Taylor & Francis
Taylor & Francis Group

Journal of Microencapsulation
Micro and Nano Carriers

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/imnc20

Recent developments in sustained-release and targeted drug delivery applications of solid lipid nanoparticles

Hanaa Ali Hussein, Fatin L. Khaphi, Ramachandran Sivaramakrishnan, Sivamani Poornima & Mohd Azmuddin Abdullah

To cite this article: Hanaa Ali Hussein, Fatin L. Khaphi, Ramachandran Sivaramakrishnan, Sivamani Poornima & Mohd Azmuddin Abdullah (29 Apr 2025): Recent developments in sustained-release and targeted drug delivery applications of solid lipid nanoparticles, Journal of Microencapsulation, DOI: 10.1080/02652048.2025.2495290

To link to this article: https://doi.org/10.1080/02652048.2025.2495290

Published online: 29 Apr 2025.

JOURNAL OF MICROENCAPSULATION
https://doi.org/10.1080/02652048.2025.2495290

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Recent developments in sustained-release and targeted drug delivery applications of solid lipid nanoparticles

Hanaa Ali Hussein[a], Fatin L. Khaphi[a], Ramachandran Sivaramakrishnan[b,c], Sivamani Poornima[d] and Mohd Azmuddin Abdullah[b,e]

[a]College of Dentistry, University of Basrah, Basrah, Iraq; [b]Laboratory of Cyanobacterial Biotechnology, Department of Biochemistry, Faculty of Science, Chulalongkorn University, Bangkok, Thailand; [c]Centre for Global Health Research, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India; [d]Centre for Stem Cell Research, Christian Medical College, Vellore, Tamil Nadu, India; [e]SIBCo Medical and Pharmaceuticals Sdn. Bhd., Shah Alam, Selangor, Malaysia

ABSTRACT

Solid Lipid Nanoparticles (SLNs) are versatile nano-carriers for wide range of applications. The advantages of SLNs include ease of preparation, low toxicity, high active compound bioavailability, flexibility of incorporating hydrophilic and lipophilic drugs, and feasibility of large-scale production. This review provides an overview on the preparation methods of the SLNs, the micro and nanostructure characteristics of the SLNs, and the different factors influencing sustained release and targeted drug delivery. The applications in agriculture and environment, cosmetics, wound healing, malarial treatment, gene therapy and nano-vaccines, and cancer therapy, are elaborated. The mechanisms such as passive, active, and co-delivery are discussed. The issues, challenges and the way forward with ionisable SLNs for delivery of gene and vaccines, RAS-targeted therapy, and bioactive compounds, are highlighted. In combination with multiple compounds and the potential for integration with nature/bio-based solutions, SLNs are proven to be effective, and practical for diverse applications.

ARTICLE HISTORY
Received 24 September 2024
Accepted 14 April 2025

KEYWORDS
Solid lipid nanoparticles; sustained release; targeted delivery; biomedical application; mechanism; ionisable lipids

1. Introduction

Nanoparticles (NPs), with sizes ranging from 1 to 100 nm, can be broadly classified into metallic, polymeric, lipid, fullerene, and ceramic NPs. The properties such as high surface area, nanoscale dimensions, sizes, and shapes, and unique physical and chemical properties, can be harnessed for applications in catalysis, imaging, medical, energy and environment (Khan *et al.* 2022). In biomedical applications, the NPs can be combined with synthetic polymers to enhance drug transport and reduce mortality (Lingayat *et al.* 2017). The issues will be in attaining sustained release, targeted delivery, biocompatibility, and biodegradability. Of great concern with metallic NPs is the types of metals and their associated toxic side effects on the biosystems and the environment (Ray *et al.* 2009).

