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Industrial-scale methods for the manufacture of liposomes and nanoliposomes: pharmaceutical, cosmetic, and nutraceutical aspects

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ABSTRACT

Liposomes are microscale lipid bilayer vesicles, widely employed for solubilizing drugs and delivering them to the body with precise targeting and controlled release. The nanoscale version of liposomes is known as nanoliposome. These biocompatible and biodegradable drug delivery systems have several advantages, such as the ability to be loaded with various drug molecules in physiological conditions. Compared with other delivery systems, such as micelles, polymeric, metallic nanocarriers, or niosomes, liposomes are the most well-established and commercially available carrier, used not only in pharmaceuticals, but also in cosmeceutical and nutraceutical products. However, scaling-up their manufacture and ensuring sufficient stability are significant challenges for liposomes. In this review, we discuss several industrial-scale methods for liposome preparation including organic solvent methods, freeze-drying of double emulsions, heating method, Mozafari method, membrane contactor method, liposome formation by curvature tuning, biomimetic liposomal self-assembly, sonication method, extrusion method, spray drying method, and microfluidic systems. Some factors leading to physicochemical or biological instability and the ways to overcome these challenges are discussed. International agencies quality control procedures and regulatory aspects for liposomal and nanoliposomal drug product development are also addressed.

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Introduction

Nanotechnology has attracted enormous attention in recent decades because of the unique properties of nanoparticles compared with bulk materials [1, 2]. Methods have been developed to synthesize organic and inorganic nanomaterials in desired sizes and shapes [3-11]. Liposomes and nanoliposomes (also known as "lipid vesicles") are good examples of these carriers in the nano or microscale that can be used for the encapsulation and loading therapeutic or nutraceutical compounds [12-14]. These cargos can have amphipathic, hydrophilic or hydrophobic properties. Liposomes can protect these cargos against degradation, and deliver them to target cells in either a passive or active manner [15]. Liposomes are supramolecular assemblies of amphiphilic lipids and phospholipids. Examples of liposomal ingredients include cholesterol, dicetyl phosphate (DCP), stearylamine (SA), dipalmitoylphosphatidylcholine (DPPC), phospholipon® 100H, phospholipon® 90H, 2-dioleoyl-sn-glycero-3-[phospho-rac-(1-glycerol)] (sodium salt) (DOPG), 1,2-dioleoyl-3-trimethylammonium propane (chloride salt) (DOTAP), 1,2-dipalmitoyl-sn-gly-cero-3-[phospho-rac-(1-glycerol)] (sodium salt) (DPPG), 1,2-dioleoyl-sn-

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glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), lyso-palmitoylphosphatidylcholine (lyso-PPC), and asolectin lipid. These compounds can self-assemble into lipid-bilayer enclosed vesicles, encapsulating hydrophilic cargos within the aqueous core, or hydrophobic cargos within the lipid bilayer [15, 16]. These carriers possess microscale or nanoscale diameters, and have attracted much attention for the encapsulation and loading of a variety of therapeutic agents, as well as the design of artificial organelles and cells. Many of the known liposome preparation methods have the disadvantages of being time-consuming and requiring the use of organic solvents. In addition, polydisperse liposomes with different sizes, shapes, and poor stability are other problems encountered in the conventional methods of liposome production. Therefore, establishing solvent-free (green) and one-step liposome preparation methods (particularly on a large scale) can help to obtain monodipserse liposomes with effective encapsulation and loading of therapeutic agents. In this review, we discuss the main liposome production methods and their advantages and disadvantages.

The major properties of liposomes are generally governed by the employed preparation technique. Although many liposome preparation methods have been well-established, new improved methods are still required. There are various synthetic strategies available to choose a suitable size, shape, and composition of liposomes, and the optimum phospholipids to prevent the rapid decay of liposomes can be employed. In this respect, controlling factors such as the melting temperature or T_m should be considered for liposome preparation. The stage transformation temperature is the temperature at which the lipid transforms from a normal, disordered conformation where the hydrocarbon chains are randomly distributed, to a translucent fluid suspension, where the hydrocarbon chains become directional and ordered within the bilayer.

