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REVIEW

Liposomes-The 21st Century's Drug Delivery System: Developments in the Last Two Decade

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Liposomes have been thoroughly investigated and are utilized for various illnesses for the past few decades starting from its first discovery in 1961. Since then, therapeutic efficiency of liposomes is enhanced by increasing drug absorbance while fast deterioration and adverse effects are avoided or minimized. This will extend the biological halfway life. Liposomes are more attractive for usage as drug delivery carriers with all of these characteristics and versatility to modify their surface to create additional specific functionalities. In various phases of research, there are numerous new liposomal compositions that improve the therapeutic efficiency of new and old medicines used in pre-clinical and clinical studies. Current multimodal imaging advances aimed at better diagnosing and monitoring liposome therapies as diagnostic tools. Liposomes are major possibilities for medication delivery improvement. Recent researches show that the liposomes can be taken widely in cancer treatments. The primary properties of these structures include minimal toxicity, cytocompatibility, reduced clearance rates, tissue targeting and sustained drug release. Liposomes offer a variety of benefits as shown by approval of Doxil, as compared to traditional chemotherapy with free medication treatment. There are a multitude of liposomes depending on their size, lamellar number, shape and composition. Diagnostic, therapeutic, improved vaccination are covered by clinical use of these systems. Drug and gene delivery are two therapeutic aspects, where due to their unique characteristics liposomes might be beneficial. Several illnesses have been examined with respect to the participation of liposomes, with some good results. Cancer is a life-threatening disease. These structures have been examined in this respect, both in imaging and in chemotherapy. These investigations have resulted in different liposome compositions in different clinical stages. We take this great opportunity to present various surface functionalization strategies and bio-applications of liposomes developed during the last two decades covering the notable work published from 2011 to 2021 in this review. In addition, we provide opinions on the liposome industry, its commercial market and the prospective developments in the field of liposome technology. It is anticipated that this review will serve as a valuable resource, fostering interest and engagement among scientists worldwide in the field of liposome research.

Keywords: Liposome, Preparation, Bioimaging, Drug delivery system, Types of liposomes, Applications.

INTRODUCTION

A number of nanoparticulate materials *e.g.*, dendrimers, nano-gold shells, nano-emulsions, drug-polymer conjugates, drug-antibody conjugates, quantum dots, aptamer-gated, nano-vehicles and solid lipid nanoparticles, liposomes, *etc.* have been designed over the last few decades for biological applications. Out of all these liposome makes its own positions and studied most by the scientist throughout the world and gained tremendous commercial success in pharma industries. Liposomes are lipid-based vesicles having bilayer or multilayer depending upon their manufacturing methods. Liposomes has attracted many scientists to its fascinating world from the very beginning of its discovery in 1961 by Alec D Bangham, British haematologist at the Babraham Institute, in Cambridge, U.K.. Lipids are one such biomolecules which has lots of resemblance with the cell membrane and this unique property make them highly suitable for biological applications. Due to the resemblance of cell membrane sometimes liposomes are also known as biomimetic membrane and various theoretical as well as practical experiments show that liposomes can be applied to mimic cell membrane thus known as artificial cells also [1-5]. A great progress has been made in the field of liposome for the last two decades. Liposomes are in general spherical bilayer having

two lipid layers where the head and tail groups of the lipids face opposite to each other and contain an aqueous core in between the bilayer. Due to the presence of both hydrophobic and hydrophilic portion in the lipids, liposome can interact with both hydrophobic as well as hydrophilic molecules. Thus, liposomes can be used to carry both lipophilic as well as lipophobic materials *e.g.*, drug molecules, biomolecules, *etc.* Based on the size and lamellarity, liposomes have been categorized into various types *e.g.* small unilamellar liposome, large unilamellar liposome, giant unilamellar liposome, multilamellar liposomes [6-9]. Liposomes due to many interesting properties *e.g.* biocompatibility, complete biodegradability, non-toxic, flexible and non-immunogenic, easy to prepare, easy surface functionalization for targeting, amphiphilicity, have been used in various branches of biomedical sciences *e.g.* drug delivery, targeted drug delivery, stimuli responsive drug delivery, efficacy improvement for drug, solubility enhancement of poorly soluble drugs, biomolecules delivery, diagnostic imaging, theranostics, gene delivery, vaccine delivery, protein and peptide delivery, *etc.* [10-13].

A number of drug delivery system (DDS) have been successfully prepared using liposomes to deliver various types of drugs including chemotherapeutic, anti-fungal, sedative, anti-inflammatory, corticosteroids, anesthetics, anti-infectives, *etc.* Doxil which is a liposomal doxorubicin developed by Sequus Pharmaceuticals in 1995 become the first liposome-based nano-drug formulations and with its introduction in the market, liposomal drug delivery system takes an exciting turn in the field of clinical applications of liposome. After that a number of drugs *e.g.* daunorubicin, mifamurtide, irinotecan, amphotericin B, verteporphin, morphine sulfate, have been successfully formulated as liposomal drug and all are commercially available. Several unique technologies *e.g.*, DepoFoam™ Liposome Technology (developed by Pacira Pharmaceuticals), Lysolipid Thermally Sensitive Liposome (LTSL) Technology have been invented utilising only liposome. Many pharmaeutical companies are investing billion dollars on liposome to invent new kind of drug delivery systems, which indicates the importance of research in liposome-based medications. Due to the overwhelming demand of liposomes for the medicinal applications various strategies have been adopted in the last two decades for the preparation of liposomes *e.g.* ethanol injection method, ether injection method, thin film hydration, free drying method, extrusion method, sonication technique, micro-emulsification method, dialysis, spray drying, gel hydration, *etc.* [14-20].

One of the major objectives of the liposome-based drug delivery system is to deliver the drug molecules as per the demands at the disease site and when it comes to anticancer drugs, the on-demand drug delivery become more important. The slow and steady release of the drug have many advantages *e.g.* reduce side effect, prolonged circulation time, low dose requirement, reduction of multiple dose, *etc.* over the conventional fast release of the naked drugs [21-25]. Targeted and controlled delivery of the drug molecules can be achieved if the liposomes are stimuli responsive. The cargo molecules inside liposomes can be delivered at the desired disease site as per the requirement by applying a number of external stimuli *e.g.* redox, pH, temperature, photo/light, magnetic, ultrasound, electrical, *etc.* [26-30]. Among all the external stimuli, pH gradients have been used for a long time to design stimuli-responsive drug-delivery systems. The reason behind the widely used pH-responsive drug-delivery system is that the pH of human body varies widely from pH ~3 to pH ~7.4, which gives an opportunity to design a system that will response towards pH change. A number of stimuli responsive liposomal drug delivery systems *e.g.* ThermoDox, Visudyne, Opaxio, Cornell dots, AuroShell, NanoXray products, NanoTherms have been formulated to deliver a number of drugs *e.g.* doxorubicin, curcumin, zoledronic acid and IR-780, camptothecin, paclitaxel, si-RNA, dexamethasone, diclofenac sodium and ciprofloxacin, irinotecan, vincristine, mifamurtide, L-asparaginase, daunorubicin, by several renowned pharma companies over the last decades to address targeted controlled release of and some of them have entered into the clinical trials [20,31-35]. A number of liposomal drug delivery systems *e.g.* Atragen (Tretinoin), Amphotec (Amphotericin B), Ambisome (Amphotericin B), Abelcet (Amphotericin B), DepoDur (Morphine), Daunoxome (Daunorubicin citrate), Depocyt (Cytarabine), Estrasorb (estradiol), Mikasome (Amikacin), Nyotran (Nystatin), Topex Br (Terbutaline sulphate) Ventus (Prostoglandin-E1) are already approved and commercialized during the last two decades and many more [*e.g.* Lipoplatin (Regulon), L-annamycin (Callisto), Alocrest (Talon), Brakiva (Talon) Exparel (Pacira), Arikace™ (Insmed)] are in various stages of clinical trials and awaiting to become commercialized [36-40]. All these indicate an exciting future is awaiting in liposome-based medications.

Due to the overwhelming interest in liposome-based DDS and its growing demand in the pharma industries makes the manufacturing of liposomes an interesting subject for many scientists. Several reviews are published in the last decades to address the preparation, functionalization and characterization of liposomes. The most common and well-known lipids which are used for the formulations of liposomes are 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dihexanoyl-sn-glycero-3-phosphocholine (DHPC), 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC), 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine (POPC), 1-palmitoyl-2-[12′-(palmitoyloxy)octadecanoyl]-sn-glycero-3-phosphoholine (PAHSA PC), 1-behenoyl-2-hydroxy-sn-glycero-3-phosphocholine (Lyso PC), L-α-phosphatidylcholine (95%) (egg, chicken), L-α-phosphatidylcholine (Soy-PC), L-α-lysophosphatidylcholine (egg, chicken), L-α-phosphatidylcholine (Heart, Bovine), L-α-phosphatidylcholine, hydrogenated (Soy), L-α-phosphatidylcholine, hydrogenated (egg, chicken), L-α-lysophosphatidylcholine (Soy) 1,2-di-O-octadecenyl-3-trimethylammonium propane (chloride salt) (DOTMA), dimethyldioctadecylammonium (bromide salt) (DDAB), 1,2-dioleoyl-3-trimethylammonium-propane (chloride salt) (DOTAP), 1,2-dioleyloxy-3-dimethylaminopropane (DODMA), N-(4-carboxybenzyl)-N,N-dimethyl-2,3-*bis*(oleoyloxy)propan-1-aminium (DOBAQ), 3β-[N-(N′,N′-dimethylaminoethane)-carbamoyl]cholesterol hydrochloride (DC-Cholesterol·HCl) [41-43].

Although the liposome has many fold advantages, but they also suffer from many drawbacks. One of the, major drawbacks of bare or naked liposome is their premature and fast release of the cargo molecules before reaching to the disease cite which leads to many side effects with respect to chemotherapeutic drug delivery [44-46]. Chemotherapeutic drugs exhibit a lack of selectivity in targeting cancer cells, resulting in the unintended destruction of healthy cells. This indiscriminate cytotoxicity has prompted the removal of numerous drugs from the market shortly after their introduction, causing significant financial setbacks for pharmaceutical companies. To address these problems many pharma companies have invested billion dollars to liposome research and the surface modification and functionalization of liposome become the hot topic of research in the past decade of biomedical research [47-50]. The liposome research in the past decade have reached a great height and various preparation methodology have been invented to create several advanced liposome formulations *e.g.* archaeosomes, niosomes, novasomes, transfersomes, ethosomes, virosomes, cryptosomes, emulsomes, vesosomes, genosomes, *etc.* [51-57] to address these challenges associated with bare liposomes. Many surface functionalization strategies have been adopted to decorate the liposome surface to remove the unwanted leakage of the cargo molecules and making it stimuli responsive [58,59]. Liposomes due to their multimodal advantages *e.g.* cargo protection, amphiphilic carrier, controlled cargo release, tunable size, tunable surface properties (charge, zeta potential *etc.*), reduction in dosage, biodegradable, biocompatible, non-immunogenicity, various administration routes, reduce cytotoxicity, increment in half-life of drug molecules, increased efficiency is already used for many applications in biomedical sciences *e.g.* synthetic cells, diagnostic imaging, targeted drug delivery, nanoreactors, biocatalysis, chelation therapy (treatment for heavy metal poisoning *e.g.* iron, mercury, arsenic, lead, *etc.*), gene therapy, enzyme replacement, protein delivery, cosmetic delivery and many more are yet to come [13,60-62]. A bright future is waiting for all of us in liposome research, which may bring lots of novel applications in science and technology. Liposome can bring the next generation medications to cure many diseases and may help to understand the various complex biological processes in more detail. Although several reviews have already been written and available in virtual space but as a never-ending process and huge commercial as well as scientific importance liposomes science must be explored continuously and needs to be revisited repeatedly [63-67]. Thus, this review is an attempt to highlight the recent progress of various preparation strategy of liposome, their surface functionalization and various biomedical applications. The next sections describe the recent progress in liposome formulations, then it discuss various types of liposomes and their surface functionalization and their applications The review also talks about the imminent opportunity and future directions of liposome technology to formulate the ideal nano-drug delivery system, which can revolutionize the current state of medical treatment and may create a history in medical science. It also report about various futuristic applications of liposomes other than biomedical briefly. It is our pleasure to write this review and hope this will attract the audience from many branches of medical science and will help the researcher over the globe.

Preparations

Ethanol injection method: One of the easiest and widely used techniques for the preparation of liposomes, first reported in 1973 by Batzri & Korn, has been used in industrial scale since 1990 to produce liposome. At the beginning, the method was employed to prepare liposome in the range 120 g to 15 kg but later on after several modification, it's scaling up ability increases up to several hundred kilograms. It also become very popular technique among the researcher due to its many advantages *e.g.* rapid, simple, low-cost, easy to handle, *etc.* In this method at first, a desired amount of lipids are dissolved in ethanol and then the lipid solution is injected through s syringe into the magnetically stirred buffer solution at above the lipids phase transition temperature. This technique most produce small unilamellar vesicle along with few large unilamellar vesicle. Although it has many advantages, but the technique suffers from many drawbacks *e.g.* heterogeneous size distribution, diluteness of the liposome, difficulty in removal of the solvent completely due to the formation of azeotropic mixture of ethanol and water, possibility of inactivation of biomolecules in presence of trace amount of ethanol, *etc.* Various modifications of this technique have been done to address these challenges over the last few decades and several injection techniques is also invented *e.g.* crossflow injection technique which can prepare liposome in bulk scale. The as prepared liposome can be characterized by a number of techniques *e.g.*, SEM, TEM, AFM, *etc.* These techniques are very useful for the liposome encap-sulation of a range of drug molecules, small molecule, biomole-cules, *etc.* [68-72].

Ether injection method: Another widely used technique for the preparation of liposome is ether injection method. This technique is also similar to ethanol injection methods. In this method, a desired amount of lipids are dissolved in ethers and slowly injected through syringe keeping the lipids in aqueous buffer solution at above the lipids phase transition temperature. Next the solvent is removed from the mixture by evaporation under reduced pressure which leads to liposome powder. The optimum liposome concentration depends on several parameters *e.g.*, concentration of lipids in ether, rate on injection, temperature of the buffer solution, volume of the injection, *etc.* Generally, the rate of injection is kept at 0.1-0.2 mL/min and the lipid concentration is kept around 1-2 μM. It can produce both SUV and LUV but not MLV. Although the technique is very simple and cost effective similar to ethanol injection technique, but it has many drawbacks *e.g.* heterogeneous size distribution, contamination due to ether, high temperature requirement, *etc.* To overcome these challenges, many modifications *e.g.* by changing the solvent to lipid ratio, changing the method of injection, injection time, *etc.* have been implemented over the decades [10,73-77].

Thin film hydration method: By thin film hydration method one can prepare both unilamellar as well as multilamellar liposomes and this makes the technique more versatile. This technique is superior over other two techniques described above with

respect to stability of the liposome, encapsulation efficiency, encapsulation capacity, homogeneous size distribution (after extrusion), rigidity, *etc.* In this method, first, the lipids and other chemicals are dissolved in an organic solvent (*e.g.* chloroform) in a round bottom flask and then the organic solvent was evaporated slowly, which forms a thin film over the bottom surface of the conical flask. Hydration is generally carried out by aqueous buffer solution at desired pH (normally the pH is kept near about 7.4 to avoid the disintegration of the liposome). The buffer solution is vortex for few minutes and then stirred magnetically over few hours to get the desired liposomes. The liposomes can be made homogeneous by utilizing extrusion. Lipid composition can be varied to get the desired concentration of liposomes [78-80].

Freeze drying method: Various techniques have been developed to address many challenges during liposome preparation and one such approach is freeze drying method. This method involves three steps: (i) Preparation of homogeneous lipid solution, (ii) Freeze drying of the lipid solution to prepare liposomes, and (iii) Reconstitution or hydration of lyophilized product. First, the required lipids component needs to be dissolved in the required solvent and a homogeneous single-phase solution to be obtained. Next the solution is filtered through the desired filter paper to remove the solid particles if any. The solution is then transferred to the freezing vial and it is freeze at -20 ºC (primary drying at very low pressure to supply heat required for sublimation) and -45 ºC (secondary drying to allow the water desorption), respectively. This lyophilized product is stable and can be store for long time under proper sealed vial. This can be hydrated using water buffer to get homogeneous liposome solution, which can be used for further study. This method has many advantages *e.g.* high encapsulation efficiency, stability for long duration, controlled size distribution, easy cargo loading, high loading capacity, *etc.* and it is now highly accepted by many pharma industries [81-85].

Extrusion method: Size of the liposome is very important with respect to its biological applications. Although three types of liposomes are available but large unilamellar vesicle and multilamellar vesicle are not suitable due to their large size. During the liposome preparation by the techniques discussed above always few amount of LUV and MLV are produced which imparts some problem during their biological application hence the SUV needs to produce exclusively. In this respect, extrusion technique is highly beneficial and used widely for the preparation of SUV. In this method, a number of membranes of various size cut off is used to filter the as prepared liposome to get the desired size. In this technique, the as-prepared liposome suspension (by thin film hydration, ethanol injection or ether injection method) is passed through the membrane of desired pore size (pore size of the membrane can vary from 100 nm to 1000 nm) for multiple times under a constant flow rate (flow rate can be varied) until the required size is obtained. Several parameters (flow rate, membrane pore size, temperature, *etc.*) play important role on the extrusion process of liposome preparation. After passing through each time, the size of the liposomes should be evaluated through dynamic light scattering or transmission electron microscopy. The main advantage of this technique is that it can tune the size of the liposome [86-89].

Sonication technique: Sonication helps in two ways during the preparation of liposomes. It breaks the larger liposomes (*e.g.* MLVs and LUV) to SUVs reducing size of the liposomes and make it homogenous. In this technique the lipids are dissolved in a desired solvent and filtered to remove the unwanted particle present if any. Then the solvent is evaporated to dryness at temperature above the phase transition temperature of the lipids to produce a thin film of the lipid layer in the container. The thin film can be prepared by other methods also *e.g.* lyophilization *etc.* Further the thin film is dried under high vacuum to remove any traces of organic solvents. The thin film should be rehydrated with aqueous buffer and vortexed for 1-2 min to get a milky suspension of the liposome. After vortexing the liposomal suspension is sonicated using various types of sonicator (water bath sonicator, probe sonicator). However, water bath sonicator is more helpful as it produces less sound and heat whereas probe sonicator creates heavy noise and more heat. This technique generally produces liposome of size 20-100 nm which is highly suitable for biological experiments. Overall, this technique is suitable for the preparation of small unilamellar liposome without using any toxic organic solvents [90-93].

Micro-emulsification method: This technique is suitable for the preparation of small unilamellar vesicle having small size staring from multilamellar vesicle. This method has two steps, hydration of the lipid thin films followed by miroemulsification through a microemulsifier. In first stage, lipid [(or lipid mixtures *e.g.* lipid + cholesterol)] are dissolved in an organic solvent (*e.g.* chloroform) and then solvent is evaporated slowly using rotavapor to make a thin film of the lipids. It is hydrated then with aqueous buffer to get the hydrated lipid suspension, which generally contain MLVs having large size. This hydrated lipid suspension is then sent through the microemulsifier. Microemulsifier has two parts, pump and interaction chamber. The instrument pumps the suspension under very high pressure at very high speed. Then the fluid is divided into two parts and entered the microchannels which allow the two parts of fluid two colloid at very high speed and it entered the collection chamber. The collected liposomes can be sent through the microemulsifier repeatedly in the same way until the desired size and morphology is obtained. This method has advantages *e.g.* liposome size can be tuned. morphology of the liposome can be controlled, by increasing the lipid concentration, one can get the desired liposome concentration, *etc.* [94-96].

Dialysis method: This method generally produces large unilamellar vesicle, but it can give small unilamellar vesicle after the extrusion. This method has four steps preparation of the lipid mixture, thin film making, hydration of the lipid film and dialysis. At first, the desired lipids are dissolved in organic solvents and the solvent is evaporated to make the thin film of the lipids. Hydration is carried out by aqueous buffer at a particular pH and then the hydrated lipids are vortexed to get the lipid suspension. Finally, this liposome suspension is dialyzed using the desired membrane having a particular molecular weight cut off in a buffer solution. The buffer solution is replaced after a certain interval of times. The liposome solution is then sent through the extruder to get the desired size. This method helps to control the liposome size distribution [97-99].

Spray drying: This is another easy and effective method of liposome preparation at laboratory scale. In this method, many parameters can be easily controlled and optimized as per the requirement. Briefly in this method, the desired lipid or lipid mixtures are dissolved in an organic solvent (*e.g.* $CHCl_3$ or CH_2Cl_2) to get the required concentration of the lipids. By changing the solvent volume or lipid amount the concentration of the lipids can be tuned easily. The lipid solution is then sonicated for 15 min to get the homogeneous lipid concentration. After sonication, the lipoid solution is sprayed through a spray drier into the drying chamber with a controlled flow rate at a controlled temperature. The temperature of both inlet and outlet of the spray dryer must be maintained properly to get the best results. The spray dried product is then collected from the inner surface of the chamber and hydrated with the buffer solution of needed pH and finally preserved in refrigerator for future use. The technique is very effective for the encapsulation of a number of cargo molecules [100-102].

Gel hydration method: This is a good technique for the encapsulation of a number of cargo molecules *e.g.* drugs, biomolecules, nanoparticles, *etc.* This technique is widely used in many R&D laboratory for day-to-day purpose. First the liposome suspension is prepared through thin film hydration technique and lyophilized under reduced pressure. Gel can be prepared from a number of gel formulating polymers (*e.g.* Carbopol 940 polymer). Once the gel is prepared, lipid suspension is added to the gel and stirred thoroughly to mix well and hydrated again with buffer solution and kept at room temperature for overnight. Liposome gel is then preserved at refrigerator for future use. This technique is superior over other techniques with respect to encapsulation efficiency, versatility stability, *etc.* [103-106].