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) (Alsaad *et al.* 2020, Borges *et al.* 2020) are generally known as safe materials or generally regarded as safe (GRAS). SLNs have the solid fats replacing the liquid fats, as alternatives to emulsions, liposomes and polymeric NPs (Hussein and Abdullah, 2022), and are composed of solid lipids, emulsifiers/surfactants, and water or other solvents. The solid lipids act as a matrix to encapsulate compounds (Kaur *et al.* 2012), and active ingredients such as drugs, antibiotics, minerals, vitamins, as well as non-polar, semipolar, and polar antioxidant compounds (Ganesan *et al.* 2018). The SLNs prepared from glycerol monostearate (monoglycerides), glycerol bahenate (diglycerides), tristearin (triglycerides), cetyl palmitate (wax), cholestrol (steroids), and stearic acid (fatty acid) are effective as a transport system for water-soluble and dynamic curative substances. Incorporating emulsifiers prevent particle clumping (Nasikkar *et al.* 2019), which otherwise could have caused ineffective or untargeted delivery.

SLN is a versatile platform for applications in diverse area such as from sustained-release of fertilisers and pesticides in agriculture, to administering and targeted delivery of various bioactive and therapeutic agents as drug-delivery systems (DDS) in the biomedical sector.

CONTACT Mohd Azmuddin Abdullah joule1602@gmail.com SIBCo Medical and Pharmaceuticals Sdn. Bhd., Shah Alam, Selangor, Malaysia.

SLNs enhance drug bioavailability and biocompatibility with high target specificity. The large surface area confers easy incorporation of hydrophilic and hydrophobic drugs, high stability and sterility, and allows for controlled-release kinetics of the compounds. Advances in nanotechnology lead to precise modifications of sizes, surface charges, and loading capacities. The controlled release and sustained delivery properties of SLNs improve the effectiveness of therapies while minimising the side effects. The drugs can be delivered to specific tissues or cells (Bukke *et al.* 2024), or the active compounds delivered with reduced impact on the environment and with lesser pollution (Wanyika *et al.* 2012). There remain some challenges that need to be overcome such as random gelation, high water content dispersion, slow incorporation rate, and lower ability to encapsulate hydrophilic compounds or drugs (Ekambaram *et al.* 2012, Sarangi and Padhi 2016, Lingayat *et al.* 2017, Nasikkar *et al.* 2019, Seo *et al.* 2023).

This review provides an overview on the sources of lipids, the synthesis, characterisation, significant findings, and various applications of solid lipid NPs.

2. Sources of lipids and methods of synthesis

Lipids can be sourced from animal fats; oleaginous plants such as oil palm, rapeseed, sunflower, soybean, or castor; or microorganisms such as bacteria, fungi, and yeast. The big hurdle is in getting adequate supply of fatty acids (FAs) and polyunsaturated fatty acids (PUFAs) from sustainable, renewable, and cost-effective sources. The composition of FA also differs depending on sources. Castor oil lipid, for example, contains 90% ricinoleic acid and 10% of mainly linoleic, oleic, stearic, and linolenic FAs (Landoni *et al.* 2023). Of increasing interest, is the use of algae as lipid sources due to the flexibility of cultivation with lower land-use, lesser conflict with the food crops (Abdullah *et al.* 2024), and high oil content of 10–70%, with significant component of eicosapentaenoic acid (EPA) (C20:5) and docosahexaenoic acid (DHA) (C22:6) as PUFAs (Cerone and Smith 2021). Microalgae can be the sources of polar and non-polar, or neutral lipids. Polar lipids, also known as membrane or synthetic lipids, are crucial in cellular signalling and cell structure processes. They make up about 20% of the total lipid in the cells and normally contain long-chain extractable fatty acids. Non-polar lipids make up 80% of the total lipids and have different biological functions, and most are as energy storage in the form of triglycerides (TAG) (Stoyneva-Gärtner *et al.* 2022).[1]H NMR metabolomics analyses of *Chlorella* sp. chloroform extract suggest the presence of choline, an aliphatic monoamine associated with phospholipid, and glycerol, the essential component of neutral and phospholipids. Based on extracting solvents, TAG, together with stearic, oleic, and linoleic acids, with EPA, are detected at different levels in the crude extracts of *Nannochloropsis oculata*, *Tetraselmis suecica*, and *Chlorella* sp. (Hussein *et al.* 2022).