To choose the best strategy for liposome synthesis, several factors should be taken into consideration: 1) the physicochemical and cytotoxicity properties of the reactants and liposomal constituents; 2) the properties of the medium in which the liposomes are dispersed; 3) the number of steps required during the liposome preparation; 4) suitable size, distribution, and half-life of the liposomes in the body; 5) reproducibility in large scale preparations; 6) the provision of stable and effective liposomal carriers for specific therapeutic aims. Liposome size is a crucial parameter governing the bioavailability of liposomes for drug delivery. Different preparation methods can be used to control the size of liposomes suitable for physiological conditions. Moreover, the encapsulation and loading of hydrophilic or hydrophobic drugs can be tuned by selecting the appropriate preparation method, which is discussed in the present review according to recent investigations.

Ethanol and ether injection (organic solvent) methods

The main problems with conventional methods of liposome synthesis are the complex multistage process, the requirement of removing toxic organic solvents, the high cost of energy, and poor stability of the final products. In methods based on ethanol and diethyl ether, the organic solvents are added to the phospholipids followed by rapid injection into an aqueous medium to generate the liposomes. Removing ethanol or ether from the liposome dispersion can be carried by rotary evaporation under reduced pressure [17]. Using the ether injection method, a liposomal formulation of asolectin lipid and erlotinib (chemotherapeutic drug for treating certain types of non-small cell lung cancer) was prepared with PDI (polydispersity index) of 0.22, mean size of 121 nm, and zeta potential of −33.7 mV, which showed a drug loading and entrapment efficiency of 15.89% and 82.60 % w/w, respectively [18].

Freeze-drying of double emulsions

This method is suitable for producing sterile unilamellar nanoliposomes. In this method, different phospholipids or combinations of lipids as emulsifiers, are employed to produce a double emulsion by a two-step emulsification process, using hydrophilic components for the initial fluid stage or lipophilic components for the oil stage. In the next stage, the double emulsions are lyophilized after sterilization by filtration through a 0.22-µm pore-size filter and sonication to produce a uniform size (Figure 1) [19]. The freeze-drying process can be carried out in three steps freezing, primary drying, and secondary drying. Finally, rehydration of the lyophilized samples brings

about lipid vesicles with moderately high exemplification productivity. Encapsulation efficiencies of 87%, 19%, and 93% have been obtained for nanoliposomomal formulations (with diameters below 200 nm) of calcein (a fluorescent dye), 5-fluorouracil (a chemotherapy medication), and flurbiprofen (nonsteroidal anti-inflammatory drugs) respectively. As an important note, applying disaccharides such as lactose, sucrose, and sucrose plus mannitol as lyoprotectants in the outer and inner phases of an emulsion is indispensable to stabilize formulation [20]. The stability of the final liposomes containing lipophilic flurbiprofen stored in sealed nitrogen gas-filled vials at 4 °C without light was reached for more than 6 months [19].