Types of liposomes

pH sensitive liposomes: Controlled release of drugs from liposome is one of the prime requirements of a liposome-based DDS and to achieve the controlled release, a number of external stimuli can be used. One such stimuli which is used widely in the field of controlled drug delivery is pH. So, pH sensitive liposomes are of great importance with respect to its medicinal applications. The pH of the cancerous cells can vary from 1.2-5.6 depending on the type and locations of cancer. The basic mechanism behind the pH sensitive liposome is based on the stability and degradation of the liposome at neutral and low pH condition respectively [107,108]. During the cargo loading in liposome the pH is generally kept at physiological pH so that lipsome can be intact until it reaches to the disease cite. Liposome then degraded at low pH inside cancerous cells. The degradation can be controlled by surface functionalization of the liposomes. A number of pH sensitive molecules *e.g.* phosphatidylethanolamine, diacetylenic-phosphatidyl-ethanolamine (DAPE), palmitoyl-oleoyl-phosphatidyl-ethanolamine (POPE), N-citraconyl-dioleoyl-phosphatidyl-ethanolamine (C-DOPE), N-citraconyl-dioleoyl-phosphatidylserine (C-DOPS), pH-sensitive peptide/proteins, pH-sensitive polymers (poly (alkyl acrylic acid)s, succinylated PEG, hyperbranched poly (glycidol) (HPG), N-isopropylacrylamide (NIPAM), oleic acid, succinic acid derivatives, aspartic acid, glutaric acid, zwitterionic lipids, phosphoethanolamine, pH-sensitive peptide, poly(2-ethyl-2-oxazoline), *ortho*-esters, vinyl ether, hydrazone, *etc.* are used to make pH sensitive liposome in the last few years [109,110]. The pH sensitive liposomes are already applied for various applications *e.g.* vaccine delivery, tumor diagnosis through bioimaging, MRI contrast agents, immunotherapy, chemotherapy, gene delivery, antigen delivery, antiulcer therapy, anti-inflammatory therapy, anti-infection therapy antiasthma therapy, cardiovascular therapy, colon drug delivery, *etc.* [60, 111,112]. Tuning of this pH sensitive liposomes are highly important to use them for specific applications and various parameters *e.g.* lipid structure, polymer materials, lipid to polymer ratio, nature of the surface functionalized molecules, *etc.* play an important role to tune the pH sensitivity of the liposomes. But there are few limitations of pH sensitive liposomes (stability, premature leakage) which urge for more research in this field which will explore this for more advanced applications in near future [113,114].

Thermosensitive liposome: Thermosensitive liposomes are another type of liposomes which can control the cargo delivery under thermal stimuli. Thermosensitive liposomes can be formulated from a variety of starting materials *e.g.* thermosensitive lipids (1-myristoyl-2-stearoyl-sn-glycero-3-phosphocholine (MSCP) monopalmitoylphosphatidylcholine (MPPC), hexadecylphosphocholine (HePC), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N- [methoxy(polyethyleneglycol)-2000] (DSPE-mPEG2000), *etc.* These lipids can be added with appropriate ratio with other lipids to prepare tunable thermosensitive liposomes. The ratio of the two or more lipids molecule can control the temperature range in which the liposomes can release the cargo in a controlled way [115]. Various synthetic thermosensitive polymer *e.g.* poly(N-vinylamides), poly-(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO) block copolymers (poloxamers/pluronics), (PEG–PLGA) block copolymers, Elastin-like oligo- and polypeptides and natural thermosensitive polymers *e.g.* agarose, gelatin, amylose, amylopectin, carageenans, gellan, xyloglucan and cellulose derivatives can be utilized to functionlaize the liposome to get thermoresponsive properties [116]. There are few thermosensitive surfactants *e.g.* polyoxyethylene (20) stearyl ether (Brij78) that can also be used to prepare thermosensitive liposomes [117]. The thermal stimuli can be provided either from a local heat source or from a localized high intensity ultrasound [118]. A number of drugs *e.g.* neomycin, methotrexate, doxorubicin, cisplatinum, gemcitabine, miltefosine, oxaliplatin, have already been incorporated in thermosensitive liposomes [119]. There are few thermosensitive liposomes-based drug delivery systems (ThermoDox, Lipoplatin) which are in the clinical trials and have shown promising results which may give few thermosensitive drug delivery systems within next few years [120]. But there are some challenges with thermosensitive liposomes with respect to availability of heat treatment and less amount of data which keeps an open platform for researchers throughout the globe to continue the research in this field [120].

Photosensitive liposome: In last few years, photosensitive liposomes becomes very important for their versatile applica-

tions including diagnosis and treatment of various diseases, delivery of various cargo molecules, *etc.* [121]. Photosensitive liposomes are generally prepared using photosensitive lipids, polymers surfactants, *etc.* following the traditional liposome preparation method as discussed in earlier section. Photosensitive lipids *e.g.* N-[(*E*)-4-(4-((4-butylphenyl)diazenyl)phenyl)-butanoyl]-D-erythro-sphingosine [ACe-1], 1-stearoyl-2-[(E)-4-(4-((4-butylphenyl)diazenyl)phenyl)butanoyl]-sn-glycerol [18:0-PhoDAG], 1-stearoyl-2-[(*E*)-4-(4-((4-butylphenyl)diazenyl)phenyl)butanoyl]-sn-glycero-3-phosphocholine [18:0-azo PC], (*E*)-4-(4-((4-butylphenyl)diazenyl)phenyl)-N-(3-hydroxy-4-methoxybenzyl)butanamide [*trans*-AzCA4], 1-(*E*)-4-(4-((4-butylphenyl)diazenyl)phenyl)butanoyl]-2-hydroxy-sn-glycero-3-phosphate (ammonium salt) [AzoLPA], (2*S*,3*R*,*E*)-2-amino-7-(4-((*E*)-(4-propylphenyl)diazenyl)phenyl)hept-4-ene-1,3-diol [Photoswitchable Sphingosine (PhotoSph)], (1,2-*bis*(tricosa-10,12-diynoyl)-sn-glycero-3-phosphocholine (DC8, 9PC), Biz-azo PC, O-nitrobenzyl conjugated lipid, NVOC-DOPE, Plasmalogen, *bis*-sorbyl phosphatidylcholine (bis-SorbPC), *etc.* [122-125]. Various light sensitive polymers *e.g.* polymer containing diazonaphtoquinones, azobenzene, cyclopropane containing polymers are synthesized and applied for the surface modification of liposomes to get photosensitive nature of liposomes [126-130]. Photosensitive liposomes have been applied to deliver varieties of molecules including drugs, nanoparticles, *etc.* Various drugs *e.g.* doxorubicin, have been formulated as photosensitive liposomal DDS [131-135]. The light source can come from external infrared radiation or laser source. Few photosensitive liposomes-based DDS (visudyne, foslip, fospeg, *etc.*) are already commercialized which encourages the researcher to work further in this field [123].

Enzyme responsive liposome: One of the main objectives of the drug delivery system is to deliver the drugs in a controlled way and the most popular approach to achieve this is using suitable external stimuli [136,137]. Two main mechanisms are observed *e.g.* active release and passive release by which the cargo molecules can be released in a controlled way from liposomes [133,138]. A number of stimuli are available as discussed earlier but enzymes remain one of the best choices for passive release due to their endogenous versatile nature [139-141]. The concentrations of many enzymes [*e.g.* Phospholipases (sPLA2)] are elevated during various disease conditions mostly in various cancer cells and these are utilized to trigger the cargo release from liposomes [142]. Enzyme responsive liposomes are explored for a long period of time and there are many approaches to prepare them. One of the approaches is to formulate the liposome composed of enzymatically cleavable lipid or lipid mixture. Few lipid molecules *e.g.* DPPC (1,2-dipalmitoyl-sn-glycero-3-phosphocholine), 1,2-distearyl-sn-glycero-3-phosphoethanolamine (DSPE), distearoylphosphatidylglycerol (DSPG), 1,2-distearyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, DSPE-PEG2000, 1,2-dioleoyl-3-trimethylammonium propane (DOTAP), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) have been already utilized to prepare the desired enzyme responsive liposomes by mixing them in a appropriate ratio [13,143-145]. Enzymes generally cleaves the phospholipid bond by hydrolysis producing fatty acid and lysophospholipids [146,147]. These enzyme responsive liposomes are applied for various purposes including intracellular, extracellular, targeted drug delivery, diagnostic imaging, *etc.* [132,148-150]. A number of enzymes (*e.g.* urease, cathepsin B, α-amilase, glucose oxidase, peroxidase, caspase 1 thrombin collagenase chymotrypsin, esterases, phosphatases, phospholipases, penicillin G amidase, β-galactosidases, *etc.*) [151,152] can be explored to investigate enzyme responsive liposomes thus gives open opportunity to all the researcher who are working in this field.

Redox responsive liposome: Redox is another external stimulus, which are successfully applied for the controlled release of the cargo molecules from liposomes. Due to the differences in concentration of various chemicals (*e.g.* glutathione) between intracellular and extracellular microenvironment, a potential gradient develops, which actually acts as triggering agents [153,154]. This redox potential control the stability of redox sensitive materials present in liposome thus control the release of the cargo molecules (*e.g.* drugs, gene, nucleic acid, *etc.*) by slow decomposition of liposome [155, 156]. The formulations of the redox sensitive liposomes are already been produced by various lipid composition *e.g.* 1,2-dioleoylsn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-distearoyl-snglycero-3-phosphoethanolamine (DSPE), 1,2-distearoyl-snglycero-3-phospho-(1′-rac-glycerol) (DSPG), egg phosphatidylcholine (EPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), palmitoyl-oleoyl-phosphoethanolamine (POPE), cholesterol, *etc.* The redox sensitive liposomes are generally composed of more than one lipid as stated above with optimized ratio [157-159]. A number of molecules *e.g.* doxorubicin, paclitaxel, si-RNA, plasmid DNA, docetaxel prodrug are used as cargo molecules to investigate the redox responsive liposomes. The basic mechanism through which redox responsive liposomes works is that, at physiological conditions they are stable and there is no release of cargo molecules but when a certain redox potential reaches due to the generation of redox potential gradient, the liposomes are destabilized thus releasing the cargo molecules. This potential gradient can also be generated by introducing some chemical reaction (*e.g.* introduction of disulphide linkage followed by its reduction) externally thus making on demand drug delivery [138,160-162]. But more studies need to be done before it come into commercialization thus making this field a challenging one.

Stealth liposomes: Although liposomal drug delivery systems are well established and there are many commercial products available in the market for the treatment of many cancer diseases based on liposomal formulations, still, conventional liposomes suffers from few problems associated with its less stability and premature cargo release [163]. Conventional liposomes are easily taken up by the reticular endoplasmic system (RES) followed by rapid degradation through a process known as phagocytosis which renders the uncontrolled cargo release before it reaches to the targeted disease cells. These problems restrict many liposomal formulations to be commer-

cialized [164,165]. These problems prompt the scientists to modify the liposomes and, an effort to solve these issues, stealth liposome are introduced. Stealth liposomes possess few interesting characteristics *e.g.* stable in nature, tunable size, shape and composition, release drugs slowly, uniform in nature, not taken up by RES, minimum toxicity, increased bioavailability, easy targeted delivery, which made them better than conventional one. Stealth liposomes are generally prepared either by surface modifications of the liposomes or by using multiple lipid formulations in an appropriate ratio [166]. A number of polymers *e.g.* polyethylene glycol (PEG), dextran (Dex), polysialic acid (PSA), hyaluronic acid (HA), chitosan (CH), heparin polyaniline (PA), polyacrylamide (PAA), polyvinylpyrrolidine (PVPA), poly[N-(2-hydroxypropyl)methacrylamide], poly-N-vinylpyrrolidones, poloxamers, poloxamines, polysorbates, poly(carboxybetaine), poly(glutamic acid) (PGA), are used to prepare the stealth liposomes in the last few decades [167-169]. Stealth liposomes can be easily prepared by any of the methods *e.g.* sonication, reverse phase evaporation, freeze-dried rehydration method, solvent injection method, *etc.* and can be easily characterized by the well-known zeta potential measurement, drug release study, polydispersity index analysis, drug quantification analysis. Many drugs *e.g.*, doxorubicin, vinorelbine, methotrexate, vincristine, imatinib, *etc.* and nucleic acids (DNA and RNA) are already encapsulated in these stealth liposomes and have been going through various phases of clinical trial [170,171].

Immunoliposome: To achieve the targeted drug delivery various approaches have been adopted but one method which become popular and found lots of applications is immunoliposomes. Immunoliposomes can be prepared by the functionalization of the liposomes with antibodies [172]. The antibody can be conjugated to lipids followed by liposomes preparation or after the preparation of liposomes, surface of the liposomes can be functionalized with antibodies [173,174]. Conventional liposomes can be functionalized with antibodies which produces type-A immunoliposomes whereas the stealth liposomes conjugated with antibodies are known as type-B immunoliposomes [175]. A number of immunoliposomes are already prepared for the last few decades to achieve targeted drug delivery of various anticancer drugs (*e.g.* doxorubicin, gemcitabine, topotecan, fenretinide, vincristine, paclitaxel, melittin, calcein, indinavir, amphotericin B, dexamethasone, chloroquine, siRNA and miRNA, *etc.*) and nucleic acids (*e.g.* luciferase gene, oligodeoxynucleotides, modified hybrid (DNA-RNA) anti-HER-2 siRNA, *etc.*) to treat various types of cancer (*e.g.* human lung cancer, human brain tumor, murine lewis lung carcinoma, murine breast adenocarcinoma, human mammary adenocarcinoma, human oestrogen receptor-sensitive breast carcinoma, ovarian cancer, Non-Hodgkin's lymphoma, small cell lung cancer, T-lymphocytes, leukemia, chronic lymphocytic leukemia, primary effusion lymphoma, human glioma and many more) [176-179]. The immunoliposome are already used to target various receptor (epidermal growth factor receptor (EGFR, ErbB), Anti-RON receptor tyrosine kinase, human epidermal growth factor receptor 2, *etc.*) for various cancer therapy. The mechanism through which the immunoliposomes works is ligand target complex formation mechanisms followed by complex internalization. After the internalization the complex gets destabilized followed by release of drug molecules and receptor degradation. The receptor then recycled again and the process continues [180]. The immunoliposomes are an exciting field of liposome research and have high potential for cancer treatment with commercialization.

Surface functionalization of liposomes

Functionalization with inorganic nanoparticles: The conventional liposome or first-generation liposomes which are composed of only traditional lipid molecules suffer from many drawbacks in terms of premature drug release and stability at physiological condition [181]. Most of the first-generation liposomes get destabilized due to internalization by reticuloendothelial system (RES) which limit their biological applications. Various methods have been adopted over the years to improve the lifespan of liposomes and to minimize the premature drug leakage [169]. Modification of liposome can be performed by two methods either before the synthesis of liposomes or through post synthetic modification [49,144]. One of the post synthetic approaches of liposome surface functionalization is carried out *via* various inorganic nanoparticles [182]. This field of liposome research is developing rapidly in the last few years and a number of nanoparticles *e.g.* silica nanoparticle, gold nanoparticle, functionalized gold nanoparticles, silver nanoparticle, iron oxide nanoparticle, super paramagnetic iron oxide nanoparticle, are already applied to modify the liposomes [183]. Among all of these, one of the best studied system is silica nanoparticles coated liposome also known as liposil [184]. Liposil is generally prepared by post-synthetic modification of multilamellar vesicle *i.e.* at first multilamellar liposome is prepared by any of the traditional method followed by silica coating following standard literature procedure *e.g.* Stober method or LaMer method. Liposil possesses many advantages over conventional liposomes due to their increased stability, high encapsulation efficiency, prolonged blood circulation time, minimum drug leakage, high kinetic stability (liposil can stable as long as up to one year which is highly suitable for industrial use), controlled release of drugs, *etc.* Liposil have been used to deliver many drugs (insulin, paclitaxel, *etc.*) and various small molecules [185,186]. Gold nanoparticle and functionalized gold nanoparticles are another promising nanoparticle which have been utilized for surface modification of liposomes for the last few years. Because of their excellent optical properties, tunable size, shape, surface area, safety, biocompatibility, *etc.* [187,188]. Gold nanoparticles also show unique photo- and thermo-responsive behaviour, which make them suitable for making photo- and thermo-responsive liposomal drug delivery system for various photodynamic therapy and diagnostic applications [189,190]. Various types of gold nanoparticle liposome complex can be formed *e.g.* gold nanoparticle can present within the lipid bilayer of liposomes, in the aqueous core of liposomes, On the surface of liposomes, aggregates with liposomes, free in liposome solution, *etc.* [189, 191,192]. Chakrabarty *et al.* [193] already showed that drug loaded liposomes can be stabilized by functionalized gold nanoparticle decorated lipo-

somes and the release of the drugs can be controlled over 6-12 h. Chakrabarty *et al.* [193,194] also reported functionalized gold nanoparticles and polymer coated liposome nanocapsules for the controlled release of cargo molecules. The size of the gold nanoparticle can vary from 2-50 nm. A number of molecules are used as cargo molecules *e.g.* calcein, prodan, ellipticine, doxorubicin, alkaloid berberine, carboxyfluorescein, *etc.* to investigate the gold nanoparticle decorated liposomes and they applied for various biomedical applications including various cancer treatment. Xia *et al.* [195] reported the gold nanoparticle decorated thermo-responsive and photo-responsive liposomes and shown the controlled release of the cargo molecules using radiation. Moreover, Cui *et al.* [196] developed SERS-active liposome-Au nanohybrids and studied them for tumor therapy. All these promising results showed that the liposome-Au nanohybrids hold great promise in biomedical applications. Silver nanoparticles are also applied to functionalize the liposome surface due to their many important properties *e.g.* low cytotoxicity, high biocompatibility, optical properties, efficient SERS enhancing, *etc.* Due to the excellent SERS response, the drug delivery can be easily monitored [197-200]. Cui *et al.* [201] reported liposome nanohybrids formulated by electrostatic interactions, leading to surface modified liposomes with excellent SERS spectral optical properties that offer excellent opportunity for the further development for intracellular applications. Silver nanoparticle are also found to have great effect on the fluidity of the lipid bilayer, which again is very important for liposome stabilization. Silver nanoparticle functionalized liposome has great potential in the investigation of interactions between nanocomposites and cells for drug delivery as well as for improving the therapeutic efficiency by further modifications [202-204]. Superparamagnetic iron oxide nanoparticles (SPIONs) are another class of nanomaterials, which are extensively used for liposome modification. SPION modified liposomes which are having magnetic characteristics have already been applied for many applications including MRI bioimaging, contrast agent, drug delivery, targeted and controlled drug delivery *etc.* [205-207]. Zhang *et al.* [208] reported tumour specific pH responsive delivery of paclitaxel using SPION-liposomes. Simiarly, Saengkrit *et al.* [209] developed SPION modified liposomes for theranostic treatment of central nervous system lymphoma, whereas Song *et al.* [210] reported iron oxide nano-particles/mitoxantrone-loaded liposomes for both magnetic resonance imaging and targeted cancer therapy [210]. Busquets *et al.* [211] reported SPION modified liposomes as T2 MRI contrast agents. There are few review articles are also available in the literature, which describes the applications of SPION modified liposomes [211-213]. Recently various other nano-particles *e.g.* zinc oxide, titanium dioxide, *etc.* are also applied by many researcher to understand their effects on lipid bilayer or liposomes. Ross *et al.* [214] extensively studied the effect of titanium dioxide and zinc oxide nanoparticles on lipid bilayer as a model of biological membrane. But this field is still highly unsaturated and lots of open challenges are there in terms of cytotoxicity, bioavailability, biocompatibility, stability of the nanoparticles upon integration with liposomes. Hence, more and more experiments and research study is required to understand the liposome-nanoparticles interaction to gather more data for further applications in future.

Functionalization with polymers: Polymers are another class of materials, which are extensively used for the surface functionalization of liposomes for the last few years [182]. A wide variety of polymers (poly(N-iso-propylacrylamide) [poly-(NIPAM)], poly(vinyl pyrrolidone), poly(2-methyl-2-oxazoline), poly(2-ethyl-2-oxazoline), poly(N-alkyl acrylamide), poly[N,N-*bis*(2-methoxyethyl)acrylamide], poly(hydroxyethyl-L-asparagine)succinyldioctadecylamine, polyvinyl pyrrolidone (PVP), polyglutamic acid (PGA), poly(hydroxyethyl-L-asparagine) (PHEA), poly(hydroxyethyl-L-glutamine), poly-(glycidol), poly(ethylene) glycol, *etc.*) are successfully applied and the surface modified liposomes were employed for varieties of application in different branches of sciences including drug delivery, bioimaging, diagnostic imaging, tumour specific drug delivery, controlled and responsive drug delivery, *etc.* [47,169, 215,216]. Among the polymers, PEG is one of the most extensively studied and used polymers for liposome modification because of its bio-inertness, thermoelasticity, linear chain, hydrophilicity, non-toxic, non-ionic character [217-220]. PEG modified liposomes are known as PEGylated liposomes or stealth liposomes and it has been successfully applied for drug delivery of many chemotherapeutic drugs *e.g.* doxorubicin (Doxil is PEGylated liposomes encapsulated doxorubicin), topotecan, *etc.* [221,222]. Temperature has been shown to affect the water solubility of certain polymers. Temperature responsive polymers that become insoluble in water or experience phase separation at a certain temperature [lower essential solution temperature (LCST)] have been used for a variety of biofunctional products, like drug carriers and functional gels. Recent advances in polymer synthesis have allowed for improved regulation of molecular weight and branching structure, as well as the application of terminal groups to the functional polymers [223]. These developments are expected to increase the versatility of practical polymer design and encourage the manufacture of multifunctional polymeric materials. The multifunctional liposomes with surface modification of these multifunctional polymers are required to have precise drug delivery [224].

