatory approaches in nanomedicines and expensive costs involved at the clinical development stage [45].

6. Conclusion

Over the last few decades, nanotechnology in cosmetics, nutraceuticals, and pharmaceuticals has been regarded as a most promising and transforming field. Researchers have developed various novel nanocarriers (i.e., vesicular and nonvesicular) to overcome the limitations and disadvantages associated with conventional drug delivery systems. Although these novel nanocarriers possess advantages over conventional drug delivery systems like

biocompatibility, better stability, high drug loading, and targeted delivery, the toxicity and safety of nanocarriers because of their nanosize are matters of utmost concern among researchers, industry, and various regulatory bodies. Due to a lack of global regulatory guidelines, high cost involved in R&D, complex clinical trial regulations, only a limited number of nanocarriers have reached the market in the pharmaceutical field. However, a large number of nanotechnology-based marketed products are available in the cosmetic field because they do not require human clinical trials. Many initiatives have been taken by regulatory bodies from different countries such as the US FDA, EMA, and PDMA/MHLW to achieve a global prospective in the development of nanotechnology-based products in the pharmaceutical field. These initiatives will surely make an influential positive contribution to nanomedicines by fabricating and implementing comprehensive regulatory policies globally.

References

[1] De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. Int J Nanomed 2008; 3:133–49.

[2] Mudshinge SR, Deore AB, Patil S, Bhalgat CM. Nanoparticles: emerging carriers for drug delivery. Saudi Pharm J 2011;19:129–41.

[3] Wilczewska AZ, Niemirowicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. Pharmacol Rep 2012;64:1020–37.

[4] Umscheid CA, Margolis DJ, Grossman CE. Key concepts of clinical trials: a narrative review. Postgrad Med 2011;123:194–204.

[5] Lawrence MJ. Microemulsions as drug delivery vehicles. Curr Opin Colloid Interface Sci 1996;1: 826–32.

[6] Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech 2015;5:123–7.

[7] Singh Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK, Chourasia MK. Nanoemulsion: concepts, development and applications in drug delivery. J Control Release 2017;252:28–49.

[8] Chen X, Peng L, Gao J. Novel topical drug delivery systems and their potential use in scars treatment. Asian J Pharm Sci 2012;7:511–20.

[9] Vaghasiya H, Kumar A, Sawant K. Development of solid lipid nanoparticles based controlled release system for topical delivery of terbinafine hydrochloride. Eur J Pharm Sci 2013;49:311–22.

[10] Muller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery-a review of the state of the art. Eur J Pharm Biopharm 2000;50:161–77.

[11] Mehnert W, Mader K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev 2001;47:165–96.

[12] Butani D, Yewale C, Misra A. Topical amphotericin B solid lipid nanoparticles: design and development. Colloids Surfaces B Biointerfaces 2016;139:17–24.

[13] Severino P, Andreani T, Macedo AS, Fangueiro JF, Santana MH, Silva AM, Souto EB. Current state-of-art and new trends on lipid nanoparticles (SLN and NLC) for oral drug delivery. J Drug Deliv 2012:1–10.

[14] Kaul S, Gulati N, Verma D, Mukherjee S, Nagaich U. Role of nanotechnology in cosmeceuticals: a review of recent advances. J Pharm 2018;2018:1–19.

[15] Battaglia L, Ugazio E. Lipid nano- and microparticles: an overview of patent-related research. J Nanomater 2019;2019:1–22.

[16] Wissing SA, Kayser O, Muller RH. Solid lipid nanoparticles for parenteral drug delivery. Adv Drug Deliv Rev 2004;56:1257–72.

[17] Escobar-Chavez J, Diaz-Torres R, Rodriguez-Cruz I, Dominguez-Delgado C, Sampere Morales R, Angeles-Anguiano E, Melgoza-Contreras L. Nanocarriers for transdermal drug delivery. Res Rep Transdermal Drug Deliv 2012;1:3–17.

[18] Joshi M, Patravale V. Nanostructured lipid carrier (NLC) based gel of celecoxib. Int J Pharm 2008;346: 124–32.

[19] Nanjwade B, Kadam V, Manvi F. Formulation and characterization of nanostructured lipid carrier of ubiquinone (Coenzyme Q10). J Biomed Nanotechnol 2013;9:450–60.

[20] Kim H, Lee JH, Kim JE, Kim YS, Ryu CH, Lee HJ, Kim HM, Jeon H, Won HJ, Lee JY, Lee J. Micro-/nano-sized delivery systems of ginsenosides for improved systemic bioavailability. J Ginseng Res 2018;42:361–9.

[21] Jawahar N, Meyyanathan S. Polymeric nanoparticles for drug delivery and targeting: a comprehensive review. Int J Health Allied Sci 2012;1:217–23.

[22] Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res 2016;33:2373–87.