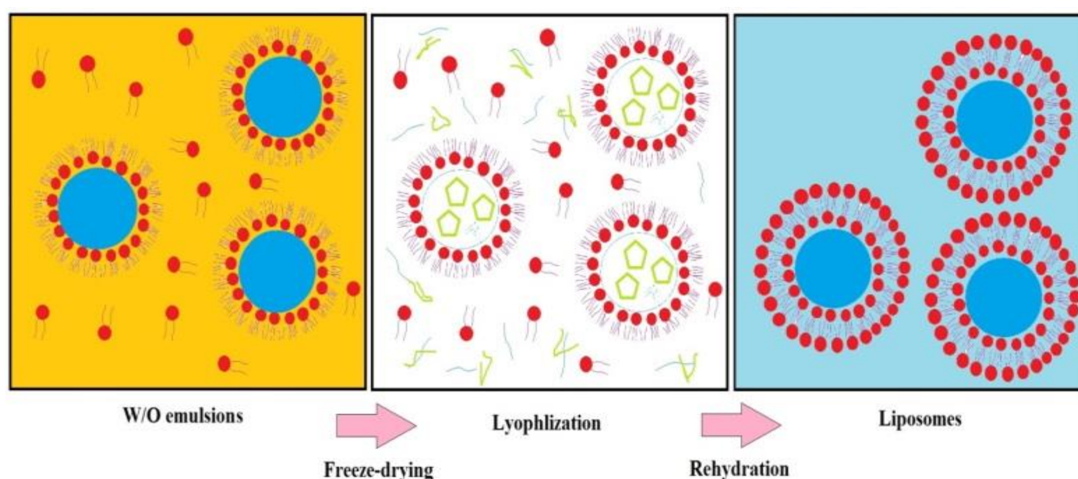

Fig. 1. Schematic illustration of freeze drying of double emulsions (Redrawn with modification from Ref. [19]).

Heating method

The use of toxic solvents such as diethyl ether, acetone, methanol, or chloroform, and the need for strong mechanical force (high shear force or high pressure) are the main hindrance to large-scale production of micro and nanoliposomes. Dialysis, vacuum, and gel filtration can reduce the toxicity of the final products; however, these methods are time-consuming and difficult in practice [15, 21, 22]. Towards this end, the heating method was developed by Prof. Mozafari to overcome the mentioned problems [23]. Using this method, 71% encapsulation efficiency was obtained for a liposomal formulation of isoniazid-hydrazone-phthalocyanine conjugate with 240 nm diameter, −57 mV Zeta potential, stable at 4 °C for 5 weeks storage, and controlled release of 40% of the drug at pH 7.4 [24].

Mozafari method

The Mozafari method is a simplified and scalable version of the heating method. Nontoxic ingredients, such as cholesterol, DCP, SA, dipalmitoylphosphatidylcholine, phospholipon 100H, and phospholipon 90H are heated (at temperatures below 70 °C) together in an aqueous medium without employing toxic solvents. This method provides a high storage stability and monodispersity as two advantages compared to conventional techniques [25]. Liposomes and nanoliposomes can be easily prepared by this safe and green method. A nanoliposomal formulation of nisin Z prepared by the Mozafari method showed an encapsulation efficiency of up to 54%, a particle size < 300 nm, and was stable for 14 months at 4 °C [26].

Membrane contactor method

As shown in Figure 2, in this strategy, the calculated amounts of phospholipids and cholesterol are dissolved in ethanol and put into a pressurized vessel. The valve to the nitrogen bottle is opened, and the nitrogen pressure is set at an appropriate level. The organic ingredients come into contact with the aqueous phase inside a membrane tube with semi-permeable pores, leading to liposome formation. Finally, the ethanol is removed by rotary evaporation under reduced pressure. Relatively high encapsulation efficiencies of 98% and 63% were found for nanoliposomes of beclomethasone dipropionate or indomethacin, respectively, with a size range of 50-160 nm [27].