PEGylation can be done in two ways either by adding PEG lipids to the lipid composition before liposome formation (preinsertion method) or by combining PEG-lipids with liposomal dispersion (mixing method) (post-insertion method). The efficiency of liposomal PEGylation is influenced by both the length and density of PEG coverage. PEG molecules with very short chains cannot inhibit protein absorption and improve blood circulation time, whereas PEG chains with very long chains result in a substantial reduction in transfection activity. Liposome modulation is usually done with medium-length PEG molecules [225-227]. The coverage density increases as the molar PEG-lipid/lipid composition ratio rises. Several drug delivery systems based on the PEGylated liposomes have been developed to date [170]. Recently, Morsbach *et al.* [50] reported the functionalization of liposomes with hydrophilic polymers (PEG and hbPG-functionalized) and their application for cellular uptake of proteins. They studied the protein corona of several functionalized liposomes (unfunctionalized, PEG and hbPG),

as well as the influence of surface modification and protein adsorption on macrophage uptake. There are few more important polymers which are also used for preparation of liposomal drug delivery system and one such example is Pluronic F127 (PF127). Pluronic F127 (PF127) is used for liposome coating as an alternative to the more conventional PEG. PF127 is a non-ionic triblock surfactant that is commonly used as a food additive and has been approved as a medicinal constituent in cancer drugs. It has a long circulating time and good bioavailability, as well as the capacity to preserve liposome preparations. PF127 can also improve liposome mucus penetration and cellular absorption. Liposomes coated with PF127 transmit coumarin 6 to enterocytes more efficiently than liposomes without the coating [228-231]. As another substitute to PEG, polymers such as poly(carboxybetaine) (PCB) can stabilize liposomes. Furthermore, even without inclusion of cholesterol to the lipid formulation, PCB-modified liposomes showed high retention of the hydrophilic drug and extended blood circulation properties *in vivo*. A unique lipid/poly-phosphocholine conjugate, on the other hand, may protect liposomes against aggregation in the same way as PEG does and allow them to operate as extremely effective lubricating components, easily achieving superlubric performance, which might be valuable in medicinal applications [232,233]. Liposomal compositions coated with hyaluronic acid have also been investigated. Hyaluronic acid, a naturally occurred negatively charged linear hydrophilic polysaccharide is a good substitute for PEG because of its biocompatibility, biodegradability, nontoxicity and nonimmunogenic properties. HA's hydrophilic coating hinders opsonin adsorption to the liposome surface, increasing drug circulation and affinity binding to tumour recognition sites, according to several studies [234-236]. Polysaccharides are another class of polymers, which have been successfully employed to functionalize the liposome surface an two important polysaccharides which are mostly used are chitosan and starch. Chitosan is commonly utilized as a protective coating since it is positively charged and rapidly interfaces with the negatively charged liposomal surfaces, resulting in a solid coating that improves liposome stability in the biological fluid in terms of both size and drug loading. Changes of the exterior of chitosan-based systems to generate multi-layered or multivesicular carriers have been reported to boost their resilience to the harsh gastrointestinal environment. Because of the ability to functionalize chitosan, copolymers such as PEG-chitosan that stabilize liposomes and encapsulate the new doxorubicin prodrug modified by stearoyl-spermine have been developed [49,237-241]. Due to its high availability, low cytotoxicity and biodegradability, starch is another polysaccharide utilized to stabilize liposomal systems. For example, Nahar *et al.* [242] formed stable starch-coated magnetic liposomes that proved to be a successful respirable carrier for fasudil drug accumulation in the pulmonary vasculature, whereas Salem *et al.* [243] investigated an ocular starch-liposome specification that improved sodium alendronate stability and efficacy.

Functionalization with polyelectrolytes: Polyelectrolyte multilayer (PEM) coatings have been one of the most frequently investigated and preferred techniques for modulating liposome surface features for eliciting particular tissue responses, regulating degradation behaviour and serving as reservoirs for active therapeutic cargo during the last decade [244,245]. From its first report around three decades ago, layer-by-layer (L-b-L) deposition has been still used to deposit these PEMs, with electrostatic interactions and other short-range interactions playing a major role. The L-b-L is a very reliable and repeatable method for creating highly ordered polymeric stacks on any substrate, regardless of its form, size or geometry [246]. The transportation of pharmaceuticals has been based on the stability of bulk chemical characteristics of these biocompatible and biodegradable polymer complexes. Furthermore, for prolonged and regulated drug release *via* PEM, the technical capacity to manage layer interdiffusion and manipulate layer stacking is critical. In (L-b-L) method, the deposition is directed by reversing of charge density at each coating phase when the substrate is permitted to dip in a mixture of oppositely charged polyelectrolyte with an intervening washing step to remove weakly bound charges [247,248]. A number of polyelectrolytes are used for surface modification of liposomes *e.g.* poly-L-lysine, poly(sodium styrene sulfonate), poly(acrylic acid), chitosan, alginate, dextran sulphate, hyaluronanic acid, chondroitin sulphate, sulfhydrylated chitosan, gentamicin sulphate, branched polyethyleneimine, fibronectin, gelatine, poly(L-glutamic acid), poly(diallyldimethylammonium chloride), poly(sodium 4-styrenesulfonate), *etc*. Chemotherapeutic medicines can be delivered into cancer cells *via* endosomal routes mediated by electrostatic attraction using these polyelectrolytes modified carriers [249]. As a result, cellular absorption increased and anticancer activities *in vitro* or *in vivo* were improved. Among them chitosan and alginate become most widely cited in the literature [240].

Chitosan is appealing as a coating polymer for biological applications of liposomes because of its less cytotoxicity, biocompatibility and biodegradable properties, as well as its distinctive cationic property in water. The positive charge on mucoadhesive liposomes is generated *via* electrostatic force interactions between negatively charge phosphate group in liposome and positively charged chitosan. The overall charge of this chitosan-liposome capsules can be controlled and tuned to either positive or negative thus allows the further modification of the surface with other polyelectrolytes using L-b-L technique [250]. Several chitosan coated liposomal drug delivery system have been developed in the past decades and utilized for the delivery of a varieties of cargo molecules including drugs (*e.g.*, ciprofloxacin, orceftriaxone, tobramycin, doxorubicin), nanoparticles (*e.g.* silver nanoparticles) biomolecules (*e.g.* DNA, *etc.*). The surface charge of these polyelectrolytes coated liposomes after each layer of coating can be easily monitored using zeta potential instruments and accordingly the polyelectrolytes can be chosen [251].

Similarly, the size of the polyelectrolyte coated capsules can also be characterized through dynamic light scattering followed by SEM and TEM techniques [252]. There are many alternative polyelectrolytes *e.g.* polylysine, polyglutamic acid to chitosan which can be applied for surface coating of the liposomes using L-b-L coating. Polylysine, a biocompatible and

readily obtainable cationic polyelectrolyte, has been widely employed in liposome surface modification and coating. Polylysine coated complexes have been shown in many studies to boost their stability, prevent aggregation and increase the accessibility of complexes into cells [253]. Polyglutamic acid (PGA) is an anionic polyelectrolyte with good biocompatibility, nontoxicity and biodegradability when compared to polylysine. It has been used for medication and gene delivery and has been proven to increase intracellular absorption. Any technology has advantages and disadvantages [254]. Although PEM has had a lot of success in biomedical applications, it still has a lot of practical obstacles to overcome before it can be used in large-scale industrial operations [255]. Most of the work on the L-b-L deposited polyelectrolyte films focuses on improving the understanding of physico-chemical conditions and multilayer manufacturing kinetics. Despite the practical obstacles, an adaptable nature of PEM still retains the promise of outstanding performance in a range of applications [256, 257].

Functionalization with biomolecules and small molecules: A number of biomolecules and small molecules *e.g.* lipids, protein, antibodies, nucleic acids, aptamers, carbohydrates, vitamins, *etc.* have been utilized for surface functionalization of liposomes over the years [258]. However, each of these options possesses distinct advantages and disadvantages. As discussed few of them in previous sections, herein only lipid, aptamers, vitamins and small molecules for surface modification of liposomes will be discussed. There are two general approaches for modifying the surface of liposomes with peptides [259,260]. To begin, ligands can be chemically bonded to lipid headgroups or polymer that extend perpendicularly from the liposomal surface. To accomplish these changes, optimized carboxyl groups can interact with amino groups making an amide bonds, dithiols can interact with thiols to make disulphide bonds, imide can react to form thioether, *etc.* In an alternate method peptide and liposome can interact electrostatically and can bind with the liposomal surface [261,262]. A number of lipids *e.g.* linear RGD, cyclic RGD, HER-2 peptide, cystabn, *etc.* are already experimented for the surface functionalization of liposomes over the globe. Out of these linear RGD and cyclic RGD are the most widely studied peptide for liposome surface modification. Linear RGD modified liposomes have been utilized for the stimuli responsive delivery of a number of drugs including docetaxel, gemcitabine and few nanoparticles *e.g.* quantum dots. Cyclic RGD are also used to increase cell specific target efficiency and liposomal stability [263-265].

Cyclic RGD lipid modified liposomes are also applied for the drug delivery. Lipid functionalized liposomes are applied to target a large number of receptors *e.g.* transferrin receptor (due to the increased metabolic demand for iron, it is overexpressed in a range of cancer forms, indicating that it is a promising target for cancer therapies), epidermal growth factor receptor (during the malignant transformation of healthy cells, it is frequently overexpressed), aminopeptidase-N (due to its overexpression on the surface of cancer cells, which is most typically found in aggressively developing phenotypes, it has been extensively studied), vascular endothelial growth factor receptor-2 (angiogenesis marker that is well-known and overexpressed in freshly generated tumour vasculature [266,267]. The activation of this tyrosine kinase receptor has been demonstrated to promote tumour proliferation and migration, as well as tumour metastasis), Integrin $\alpha_v\beta_3$ and $\alpha_5\beta_1$ receptors (due to their elevated expression, which contributes to cell adhesion, migration, infiltration and metastasis, they are likely targets on the cell membrane of cancer cells), gastrin-releasing peptide receptor (several forms of cancer, including pancreatic cancer, glioma and lung cancer, this receptor is are overexpressed), Interleukin-13 receptor a2 (interleukin-13 receptor is a plasma membrane protein that is overexpressed in glioblastoma multiforme), glycoprotein 130 (is highly expressed in glioma cells), *etc.* [268-270].

Another important biomolecule which is applied extensively for liposome surface modification is aptamers. Small single-stranded RNA or DNA (oligonucleotide) motifs capable of binding receptors on the surface of cancerous cells are known as aptamars [271]. The systematic-evolution of ligand by exponential-enrichment technique was used to create aptamers with high affinity for target compounds. Liposomes with a targeting aptamer ligand attached to the liposome surface and encapsulating anticancer cisplatin have indeed been already described. When compared to non-targeted drug loaded liposomes and free drug, aptamer targeted liposomes showed improved antiproliferative action in breast cancer (MCF-7 cells) over expressing nucleolins [272-274]. Another important biomolecule which has been used since last two decades for liposome modification is vitamins. The use of vitamins as liposome ligands for effective and targeted drug delivery has created a whole new world of possibilities. Various types of cancer cells overexpress vitamin receptors more than normal cells, therefore understanding receptors is critical for docking vitamin-ligand liposomes. In malignant phenotypes, the expression of several vitamin receptors is frequently increased. There are two ways by which liposome surface can be functionalized with vitamins. Phospholipids can be used to conjugate directly with the vitamins or a linker (one of the most widely used linker is PEG) can be used to conjugate phospholipids and vitamins. Due to the lack of biding ability of folic receptor with the first one the later method become more popular and have been used extensively. A wide variety of vitamins *e.g.* biotin, nicotinamide, vitamin A, pyridoxal phosphate, riboflavin, tocopherol, folic acid, have been already used for surface engineering of liposomes [275-277]. These surface engineered liposomes are applied for various applications including sensing of nucleic acids (DNA and siRNA), delivery of drugs, quantum dots, radiotherapy, *etc.* The biocompatibility of liposomes is one of the prime requirements of any type of biological applications and one of the approaches to make biocompatible liposome is to apply highly biocompatible carbohydrates. A number of carbohydrates *e.g.* glucose, mannose, galactose, sucrose, maltose, lactose, oligosaccharides, lectins, tomato lectin, wheat germ, agglutinin, are also employed to decorate liposome surface. These carbohydrates modified liposomes are used for a few applications including drug delivery, therapeutic study, *etc.* [275,278,279]. Compatibility with biological and chemical

systems is also a possible issue. For example, the presence with one protein on the liposome surface may impair the coupling techniques' ability to attach another protein. To overcome these challenges, the liposome surface is decorated with a variety of physiologically suitable and structurally selective protein molecules. As a result, more flexible and site-specific coupling strategies for protein attachment to liposomes are needed. It has been demonstrated that concentrating a significant amount of protein on the liposome membrane's outer surface causes membrane tabulation and distortion [280-282]. There have been reports of methods to localise proteins on a single side of a liposome. However, *in vitro* localization of various proteins on the inner and outer leaflets of the liposome has proven problematic. Thus, there are great opportunities and challenges awaiting in this area of liposome research which needs the attention of young researcher throughout the globe [283,284].

Applications

Liposomes for anticancer drug delivery: Cancer is a life-threatening disease that causes malignant cells to develop in an uncontrolled and irregular pattern. These unregulated cells can infiltrate healthy tissues and organs, generating unfavourable development and responses that eventually lead to their destruction. Cancer cells can travel throughout the body *via* blood arteries and lymphatic systems, resulting in metastasis and the formation of a secondary tumour [285]. Anticancer drugs are commonly given to cancer patients in order to destroy cancer cells. These medications function in two ways *i.e.* they destroy cancer cells by exposing them to a chemical agent directly and they induce apoptosis (cancer cell death). Liposomal medication compositions have the potential to improve chemotherapeutic treatment effectiveness while decreasing hazardous adverse effects. They can also have an effect on the chemotherapeutic compound's pharmacokinetics and tissue distribution. They have been termed as "alternative drug delivering systems" that have been employed to improve the therapeutic efficacy of anticancer drugs while also lowering their toxicity in surrounding healthy cells [170,286]. A number of anticancer drugs are administered using liposomal drug delivery system including methotrexate, cytarabine, cisplatin, doxorubicin, oxaplatin, daunorubicin, vincristine, paclitaxel, camptothecin, vinblastine, vinorelbine, *etc.* [60,287,288]. Doxil® is the world's first PEGylated liposome-based medication delivery system. It contains liposomal doxorubicin hydrochloride, an anthracycline chemotherapeutic medication that causes apoptosis in cancer cells by inhibiting topoisomerase II, an enzyme required for tumor cells to reproduce and develop. Non-liposomal or traditional anthracyclines, such as doxorubicin and daunorubicin, have a substantial disadvantage in terms of cardiotoxicity. To solve the problems associated with the use of conventional doxorubicin, liposomal formulation was created [289]. Irinotecan is a water-soluble semi-synthetic counterpart of the natural alkaloid camptothecin, often known as CPT-11. By inhibiting topoisomerase-I, it stops DNA from unwinding and reproducing. It is applied to treat malignancies, diarrhoea and myelosuppression as an antineoplastic drug. The FDA in the United States and the European Medicines Agency have authorized Onivyde® (nal-IRI), a nanoliposomal hydrochloride irinotecan formulation. The chemotherapeutic medicine's pharmacokinetic properties were enhanced by using a liposomal dose form, which had no additional side effects than the medication itself [290]. Docetaxel is a another anticancer drug extracted from the natural product and purified in laboratory coming from a taxane type of species and antimitotic drug that binds to tubulin's beta subunit and causes tubulin polymerization to be stabilized. Microtubules are disrupted as a result of this stabilization and the cell cycle is arrested during the G2/M phase, preventing mitosis. It has a low water solubility and is often used to treat a variety of solid tumours [291-293]. The commercialized docetaxel (Taxotere) is prepared in Tween 80 and ethanol because of its insolubility. However, infusion-related toxicity, acute hypersensitivity responses and cumulative fluid retention have all been linked to this drug. Various delivery technologies without Tween 80-free and ethanol such as nanosomes, polymeric micelles, protein and nanospheres, have been developed and clinically evaluated to prevent such unpleasant side effects [294-296]. Mepact® is an encapsulated mifamurtide formulation recognized for the therapy of osteosarcoma by the European Union, Switzerland and other nations [297].

To circumvent the dosage, the pharmacokinetic and pharmacodynamic constraints of non-liposomal vincristine, the semi-synthetic chemotherapeutic drug vincristine sulphate has been encapsulated in sphingomyelin/cholesterol nanoliposomes. The FDA has authorized this vincristine injectable dosage form (VSLI, Marqibo®) because it has been proven to be safe [298, 299]. Topotecan is a powerful anticancer drug that inhibits the topoisomerase enzyme. It is a water-soluble natural analogue of cisplatin. It is sold as Hycamtin^{R} (topotecan hydrochloride) and has been linked to the treatment of lung, ovarian and other malignancies. For the targeted delivery of topotecan, a variety of nanocarriers, including liposomes, have been developed. The co-encapsulation of phenyl ketone carboxylate derivatives with the anticancer medicine topotecan and DNR as a co-delivery regimen for use in different tumours for human trials was revealed in a Canadian patent [300-304]. Cisplatin, also known as *cis*-diamine-dichloroplatinum (CPT), is an active anticancer platinate that is used to treat a variety of solid malignancies. The use of cisplatin in clinical trials revealed nephrotoxicity and dose-induced acute renal failures. Due to its high hydrophobic nature, cisplatin, on the other hand, is difficult to adequately entrap into liposomes. The responsiveness of deterrent of the tissue sample caused by loss of cancer cells after treatment with cisplatin-loaded liposomes. This composition improved the efficacy of cisplatin in the A427 human non-small-cell lung cancer model. PEGylated liposomes were more effective *in vivo* than cisplatin in mice carrying human xenograft A427 for the same amounts of cisplatin-delivered dosages, according to the findings [305-307]. A patent was recently granted for an oxaliplatin-encapsulated aqueous liposomal formulation with dramatically improved storage stability. To make the formulation at pH 6-8, aqueous dispersion comprised 2-morpholino-ethane-sulfonic acid/salt, which formed liposomal vesicles from hydrogenated soybean-sourced PC, CHL,

mPEG2000, DSPE and oxaliplatin [308-310]. Vincristine is a natural vinca alkaloid isolated from the pink periwinkle plant that has anticancer action which is unique to the cell cycle. The vincristine sulphate liposomal injection (VSLI), marketed as Marqibo^{R} (Spectrum Pharmaceuticals, Inc., NV, USA), has been proven to enhance pharmacokinetics and pharmacodynamics of vincristine [311-313]. Different polymeric materials, the active ingredient curcumin and/or curcumin–PLGA conjugates were employed in the liposomal formulation, which consisted of a polymeric core with surface-extruding lipidic elements. Human embryonic kidney (HEK 293) cell lines transfected with hERG were used to test it. The whole-cell release current acquisition and analysis techniques were used to investigate the *in vitro* effects of the curcumin liposomal formulation on potassium-selective IKr currents produced in normoxic conditions in stably transfected HEK 293 cells [314-317]. So, liposomal systems for the supply of anticancer drugs should be designed to meet stable, soluble and permeable requirements. These systems must be useful, efficient, safe and inexpensive. In addition, using multifunctional materials to alter the liposome surfaces for drug delivery, 'smart' vesicles such as pH responsive and controlled release systems may be produced [49].

Gene delivery using liposome: Gene therapy is a one-of-a-kind method of using genes to cure or treat diseases. Instead of administering medications or surgery, doctors could use gene therapy to treat a problem by delivering a gene into the patient's cell. Multiple approaches to gene therapy are being investigated by some scientists and physicians, including replacing a disease causing mutated gene with a healthy gene, 'knocking out' or inhibiting a mutated gene that is malfunctioning; and bringing new genes into the cells to protect against diseases [318,319]. Gene therapy was developed to send genetic information to a patient's somatic cells in order for them to produce specialized therapeutic proteins to modify genetic disease. Nevertheless, numerous important barriers must be addressed before nucleic acid-based treatments may be utilized clinically effectively and safely. Nucleic acids' cellular absorption is limited by their short half-life, high molecular size and large negative charge density [320-322]. Nucleases efficiently breakdown naked nucleic acids and the liver and kidneys quickly remove them from the bloodstream. Furthermore, once within the cell, nucleic acids only induce temporary gene silence. As a result, successful nucleic acid distribution requires a delivery method that protects the molecules from degradation, improves their stability and allows them to be internalized into the target cells. A plasmid based gene expression system that regulates the gene activity inside the targeting cell, a gene that contains an effective targeted protein and a gene delivery system that governs the delivery of the genomic plasmid to a specific location within the body are the three components of the gene delivery systems. The foreign genetic material must remain stable within the host cells for the gene delivery mechanism to work [323,324]. Liposomes are made up of homologous lipid molecules with a head group and hydrophobic hydrocarbon tails linked by a backbone linker like glycerol. One and sometimes more amines present in the polar head group give cationic lipids their positive charge. The existence of positively charged amines makes it easier for anions like those present in DNA to attach to them [325]. The liposome is produced as a result of energy contributions from van der Waals forces and electrostatic attraction to DNA, which controls liposome morphologies in part. Due to the polyanionic nature of DNA, cationic (and neutral) lipids are widely applied for gene delivery, while anionic liposomes are generally utilized for other therapeutic macromolecule delivery. The size of the head group and the length of the hydrocarbon tail varies amongst lipids. These properties provide the lipid/DNA complex unique properties, which impact its interaction with and absorption into the cell [326]. Cationic lipids, on the other hand, have a fundamental structure that is similar to biological lipids in terms of chemical and physical properties. The positive charge on the head group enables spontaneous electrostatic contact with DNA, as well as binding of the resultant lipoplexes to the cell membrane's negatively charged components prior to cellular absorption. Almost all chemically mediated gene transport vectors, including polymers, lipids and non-degradable nanoparticles, employ a cation [327-329]. A number of cationic lipids *e.g.* DOTMA, N-[1-(2,3-dioleyloxy) propyl]-N,N,N-trimethylammonium chloride; DOTAP, [1,2-*bis*(oleoyloxy)-3-(trimethylammonio)propane]; DC-Chol 3β[N-(N′,N′-dimethylaminoethane)carbamoyl]cholesterol; DOSPA, 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-l-propanaminium trifluoroacetate; DOGS, di-octadecylamidoglycyl-spermine have been already used for the delivery of genes.

Few neutral lipids *e.g.*, dioleoylphosphatidylethanolamine (DOPE), dioleoylphosphatidylcholine (DOPC) are also applied for gene delivery. Gene transport by anionic lipids is inefficient in general [330-333]. Due to repulsive electrostatic interactions between the phosphate backbone of DNA and the anionic head groups of the lipids, the negatively charged head group hinders effective DNA compaction. The utilization of divalent cations to eliminate mutual electrostatic repulsion and enhance lipoplex assembly can be used to form DNA-containing liposomes utilising anionic lipids. Anionic lipoplexes are made up of components that are physiologically safe, such as anionic lipids, cations and plasmid DNA [334-336]. The development of therapeutically useful vectors to treat elusive illnesses such as chronic granulomatus disorder, hemophilia, blindness, neurodegenerative diseases, mesothelioma, AIDS, cancer, Alzheimer's and other diseases is an essential objective for gene delivery system research. The viral vectors are used to transfer genetic materials to the host cells in DNA-based viral vectors for gene delivery systems. The delivery of genetic resources to host cells is facilitated by DNA viral vectors [337-339]. However, one of the most promising RNA vectors has emerged, which uses naked syn-mRNA, viral or non-viral RNA contained within viral particles and self-amplifying RNA replicons. The RNA-based systems appear to be superior to DNA-based ones. In terms of immunogenicity, RNA stability, formulation and manufacturing, RNA technologies have advanced significantly. Improvements in these characteristics have resulted in potential gene transfer systems that can be used *in vivo* [340-342]. The next stage in research will most likely be to advance DNA and RNA molecular technologies to the point where they may be used as routine treatment choices in biomedical applications.