[23] Varde NK, Pack DW. Microspheres for controlled release drug delivery. Expert Opin Biol Ther 2004;4: 35–51.
[24] Sinha VR, Trehan A. Biodegradable microspheres for protein delivery. J Control Release 2003;90:261–80.
[25] Mao S, Guo C, Shi Y, Chiu Li L. Recent advances in polymeric microspheres for parenteral drug delivery. Part 1. Expert Opin Drug Deliv 2012;9:1161–76.
[26] Sala M, Diab R, Elaissari A, Fessi H. Lipid nanocarriers as skin drug delivery systems: properties, mechanisms of skin interactions and medical applications. Int J Pharm 2018;535:1–17.
[27] Rai S, Pandey V, Rai G. Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: the state of the art. Nano Rev Exp 2017;8:1–18.
[28] Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes – novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release 2000;65:403–18.
[29] Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm 1998;172: 33–70.
[30] Khanam N, Alam M, Sachan A, Sharma R. Recent trends in drug delivery by niosomes: a review. Asian J Pharmaceut Res Dev 2013;1:115–22.
[31] Rizvi SAA, Saleh AM. Applications of nanoparticle systems in drug delivery technology. Saudi Pharm J 2018;26:64–70.
[32] Shah LK, Amiji MM. Intracellular delivery of saquinavir in biodegradable polymeric nanoparticles for HIV/AIDS. Pharm Res 2006;23:2638–45.
[33] Mallipeddi R, Rohan LC. Progress in antiretroviral drug delivery using nanotechnology. Int J Nanomed 2010;5:533–47.
[34] Destache CJ, Belgum T, Christensen K, Shibata A, Sharma A, Dash A. Combination antiretroviral drugs in PLGA nanoparticle for HIV-1. BMC Infect Dis 2009;9:198.
[35] Spudich SS, Ances BM. Central nervous system complications of HIV infection. Topics Antivir Med 2011;19: 48–57.
[36] Rao KS, Ghorpade A, Labhasetwar V. Targeting anti-HIV drugs to the CNS. Expert Opin Drug Deliv 2009; 6:771–84.
[37] Nowacek AS, McMillan J, Miller R, Anderson A, Rabinow B, Gendelman HE. Nanoformulated antiretroviral drug combinations extend drug release and antiretroviral responses in HIV-1-infected macrophages: implications for neuroAIDS therapeutics. J Neuroimmune Pharmacol 2010;5:592–601.
[38] Acosta E. Bioavailability of nanoparticles in nutrient and nutraceutical delivery. Curr Opin Colloid Interface Sci 2009;14:3–15.
[39] McClements DJ. Nanoscale nutrient delivery systems for food applications: improving bioactive dispersibility, stability, and bioavailability. J Food Sci 2015;80: N1602–11.
[40] McClements DJ, Li F, Xiao H. The nutraceutical bioavailability classification scheme: classifying nutraceuticals according to factors limiting their oral bioavailability. Ann Rev Food Sci Technol 2015;6: 299–327.
[41] Mohanty C, Sahoo SK. The in vitro stability and in vivo pharmacokinetics of curcumin prepared as an aqueous nanoparticulate formulation. Biomaterials 2010;31: 6597–611.
[42] Carvalho DdM, Takeuchi KP, Geraldine RM, Moura CJd, Torres MCL. Production, solubility and antioxidant activity of curcumin nanosuspension. Food Sci Technol 2015;35:115–9.
[43] Goindi S, Kaur A, Kaur R, Kalra A, Chauhan P. Nanoemulsions: an emerging technology in the food industry. In: Emulsions. Elsevier; 2016. p. 651–88.
[44] Bromley PJ. Nanoemulsion including sucrose fatty acid ester. 2013. http://www.google.com/patents/EP2563164A1?cl=en.
[45] Sainz V, Conniot J, Matos AI, Peres C, Zupancic E, Moura L, Silva LC, Florindo HF, Gaspar RS. Regulatory aspects on nanomedicines. Biochem Biophys Res Commun 2015;468:504–10.
[46] www.clinicaltrials.gov. 2019. https://clinicaltrials.gov/ct2/results?cond=&term=microemulsions&cntry=&state=&city=&dist=.
[47] www.clinicaltrials.gov. 2019. https://www.clinicaltrials.gov/ct2/results?cond=&term=ethosomes&cntry=&state=&city=&dist=.
[48] www.clinicaltrials.gov. 2019. https://www.clinicaltrials.gov/ct2/results?cond=&term=liposomes&cntry=&state=&city=&dist=.
[49] www.clinicaltrials.gov. 2019. https://www.clinicaltrials.gov/ct2/results?cond=&term=niosomes&cntry=&state=&city=&dist=.
[50] www.clinicaltrials.gov. 2019. https://www.clinicaltrials.gov/ct2/results?term=transfersome.
[51] www.clinicaltrials.gov. 2019. https://clinicaltrials.gov/ct2/results?cond=&term=solid+lipid+nanoparticles&cntry=&state=&city=&dist=.
[52] www.clinicaltrials.gov. 2019. https://www.clinicaltrials.gov/ct2/results?cond=&term=microspheres&cntry=&state=&city=&dist=.