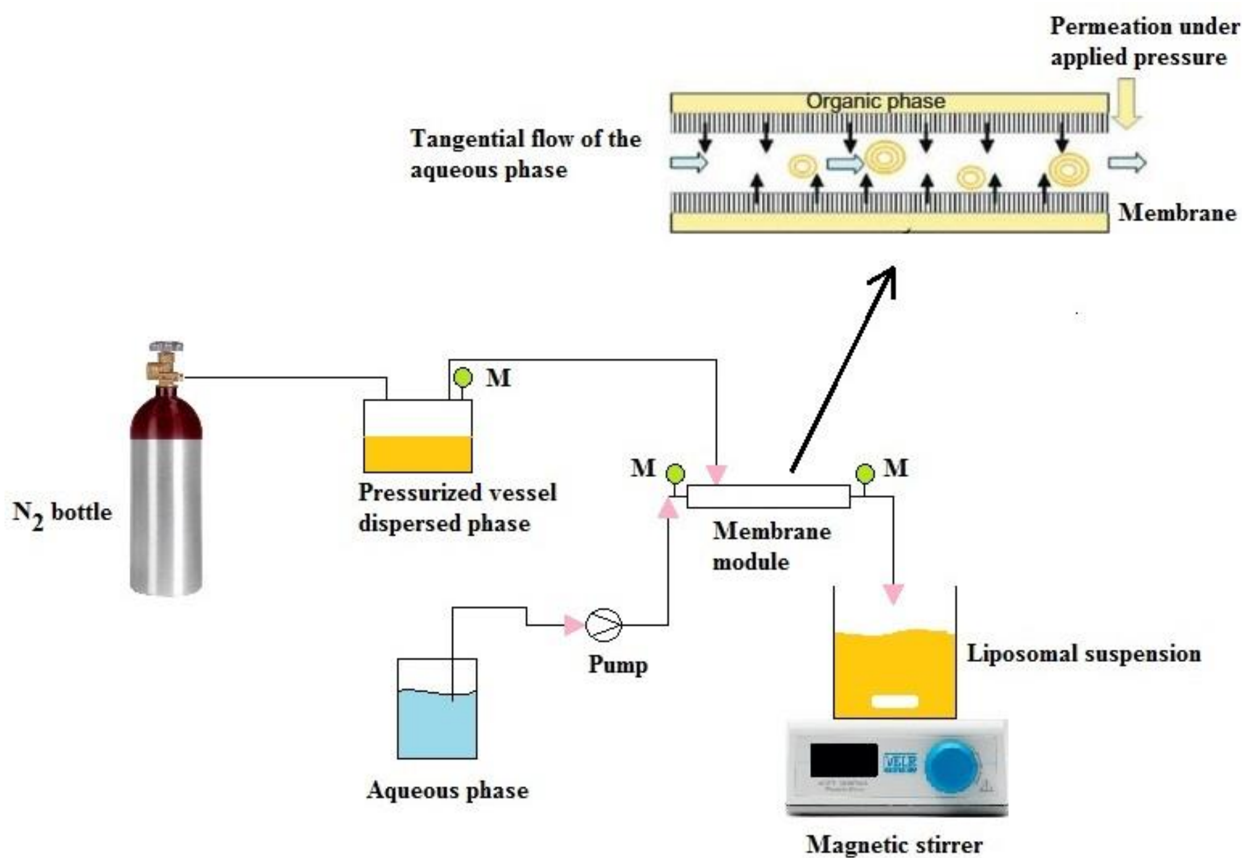

Fig. 2. Schematic illustration of the membrane contactor method (Redrawn with modification from Ref. [27]).

Liposome formation by curvature tuning

This method is based on a rapid change in pH (pH jump). As an alternative to the thin-film preparation step, a lipid mixture is directly hydrated in a buffer such as PBS (phosphate buffered saline), 2-morpholinoethane sulfonic acid (MES), 2-(N-morpholino) ethanesulfonic acid), and HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) which was heated to a predetermined temperature (T_o). After adding glycerol to the stirrer for ~15 min, the pH is then subsequently increased to a maximum (pH ~11) by the addition of sodium hydroxide (NaOH) and then adjusted to pH 7.4 by hydrochloric acid (HCl) for a fixed time incubation, called the "pH jumping time" [28]. These liposomes can be used as nanoreactors to prepare nanoparticles (NPs) by a green synthesis method. Liposomes prepared by the curvature-tuned method were used as nanoreactors to synthesize spherical gold NPs with a size range of 2-8 nm, depending on the glycerol concentration. The use of different glycerol concentrations, 3%, 10%, or 15% v/v resulted in 7.7, 7.3, or 6.4 nm diameter gold NPs, respectively [29].