Vaccine delivery using liposome: Vaccination has saved millions of lives and is the most successful approach for preventing infectious illnesses. Smallpox has been eradicated thanks to a worldwide vaccination effort, while other diseases are on the cusp of extinction (*e.g.* polio, measles, *etc.*). Vaccines are generally made from attenuated or dead microorganisms or pieces of them. However, such vaccinations are frequently linked to negative side effects (*e.g.* allergic responses). Furthermore, they frequently need the use of a cold chain to ensure stability and large manufacturing of such vaccines is not always possible [343-345]. However, more effective and safer alternative delivery systems for human usage are still needed, as the currently available delivery systems are ineffective and have safety and effectiveness concerns, especially in immunocompromised and elderly people. Delivering antigens by enclosing them in delivery vehicles such as liposomes is one of the most used alternate ways to increasing immunogenicity [346,347]. Because of their potential as immunostimulants and their ability to transport antigenic components, liposomes have been extensively investigated. Some of the characteristics that make liposomal medication delivery systems successfully apply to vaccine delivery [348,349]. To begin with, liposomes effectively shield tiny peptide/protein antigens from host cell enzymatic degradation. These hydrophilic components can be enclosed in or adsorbed onto the liposomal surface thanks to the bilayer structure of liposomes, while the hydrophobic part of the liposomes permits additional lipids or apolar polymeric components to be incorporated in the membrane bilayer. Second, liposomes can have varied pharmacokinetics and be designed to achieve optimal retention and presentation of vaccination antigens based on their composition, charge and size. Liposomes are also readily absorbed by antigen-presenting cells (APCs) due to their particle structure. This capability is arguably the most significant feature of liposomes for vaccine administration, since it allows for simultaneous processing and presentation of ingested antigen on MHC molecules [350-352]. A number of liposomal vaccine delivery systems *e.g.*, VaxiSome, Vaxfectin, *etc*. have been successfully prepared and used to treat a range of diseases *e.g.* influenza, chlamydia, malaria, tuberculosis, house dust mite allergy, *etc.* [353,354]. Exploring the interaction between drug delivery system and antigen is critical in vaccine development, not only because it can significantly impact vaccine efficacy, but rather because production considerations like formulation stability and antigen organization inconsistencies can cause immunogenically sound vaccines to fail. Most approved adjuvants bind to antigen on the outside, either by adsorption or by being combined together. Crucell's FDA approved influenza vaccine Inflexal V, which is made up of virosomes with antigenic moieties injected into the membrane, is the only exception [355].

Cell transfection reagents and vaccination adjuvants commonly employ cationic liposomes. Although most cationic lipids produce bilayer liposomes, extra lipids are frequently required. Liposome adsorption on the negatively charged cell surfaces is aided by the high surface density of positive charges. Depending on the cell type, cationic lipid nature, formulation kinds and liposome size, cationic liposomes infiltrate cells through distinct methods and activate different cellular pathways [356,357]. To combat the pulmonary fungal illness, liposomes were utilized to transfer plasmid DNA protein, resulted in a protective immune response and decreased fungal load. Liposomes are the artificial microorganisms that can be taught to generate specific antigens for immunisation. A bacterial transcription and translation machinery was entrapped in liposomes, along with a gene construct producing galactosidase or a luciferase–nucleoprotein fusion epitope as antigens. Antigen producing liposomes induced greater specific immune responses to the manufactured antigen in mice when compared to a control vaccination. Alternatives to inhibited bacterial antigens, protein or peptide vaccinations include nucleic acid vaccines [358-360]. Rodriguez *et al*. [361] utilized MLVs as low-cost carriers to transfer DNA to mice carrying plasmids expressing bovine herpesvirus type 1. The IgG responses were produced in vaccinated mice. Liu *et al.* [362] utilized the influenza A virus's M1 gene to create a cationic liposome/DNA vaccine with an M1-encoding plasmid for oral vaccination, which resulted in M1 gene expression in vaccinated mice's intestines, robust immune responses and protection against trial infection. One of the most significant advantages of utilizing liposomes as delivery system is their versatility in terms of biophysical and antigenic characteristics. Making minor changes to the lipid subunits, the size of liposomes or the delivery method has dramatic impacts on the vaccine's effectiveness, as well as which part of the immune system is targeted preferentially [363-365].

Liposomes have a significant advantage over already approved aluminum-based vaccine delivery system because they are highly flexible and capable of activating a wide range of stimulators. As a result, this novel liposome-based adjuvant system is a highly promising platform technology that meets many of the requirements, both as an adjuvant and from a pharmacological standpoint. Much researches have been done on subunit protein or peptide vaccines in order to produce effective vaccines with acceptable safety profiles while yet producing significant immunogenicity. However, enhanced safety comes at the cost of low immunogenicity and higher metabolic degradation of sensitive antigens [366-368]. Liposomes are an intriguing approach for addressing these issues because they can provide two key qualities *i.e.* antigen delivery and adjuvant characteristics [369-371].

Ophthalmic drug delivery using liposomes: Over the last five decades, ocular drug delivery research has contributed significantly, pushing scientists to consider the benefits and drawbacks of this drug delivery method. The most frequent ocular medication delivery formulation is topical eye drops. Given the substantial precorneal loss of medicines due to tears formation and ocular obstacles, this topical administration is only focused on anterior ocular disorders and has a high precorneal loss of pharmaceuticals [372-374]. Antibiotics are commonly utilized for the ocular route in the form of a solution or a cream. Nevertheless, their localized bioavailability must be enhanced in order to reduce administration frequency and adverse effects while increasing therapeutic efficacy. Controlled release formulations for ocular antibiotic administration

were proposed for this purpose [375]. *In situ* gel and hydrogels, liposomes, nanoparticles, niosomes, nanoemulsions and microemulsions are among the new ocular drug delivery types. They can be used with hydrophilic or lipophilic medicines, can target a specific location and can be administered in a variety of ways. *In situ* gelling systems can enhance the precorneal residence duration and reduce medication loss owing to the tear by using the right excipients. Different polymers, production techniques and compositions enable nanoparticles to react to a requirement for mucoadhesion, topical, periocular or intraocular delivery and to achieve a stable, effective and non-irritating formulation for the patient [376-380]. Liposomes have been studied as a carrier system for ocular medication administration because of their benefits. It's a biocompatible, biodegradable nanocarrier. By adhering to the ocular surface and increasing residence duration, it can improve the penetration of poorly absorbed drug molecules. Both hydrophilic and hydrophobic drug molecules can be encapsulated in it. Liposomes can also improve pharmacokinetic profiles, increase therapeutic efficacy and minimise toxicity associated with larger doses. Liposomes have been studied extensively for the treatment of both anterior and posterior segment eye diseases due to their versatility [381-384].

Incorporating different bioadhesive and penetration boosting polymers into current methods for anterior segment medication administration focuses on increasing corneal adherence and permeation. Improvements in intravitreal half-life and tailored medication administration to the retina are required in the case of posterior segment diseases. Ophthalmic medication delivery has been investigated using liposome technology [385,386]. However, there are certain difficulties to be addressed, such as the challenging manufacturing and storage of liposomes, which are known to produce long-term adverse effects. Vitreal condensation, vitreal bodies in the lower portion of the eye and retinal anomalies have all been reported because of intravitreal liposome injection. As a result, while designing liposomal formulations for ophthalmic use, all of these variables must be considered [387-389]. Several antibacterial, antifungal, anti-inflammatory, antiglaucoma, immuno-modulatory, antioxidants medicines *e.g.* tetracyclines, amino-glycoside group of antibiotics, gentamycin, ciprofloxacin, amphotericin B, diclofenac, norfloxacin, chloramphenicol, 2-(2,6-dichloroanilino)phenyl acetic acid, cyclosporin, afouna, pilo-carpine, latanoprost, acetazolamide, edavarone have been developed as liposomal formulations to improve their ocular bioavailability in the treatment of various diseases [390-392]. The most frequent route of administration for the treatment of ocular disorders is the topical route. However, many layers of permeation barriers, ranging from the tear film to the inner layers of the cornea, make therapeutic concentrations in the target tissue within the eye difficult to obtain. To overcome these obstacles and offer continuous and targeted medication delivery, significant progress has been achieved in the development of drug carriers. Liposomal drug delivery methods are advantageous because of their unusual structure, which allows them to entrap both hydrophilic and hydrophobic medicines. Despite this, most of the researchers looking at the topical use of liposomes for a variety of ocular diseases are still in the preclinical stage, with none moving on to clinical trials [393-395]. The development of customised liposomes will be based on the finding of appropriate target molecules on the corneal epithelial cells or maybe tight junctions. Immunoliposomes and cationic liposomes are also predicted to be used increasingly often in the administration of topical ophthalmic medications [393,397].

Liposome for diagnostic imaging: Current accuracy and personalized medicines rely heavily on various imaging techniques to detect a number of diseases including various types of cancer. Imaging has a wide range of uses in clinic, including medication delivery monitoring, accurate illness diagnosis, assessing response to therapy and directing minimally invasive operations [398,399]. Traditional imaging techniques including computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) all have target specificity, which limits their therapeutic value. Due to recent developments in imaging techniques, molecular genetics and chemistry, substantial progress has been made in the field of molecular imaging [400,401]. The measurement, characterization and visualization of biological processes at the cellular and molecular level in humans and other living systems is referred to as molecular imaging [402]. Liposomes have a lengthy history of being used to deliver imaging agents. Liposomes are ideal for transporting diagnostic moieties utilized in all imaging modalities because of their capacity to trap various compounds in both the aqueous phase and the liposome membrane segment. Since the chemical composition of the reporter moieties employed in the various modalities differs, a variety of methods for loading liposomes with the specified contrast agent are required. Moreover, the responsiveness and clarity of imaging modalities varies, requiring various quantities of a diagnostic label to be given to the region of interest [403-405]. These broad concerns have resulted in the creation of a family of liposomal contrast agents for a variety of applications. Liposomes containing hydrophilic polymers like PEG on their surfaces linger in the bloodstream longer and eventually localise in greater quantities in the tumour location due to the EPR effect. Active targeting of medicines or delivery systems to the desired particular cell, sub-cell, molecule, receptors, protein, peptide, hormone, or enzyme relevant to the illness is the only way of achieving targeted specifically molecular imaging of pharmaceuticals or delivery systems [406-408]. Liposomes have also been investigated for theranostic applications, such as imaging and treatment for a range of illnesses, primarily cancer. Imaging and treatment may be done simultaneously with the use of nano-sized, theranostic liposomes. Furthermore, such target-specific, nano-sized theranostic liposomes can be used for molecular imaging. *In vitro* TN-C overexpressed cancer cell lines, Gd-loaded, active-targeted liposomes were shown to have promise as MRI contrast agents for tumour diagnosis as compared to non-targeted ones at 37 ºC. Zhang *et al.* [148,409,410] developed Gd-DTPA encapsulated, AS1411 modified, aptamer-modified thermosensitive liposomes. When compared to non-targeted liposomes, these liposomes were proven to be effective tumour imaging MRI agents in an *in vitro* MCF-7 cell line. The use of

diagnostic liposomes in skeletal magnetic resonance imaging was also studied. Intervertebral injection of gadolinium enhances articular surface visibility by compensating for the poor inherent contrast of joint components. However, precise imaging of the cartilage surface with regard to early arthrotic change and chondral defects is limited due to intracartilaginous dispersion of the contrast medium in the cartilage layer. By encasing gadolinium in liposomes, researchers were able to distinguish the joint space from the hyaline cartilage surface, enabling for the early identification of tiny articular cartilage lesions in living organisms [411-414]. To assess the real advantage of encapsulating paramagnetic compounds, more research is required contrasting liposomally encapsulated contrast agents for magnetic resonance imaging to standard nonliposomal formulations [415].

Liposome industry and commercial market of liposome: Recently, the COVID-19 pandemic has brought attention to the vulnerabilities inside the healthcare system. As a result of the growing number of COVID-19 patients, in particular in the United States and Europe, research institutes are being pressured to expedite R&D work to produce medicines and coronavirus vaccines [416]. Companies on the liposome medicines market are thus exploiting the chance for their research on efficient antiviral agents nanomaterials like nanocrystals, liposomes and nanoparticles. For normal clinical procedures, liposome pharmacology is used by enhanced drug activity *in vivo* and *in vitro*. Companies in the market for liposomal drug delivery are focused more on nanosystems of drug delivery that involve key antivirals and their transportation through cell and intracellular barriers. Liposomes therefore provide considerable potential for the treatment of coronavirus in ongoing research investigations conducted by medical firms [417,418].

New techniques for liposome surface functionalization are giving pharmaceutical industry additional opportunity. As a helpful biocompatible instrument for vehiculate and deliver lipophilic, hydrophilic and amphiphilic chemicals, liposome drug delivery is widely recognized. Nevertheless, some of the limits of liposome drug delivery are significant toxicity and resistance at large dosages. Through the adjustment of lipid content and surface with various ligands, firms therefore move from simple traditional to second or third generation liposomes. Many preparation procedures for this aim were developed in the previous decades, but most them particularly for the laboratory and fewer for the industrial approach. However, the manufacturing of clinical material and marketed products delivering sterile, well-known and stable products requires a high scale capacity. Unfortunately, dependent on the properties of the lipids themselves the availability of specific techniques and quality factors. The variety of liposome types to be selected for liposome based medication is therefore restricted [181,419-421].

The liposomal drugs trade includes sales by companies (organizations, traders and partnerships) of liposomal drug delivery systems and related services that produce liposomal medicinal products. Several prominent firms undertake strategic efforts such as partnerships and the development of new products which will likely be a significant tendency for the market in liposomal drug supply systems. Several firms are uniting to create liposome drug supply systems in order to extend their global array of products and operations [36,171]. The increase in the number of instances of cancer worldwide will likely lead to the enhancement of the business for liposomal medicinal products during the projected timeline. As a directed therapeutics of cancer, the liposomal drug delivery systems are utilized for radiation, chemotherapy and surgery [221]. The worldwide liposome medicines market in 2018 was worth $3.6 trillion and is expected to increase from 2021 to 2030 on a substantial CAGR. Increases in cancer incidence are driving the global market in the supply of pharmaceuticals with liposomes, particularly liposoma embodied drugs, increases of liposomes as systems for the supply of drugs, their benefits, technical developments and strong drug pipelines. The benefits given by the administration of liposome medications, including the uniqueness of both hydrophilic and lipophilic substances and the fact that a variety of medicines are encapsulated by these vesicles, help the world market to flourish [60,422]. Liposomes can be separated into diagnostic and therapeutic applications in pharmaceutical delivery. In contrast to medicinal gene delivery, these uses include antimicrobial, cancer and antifungal medicines. Doxil, AmBisome and DepoDur are the major substances created by the use of liposome drug delivery. The rise in liposome application systems as pharmaceutical systems is helping to increase the global market for liposome drugs. During the projected period, the high cost of liposomal medicines supply equipment would hinder market expansion. The high cost of the devices increases the expense and cost of liposomal therapy, which impedes market expansion [423-425].

Conclusion and future scope of liposome

Increase the effects and decrease in the adverse effects of existing and new anticancer medicines are more important for the expansion of these sophisticated medicine supply systems. In this respect, the primary arguments for the application of liposomal transporters are still the improved pharmacokinetic characteristics of liposomes, which can be associated with a superior quality toxicity profile. There are other novel methods to the physiology of and pharmacokinetic behaviour of liposomes, such as the anti-angiogenic characteristics of cationic liposomes and the development of immunoliposomes [426]. Furthermore, liposomes provide various targets and have demonstrated their ability to develop as a novel cancer therapy group. Some major questions and many obstacles are silent, with their full effectiveness and safety limits. Further knowledge of clinical data will lead to the further streamlining of improved liposomes with increased selectivity, effectiveness and safety in cancer treatment. Customized liposome has been shown to be an important tool of targeting the heart, liver, kidney, brain, lung and bone [59]. For malignancies, the treatment of breast cancer and liver cancer with the modified liposome is discussed in several articles [427,428]. Liposome has been identified as a multifaceted medicine carrier. The medication administration mediated by liposomes offers wide variety of applications and functions including the usage of a cell ligand specifically designed for the surface due to easy structural

modification. Liposomes also have certain disadvantage in the mediated distribution of medicinal products. The major difficulty is that the most typical film barriers cannot be crossed owing to their size. In future, liposome mediated drug provision will nonetheless have a more prominent function to play in the clinical setting with the advancement of liposome technology [429].

What else can we expect from liposomes? As far as technology is concerned, found in nature phospholipids are expected (already) to be substituted with low cost synthesized, well defining amphipathic lipids with different chain lengths and phase transition temperature.

Techniques of liposome production aim to progress in the higher loads of drug to lipid mass, narrower distribution of the size of the vesicle, shelf life and freeze drained formulations. It is anticipated that there would be an increased utilization of lipid-based medications within bilayers, while the prevalence of water-soluble pharmaceuticals administered in aqueous solutions is expected to diminish. There seem to be a variety of therapeutic areas in which liposomes seem promising. For example, in the formation of lipid-conjugated preparations, which might prevent quantitative localization in RES and show certain positioning in tumour tissues, it appears to be short- to medium term in cancer therapy in the future. These compositions are intended to decrease side effects, enhance the quality of life and perhaps expand the wellbeing of cancer patients [13,430,431]. In antibiotic treatment the potential of liposomes is significant since many intracellular microbial illnesses are located in lysosomes where liposomes finish following cell absorption. Nevertheless, designed antimicrobial medicines that have adequate access to ICS may be unnecessary for delivery systems. One field in which liposomes already have had an important influence is external uses for aesthetic skin treatment. Indeed, liposome-based cosmetics have benefited by showing that robust vesicles may be produced on an industrial level in the liposomological area. A variety of drugs may be transported in liposomes, which has been acknowledged as such by many. A particular cell ligand can be targeted on the liposome's interface because of the ease with which their shape can be changed. Liposome-mediated drug delivery will, however, become increasingly relevant in the clinical context with the advancement of liposome technologies. The modern technologies are therefore highly developed and the non-invasive character of topical usage combined with sophisticated absorption techniques imply that a range of eye, skin and external mucosal-treated products can emerge [432-434]. Hence, a fantastic potential of liposome is awaiting and more researchers must join to contribute in this emerging field with elevated commercial prospects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. V.P. Torchilin, *Nat. Rev. Drug Discov.*, **4**, 145 (2005); https://doi.org/10.1038/nrd1632
2. R.R. Sawant and V.P. Torchilin, *Soft Matter*, **6**, 4026 (2010); https://doi.org/10.1039/b923535n
3. D.D. Lasic and D. Papahadjopoulos, *Science*, **267**, 1275 (1995); https://doi.org/10.1126/science.7871422
4. K. Kamiya and S. Takeuchi, *J. Mater. Chem. B Mater. Biol. Med.*, **5**, 5911 (2017); https://doi.org/10.1039/C7TB01322A
5. D. Konetski, D. Zhang, D.K. Schwartz and C.N. Bowman, *Chem. Mater.*, **30**, 8757 (2018); https://doi.org/10.1021/acs.chemmater.8b02608
6. U. Kauscher, M.C.A. Stuart, P. Drücker, H.-J. Galla and B.J. Ravoo, *Langmuir*, **29**, 7377 (2013); https://doi.org/10.1021/la3045434
7. M. Petaccia, M. Condello, L. Giansanti, A. La Bella, F. Leonelli, S. Meschini, D. Gradella Villalva, E. Pellegrini, F. Ceccacci, L. Galantini and G. Mancini, *MedChemComm*, **6**, 1639 (2015); https://doi.org/10.1039/C5MD00077G
8. T. Elbayoumi and V. Torchilin, *Methods Mol. Biol.*, **605**, 1 (2010); https://doi.org/10.1007/978-1-60327-360-2_1
9. S. Bhattacharjee, Liposomes; In: Principles of Nanomedicine, Jenny Stanford Publishing, Edn. 1 (2019).
10. A. Akbarzadeh, R. Rezaei-Sadabady, S. Davaran, S.W. Joo, N. Zarghami, Y. Hanifehpour, M. Samiei, M. Kouhi and K. Nejati-Koshki, *Nanoscale Res. Lett.*, **8**, 102 (2013); https://doi.org/10.1186/1556-276X-8-102
11. M. Bally, K. Bailey, K. Sugihara, D. Grieshaber, J. Vörös and B. Städler, *Small*, **6**, 2481 (2010); https://doi.org/10.1002/smll.201000644
12. M. Rudokas, M. Najlah, M.A. Alhnan and A. Elhissi, *Med. Princ. Pract.*, **25(suppl 2)**, 60 (2016); https://doi.org/10.1159/000445116
13. K.S. Ahmed, S.A. Hussein, A.H. Ali, S.A. Korma, Q. Lipeng and C. Jinghua, *J. Drug Target.*, **27**, 742 (2019); https://doi.org/10.1080/1061186X.2018.1527337
14. T. Allen and P. Cullis, *Adv. Drug Deliv. Rev.*, **65**, 36 (2013); https://doi.org/10.1016/j.addr.2012.09.037
15. P. Goyal, K. Goyal, S. Kumar, A. Singh, O. Katare and D. Mishra, *Acta Pharm.*, **55**, 1 (2005).
16. A. Hussain, M.N. Ahsan and A. Samad, Transdermal Liposomal Drug Delivery System; In: Liposomal Delivery Systems: Advances and Challenges, Future Medicine Ltd., pp 36-49 (2015).
17. A. Maheswaran, P. Brindha, A.R. Mullaicharam and K. Masilamani, *Int. J. Pharm. Sci. Rev. Res.*, **23**, 295 (2013).
18. N. Maurer, D. Fenske and P. Cullis, *Expert Opin. Biol. Ther.*, **1**, 923 (2001); https://doi.org/10.1517/14712598.1.6.923
19. N.A. Kshirsagar, S.K. Pandya, G.B. Kirodian and S. Sanath, *J. Postgrad. Med.*, **51 Suppl 1**, S5 (2005).
20. T. Olusanya, R.H. Ahmad, M. Ibegbu, J. Smith and A. Elkordy, *Molecules*, **23**, 907 (2018); https://doi.org/10.3390/molecules23040907
21. C. Kiparissides and O. Kammona, *Can. J. Chem. Eng.*, **91**, 638 (2013); https://doi.org/10.1002/cjce.21685
22. F. Li and J.-Y. Wang, *Expert Opin. Drug Deliv.*, **6**, 531 (2009); https://doi.org/10.1517/17425240902936834
23. V. Muzykantov and S. Muro, *Int. J. Transp. Phenom.*, **12**, 41 (2011).
24. S.S. Krishna, M.S. Sudheesh and V. Viswanad, *J. Liposome Res.*, (2023); https://doi.org/10.1080/08982104.2023.2199068
25. E. Lavelle, *Crit. Rev. Ther. Drug Carrier Syst.*, **18**, 46 (2001); https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v18.i4.10
26. L. van der Koog, T.B. Gandek and A. Nagelkerke, *Adv. Healthcare Mater.*, **11**, 2100 (2022); https://doi.org/10.1002/adhm.202100639
27. M. Preiss and G. Bothun, *Expert Opin. Drug Deliv.*, **8**, 1025 (2011); https://doi.org/10.1517/17425247.2011.584868