Biomimetic liposomal self-assembly

Under the right conditions and in the presence of an appropriate template, liposomes can be produced by spontaneous supramolecular assembly of amphiphilic lipids to encapsulate hydrophilic cargos within the aqueous core. DNA nanostructures can function as high-precision templates to assemble artificial lipid membranes in this biomimetic liposomal self-assembly process. For example, a DNA octahedron within a lipid bilayer, a DNA-framework, and curved DNA origami scaffolds were all used to promote the self-assembly of an artificial membrane (Figure 3) [30-32]. It is worth noting that DNA origami can guide the assembly of lipid components to produce channels in the lipid membranes [33, 34].

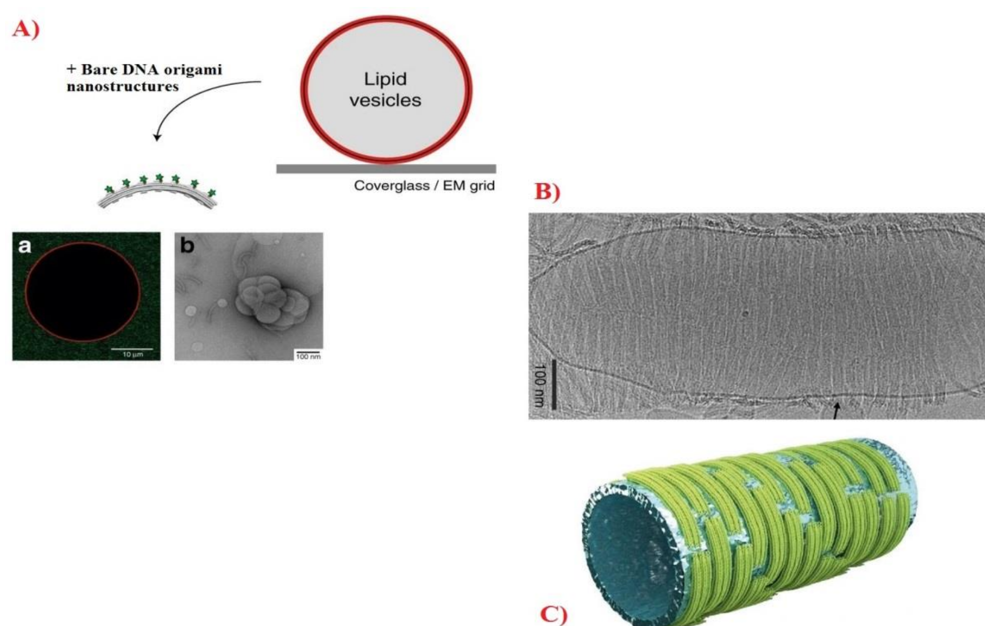

Fig. 3. Template mediated liposomal self-assembly. A) Assembly of lipid model membranes by curved origami nanostructures. B) The cryo-EM electron microscopy image. C) Schematic illustration of a lipid nanotube decorated with DNA origami (adapted from [32]).

Sonication method

This method has been widely applied to prepare various types of lipid vesicles of different sizes. This method uses acoustic energy from a probe tip sonicator or an ultrasound bath to mix the lipids in a solution. For this method, the diameter of liposomes is not dependent on the length of the phospholipid hydrocarbon chains. Still, it is determined by the time during which the lipid suspensions are sonicated [35]. By changing the time, using thin film hydration and probe-sonication method, different sizes of liposomes encapsulating ibuprofen were prepared with sizes of 159.2, 136.6, 123.7, and 98.9 nm after sonication with 120 W power for 5, 10, 15, and 20 min. In addition, at different sonication powers of 180, 150, 120, 90, or 60 W, the liposomes had sizes of 53.3, 83.5, 98.9, 108.8, or 171.6 nm. Higher encapsulation efficiency of 99.53 % was found after sonication at 120 W for 20 min [36]. In contrast to the extrusion method (see below), batch-to-batch average size and the size distribution of the liposomes prepared by the sonication method are not very reproducible.

Extrusion method

The extrusion method uses a polycarbonate membrane with a well-defined pore diameter, to prepare vesicles from a lipid suspension with a diameter close to the pore diameter of the polycarbonate membrane. Vesicles are extruded by passing the suspension through the membrane several times to produce homogenous large unilamellar vesicles, or nanoliposomes depending on the pore size (Figure 4) [22]. The significant advantages of this technique are that there is no requirement to remove detergents or organic solvents from the final product. Moreover, the average liposomal size and size distribution show acceptable reproducibility [35]. One study compared two liposomal preparation methods for scale-up objectives. Liposomes composed of cholesterol/sphingomyelin containing vinblastine-N-oxide prepared by the extrusion method showed a lower PDI of 0.1 and mean size of 64.26 nm compared to a state-of-the-art microfluidics method with a PDI of 0.2 and an average size of 56.02 nm [37].

Spray drying method

Figure 5 illustrates the spray drying process of liposome production. This method can be used as a post-processing technique similar to freeze drying and spray drying [38, 39]. In contrast to freeze-drying, the spray drying method converts aqueous materials into a dried and powdery form, and is inexpensive and rapid. The main disadvantages of this method are the leakage

of the loaded bioactive compounds during storage and liposome aggregation [39]. An extract containing black carrot anthocyanins was encapsulated in non-coated and chitosan-coated liposomes by a spray drying process. The chitosan (0.1%)-coated vesicles prepared by the spray drying process had a zeta potential of 51.4 mV and a mean diameter of 82.7 nm, with good storage stability [40].

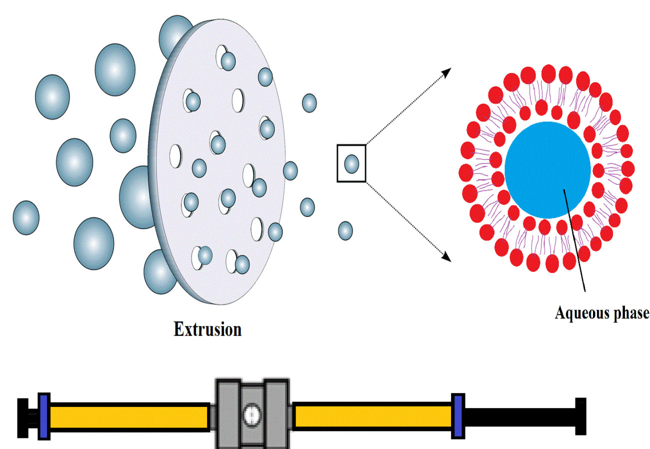

Fig. 4. The extrusion method based on a polycarbonate membrane [41, 42].

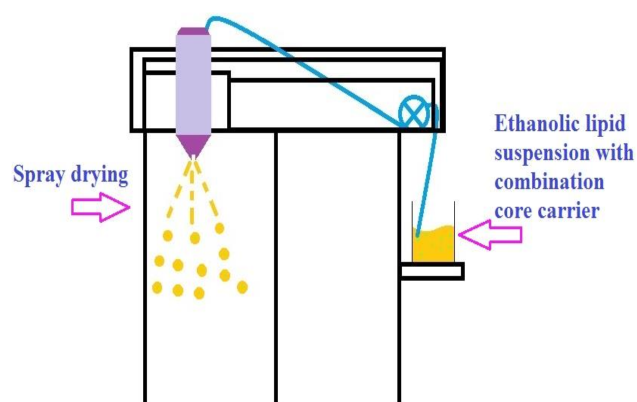

Fig. 5. Schematic illustration of the spray drying method [38].