28. X. An and R. Gui, Stimuli-Responsive Liposome and Control Release Drug, In: Nanostructures for Drug Delivery, Chap. 28, pp 887-917 (2017); https://doi.org/10.1016/B978-0-323-46143-6.00028-2
29. E. Heidarli, S. Dadashzadeh and A. Haeri, *Iran. J. Pharm. Res.*, **16**, 1273 (2017).
30. D. Pornpattananangkul, S. Olson, S. Aryal, M. Sartor, C.-M. Huang, K. Vecchio and L. Zhang, *ACS Nano*, **4**, 1935 (2010); https://doi.org/10.1021/nn9018587
31. D. v and K. an, *RGUHS J. Pharm. Sci.*, **4**, 47 (2014); https://doi.org/10.5530/rjps.2014.2.3
32. J.-S. Kim, *J. Pharm. Investig.*, **46**, 387 (2016); https://doi.org/10.1007/s40005-016-0260-1
33. J. Tang, R. Liu and Z. Dai, *Huaxue Jinzhan*, **30**, 1669 (2018); https://doi.org/10.7536/PC180205
34. M. Ranson, A. Howell, S. Cheeseman and J. Margison, *Cancer Treat. Rev.*, **22**, 365 (1996); https://doi.org/10.1016/S0305-7372(96)90009-2
35. G. Smistad, S. Bøyum, S. Alund, A. Samuelsen and M. Hiorth, *Carbohydr. Polym.*, **90**, 1337 (2012); https://doi.org/10.1016/j.carbpol.2012.07.002
36. C. Zylberberg and S. Matosevic, *Drug Deliv.*, **23**, 3319 (2016); https://doi.org/10.1080/10717544.2016.1177136
37. J. Kraft, J. Freeling, Z. Wang and R. Ho, *J. Pharm. Sci.*, **103**, 29 (2014); https://doi.org/10.1002/jps.23773
38. M. Hossann, B. Kneidl, M. Peller, L. Lindner and G. Winter, *Int. J. Nanomedicine*, **9**, 4387 (2014); https://doi.org/10.2147/IJN.S49297
39. G. Caracciolo, *Nanoscale*, **10**, 4167 (2018); https://doi.org/10.1039/C7NR07450F
40. U. Bulbake, S. Doppalapudi, N. Kommineni and W. Khan, *Pharmaceutics*, **9**, 12 (2017); https://doi.org/10.3390/pharmaceutics9020012
41. G. Amoabediny, F. Haghiralsadat, S. Naderinezhad, M.N. Helder, E.A. Kharanaghi, J.M. Arough and B. Zandieh-Doulabi, *Int. J. Polym. Mater.*, **67**, 383 (2018); https://doi.org/10.1080/00914037.2017.1332623
42 V. Nele, F. D'Aria, V. Campani, T. Silvestri, M. Biondi, C. Giancola and G. De Rosa, *J. Liposome Res*., (2023); https://doi.org/10.1080/08982104.2023.2224449
43. Y. Oda, R. Suzuki and K. Maruyama, *Drug Deliv. Syst.*, **31**, 370 (2016); https://doi.org/10.2745/dds.31.370
44. M. Slingerland, H.-J. Guchelaar and H. Gelderblom, *Drug Discov. Today*, **17**, 160 (2012); https://doi.org/10.1016/j.drudis.2011.09.015
45. M.S. Mufamadi, V. Pillay, Y.E. Choonara, L.C. Du Toit, G. Modi, D. Naidoo and V.M.K. Ndesendo, *J. Drug Deliv.*, **2011**, 1 (2011); https://doi.org/10.1155/2011/939851
46. A. Schroeder, J. Kost and Y. Barenholz, *Chem. Phys. Lipids*, **162**, 1 (2009); https://doi.org/10.1016/j.chemphyslip.2009.08.003
47. A.A. Khan, K.S. Allemailem, S.A. Almatroodi, A. Almatroudi and A.H. Rahmani, *3 Biotech*, **10**, 163 (2020); https://doi.org/10.1007/s13205-020-2144-3
48. M. Riaz, M. Riaz, X. Zhang, C. Lin, K. Wong, X. Chen, G. Zhang, A. Lu and Z. Yang, *Int. J. Mol. Sci.*, **19**, 195 (2018); https://doi.org/10.3390/ijms19010195
49. T.X. Nguyen, L. Huang, M. Gauthier, G. Yang and Q. Wang, *Nanomedicine*, **11**, 1169 (2016); https://doi.org/10.2217/nnm.16.9
50. C. Weber, M. Voigt, J. Simon, A.-K. Danner, H. Frey, V. Mailänder, M. Helm, S. Morsbach and K. Landfester, *Biomacromolecules*, **20**, 2989 (2019); https://doi.org/10.1021/acs.biomac.9b00539
51. D. Mishra, R. Shandilya and P. Mishra, *Nanomedicine*, **14**, 2023 (2018); https://doi.org/10.1016/j.nano.2018.05.021
52. S. Gorgieva, Preparative Methods and Devices of Bioinspired Materials in Drug-Delivery Systems, In: Bioinspired Materials for Medical Applications, Woodhead Publishing, Chap. 2, pp 45-67 (2007); https://doi.org/10.1016/B978-0-08-100741-9.00002-4
53. N. Marasini, K.A. Ghaffar, M. Skwarczynski and I. Toth, Liposomes as a Vaccine Delivery System, Chap. 12, pp 221–239 (2016); https://doi.org/10.1016/B978-0-323-39981-4.00012-9
54. M. Gharbavi, J. Amani, H. Kheiri-Manjili, H. Danafar and A. Sharafi, *Adv. Pharmacol. Sci.*, **2018**, 1 (2018); https://doi.org/10.1155/2018/6847971
55. M.A. Pinsky, *J. Clin. Aesthet. Dermatol.*, **10**, 27 (2017).
56. M. Alavi, N. Karimi and M. Safaei, *Adv. Pharm. Bull.*, **7**, 3 (2017); https://doi.org/10.15171/apb.2017.002
57. N.G. Kotla, B. Chandrasekar, P. Rooney, G. Sivaraman, A. Larrañaga, K.V. Krishna, A. Pandit and Y. Rochev, *ACS Biomater. Sci. Eng.*, **3**, 1262 (2017); https://doi.org/10.1021/acsbiomaterials.6b00681
58. S. Rayamajhi and S. Aryal, *J. Mater. Chem. B Mater. Biol. Med.*, **8**, 4552 (2020); https://doi.org/10.1039/D0TB00744G
59. W. Yan, S.S.Y. Leung and K.K.W. To, *Nanomedicine*, **15**, 303 (2020); https://doi.org/10.2217/nnm-2019-0308
60. H. Daraee, A. Etemadi, M. Kouhi, S. Alimirzalu and A. Akbarzadeh, *Artif. Cells Nanomed. Biotechnol.*, **44**, 381 (2016); https://doi.org/10.3109/21691401.2014.953633
61. Y. Panahi, M. Farshbaf, M. Mohammadhosseini, M. Mirahadi, R. Khalilov, S. Saghfi and A. Akbarzadeh, *Artif. Cells Nanomed. Biotechnol.*, **45**, 788 (2017); https://doi.org/10.1080/21691401.2017.1282496
62. C. Pucci, C. Martinelli and G. Ciofani, *Future Oncol.*, **16**, 81 (2020); https://doi.org/10.2217/fon-2019-0767
63. Y. Rahimpour and H. Hamishehkar, *Expert Opin. Drug Deliv.*, **9**, 443 (2012); https://doi.org/10.1517/17425247.2012.666968
64. P.S. Zangabad, S. Mirkiani, S. Shahsavari, B. Masoudi, M. Masroor, H. Hamed, Z. Jafari, Y.D. Taghipour, H. Hashemi, M. Karimi and M.R. Hamblin, *Nanotechnol. Rev.*, **7**, 95 (2018); https://doi.org/10.1515/ntrev-2017-0154
65. E. Rideau, R. Dimova, P. Schwille, F.R. Wurm and K. Landfester, *Chem. Soc. Rev.*, **47**, 8572 (2018); https://doi.org/10.1039/C8CS00162F
66. C. Has and P. Sunthar, *J. Liposome Res.*, **30**, 336 (2019); https://doi.org/10.1080/08982104.2019.1668010
67. E. Khanniri, N. Bagheripoor-Fallah, S. Sohrabvandi, A.M. Mortazavian, K. Khosravi-Darani and R. Mohammad, *Crit. Rev. Food Sci. Nutr.*, **56**, 484 (2016); https://doi.org/10.1080/10408398.2013.779571
68. C. Jaafar-Maalej, R. Diab, V. Andrieu, A. Elaissari and H. Fessi, *J. Liposome Res.*, **20**, 228 (2010); https://doi.org/10.3109/08982100903347923
69. G.H. Shin, S.K. Chung, J.T. Kim, H.J. Joung and H.J. Park, *J. Agric. Food Chem.*, **61**, 11119 (2013); https://doi.org/10.1021/jf4035404
70. K. Yang, J.T. Delaney, U.S. Schubert and A. Fahr, *J. Liposome Res.*, **22**, 31 (2012); https://doi.org/10.3109/08982104.2011.584319
71. C. Ou, Y. Liang, S. Shen and X. Han, *Nanfang Nongye Xuebao*, **42**, 1259 (2011).
72. P. Gentine, L. Bourel-Bonnet and B. Frisch, *J. Liposome Res.*, **23**, 11 (2013); https://doi.org/10.3109/08982104.2012.717298
73. J.C. Mathai and V. Sitaraman, *Biochem. Educ.*, **15**, 147 (1987); https://doi.org/10.1016/0307-4412(87)90052-5
74. A.K. Sailaja and M. Shreya, *Nano Biomed. Eng.*, **10**, 174 (2018); https://doi.org/10.5101/nbe.v10i2.p174-180
75. V. Ravalika and A.K. Sailaja, *Nano Biomed. Eng.*, **9**, 242 (2017); https://doi.org/10.5101/nbe.v9i3.p242-248
76. D. Deamer, *Ann. N.Y. Acad. Sci.*, **308**, 250 (1978); https://doi.org/10.1111/j.1749-6632.1978.tb22027.x
77. E. Chioma, *Universal J. Pharm. Res.*, **1**, 1 (2016); https://doi.org/10.22270/ujpr.v1i1.R1
78. S. Varona, Á. Martín and M.J. Cocero, *Ind. Eng. Chem. Res.*, **50**, 2088 (2011); https://doi.org/10.1021/ie102016r

79. S. Ghanbarzadeh, H. Valizadeh and P. Zakeri-Milani, *Bioimpacts*, **3**, 75 (2013); https://doi.org/10.5681/bi.2013.016
80. H. Elsana, T.O.B. Olusanya, J. Carr-wilkinson, S. Darby, A. Faheem and A.A. Elkordy, *Sci. Rep.*, **9**, 15120 (2019); https://doi.org/10.1038/s41598-019-51065-4
81. S. Franzé, F. Selmin, E. Samaritani, P. Minghetti and F. Cilurzo, *Pharmaceutics*, **10**, 139 (2018); https://doi.org/10.3390/pharmaceutics10030139
82. B. Sylvester, A. Porfire, M. Achim, L. Rus and I. Tomutã, *Drug Dev. Ind. Pharm.*, **44**, 385 (2018); https://doi.org/10.1080/03639045.2017.1395457
83. Y. Wang and D.W. Grainger, *Adv. Drug Deliv. Rev.*, **151-152**, 56 (2019); https://doi.org/10.1016/j.addr.2019.03.003
84. A. Porfire, D.M. Muntean, L. Rus, B. Sylvester and I. Tomutã, *Saudi Pharm. J.*, **25**, 981 (2017); https://doi.org/10.1016/j.jsps.2017.01.007
85. P. Savadi, T. Taghavi-Fard, M. Milani, N. Hashemzadeh, V. Panahi, N.A.J. McMillan and S. Hallaj-Nezhadi, *Curr. Microbiol.*, **77**, 2356 (2020); https://doi.org/10.1007/s00284-020-02008-0
86. S.G.M. Ong, M. Chitneni, K.S. Lee, L.C. Ming and K.H. Yuen, *Pharmaceutics*, **8**, 36 (2016); https://doi.org/10.3390/pharmaceutics8040036
87. A. Hinna, F. Steiniger, S. Hupfeld, P. Stein, J. Kuntsche and M. Brandl, *J. Liposome Res.*, **26**, 11 (2016); https://doi.org/10.3109/08982104.2015.1022556
88. P. Guo, J. Huang, Y. Zhao, C.R. Martin, R.N. Zare and M.A. Moses, *Small*, **14**, 1703493 (2018); https://doi.org/10.1002/smll.201703493
89. N. Berger, A. Sachse, J. Bender, R. Schubert and M. Brandl, *Int. J. Pharm.*, **223**, 55 (2001); https://doi.org/10.1016/S0378-5173(01)00721-9
90. R. Mendez and S. Banerjee, *Methods Mol. Biol.*, **1609**, 255 (2017); https://doi.org/10.1007/978-1-4939-6996-8_21
91. M.M. Lapinski, A. Castro-Forero, A.J. Greiner, R.Y. Ofoli and G.J. Blanchard, *Langmuir*, **23**, 11677 (2007); https://doi.org/10.1021/la7020963
92. M.J. Valle and A. Navarro, *Curr. Pharm. Anal.*, **11**, 86 (2015); https://doi.org/10.2174/1573412910666141114221935
93. M. Mozafari, *Methods Mol. Biol.*, **605**, 29 (2010); https://doi.org/10.1007/978-1-60327-360-2_2
94. B. Pradhan, N. Kumar, S. Saha and A. Roy, *J. Appl. Pharm. Res*., **3**, 1 (2015).
95. E. Mayhew, R. Lazo, W. Vail, J. King and A. Green, *Biochim. Biophys. Acta Biomembr.*, **775**, 169 (1984); https://doi.org/10.1016/0005-2736(84)90167-6
96. R.K. Gunda, J.N. Suresh Kumar, G. Bhargavi, S.P.A. Bhavani, B. Sandhya, K.N.V.L. Padmaja and S. Praveen, *British J. Multidiscipl. Adv. Stud*., **4**, 31 (2023); https://doi.org/10.37745/bjmas.2022.0268
97. D. Liu and L. Huang, *Biochim. Biophys. Acta Biomembr.*, **981**, 254 (1989); https://doi.org/10.1016/0005-2736(89)90035-7
98. M.E. Bosworth, C. Anthony Hunt and D. Pratt, *J. Pharm. Sci.*, **71**, 806 (1982); https://doi.org/10.1002/jps.2600710722
99. N. Dimov, E. Kastner, M. Hussain, Y. Perrie and N. Szita, *Sci. Rep.*, **7**, 12045 (2017); https://doi.org/10.1038/s41598-017-11533-1
100. H. Kukuchi, H. Yamauchi and S. Hirota, *Chem. Pharm. Bull. (Tokyo)*, **39**, 1522 (1991); https://doi.org/10.1248/cpb.39.1522
101. J.Y. Chun, F.C. Godoi, N. Bansal, M. Morand and B. Bhandari, *Dry. Technol.*, **35**, 1020 (2017); https://doi.org/10.1080/07373937.2016.1229333
102. M.G. Maniyar and C.R. Kokare, *J. Pharm. Investig.*, **49**, 259 (2019); https://doi.org/10.1007/s40005-018-0403-7
103. A. Polozova, X. Li, T. Shangguan, P. Meers, D. Schuette, N. Ando, S. Gruner and W. Perkins, *Biochim. Biophys. Acta Biomembr.*, **1668**, 117 (2005); https://doi.org/10.1016/j.bbamem.2004.11.012
104. M. Glavas-Dodov, K. Goracinova, K. Mladenovska and E. Fredro-Kumbaradzi, *Int. J. Pharm.*, **242**, 381 (2002); https://doi.org/10.1016/S0378-5173(02)00221-1
105. S. Madan, C. Nehate, T.K. Barman, A.S. Rathore and V. Koul, *Drug Dev. Ind. Pharm.*, **45**, 395 (2019); https://doi.org/10.1080/03639045.2018.1546310
106. M. Glavas-Dodov, E. Fredro-Kumbaradzi, K. Goracinova, S. Calis, M. Simonoska and A.A. Hincal, *Acta Pharm.*, **53**, 241 (2003).
107. S.R. Paliwal, R. Paliwal and S.P. Vyas, *Drug Deliv.*, **22**, 231 (2015); https://doi.org/10.3109/10717544.2014.882469
108. D.S. Ferreira, S.C.A. Lopes, M.S. Franco and M.C. Oliveira, *Ther. Deliv.*, **4**, 1099 (2013); https://doi.org/10.4155/tde.13.80
109. Y. Fan, C. Chen, Y. Huang, F. Zhang and G. Lin, *Colloids Surf. B Biointerfaces*, **151**, 19 (2017); https://doi.org/10.1016/j.colsurfb.2016.11.042
110. X. Liu and G. Huang, *Asian J. Pharm. Sci.*, **8**, 319 (2013); https://doi.org/10.1016/j.ajps.2013.11.002
111. Y. Kumar, K. Kuche, R. Swami, S.S. Katiyar, D. Chaudhari, P.B. Katare, S.K. Banerjee and S. Jain, *Int. J. Pharm.*, **573**, 118889 (2020); https://doi.org/10.1016/j.ijpharm.2019.118889
112. A. Yaroslavov, A. Efimova, N. Smirnova, D. Erzunov, N. Lukashev, I. Grozdova and N. Melik-Nubarov, *Colloids Surf. B Biointerfaces*, **190**, 110906 (2020); https://doi.org/10.1016/j.colsurfb.2020.110906
113 S. Saraf and S.K. Jain, *Drug Deliv. Transl. Res.*, **13**, 2961 (2023); https://doi.org/10.1007/s13346-023-01364-1
114. K.M. Huh, H.C. Kang, Y.J. Lee and Y.H. Bae, *Macromol. Res.*, **20**, 224 (2012); https://doi.org/10.1007/s13233-012-0059-5
115. H. Bi, J. Xue, H. Jiang, S. Gao, D. Yang, Y. Fang and K. Shi, *Asian J. Pharm. Sci.*, **14**, 365 (2019); https://doi.org/10.1016/j.ajps.2018.07.006
116. A.K. Teotia, H. Sami and A. Kumar, Ed.: Z. Zhang, Thermo-responsive Polymers: Structure and Design of Smart Materials, In: Switchable and Responsive Surfaces and Materials for Biomedical Applications, Ed. Woodhead Publishing: Oxford, Chap. 1, pp 3-43 (2015).
117. M. Abri Aghdam, R. Bagheri, J. Mosafer, B. Baradaran, M. Hashemzaei, A. Baghbanzadeh, M. de la Guardia and A. Mokhtarzadeh, *J. Control. Release*, **315**, 1 (2019); https://doi.org/10.1016/j.jconrel.2019.09.018
118. L. Li, T.L.M. ten Hagen, D. Schipper, T.M. Wijnberg, G.C. van Rhoon, A.M.M. Eggermont, L.H. Lindner and G.A. Koning, *J. Control. Release*, **143**, 274 (2010); https://doi.org/10.1016/j.jconrel.2010.01.006
119. B. Kneidl, M. Peller, G. Winter, L.H. Lindner and M. Hossann, *Int. J. Nanomedicine*, **2014**, 4387 (2014); https://doi.org/10.2147/IJN.S49297
120. Y. Dou, K. Hynynen and C. Allen, *J. Control. Release*, **249**, 63 (2017); https://doi.org/10.1016/j.jconrel.2017.01.025
121. Y. Suzuki, K.H. Nagai, A. Zinchenko and T. Hamada, *Langmuir*, **33**, 2671 (2017); https://doi.org/10.1021/acs.langmuir.7b00448
122. S.J. Leung and M. Romanowski, *Theranostics*, **2**, 1020 (2012); https://doi.org/10.7150/thno.4847
123. S. Ghosh, K.A. Carter and J.F. Lovell, *Biomaterials*, **218**, 119341 (2019); https://doi.org/10.1016/j.biomaterials.2019.119341
124. C. Pernpeintner, J.A. Frank, P. Urban, C.R. Roeske, S.D. Pritzl, D. Trauner and T. Lohmüller, *Langmuir*, **33**, 4083 (2017); https://doi.org/10.1021/acs.langmuir.7b01020
125. A. Aygun, K. Torrey, A. Kumar and L.D. Stephenson, *Appl. Biochem. Biotechnol.*, **167**, 743 (2012); https://doi.org/10.1007/s12010-012-9724-6
126. K.G. Guliyev, A.E. Rzayeva and A.M. Guliyev, *Russ. J. Appl. Chem.*, **92**, 1215 (2019); https://doi.org/10.1134/S1070427219090052
127. M.-C. Fu, T. Higashihara and M. Ueda, *Polym. J.*, **50**, 57 (2018); https://doi.org/10.1038/pj.2017.46
128. O. Bertrand and J.-F. Gohy, *Polym. Chem.*, **8**, 52 (2017); https://doi.org/10.1039/C6PY01082B