Microfluidic systems

Bulk methods and batch techniques are two approaches to obtaining liposomes and nanoliposomes. Microfluidic systems are batch processes relying on fluid flow in channels with cross-sectional dimensions of 5–500 μm [43]. Three main microfluidic systems are classified as single-phase flow, gas-liquid multiphase flow, and liquid-liquid multiphase flow. The microfluidics method is based on diffusion-dominated mass transfer and laminar flow in the microchannels (low Reynolds number) [44]. Hydrodynamic focusing, droplet emulsion transfer (Figure 6), transient membrane ejection, ice droplet hydration, double emulsion templates, pulsed microfluidic jetting, extrusion, electroformation, and thin-film hydration can be employed to produce liposomes in a microfluidic system [45]. We have discussed this liposome preparation method in a previous review [46].

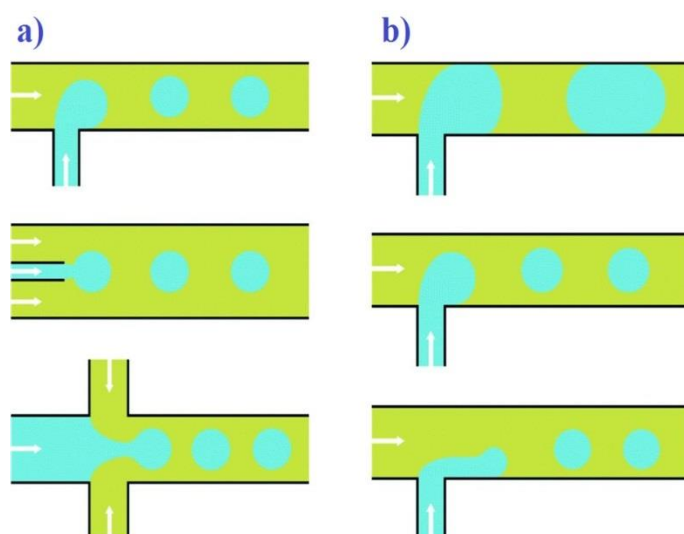

Fig. 6. Microfluidics for liposome preparation. (a) Microfluidic droplet production; (b) Different ways of droplet break up in a microfluidic device (Extracted from [45] under a Creative Commons Attribution 3.0 Unported Licence).

Dried reconstituted vesicles (DRVs)

Liposomes are created in this process under gentle, non-stressful settings, which are ideal for creating liposomes encapsulating delicate and/or easily damaged molecules such as proteins, peptides, and enzymes [47]. In compared to other liposome manufacturing methods, this approach can result in high encapsulation effectiveness of water-soluble compounds, which is a useful benefit, particularly when expensive pharmaceuticals are to be encapsulated. Because of the high encapsulation effectiveness, fewer lipids is required to deliver a given quantity of a medicine to the cells, minimizing lipid-induced cell toxicity as well as other cellular consequences associated with high lipid concentration. The hydrophilic elements to be encapsulated are combined with the empty SUVs and freeze-dried

together. During the freeze-drying stage, the SUVs are fragmented, and then during the controlled rehydration process, additional solute molecules enter the previously disrupted vesicles, which fuse form huge oligolamellar or multilamellar vesicles encapsulating vast amounts of the solutes. This approach may be used to encapsulate hydrophilic pharmaceuticals with low and (particularly) large molecular weights, such as proteins, peptides, enzymes, and DNA. Lipophilic medicines can also be encapsulated using this approach; but, due to the dilution effect, these medications will leak fast from the liposomes when supplied intravenously (in the much larger sink of the blood). One solution is to create water-soluble cyclodextrin drug complexes that are encapsulated in the aqueous compartment of the liposomes [48].