129. S. Sun, S. Liang, W.-C. Xu, G. Xu and S. Wu, *Polym. Chem.*, **10**, 4389 (2019); https://doi.org/10.1039/C9PY00793H
130. J. Cui and A. Del Campo, Eds.: M.R. Aguilar and J. San Román, Photo-Responsive Polymers: Properties, Synthesis and Applications, In: Smart Polymers and their Applications, Eds. Woodhead Publishing, Chap. 4, pp 93-133 (2014).
131. S.S. Das, P. Bharadwaj, M. Bilal, M. Barani, A. Rahdar, P. Taboada, S. Bungau and G.Z. Kyzas, *Polymers*, **12**, 1397 (2020); https://doi.org/10.3390/polym12061397
132. U. Kauscher, M.N. Holme, M. Björnmalm and M.M. Stevens, *Adv. Drug Deliv. Rev.*, **138**, 259 (2019); https://doi.org/10.1016/j.addr.2018.10.012
133. Y. Lee and D.H. Thompson, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.*, **9**, e1450 (2017); https://doi.org/10.1002/wnan.1450
134. T.L. Rapp and C.A. DeForest, *Adv. Drug Deliv. Rev.*, **171**, 94 (2021); https://doi.org/10.1016/j.addr.2021.01.009
135. X. Zhang, B. Lei, Y. Wang, S. Xu and H. Liu, *Langmuir*, **35**, 5213 (2019); https://doi.org/10.1021/acs.langmuir.8b04094
136. F. Fouladi, K.J. Steffen and S. Mallik, *Bioconjug. Chem.*, **28**, 857 (2017); https://doi.org/10.1021/acs.bioconjchem.6b00736
137. M. Shahriari, M. Zahiri, K. Abnous, S.M. Taghdisi, M. Ramezani and M. Alibolandi, *J. Control. Release*, **308**, 172 (2019); https://doi.org/10.1016/j.jconrel.2019.07.004
138. F. Movahedi, R.G. Hu, D.L. Becker and C. Xu, *Nanomedicine*, **11**, 1575 (2015); https://doi.org/10.1016/j.nano.2015.03.006
139. E.S. Shchegravina, D.S. Tretiakova, A.S. Alekseeva, T.R. Galimzyanov, Y.N. Utkin, Y.A. Ermakov, E.V. Svirshchevskaya, V.V. Negrebetsky, N.Y. Karpechenko, V.P. Chernikov, N.R. Onishchenko, E.L. Vodovozova, A.Y. Fedorov and I.A. Boldyrev, *Bioconjug. Chem.*, **30**, 1098 (2019); https://doi.org/10.1021/acs.bioconjchem.9b00051
140. F.F. Sahle, M. Gulfam and T.L. Lowe, *Drug Discov. Today*, **23**, 992 (2018); https://doi.org/10.1016/j.drudis.2018.04.003
141. Y. Qiao, J. Wan, L. Zhou, W. Ma, Y. Yang, W. Luo, Z. Yu and H. Wang, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.*, **11**, e1527 (2019); https://doi.org/10.1002/wnan.1527
142. H. Pourhassan, G. Clergeaud, A.E. Hansen, R.G. Østrem, F.P. Fliedner, F. Melander, O.L. Nielsen, C.K. O'Sullivan, A. Kjær and T.L. Andresen, *J. Control. Release*, **261**, 163 (2017); https://doi.org/10.1016/j.jconrel.2017.06.024
143. A. Scomparin, H.F. Florindo, G. Tiram, E.L. Ferguson and R. Satchi-Fainaro, *Adv. Drug Deliv. Rev.*, **118**, 52 (2017); https://doi.org/10.1016/j.addr.2017.09.011
144. M. Li, C. Du, N. Guo, Y. Teng, X. Meng, H. Sun, S. Li, P. Yu and H. Galons, *Eur. J. Med. Chem.*, **164**, 640 (2019); https://doi.org/10.1016/j.ejmech.2019.01.007
145. R.G. Østrem, L. Parhamifar, H. Pourhassan, G. Clergeaud, O.L. Nielsen, A. Kjær, A.E. Hansen and T.L. Andresen, *J. Control. Release*, **262**, 212 (2017); https://doi.org/10.1016/j.jconrel.2017.07.031
146. A.H. Hansen, O.G. Mouritsen and A. Arouri, *Int. J. Pharm.*, **491**, 49 (2015); https://doi.org/10.1016/j.ijpharm.2015.06.005
147. V. Kumar, T.M. Koyasseril-Yehiya and S. Thayumanavan, Eds.: R. Nagarajan, Enzyme-Triggered Nanomaterials and Their Applications, In: Molecular Assemblies: Characterization and Applications, ACS Symposium Series, American Chemical Society, **1355**, pp 95-107 (2020); https://doi.org/10.1021/bk-2020-1355.ch007
148. H. Xing, K. Hwang and Y. Lu, *Theranostics*, **6**, 1336 (2016); https://doi.org/10.7150/thno.15464
149. E. Yuba, Eds.: N.Y. Abu-Thabit and A.S.H. Makhlouf, Stimuli-Responsive Polymer-Modified Liposomes and their Application to DDS; In: Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications, Woodhead Publishing, Chap. 11, pp 305-319 (2019).
150. E. Yuba, *J. Mater. Chem. B Mater. Biol. Med.*, **8**, 1093 (2020); https://doi.org/10.1039/C9TB02470K
151. M.T. Basel, T.B. Shrestha, D.L. Troyer and S.H. Bossmann, *ACS Nano*, **5**, 2162 (2011); https://doi.org/10.1021/nn103362n
152. R. de la Rica, D. Aili and M.M. Stevens, *Adv. Drug Deliv. Rev.*, **64**, 967 (2012); https://doi.org/10.1016/j.addr.2012.01.002
153. Y. Zeng, J. Ma, Y. Zhan, X. Xu, Q. Zeng, J. Liang and X. Chen, *Int. J. Nanomedicine*, **13**, 6551 (2018); https://doi.org/10.2147/IJN.S173431
154. A. Raza, U. Hayat, T. Rasheed, M. Bilal and H.M.N. Iqbal, *Eur. J. Med. Chem.*, **157**, 705 (2018); https://doi.org/10.1016/j.ejmech.2018.08.034
155. Y. Chi, X. Yin, K. Sun, S. Feng, J. Liu, D. Chen, C. Guo and Z. Wu, *J. Control. Release*, **261**, 113 (2017); https://doi.org/10.1016/j.jconrel.2017.06.027
156. M. Chen, D. Liu, F. Liu, Y. Wu, X. Peng and F. Song, *J. Control. Release*, **332**, 269 (2021); https://doi.org/10.1016/j.jconrel.2021.02.030
157. T.M. Allen and P.R. Cullis, *Adv. Drug Deliv. Rev.*, **65**, 36 (2013); https://doi.org/10.1016/j.addr.2012.09.037
158. G. Ren, M. Jiang, W. Guo, B. Sun, H. Lian, Y. Wang and Z. He, *Pharm. Dev. Technol.*, **23**, 22 (2018); https://doi.org/10.1080/10837450.2017.1287728
159. V. Kumar, P. Kewlani, A. Singh, Sanjay, A.K. Gautam and V.M. Rajamanickam, Multifunctional Liposomes to Attain Targeting, Stimuli Sensitive Drug Release and Imaging Cancer, In: Advanced Drug Delivery: Methods and Applications, Singapore: Springer Nature Singapore, pp. 49-87 (2023).
160. T. Li and S. Takeoka, 3 - Smart Liposomes for Drug Delivery. In *Smart Nanoparticles for Biomedicine*, Ciofani, G., Ed. Elsevier: 2018; pp 31-47.
161. X. Chen, Y. Zhang, C. Tang, C. Tian, Q. Sun, Z. Su, L. Xue, Y. Yin, C. Ju and C. Zhang, *Int. J. Pharm.*, **529**, 102 (2017); https://doi.org/10.1016/j.ijpharm.2017.06.071
162. X. Yin, Y. Chi, C. Guo, S. Feng, J. Liu, K. Sun and Z. Wu, *Pharm. Res.*, **34**, 2172 (2017); https://doi.org/10.1007/s11095-017-2225-0
163. L. Sercombe, T. Veerati, F. Moheimani, S.Y. Wu, A.K. Sood and S. Hua, *Front. Pharmacol.*, **6**, 286 (2015); https://doi.org/10.3389/fphar.2015.00286
164. W. Liu, A. Ye, F. Han and J. Han, *Adv. Colloid Interface Sci.*, **263**, 52 (2019); https://doi.org/10.1016/j.cis.2018.11.007
165. G.T. Noble, J.F. Stefanick, J.D. Ashley, T. Kiziltepe and B. Bilgicer, *Trends Biotechnol.*, **32**, 32 (2014); https://doi.org/10.1016/j.tibtech.2013.09.007
166. K.P. Mineart, S. Venkataraman, Y.Y. Yang, J.L. Hedrick and V.M. Prabhu, *Macromolecules*, **51**, 3184 (2018); https://doi.org/10.1021/acs.macromol.8b00361
167. M. Rastogi, R.N. Saha, A. Alexander, G. Singhvi, A. Puri and S.K. Dubey, *Chem. Phys. Lipids*, **235**, 105036 (2021); https://doi.org/10.1016/j.chemphyslip.2020.105036
168. V. De Leo, F. Milano, A. Agostiano and L. Catucci, *Polymers*, **13**, 1027 (2021); https://doi.org/10.3390/polym13071027
169. O.K. Nag and V. Awasthi, *Pharmaceutics*, **5**, 542 (2013); https://doi.org/10.3390/pharmaceutics5040542.
170. E. Beltrán-Gracia, A. López-Camacho, I. Higuera-Ciapara, J.B. Velázquez-Fernández and A.A. Vallejo-Cardona, *Cancer Nanotechnol.*, **10**, 11 (2019); https://doi.org/10.1186/s12645-019-0055-y
171. H. Nsairat, W. Alshaer, F. Odeh, E. Esawi, D. Khater, A. Al Bawab, M. El-Tanani, A. Awidi and M.S. Mubarak, *OpenNano*, **11**, 100132 (2023); https://doi.org/10.1016/j.onano.2023.100132
172. J.O. Eloy, R. Petrilli, L.N.F. Trevizan and M. Chorilli, *Colloids Surf. B Biointerfaces*, **159**, 454 (2017); https://doi.org/10.1016/j.colsurfb.2017.07.085
173. D. Wang, Y. Sun, Y. Liu, F. Meng and R.J. Lee, *Expert Opin. Drug Deliv.*, **15**, 893 (2018); https://doi.org/10.1080/17425247.2018.1517747

174. M. Merino, S. Zalba and M.J. Garrido, *J. Control. Release*, **275**, 162 (2018); https://doi.org/10.1016/j.jconrel.2018.02.015
175. L.B. Thomsen, T. Linemann, S. Birkelund, G.A. Tarp and T. Moos, *Materials*, **12**, 3576 (2019); https://doi.org/10.3390/ma12213576
176. Y. Chen, L. Cheng, D. Yu, J. Shen, Z. Zhou and S. He, *J. Nanosci. Nanotechnol.*, **21**, 4565 (2021); https://doi.org/10.1166/jnn.2021.19347
177. T.M. Allen, P. Sapra, E. Moase, J. Moreira and D. Iden, *J. Liposome Res.*, **12**, 5 (2002); https://doi.org/10.1081/LPR-120004771
178. K. Maruyama, *Biosci. Rep.*, **22**, 251 (2002); https://doi.org/10.1023/A:1020138622686
179. G. Bendas, *BioDrugs*, **15**, 215 (2001); https://doi.org/10.2165/00063030-200115040-00002
180. E. Paszko and M.O. Senge, *Curr. Med. Chem.*, **19**, 5239 (2012); https://doi.org/10.2174/092986712803833362
181. B. Maherani, E. Arab-Tehrany, M. R. Mozafari, C. Gaiani and M. Linder, *Curr. Nanosci.*, **7**, 436 (2011); https://doi.org/10.2174/157341311795542453
182. E.D. Namiot, A.V. Sokolov, V.N. Chubarev, V.V. Tarasov and H.B. Schiöth, *Int. J. Mol. Sci*., **24**, 787 (2023); https://doi.org/10.3390/ijms24010787
183. D. Qiu, X. An, Z. Chen and X. Ma, *Chem. Phys. Lipids*, **165**, 563 (2012); https://doi.org/10.1016/j.chemphyslip.2012.06.004
184. S.G. Ingle, R.V. Pai, J.D. Monpara and P.R. Vavia, *Eur. J. Pharm. Sci.*, **122**, 51 (2018); https://doi.org/10.1016/j.ejps.2018.06.025
185. V.J. Mohanraj, T.J. Barnes and C.A. Prestidge, *Int. J. Pharm.*, **392**, 285 (2010); https://doi.org/10.1016/j.ijpharm.2010.03.061
186. N.V. Beloglazova, O.A. Goryacheva, E.S. Speranskaya, T. Aubert, P.S. Shmelin, V.R. Kurbangaleev, I.Y. Goryacheva and S. De Saeger, *Talanta*, **134**, 120 (2015); https://doi.org/10.1016/j.talanta.2014.10.044
187. H. Chen, J. Fan, X. Chen, Z. Ma, L. Zhang and X. Chen, *Anal. Lett*., **56**, 2021 (2023); https://doi.org/10.1080/00032719.2022.2153256
188. X. Liu, X. Li, W. Xu, X. Zhang, Z. Huang, F. Wang and J. Liu, *Langmuir*, **34**, 6628 (2018); https://doi.org/10.1021/acs.langmuir.8b01138
189. S.P. Singh, S.B. Alvi, D.B. Pemmaraju, A.D. Singh, S.V. Manda, R. Srivastava and A.K. Rengan, *Int. J. Biol. Macromol.*, **110**, 375 (2018); https://doi.org/10.1016/j.ijbiomac.2017.11.163
190. M. Mathiyazhakan, C. Wiraja and C. Xu, *Nano-Micro Lett.*, **10**, 10 (2018); https://doi.org/10.1007/s40820-017-0166-0
191. B. Acharya and V. Chikan, *Magnetochemistry*, **6**, 52 (2020); https://doi.org/10.3390/magnetochemistry6040052
192. G.A. Dichello, T. Fukuda, T. Maekawa, S.V. Mikhalovsky, M. Alavijeh, R.L.D. Whitby, A.S. Pannala and D.K. Sarker, *Eur. J. Pharm. Sci.*, **105**, 55 (2017); https://doi.org/10.1016/j.ejps.2017.05.001
193. N. Kanwa, S.K. De, C. Adhikari and A. Chakraborty, *J. Phys. Chem. B*, **121**, 11333 (2017); https://doi.org/10.1021/acs.jpcb.7b08455
194. C. Adhikari, A. Das and A. Chakraborty, *ChemPhysChem*, **16**, 866 (2015); https://doi.org/10.1002/cphc.201402748
195. D. Zhu, Z.Y. Wang, S.F. Zong, H. Chen, P. Chen, M.Y. Li, L. Wu and Y.P. Cui, *Proc. SPIE*, 954316 (2015); https://doi.org/10.1117/12.2182146
196. Y. Xia, S. Qi, X. Zhang, L. Li, X. Qu, X. Zhang and J. Liang, *RSC Adv.*, **4**, 44568 (2014); https://doi.org/10.1039/C4RA07600A
197. I. Castangia, F. Marongiu, M.L. Manca, R. Pompei, F. Angius, A. Ardu, A.M. Fadda, M. Manconi and G. Ennas, *Eur. J. Pharm. Sci.*, **97**, 62 (2017); https://doi.org/10.1016/j.ejps.2016.11.006
198. A. Yusuf and A. Casey, *Toxicol. In Vitro*, **61**, 104641 (2019); https://doi.org/10.1016/j.tiv.2019.104641
199. J.-H. Lee, Y. Shin, W. Lee, K. Whang, D. Kim, L.P. Lee, J.-W. Choi and T. Kang, *Sci. Adv.*, **2**, e1601838 (2016); https://doi.org/10.1126/sciadv.1601838
200. H. Barani, M. Montazer, T. Toliyat and N. Samadi, *J. Liposome Res.*, **20**, 323 (2010); https://doi.org/10.3109/08982100903544177
201. D. Zhu, Z. Wang, S. Zong, H. Chen, X. Wu, Y. Pei, P. Chen, X. Ma and Y. Cui, *Nanoscale*, **6**, 8155 (2014); https://doi.org/10.1039/c4nr00557k
202. A. Yusuf, A. Brophy, B. Gorey and A. Casey, *J. Appl. Toxicol.*, **38**, 616 (2018); https://doi.org/10.1002/jat.3566
203. C. Guilleux, P.G.C. Campbell and C. Fortin, *Arch. Environ. Contam. Toxicol.*, **75**, 634 (2018); https://doi.org/10.1007/s00244-018-0562-6
204. S.-H. Park, S.-G. Oh, J.-Y. Mun and S.-S. Han, *Colloids Surf. B Biointerfaces*, **44**, 117 (2005); https://doi.org/10.1016/j.colsurfb.2005.06.002
205. L.-A. Tai, P.-J. Tsai, Y.-C. Wang, Y.-J. Wang, L.-W. Lo and C.-S. Yang, *Nanotechnology*, **20**, 135101 (2009); https://doi.org/10.1088/0957-4484/20/13/135101
206. N.C.V. Rost, K. Sen, S. Savliwala, I. Singh, S. Liu, M. Unni, L. Raniero and C. Rinaldi, *J. Magn. Magn. Mater.*, **504**, 166675 (2020); https://doi.org/10.1016/j.jmmm.2020.166675
207. B. Li, B. Li, D. He, C. Feng, Z. Luo and M. He, *Curr. Drug Deliv.*, **16**, 254 (2019); https://doi.org/10.2174/1567201816666181114124333
208. X.-C. Zheng, W. Ren, S. Zhang, T. Zhong, X.-C. Duan, Y.-F. Yin, M.-Q. Xu, Y.-L. Hao, Z.-T. Li, H. Li, M. Liu, Z.-Y. Li and X. Zhang, *Int. J. Nanomedicine*, **13**, 1495 (2018); https://doi.org/10.2147/IJN.S157082
209. S. Saesoo, S. Sathornsumetee, P. Anekwiang, C. Treetidnipa, P. Thuwajit, S. Bunthot, W. Maneeprakorn, H. Hofmann, R.U. Rungsardthong, L. Maurizi and N. Saengkrit, *Colloids Surf. B Biointerfaces*, **161**, 497 (2018); https://doi.org/10.1016/j.colsurfb.2017.11.003
210. Y. He, L. Zhang, C. Song and D. Zhu, *Int. J. Nanomedicine*, **9**, 4055 (2014); https://doi.org/10.2147/IJN.S61880
211. Z. Liao, H. Wang, R. Lv, P. Zhao, X. Sun, S. Wang, W. Su, R. Niu and J. Chang, *Langmuir*, **27**, 3100 (2011); https://doi.org/10.1021/la1050157
212. A. Floris, A. Ardu, A. Musinu, G. Piccaluga, A.M. Fadda, C. Sinico and C. Cannas, *Soft Matter*, **7**, 6239 (2011); https://doi.org/10.1039/c1sm05059a
213. R. Martínez-González, J. Estelrich and M.A. Busquets, *Int. J. Mol. Sci.*, **17**, 1209 (2016); https://doi.org/10.3390/ijms17081209
214. O.M. Fadoju, O.A. Osinowo, O.I. Ogunsuyi, I.T. Oyeyemi, O.A. Alabi, C.G. Alimba and A.A. Bakare, *Nucleus*, **63**, 159 (2020); https://doi.org/10.1007/s13237-020-00308-1
215. C.H. Kim, S.G. Lee, M.J. Kang, S. Lee and Y.W. Choi, *J. Pharm. Investig.*, **47**, 203 (2017); https://doi.org/10.1007/s40005-017-0329-5
216. M. Sheikhpour, L. Barani and A. Kasaeian, *J. Control. Release*, **253**, 97 (2017); https://doi.org/10.1016/j.jconrel.2017.03.026
217. A.S. Patel, S. Lakshmibalasubramaniam, B. Nayak, C. Tripp, A. Kar and P.K. Sappati, *Int. J. Biol. Macromol.*, **163**, 209 (2020); https://doi.org/10.1016/j.ijbiomac.2020.06.262
218. D. Gao, Tang, Duan and Tong, *Int. J. Nanomedicine*, **7**, 3517 (2012); https://doi.org/10.2147/IJN.S31725
219. Y. Liu, D. Gao, X. Zhang, Z. Liu, K. Dai, B. Ji, Q. Wang and L. Luo, *Mater. Sci. Eng. C*, **64**, 124 (2016); https://doi.org/10.1016/j.msec.2016.03.080
220. K. Nakamura, K. Yamashita, Y. Itoh, K. Yoshino, S. Nozawa and H. Kasukawa, *Biochim. Biophys. Acta Biomembr.*, **1818**, 2801 (2012); https://doi.org/10.1016/j.bbamem.2012.06.019
221. S. Saraf, A. Jain, A. Tiwari, A. Verma, P.K. Panda and S.K. Jain, *J. Drug Deliv. Sci. Technol.*, **56**, 101549 (2020); https://doi.org/10.1016/j.jddst.2020.101549

222. A.J. Coukell and C.M. Spencer, *Drugs*, **53**, 520 (1997); https://doi.org/10.2165/00003495-199753030-00011
223. P. Zarrintaj, M. Jouyandeh, M.R. Ganjali, B.S. Hadavand, M. Mozafari, S.S. Sheiko, M. Vatankhah-Varnoosfaderani, T.J. Gutiérrez and M.R. Saeb, *Eur. Polym. J.*, **117**, 402 (2019); https://doi.org/10.1016/j.eurpolymj.2019.05.024
224. M. Miyazaki, E. Yuba, H. Hayashi, A. Harada and K. Kono, *Bioconjug. Chem.*, **29**, 44 (2018); https://doi.org/10.1021/acs.bioconjchem.7b00551
225. F. Zare Kazemabadi, A. Heydarinasab, A. Akbarzadeh and M. Ardjmand, *Artif. Cells Nanomed. Biotechnol.*, **47**, 3222 (2019); https://doi.org/10.1080/21691401.2019.1646265
226. Y.-D. Dong, E. Tchung, C. Nowell, S. Kaga, N. Leong, D. Mehta, L.M. Kaminskas and B.J. Boyd, *J. Liposome Res.*, **29**, 1 (2019); https://doi.org/10.1080/08982104.2017.1391285
227. V. Dave, A. Gupta, P. Singh, C. Gupta, V. Sadhu and K.R. Reddy, *Nano-Structures & Nano-Objects*, **18**, 100288 (2019); https://doi.org/10.1016/j.nanoso.2019.100288
228. V. De Leo, S. Ruscigno, A. Trapani, S. Di Gioia, D. Mandracchia, F. Milano, R. Comparelli, S. Castellani, A. Agostiano, G. Trapani, L. Catucci and M. Conese, *Int. J. Pharm.*, **545**, 378 (2018); https://doi.org/10.1016/j.ijpharm.2018.04.030
229. H. Ahn and J.-H. Park, *Biomater. Res.*, **20**, 36 (2016); https://doi.org/10.1186/s40824-016-0083-1
230. T. Zhang, X. Xu, Y. Pan, H. Yang, J. Han, J. Liu and W. Liu, *Compreh. Rev. Food Sci. Food Safety*, **22**, 3685 (2023); https://doi.org/10.1111/1541-4337.13224
231. F.A.P. de Morais, R.S. Gonçalves, G. Braga, I.R. Calori, P.C.S. Pereira, V.R. Batistela, W. Caetano and N. Hioka, *ACS Appl. Nano Mater.*, **3**, 4530 (2020); https://doi.org/10.1021/acsanm.0c00386
232. W. Lin, N. Kampf, R. Goldberg, M.J. Driver and J. Klein, *Langmuir*, **35**, 6048 (2019); https://doi.org/10.1021/acs.langmuir.9b00610
233. Z. Cao, L. Zhang and S. Jiang, *Langmuir*, **28**, 11625 (2012); https://doi.org/10.1021/la302433a
234. W. Liu, J. Liu, W. Liu, T. Li and C. Liu, *J. Agric. Food Chem.*, **61**, 4133 (2013); https://doi.org/10.1021/jf305329n
235. F. Ravar, E. Saadat, M. Gholami, P. Dehghankelishadi, M. Mahdavi, S. Azami and F.A. Dorkoosh, *J. Control. Release*, **229**, 10 (2016); https://doi.org/10.1016/j.jconrel.2016.03.012
236. A.S. Abu Lila, K. Nawata, T. Shimizu, T. Ishida and H. Kiwada, *Int. J. Pharm.*, **456**, 235 (2013); https://doi.org/10.1016/j.ijpharm.2013.07.059
237. L.N.M. Ribeiro, A.C.S. Alcântara, G.H. Rodrigues da Silva, M. Franz-Montan, S.V.G. Nista, S.R. Castro, V.M. Couto, V.A. Guilherme and E. de Paula, *Int. J. Polym. Sci.*, **2017**, 1231464 (2017); https://doi.org/10.1155/2017/1231464
238. M. Manconi, A. Nácher, V. Merino, M. Merino-Sanjuan, M.L. Manca, C. Mura, S. Mura, A.M. Fadda and O. Diez-Sales, *AAPS PharmSciTech*, **14**, 485 (2013); https://doi.org/10.1208/s12249-013-9926-4
239. M.J. Barea, M.J. Jenkins, Y.S. Lee, P. Johnson and R.H. Bridson, *Int. J. Biomater.*, **2012**, 458712 (2012); https://doi.org/10.1155/2012/458712
240. S. Jain, D. Kumar, N.K. Swarnakar and K. Thanki, *Biomaterials*, **33**, 6758 (2012); https://doi.org/10.1016/j.biomaterials.2012.05.026
241. S. Jain, S.R. Patil, N.K. Swarnakar and A.K. Agrawal, *Mol. Pharm.*, **9**, 2626 (2012); https://doi.org/10.1021/mp300202c
242. K. Nahar, S. Absar, B. Patel and F. Ahsan, *Int. J. Pharm.*, **464**, 185 (2014); https://doi.org/10.1016/j.ijpharm.2014.01.007
243. H.F. Salem, R.M. Kharshoum, M. Mahmoud, S.A. Azim and E.-Z.M. Ebeid, *ARS Pharm.*, **59**, 9 (2018).
244. M. Ruano, A. Mateos-Maroto, F. Ortega, H. Ritacco, J.E.F. Rubio, E. Guzmán and R.G. Rubio, *Langmuir*, **37**, 6189 (2021); https://doi.org/10.1021/acs.langmuir.1c00341
245. A.A. Yaroslavov, A.A. Rakhnyanskaya, E.G. Yaroslavova, A.A. Efimova and F.M. Menger, *Adv. Colloid Interface Sci.*, **142**, 43 (2008); https://doi.org/10.1016/j.cis.2008.04.004
246. J.J. Richardson, M. Björnmalm and F. Caruso, *Science*, **348**, aaa2491 (2015); https://doi.org/10.1126/science.aaa2491
247. H. Ai, S.A. Jones and Y.M. Lvov, *Cell Biochem. Biophys.*, **39**, 23 (2003); https://doi.org/10.1385/CBB:39:1:23
248. N.A. Kotov, *Nanostruct. Mater.*, **12**, 789 (1999); https://doi.org/10.1016/S0965-9773(99)00237-8
249. A.B. Scranton, B. Rangarajan and J. Klier, Eds.: N.A. Peppas and R.S. Langer, Biomedical applications of polyelectrolytes, In: Biopolymers II, Berlin, Heidelberg, pp 1-54 (1995).
250. M. Chen, Z. Zeng, X. Qu, Y. Tang, Q. Long and X. Feng, *Int. J. Pharm.*, **490**, 173 (2015); https://doi.org/10.1016/j.ijpharm.2015.05.046
251. M.C.F. Gonçalves, O. Mertins, A.R. Pohlmann, N.P. Silveira and S.S. Guterres, *J. Biomed. Nanotechnol.*, **8**, 240 (2012); https://doi.org/10.1166/jbn.2012.1375
252. Y. Fan, M. Marioli and K. Zhang, *J. Pharm. Biomed. Anal.*, **192**, 113642 (2021); https://doi.org/10.1016/j.jpba.2020.113642
253. S. Pahal, R. Gakhar, A.M. Raichur and M.M. Varma, *IET Nanobiotechnol.*, **11**, 903 (2017); https://doi.org/10.1049/iet-nbt.2017.0007
254. Y. Xia, X. Wang, H. Cheng, M. Fang, P. Ning, Y. Zhou, W. Chen and H. Song, *Colloids Surf. B Biointerfaces*, **159**, 427 (2017); https://doi.org/10.1016/j.colsurfb.2017.08.011
255. M. Rubinstein and G.A. Papoian, *Soft Matter*, **8**, 9265 (2012); https://doi.org/10.1039/c2sm90104h
256. A.S. Sergeeva, D.A. Gorin and D.V. Volodkin, *Bionanoscience*, **4**, 1 (2014); https://doi.org/10.1007/s12668-013-0121-6
257. R. Kurapati, T.W. Groth and A.M. Raichur, *ACS Appl. BioMater.*, **2**, 5512 (2019); https://doi.org/10.1021/acsabm.9b00703
258. B. Almeida, O.K. Nag, K.E. Rogers and J.B. Delehanty, *Molecules*, **25**, 5672 (2020); https://doi.org/10.3390/molecules25235672
259. C. Su, Y. Xia, J. Sun, N. Wang, L. Zhu, T. Chen, Y. Huang and D. Liang, *Langmuir*, **30**, 6219 (2014); https://doi.org/10.1021/la501296r
260. G. Morelli, A. Accardo, D. Tesauro, C. Cicala, G. Salzano, G. De Rosa, A. Morisco, L. Aloj, M. Aurilio, F. Maione and A. Parisi, *Int. J. Nanomedicine*, **7**, 2007 (2012); https://doi.org/10.2147/IJN.S29242
261. B.O. Yuan, Y. Zhao, S. Dong, Y. Sun, F.E.I. Hao, J. Xie, L. Teng, R.J. Lee, Y. Fu and Y.E. Bi, *Anticancer Res.*, **39**, 237 (2019); https://doi.org/10.21873/anticanres.13103
262. M.R. Aronson, S.H. Medina and M.J. Mitchell, *APL Bioeng.*, **5**, 011501 (2021); https://doi.org/10.1063/5.0029860
263. S. Ye, Y. Liu, Y. Lu, Y. Ji, L. Mei, M. Yang, X. Gong, Q. Gu, D. Li, F. Yang and C.-J. Li, *J. Mater. Chem. B Mater. Biol. Med.*, **8**, 447 (2020); https://doi.org/10.1039/C9TB01834D
264. F. Khosravani, H. Mir, A. Mirzaei, F. Kobarfard, H. Bardania and E. Hosseini, *Biotechnol. Appl. Biochem.*, **70**, 811 (2023); https://doi.org/10.1002/bab.2401
265. Z. Song, Y. Lin, X. Zhang, C. Feng, Y. Lu, Y. Gao and C. Dong, *Int. J. Nanomedicine*, **12**, 1941 (2017); https://doi.org/10.2147/IJN.S125573
266. P.P. Deshpande, S. Biswas and V.P. Torchilin, *Nanomedicine*, **8**, 1509 (2013); https://doi.org/10.2217/nnm.13.118
267. F. Khosravani, F. Amiri, R. Mahmoudi, D. Morshedi, F. Kobarfard, M. Alipour, E. Hosseini and H. Bardania, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, (2023); https://doi.org/10.1007/s00210-023-02752-7
268. Q. Zhang, L. Lu, L. Zhang, K. Shi, X. Cun, Y. Yang, Y. Liu, H. Gao and Q. He, *Sci. Rep.*, **6**, 19800 (2016); https://doi.org/10.1038/srep19800
269. L. Chen, Y. Liu, W. Wang and K. Liu, *Oncol. Lett.*, **10**, 77 (2015); https://doi.org/10.3892/ol.2015.3242
270. Y. Cheng and Y. Ji, *Eur. J. Pharm. Sci.*, **128**, 8 (2019); https://doi.org/10.1016/j.ejps.2018.11.023

271. S. Catuogno, C.L. Esposito and V. De Franciscis, *Pharmaceuticals*, **9**, 69 (2016); https://doi.org/10.3390/ph9040069
272. Y. Zhang, J. He, L. Shen, T. Wang, J. Yang, Y. Li, Y. Wang and D. Quan, *J. Control. Release*, **329**, 1117 (2021); https://doi.org/10.1016/j.jconrel.2020.10.039
273. M.N. Ara, T. Matsuda, M. Hyodo, Y. Sakurai, H. Hatakeyama, N. Ohga, K. Hida and H. Harashima, *Biomaterials*, **35**, 7110 (2014); https://doi.org/10.1016/j.biomaterials.2014.04.087
274. S.A. Moosavian and A. Sahebkar, *Cancer Lett.*, **448**, 144 (2019); https://doi.org/10.1016/j.canlet.2019.01.045
275. R. Lu, L. Zhou, Q. Yue, Q. Liu, X. Cai, W. Xiao, L. Hai, L. Guo and Y. Wu, *Bioorg. Med. Chem.*, **27**, 3115 (2019); https://doi.org/10.1016/j.bmc.2019.05.039
276. R.I. Jølck, L.N. Feldborg, S. Andersen, S.M. Moghimi and T.L. Andresen, Eds.: G.S. Nyanhongo, W. Steiner and G. Gübitz, Engineering Liposomes and Nanoparticles for Biological Targeting; In: Biofunctionalization of Polymers and their Applications, Springer Berlin Heidelberg: Berlin, Heidelberg, pp 251-280 (2011).
277 M.A. Chaves, L.S. Ferreira, L. Baldino, S.C. Pinho and E. Reverchon, *Nanomaterials*, **13**, 1557 (2023); https://doi.org/10.3390/nano13091557
278. H. Zhang, Y. Ma and X.-L. Sun, Rds.: S.S. Mark, Chemically Selective Liposome Surface Glyco-functionalization, In: Bioconjugation Protocols: Strategies and Methods, Humana Press: Totowa, NJ, pp 269-280 (2011).
279. V.M. Platt, Ph.D Thesis, Surface Functionalization of Liposomes with Proteins and Carbohydrates for Use in Anticancer Applications, University of California, Berkeley, USA (2010).
280. V.P. Torchilin, R. Rammohan, V. Weissig and T.S. Levchenko, *Proc. Natl. Acad. Sci. USA*, **98**, 8786 (2001); https://doi.org/10.1073/pnas.151247498
281. K. Maruyama, A. Mori, S. Bhadra, M.T. Ravi Subbiah and L. Huang, *Biochim. Biophys. Acta Biomembr.*, **1070**, 246 (1991); https://doi.org/10.1016/0005-2736(91)90171-4
282. M. Alavi, K. Asare-Addo and A. Nokhodchi, *Biomedicines*, **8**, 580 (2020); https://doi.org/10.3390/biomedicines8120580
283. F. Giulimondi, L. Digiacomo, D. Pozzi, S. Palchetti, A.L. Capriotti, E. Vulpis, R.Z. Chiozzi, A. Laganà, H. Amenitsch, L. Masuelli, G. Peruzzi, M. Mahmoudi, I. Screpanti, A. Zingoni and G. Caracciolo, *Nat. Commun.*, **10**, 3686 (2019); https://doi.org/10.1038/s41467-019-11642-7
284. G. Caracciolo, *Nanomedicine*, **11**, 543 (2015); https://doi.org/10.1016/j.nano.2014.11.003
285. B.N. Ames, L.S. Gold and W.C. Willett, *Proc. Natl. Acad. Sci. USA*, **92**, 5258 (1995); https://doi.org/10.1073/pnas.92.12.5258
286. S. Senapati, A.K. Mahanta, S. Kumar and P. Maiti, *Signal Transduct. Target. Ther.*, **3**, 7 (2018); https://doi.org/10.1038/s41392-017-0004-3
287. N. Bhagya and K.R. Chandrashekar, *Int. J. Pharm.*, 642, 123105 (2023); https://doi.org/10.1016/j.ijpharm.2023.123105
288. S. Marchal, A.E. Hor, M. Millard, V. Gillon and L. Bezdetnaya, *Drugs*, **75**, 1601 (2015); https://doi.org/10.1007/s40265-015-0453-3
289. Y. Barenholz, *J. Control. Release*, **160**, 117 (2012); https://doi.org/10.1016/j.jconrel.2012.03.020
290. Y.N. Lamb and L.J. Scott, *Drugs*, **77**, 785 (2017); https://doi.org/10.1007/s40265-017-0741-1
291. S. Pereira, R. Egbu, G. Jannati and W.T. Al-Jamal, *Int. J. Pharm.*, **514**, 150 (2016); https://doi.org/10.1016/j.ijpharm.2016.06.057
292. S. Naik, D. Patel, N. Surti and A. Misra, *J. Supercrit. Fluids*, **54**, 110 (2010); https://doi.org/10.1016/j.supflu.2010.02.005
293. Q. Tan, X. Liu, X. Fu, Q. Li, J. Dou and G. Zhai, *Expert Opin. Drug Deliv.*, **9**, 975 (2012); https://doi.org/10.1517/17425247.2012.696606
294. D.K. Wang, C.X. Zhang, W.T. Zhang, C.H. Zhao and S.X. Guan, *J. Drug Deliv. Sci. Technol.*, **18**, 253 (2008); https://doi.org/10.1016/S1773-2247(08)50049-9
295. J. Verweij, *Br. J. Cancer*, **70**, 183 (1994); https://doi.org/10.1038/bjc.1994.276
296. D.E. Goertz, M. Todorova, O. Mortazavi, V. Agache, R. Karshafian, B. Chen and K. Hynynen, *PLoS One*, **7**, e52307 (2012); https://doi.org/10.1371/journal.pone.0052307
297. K. Venkatakrishnan, Y. Liu, D. Noe, J. Mertz, M. Bargfrede, T. Marbury, K. Farbakhsh, C. Oliva and A. Milton, *Br. J. Clin. Pharmacol.*, **77**, 986 (2014); https://doi.org/10.1111/bcp.12260
298. D. Douer, *Oncologist*, **21**, 840 (2016); https://doi.org/10.1634/theoncologist.2015-0391
299. N.N. Shah, M.S. Merchant, D.E. Cole, N. Jayaprakash, D. Bernstein, C. Delbrook, K. Richards, B.C. Widemann and A.S. Wayne, *Pediatr. Blood Cancer*, **63**, 997 (2016); https://doi.org/10.1002/pbc.25937
300. D. Patel and N. Patel, *Future J. Pharm. Sci.*, **6**, 79 (2020); https://doi.org/10.1186/s43094-020-00089-z
301. C. Du, S. Li, Y. Li, H. Galons, N. Guo, Y. Teng, Y. Zhang, M. Li and P. Yu, *Drug Deliv.*, **27**, 836 (2020); https://doi.org/10.1080/10717544.2020.1772409
302. Y. Yang, Y. Ma and S. Wang, *Eur. J. Pharm. Biopharm.*, **80**, 332 (2012); https://doi.org/10.1016/j.ejpb.2011.10.013
303. L. Chernov, R.J. Deyell, M. Anantha, N. Dos Santos, R. Gilabert-Oriol and M.B. Bally, *Cancer Med.*, **6**, 1240 (2017); https://doi.org/10.1002/cam4.1083
304. S. Saraf, A. Jain, P. Hurkat and S.K. Jain, *Crit. Rev. Ther. Drug Carrier Syst.*, **33**, 401 (2016); https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2016015926
305. F. Zahednezhad, P. Zakeri-Milani, J. Shahbazi Mojarrad and H. Valizadeh, *Expert Opin. Drug Deliv.*, **17**, 523 (2020); https://doi.org/10.1080/17425247.2020.1737672
306. Y. Wang, J. Zhou, L. Qiu, X. Wang, L. Chen, T. Liu and W. Di, *Biomaterials*, **35**, 4297 (2014); https://doi.org/10.1016/j.biomaterials.2014.01.035
307. M.A. Farooq, M. Aquib, A. Farooq, D. Haleem Khan, M.B. Joelle Maviah, M. Sied Filli, S. Kesse, K.O. Boakye-Yiadom, R. Mavlyanova, A. Parveen and B. Wang, *Artif. Cells Nanomed. Biotechnol.*, **47**, 1674 (2019); https://doi.org/10.1080/21691401.2019.1604535
308. T. Shoeib and A.Z.-e. Mohamed, Liposomal Delivery Systems for Oxaliplatin and in Dual Drug Delivery in Combination with Chemo-sensitizing and Chemo-therapeutic agents, Google Patents WO2017192502A1 (2019).
309. C. Zeng, F. Yu, Y. Yang, X. Cheng, Y. Liu, H. Zhang, S. Zhao, Z. Yang, M. Li, Z. Li and X. Mei, *PLoS One*, **11**, e0158517 (2016); https://doi.org/10.1371/journal.pone.0158517
310. C. Yang, H.Z. Liu, Z.X. Fu and W.D. Lu, *BMC Biotechnol.*, **11**, 21 (2011); https://doi.org/10.1186/1472-6750-11-21
311. S. Duan, Y. Yu, C. Lai, D. Wang, Y. Wang, D. Xue, Z. Hu and X. Lu, *J. Biomed. Nanotechnol.*, **14**, 910 (2018); https://doi.org/10.1166/jbn.2018.2530
312. F. Yang, M. Jiang, M. Lu, P. Hu, H. Wang and J. Jiang, *Front. Pharmacol.*, **9**, 991 (2018); https://doi.org/10.3389/fphar.2018.00991
313. J.A. Silverman and S.R. Deitcher, *Cancer Chemother. Pharmacol.*, **71**, 555 (2013); https://doi.org/10.1007/s00280-012-2042-4
314. X.-Q. Wei and K. Ba, *ACS Omega*, **5**, 16502 (2020); https://doi.org/10.1021/acsomega.0c00930
315. B. Sinjari, J. Pizzicannella, M. D'Aurora, R. Zappacosta, V. Gatta, A. Fontana, O. Trubiani and F. Diomede, *Front. Physiol.*, **10**, 633 (2019); https://doi.org/10.3389/fphys.2019.00633
316. A. Sethiya, D.K. Agarwal and S. Agarwal, *Mini Rev. Med. Chem.*, **20**, 1190 (2020); https://doi.org/10.2174/1389557520666200429103647
317. S.S. Bansal, M. Goel, F. Aqil, M.V. Vadhanam and R.C. Gupta, *Cancer Prev. Res.*, **4**, 1158 (2011); https://doi.org/10.1158/1940-6207.CAPR-10-0006
318. H. Xu, Z. Li and J. Si, *J. Biomed. Nanotechnol.*, **10**, 3483 (2014); https://doi.org/10.1166/jbn.2014.2044