Remote loading

The fundamental benefit of remote loading is that it achieves greater drug-to-lipid ratios and encapsulation efficiencies than traditional passive trapping procedures such as hydration of dry lipid films with aqueous drug solutions. The ideal loading process should be chosen using scientific reasoning. There are four alternative methods for putting doxorubicin into liposomes. The utilization of a pH-, manganese-, sulfate-, or citrate gradient drives the various loading strategies. All of these ideas are based on the same principle: free doxorubicin base diffuses within the liposome, where it undergoes a change that limits membrane release, resulting in drug accumulation inside the liposomes. The development of an intravesicular doxorubicin-Mn^{2+}complex provides the basis for doxorubicin loading into liposomes through a transmembrane manganese gradient [49]. Liposome integrity and stability are critical in the pharmaceutical industry, so risk assessment is one of the key factors to achieve proper quality. Among the things that lead to physicochemical or biological instability in the manufacture of liposomes, it is possible to mention the failure to follow the protocol of the formulation process during manufacture. Identification of risk process at each stage and ways to overcome these challenges are discussed. Quality control methods for liposomal product development, risk assessment and identification techniques can produce a good quality product [50].

Conclusions

Functionalized liposomes can be used to increase the bioavailability and biodegradability of bioactive agents in physiological conditions and control the drug release at the target site. Several new methods for liposome preparation have been described in recent years. However, each method has its advantages and limitations. Therefore, the choice of preparation method should be determined based on the therapeutic objectives. Aggregation, coalescence, agglomeration, or the precipitation of vesicles during preparation or storage can result in the degradation of the vesicle structure. This review has focused on new techniques and addressed their challenges for micro and nanoformulations. The stability of liposomes during storage is affected by the spray drying and freeze-drying processes. Solubility properties, functionalization methods, stability of liposomes in physiological conditions, and storage outside the body are the main factors that govern the choice of preparation method. Microfluidic systems are recently introduced methods for controlling physical properties, including vesicle size and size distribution. However, the primary concern of the microfluidics method is the difficulty in scaling up for the industrial application, owing to the inherent volume limitations of the microfluidic devices. Therefore, a smart strategy would be to use several methods, depending on the therapeutic or industrial aims.

Study Highlights

- Functionalized liposomes can be employed to increase the bioavailability and biodegradability of bioactive agents in physiological conditions.
- The choice of preparation method should be determined based on the therapeutic objectives.
- Aggregation, coalescence, agglomeration, or the precipitation of vesicles during preparation or storage can lead to the degradation of the vesicle structure.
- Solubility properties, functionalization methods, stability of liposomes in physiological conditions, and storage outside the body are the main factors that govern the choice of preparation method.
- The stability of liposomes during storage is affected by the spray drying and freeze-drying processes.
- The primary concern of the microfluidics method is the difficulty in scaling up for the industrial

application, owing to the inherent volume limitations of the microfluidic devices.

Abbreviations
DCP: Dicetyl phosphate
DOPC: 1,2-dioleoyl-sn-glycero-3-phosphocholine
DOPG: 2-dioleoyl-sn-glycero-3-[phospho-rac-(1-glycerol)]
DOTAP: 1,2-dioleoyl-3-trimethylammonium propane (chloride salt)
DPPC: 1,2-dipalmitoyl-sn-glycero-3-phosphocholine
lyso-PPC: lyso-palmitoylphosphatidylcholine
DPPC: Dipalmitoylphosphatidylcholine
DPPG: 1,2-dipalmitoyl-sn-gly-cero-3-[phospho-rac-(1-glycerol)] (sodium salt)
DRVs: Dried reconstituted vesicles
HEPES:4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
MES: 2-morpholinoethane sulfonic acid
NPs: Nanoparticles
PBS: Phosphate buffered saline
SA: Stearylamine

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Conflict of interest
The authors declare that they have no conflict of interest.

Ethical approval
This article does not contain any studies with animals or human participants.

Authors' contribution
MA: conceptualization and preparing the first draft; MRM, MRH, MH, MH, and IK: revising of the manuscript.

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