319. K. Bulaklak and C.A. Gersbach, *Nat. Commun.*, **11**, 5820 (2020); https://doi.org/10.1038/s41467-020-19505-2
320. C.E. Dunbar, K.A. High, J.K. Joung, D.B. Kohn, K. Ozawa and M. Sadelain, *Science*, **359**, eaan4672 (2018); https://doi.org/10.1126/science.aan4672
321. T. Wirth, N. Parker and S. Ylä-Herttuala, *Gene*, **525**, 162 (2013); https://doi.org/10.1016/j.gene.2013.03.137
322. S. Han, R.I. Mahato, Y.K. Sung and S.W. Kim, *Mol. Ther.*, **2**, 302 (2000); https://doi.org/10.1006/mthe.2000.0142
323. Y.K. Sung and S.W. Kim, *Biomater. Res.*, **23**, 8 (2019); https://doi.org/10.1186/s40824-019-0156-z
324. D. Ibraheem, A. Elaissari and H. Fessi, *Int. J. Pharm.*, **459**, 70 (2014); https://doi.org/10.1016/j.ijpharm.2013.11.041
325. C. Zylberberg, K. Gaskill, S. Pasley and S. Matosevic, *Gene Ther.*, **24**, 441 (2017); https://doi.org/10.1038/gt.2017.41
326. F. Xiong, Z. Mi and N. Gu, *J. Pharm. Sci.*, **66**, 158 (2011); https://doi.org/10.1691/ph.2011.0768
327. G. Caracciolo and H. Amenitsch, *Eur. Biophys. J.*, **41**, 815 (2012); https://doi.org/10.1007/s00249-012-0830-8
328. C.R. Safinya, K.K. Ewert and C. Leal, *Liq. Cryst.*, **38**, 1715 (2011); https://doi.org/10.1080/02678292.2011.624364
329. C.R. Safinya, K.K. Ewert, R.N. Majzoub and C. Leal, *New J. Chem.*, **38**, 5164 (2014); https://doi.org/10.1039/C4NJ01314J
330. E. Junquera and E. Aicart, *Adv. Colloid Interface Sci.*, **233**, 161 (2016); https://doi.org/10.1016/j.cis.2015.07.003
331. D. Zhi, Y. Bai, J. Yang, S. Cui, Y. Zhao, H. Chen and S. Zhang, *Adv. Colloid Interface Sci.*, **253**, 117 (2018); https://doi.org/10.1016/j.cis.2017.12.006
332. D. Zhi, S. Zhang, S. Cui, Y. Zhao, Y. Wang and D. Zhao, *Bioconjug. Chem.*, **24**, 487 (2013); https://doi.org/10.1021/bc300381s
333. E. Junquera and E. Aicart, *Curr. Top. Med. Chem.*, **14**, 649 (2014); https://doi.org/10.2174/1568026614666140118203128
334. N. Yilmaz, Y. Kodama and K. Numata, *Langmuir*, **37**, 1882 (2021); https://doi.org/10.1021/acs.langmuir.0c03320
335. D. Scherman, A. Rousseau, P. Bigey and V. Escriou, *Gene Ther.*, **24**, 151 (2017); https://doi.org/10.1038/gt.2017.6
336. M. Kapoor and D.J. Burgess, *Int. J. Pharm.*, **432**, 80 (2012); https://doi.org/10.1016/j.ijpharm.2012.04.058
337. S.M. Alnasser, *Gene*, **769**, 145246 (2021); https://doi.org/10.1016/j.gene.2020.145246
338. M.A.J. Shaikh, O. Afzal, W.H. Almalki, I. Kazmi, S.I. Alzarea, M. Jafar, A.S.A. Altamimi, V. Jakhmola, K. Anand, S.K. Singh, K. Dua and G. Gupta, *J. Drug Deliv. Sci. Technol.*, **85**, 104619 (2023); https://doi.org/10.1016/j.jddst.2023.104619
339. C. Roma-Rodrigues, L. Rivas-García, P.V. Baptista and A.R. Fernandes, *Pharmaceutics*, **12**, 233 (2020); https://doi.org/10.3390/pharmaceutics12030233
340. J.O. Eloy, R. Petrilli, G.L. Raspantini and R.J. Lee, *Curr. Pharm. Des.*, **24**, 2664 (2018); https://doi.org/10.2174/1381612824666180807121935
341. E. Abeyratne, K. Tharmarajah, J.R. Freitas, H. Mostafavi, A. Zaid, S. Mahalingam, M. Zaman and A. Taylor, *Front. Immunol.*, **11**, 304 (2020); https://doi.org/10.3389/fimmu.2020.00304
342. J. Qian, Y. Guo, Y. Xu, X. Wang, J. Chen and X. Wu, *Drug Deliv. Transl. Res.*, **13**, 2960 (2023); https://doi.org/10.1007/s13346-023-01394-9
343. R. Pati, M. Shevtsov and A. Sonawane, *Front. Immunol.*, **9**, 2224 (2018); https://doi.org/10.3389/fimmu.2018.02224
344. J.-L. Excler, M. Saville, S. Berkley and J.H. Kim, *Nat. Med.*, **27**, 591 (2021); https://doi.org/10.1038/s41591-021-01301-0
345. P.L. Stern, *Ann. Allergy Asthma Immunol.*, **125**, 17 (2020); https://doi.org/10.1016/j.anai.2020.01.025
346. A.E. Gregory, R. Titball and D. Williamson, *Front. Cell. Infect. Microbiol.*, **3**, (2013); https://doi.org/10.3389/fcimb.2013.00013
347. J.F. Correia-Pinto, N. Csaba and M.J. Alonso, *Int. J. Pharm.*, **440**, 27 (2013); https://doi.org/10.1016/j.ijpharm.2012.04.047
348. R.A. Schwendener, *Ther. Adv. Vaccines*, **2**, 159 (2014); https://doi.org/10.1177/2051013614541440
349. M. Henriksen-Lacey, K.S. Korsholm, P. Andersen, Y. Perrie and D. Christensen, *Expert Opin. Drug Deliv.*, **8**, 505 (2011); https://doi.org/10.1517/17425247.2011.558081
350. R. Yu, Y. Mai, Y. Zhao, Y. Hou, Y. Liu and J. Yang, *J. Drug Target.*, **27**, 780 (2019); https://doi.org/10.1080/1061186X.2018.1547734
351. A.K. Giddam, M. Zaman, M. Skwarczynski and I. Toth, *Nanomedicine*, **7**, 1877 (2012); https://doi.org/10.2217/nnm.12.157
352. N. Marasini, K.A. Ghaffar, M. Skwarczynski and I. Toth, Eds.: M. Skwarczynski and I. Toth, Liposomes as a Vaccine Delivery System. In Micro and Nanotechnology in Vaccine Development, William Andrew Publishing: Chap. 12, pp 221-239 (2017).
353. S.M. Sullivan, J. Doukas, J. Hartikka, L. Smith and A. Rolland, *Expert Opin. Drug Deliv.*, **7**, 1433 (2010); https://doi.org/10.1517/17425247.2010.538047
354. O. Even-Or, S. Samira, R. Ellis, E. Kedar and Y. Barenholz, *Expert Rev. Vaccines*, **12**, 1095 (2013); https://doi.org/10.1586/14760584.2013.825445
355. R. Mischler and I.C. Metcalfe, *Vaccine*, **20**, B17 (2002); https://doi.org/10.1016/S0264-410X(02)00512-1
356. J. Heuts, E.M. Varypataki, K. van der Maaden, S. Romeijn, J.W. Drijfhout, A.T. van Scheltinga, F. Ossendorp and W. Jiskoot, *Pharm. Res.*, **35**, 207 (2018); https://doi.org/10.1007/s11095-018-2490-6
357. D. Christensen, K.S. Korsholm, I. Rosenkrands, T. Lindenstrøm, P. Andersen and E.M. Agger, *Expert Rev. Vaccines*, **6**, 785 (2007); https://doi.org/10.1586/14760584.6.5.785
358. Y.-F. Du, M. Chen, J.-R. Xu, Q. Luo and W.-L. Lu, Eds.: W.-L. Lu and X.-R. Qi, Preparation and Characterization of DNA Liposomes Vaccine; In: Liposome-Based Drug Delivery Systems, Springer Berlin Heidelberg: Berlin, Heidelberg, pp. 259-275 (2021).
359. Y. Inoh, M. Nagai, K. Matsushita, M. Nakanishi and T. Furuno, *Eur. J. Pharm. Sci.*, **102**, 230 (2017); https://doi.org/10.1016/j.ejps.2017.03.023
360. D. Jiang, H. Lee and W.M. Pardridge, *Sci. Rep.*, **10**, 13334 (2020); https://doi.org/10.1038/s41598-020-70290-w
361. A.E. Rodriguez, P. Zamorano, S. Wilkowsky, F. Torrá, L. Ferreri, M. Dominguez and M. Florin-Christensen, *Vet. J.*, **196**, 550 (2013); https://doi.org/10.1016/j.tvjl.2012.10.036
362. J. Liu, J. Wu, B. Wang, S. Zeng, F. Qi, C. Lu, Y. Kimura and B. Liu, *J. Med. Virol.*, **86**, 886 (2014); https://doi.org/10.1002/jmv.23768
363. R. Tenchov, R. Bird, A.E. Curtze and Q. Zhou, *ACS Nano*, **15**, 16982 (2021); https://doi.org/10.1021/acsnano.1c04996
364. K.C. Petkar, S.M. Patil, S.S. Chavhan, K. Kaneko, K.K. Sawant, N.K. Kunda and I.Y. Saleem, *Pharmaceutics*, **13**, 455 (2021); https://doi.org/10.3390/pharmaceutics13040455
365. M. Kaurav, J. Madan, M.S. Sudheesh and R.S. Pandey, *Artif. Cells Nanomed. Biotechnol.*, **46**, 818 (2018); https://doi.org/10.1080/21691401.2018.1513941
366. S. Beg, K.S. Alharbi, N.K. Alruwaili, N.H. Alotaibi, W.H. Almalki, S.K. Alenezi, W.M. Altowayan, M.S. Alshammari and M. Rahman, *Nanomedicine*, **15**, 1527 (2020); https://doi.org/10.2217/nnm-2020-0046
367. Y. Azadi, E. Ahmadpour and A. Ahmadi, *Curr. Drug Targets*, **21**, 541 (2020); https://doi.org/10.2174/1389450120666191023151423
368. D. Kim, Y. Wu, Y.B. Kim and Y.-K. Oh, *Drug Deliv. Transl. Res.*, **11**, 1401 (2021); https://doi.org/10.1007/s13346-021-00945-2
369. V.-A. Duong, T.-T.-L. Nguyen and H.-J. Maeng, *Pharmaceutics*, **15**, 207 (2021); https://doi.org/10.3390/pharmaceutics15010207

370. H. Moulahoum, F. Ghorbanizamani, F. Zihnioglu and S. Timur, *Bioconjug. Chem.*, **32**, 1491 (2021); https://doi.org/10.1021/acs.bioconjchem.1c00285
371. R. Liang, J. Xie, J. Li, K. Wang, L. Liu, Y. Gao, M. Hussain, G. Shen, J. Zhu and J. Tao, *Biomaterials*, **149**, 41 (2017); https://doi.org/10.1016/j.biomaterials.2017.09.029
372. S. Gause, K.-H. Hsu, C. Shafor, P. Dixon, K.C. Powell and A. Chauhan, *Adv. Colloid Interface Sci.*, **233**, 139 (2016); https://doi.org/10.1016/j.cis.2015.08.002
373. K.H. Hsu, S. Gause and A. Chauhan, *J. Drug Deliv. Sci. Technol.*, **24**, 123 (2014); https://doi.org/10.1016/S1773-2247(14)50021-4
374. P.W.J. Morrison and V.V. Khutoryanskiy, *Ther. Deliv.*, **5**, 1297 (2014); https://doi.org/10.4155/tde.14.75
375. M. Dubald, S. Bourgeois, V. Andrieu and H. Fessi, *Pharmaceutics*, **10**, 10 (2018); https://doi.org/10.3390/pharmaceutics10010010
376. Y. Wu, Y. Liu, X. Li, D. Kebebe, B. Zhang, J. Ren, J. Lu, J. Li, S. Du and Z. Liu, *Asian J. Pharm. Sci.*, **14**, 1 (2019); https://doi.org/10.1016/j.ajps.2018.04.008
377. L. Gan, J. Wang, M. Jiang, H. Bartlett, D. Ouyang, F. Eperjesi, J. Liu and Y. Gan, *Drug Discov. Today*, **18**, 290 (2013); https://doi.org/10.1016/j.drudis.2012.10.005
378. V. Gote, S. Sikder, J. Sicotte and D. Pal, *J. Pharmacol. Exp. Ther.*, **370**, 602 (2019); https://doi.org/10.1124/jpet.119.256933
379. D. Achouri, K. Alhanout, P. Piccerelle and V. Andrieu, *Drug Dev. Ind. Pharm.*, **39**, 1599 (2013); https://doi.org/10.3109/03639045.2012.736515
380. A. Patel, K. Cholkar, V. Agrahari and A.K. Mitra, *World J. Pharmacol.*, **2**, 47 (2013); https://doi.org/10.5497/wjp.v2.i2.47
381. H. Chen, Y. Jin, L. Sun, X. Li, K. Nan, H. Liu, Q. Zheng and B. Wang, *Colloid Interface Sci. Commun.*, **24**, 54 (2018); https://doi.org/10.1016/j.colcom.2018.03.008
382. X. Zhang, X. Cao and P. Qi, *J. Biomater. Sci. Polym. Ed.*, **31**, 549 (2020); https://doi.org/10.1080/09205063.2020.1712175
383. J.J. López-Cano, M.A. González-Cela-Casamayor, V. Andrés-Guerrero, R. Herrero-Vanrell and I.T. Molina-Martínez, *Expert Opin. Drug Deliv.*, **18**, 819 (2021); https://doi.org/10.1080/17425247.2021.1872542
384. R. Agarwal, I. Iezhitsa, P. Agarwal, N.A. Abdul Nasir, N. Razali, R. Alyautdin and N.M. Ismail, *Drug Deliv.*, **23**, 1075 (2016); https://doi.org/10.3109/10717544.2014.943336
385. A.J. Urquhart and A.Z. Eriksen, *Drug Discov. Today*, **24**, 1660 (2019); https://doi.org/10.1016/j.drudis.2019.04.004
386. H. Sasaki, K. Karasawa, K. Hironaka, K. Tahara, Y. Tozuka and H. Takeuchi, *Eur. J. Pharm. Biopharm.*, **83**, 364 (2013); https://doi.org/10.1016/j.ejpb.2012.10.014
387. J. Wang, A. Jiang, M. Joshi and J. Christoforidis, *Mediators Inflamm.*, **2013**, 780634 (2013); https://doi.org/10.1155/2013/780634
388. S. Tavakoli, K. Peynshaert, T. Lajunen, J. Devoldere, E.M. del Amo, M. Ruponen, S.C. De Smedt, K. Remaut and A. Urtti, *J. Control. Release*, **328**, 952 (2020); https://doi.org/10.1016/j.jconrel.2020.10.028
389. A. Bochot and E. Fattal, *J. Control. Release*, **161**, 628 (2012); https://doi.org/10.1016/j.jconrel.2012.01.019
390. R.L. Jain and J.P. Shastri, *Int. J. Pharm. Investig.*, **1**, 35 (2011); https://doi.org/10.4103/2230-973X.76727
391. M. Honda, T. Asai, N. Oku, Y. Araki, M. Tanaka and N. Ebihara, *Int. J. Nanomedicine*, **8**, 495 (2013); https://doi.org/10.2147/IJN.S30725
392. T. Lajunen, R. Nurmi, L. Kontturi, L. Viitala, M. Yliperttula, L. Murtomäki and A. Urtti, *J. Control. Release*, **244**, 157 (2016); https://doi.org/10.1016/j.jconrel.2016.08.024
393. A. Santos, J.C. Altamirano, J. Navarro-Partida, A.G.-De la Rosa and J.H. Hsiao, Eds.: R.V. Tyagi, N. Garg, R. Shukla and B.P. Singh, Breaking Down the Barrier: Topical Liposomes as Nanocarriers for Drug Delivery into the Posterior Segment of the Eyeball, In: Role of Novel Drug Delivery Vehicles in Nanobiomedicine, IntechOpen (2019); https://doi.org/10.5772/intechopen.86601
394. H. Almeida, M. Amaral, P. Lobao, C. Frigerio and J. Sousa-Lobo, *Curr. Pharm. Des.*, **21**, 5212 (2015); https://doi.org/10.2174/1381612821666150923095155
395. S. Gorantla, V.K. Rapalli, T. Waghule, P.P. Singh, S.K. Dubey, R.N. Saha and G. Singhvi, *RSC Adv.*, **10**, 27835 (2020); https://doi.org/10.1039/D0RA04971A
396. L. He, H. Xu, S. Nie, X. Yang, J. Yin and W. Pan, *J. Appl. Polym. Sci.*, **123**, 3363 (2012); https://doi.org/10.1002/app.33883
397. F. Dilnawaz and S.K. Sahoo, Eds.: A.J. Domb and W. Khan, Nanotechnology Based Ophthalmic Drug Delivery System, In: Focal Controlled Drug Delivery, Springer US: Boston, MA, pp. 225-241 (2014).
398. P. Morris and A. Perkins, *Lancet*, **379**, 1525 (2012); https://doi.org/10.1016/S0140-6736(12)60429-2
399. R. Vadivambal and D.S. Jayas, Bio-imaging: Principles, Techniques, and Applications, CRC Press (2015).
400. A.M. Mills, A.S. Raja, J.R. Marin, Optimizing Diagnostic Imaging in the Emergency Department, *Acad. Emerg. Med.*, **22**, 625 (2015); https://doi.org/10.1111/acem.12640
401. M. Aiello, C. Cavaliere, A. D'Albore and M. Salvatore, *J. Clin. Med.*, **8**, 316 (2019); https://doi.org/10.3390/jcm8030316
402. M. Wu and J. Shu, *Contrast Media Mol. Imaging*, **2018**, 1382183 (2018); https://doi.org/10.1155/2018/1382183
403. Y. Xia, C. Xu, X. Zhang, P. Ning, Z. Wang, J. Tian and X. Chen, *Nanoscale*, **11**, 5822 (2019); https://doi.org/10.1039/C9NR00207C
404. A.L. Petersen, A.E. Hansen, A. Gabizon and T.L. Andresen, *Adv. Drug Deliv. Rev.*, **64**, 1417 (2012); https://doi.org/10.1016/j.addr.2012.09.003
405. A.M. Syed, P. MacMillan, J. Ngai, S. Wilhelm, S. Sindhwani, B.R. Kingston, J.L.Y. Wu, P. Llano-Suárez, Z.P. Lin, B. Ouyang, Z. Kahiel, S. Gadde and W.C.W. Chan, *Nano Lett.*, **20**, 1362 (2020); https://doi.org/10.1021/acs.nanolett.9b04853
406. N. Kostevšek, C.C.L. Cheung, I. Serša, M.E. Kreft, I. Monaco, M. Comes-Franchini, J. Vidmar and W.T. Al-Jamal, *Nanomaterials*, **10**, 889 (2020); https://doi.org/10.3390/nano10050889
407. S.V. German, N.A. Navolokin, N.R. Kuznetsova, O.A. Inozemtseva, V.V. Zuev, A.A. Anis'kov, A.B. Bucharskaya, G.N. Maslyakova, R.F. Fakhrullin, E.K. Volkova, G.S. Terentyuk, E.L. Vodovozova and D.A. Gorin, *Colloids Surf. B Biointerfaces*, **135**, 109 (2015); https://doi.org/10.1016/j.colsurfb.2015.07.042
408. N. Mitchell, T.L. Kalber, M.S. Cooper, K. Sunassee, S.L. Chalker, K.P. Shaw, K.L. Ordidge, A. Badar, S.M. Janes, P.J. Blower, M.F. Lythgoe, H.C. Hailes and A.B. Tabor, *Biomaterials*, **34**, 1179 (2013); https://doi.org/10.1016/j.biomaterials.2012.09.070
409. W. Lee and H.-J. Im, *Nucl. Med. Mol. Imaging*, **53**, 242 (2019); https://doi.org/10.1007/s13139-019-00603-z
410. M.S. Muthu and S.-S. Feng, *Expert Opin. Drug Deliv.*, **10**, 151 (2013); https://doi.org/10.1517/17425247.2013.729576
411. A.G. Robertson and L.M. Rendina, *Chem. Soc. Rev.*, **50**, 4231 (2021); https://doi.org/10.1039/D0CS01075H
412. D.C.F. Soares, G.F. de Sousa, A.L.B. de Barros, V.N. Cardoso, M.C. de Oliveira and G.A. Ramaldes, *J. Drug Deliv. Sci. Technol.*, **30**, 7 (2015); https://doi.org/10.1016/j.jddst.2015.09.003
413. B. Wereszczyñska and T. Zalewski, *Appl. Magn. Reson.*, **52**, 143 (2021); https://doi.org/10.1007/s00723-020-01297-9
414. A. Pitchaimani, T.D. Thanh Nguyen, H. Wang, S.H. Bossmann and S. Aryal, *RSC Adv.*, **6**, 36898 (2016); https://doi.org/10.1039/C6RA00552G
415. S. Langereis, T. Geelen, H. Grüll, G.J. Strijkers and K. Nicolay, *NMR Biomed.*, **26**, 728 (2013); https://doi.org/10.1002/nbm.2971
416. G.M. Jensen and D.F. Hodgson, *Adv. Drug Deliv. Rev.*, **154-155**, 2 (2020); https://doi.org/10.1016/j.addr.2020.07.016
417. V.K. Sharma and M.K. Agrawal, *Mater. Today Proc.*, **45**, 2963 (2021); https://doi.org/10.1016/j.matpr.2020.11.952

418. S. Handali, I. Haririan, M. Vaziri and F.A. Dorkoosh, *Drug Deliv. Lett.*, **13**, 83 (2023); https://doi.org/10.2174/2210303112666220829125054
419. D.J.A. Crommelin, P. van Hoogevest and G. Storm, *J. Control. Release*, **318**, 256 (2020); https://doi.org/10.1016/j.jconrel.2019.12.023
420. N. Filipczak, J. Pan, S.S.K. Yalamarty and V.P. Torchilin, *Adv. Drug Deliv. Rev.*, **156**, 4 (2020); https://doi.org/10.1016/j.addr.2020.06.022
421. L. Shetye, A. Sherlekar and V. Mendhulkar, Liposome-Based Drug Delivery—A New Therapeutic Paradigm, In: Advanced Drug Delivery: Methods and Applications, Singapore: Springer Nature Singapore, pp. 21-48 (2023).
422. I.A.H. Khalil, I.A. Arida and M.J.C. Ahmed, Nanomedicine, F. A. o., Introductory Chapter: Overview on Nanomedicine Market, In: Current and Future Aspects of Nanomedicine, IntechOpen (2020); https://doi.org/10.5772/intechopen.91890
423. D.E. Large, R.G. Abdelmessih, E.A. Fink and D.T. Auguste, *Adv. Drug Deliv. Rev.*, **176**, 113851 (2021); https://doi.org/10.1016/j.addr.2021.113851
424. V. Gupta and N. Sharma, *PEXACY Int. J. Pharm. Sci.*, **2**, 1 (2023).
425. G.M. Jensen, *J. Liposome Res.*, **27**, 173 (2017); https://doi.org/10.1080/08982104.2017.1380664
426. I. Pont, A. Calatayud-Pascual, A. López-Castellano, E.P. Albelda, E. García-España, L. Martí-Bonmatí, J.C. Frias and M.T. Albelda, *PLoS One*, **13**, e0190540 (2018); https://doi.org/10.1371/journal.pone.0190540
427. Y.E. Bi, Y. Zhou, M. Wang, L. Li, R.J. Lee, J. Xie and L. Teng, *Anticancer Res.*, **37**, 5207 (2017).
428. D. Cao, X. Zhang, M.D. Akabar, Y. Luo, H. Wu, X. Ke and T. Ci, *Artif. Cells Nanomed. Biotechnol.*, **47**, 181 (2019); https://doi.org/10.1080/21691401.2018.1548470
429. L. Maja, K. •eljko and P. Mateja, *J. Supercrit. Fluids*, **165**, 104984 (2020); https://doi.org/10.1016/j.supflu.2020.104984
430. M.G. Sá Correia, M.L. Briuglia, F. Niosi and D.A. Lamprou, *Int. J. Pharm.*, **516**, 91 (2017); https://doi.org/10.1016/j.ijpharm.2016.11.025
431. H. Tamam, J. Park, H.H. Gadalla, A.R. Masters, J.A. Abdel-Aleem, S.I. Abdelrahman, A.A. Abdelrahman, L.T. Lyle and Y. Yeo, *Mol. Pharm.*, **16**, 2858 (2019); https://doi.org/10.1021/acs.molpharmaceut.8b01284
432. S. Shukla, Y. Haldorai, S.K. Hwang, V.K. Bajpai, Y.S. Huh and Y.-K. Han, *Front. Microbiol.*, **8**, 2398 (2017); https://doi.org/10.3389/fmicb.2017.02398
433. H.R. Ahmadi Ashtiani, P. Bishe, N. Lashgari, M.A. Nilforoushzadeh and S. Zare, *J. Skin Stem Cell*, **3**, e65815 (2016); https://doi.org/10.5812/jssc.65815
434. W. Liu, Y. Hou, Y. Jin, Y. Wang, X. Xu and J. Han, *Trends Food Sci. Technol.*, **104**, 177 (2020); https://doi.org/10.1016/j.tifs.2020.08.012