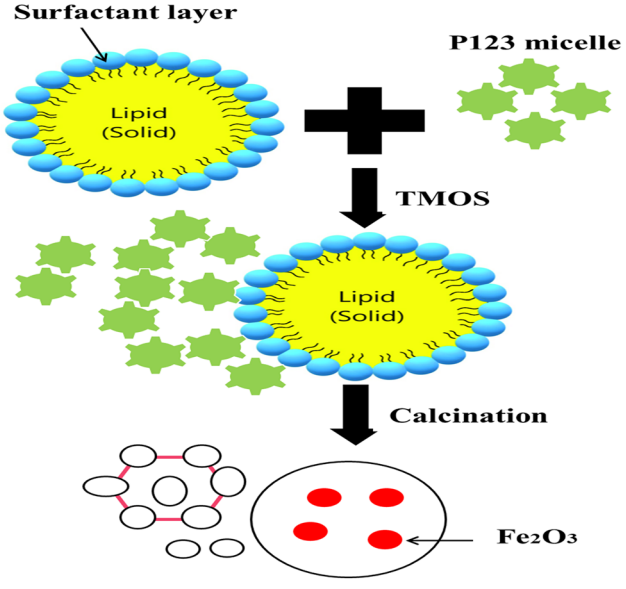


Figure 1. Synthetic strategy based on Fe_2O_3@meso – macroporous silica-SLNs. Preparation of magnetic SLN based on cetyl palmitate, magnetic surfactant, and plauronic acid P123 by ultra-sonication of hot emulsions, followed by solidification. Magnetic surfactant is developed from cetyltrimethylammonium bromide (CTAB) and iron (III) chloride, with TMOS as silica precursor, and mixed with CTAFe to synthesise Fe_2O_3-based mesomacroporous silica (Adapted from Kim 2018).

SLNs can be synthesised from fatty acids (e.g. palmitic, myristic, and stearic acids), glycerides (e.g. glyceryl monostearate and caprate), steroids (e.g. cholesterol), phospholipids (e.g. soybean phosphatidylcholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, hydrogenated soy phosphatidylcholine, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine, and lecithin), cetyl alcohol, cetyl palmitate, tripalmitin, trimyristin, and tristearin, and synthetic lipids such as 1,2-dioleoyl 3-trimethylammonium propane (DOTAP) and 1,2-dipalmi toyl-3-trimethylammonium propane (DPTAP) (Barba *et al.* 2015, Zhang *et al.* 2017, Stanisic *et al.* 2018, Kumar, 2019). SLNs have been prepared using only stearic acid as the lipid phase, without the addition of any liquid oil (Wang *et al.* 2014). The core-shell micro-capsules of SLN and mineralisation with Tetramethylorthosilicate (TMOS) as silica source has been developed (Diab *et al.* 2017). As shown in Figure 1 for the synthesis of Fe_2O_3@meso – macroporous silica-SLNs, hydrochloric acid is added to the SLN@Cetyltrimethylammonium trichloromonobromoferrate (CTAFe) to form dispersion, and TMOS is added dropwise at the

surfactant/silica precursor ratio of 0.016. The mixture is stirred for 1 h at 40 °C for 24 h and heated further at 100 °C for 24 h. The silica-based material is then dried at 30 °C for 24 h and calcined at 550 °C for 6 h to remove organic matter to form iron oxide particles, giving the final product, Fe_2O_3@meso-macroporous silica (Kim 2018). For the synthesis of fine SLNs, the common methods include high shear homogenisation (HSH), ultrasonication, microemulsion, supercritical fluid technology, solvent emulsification/evaporation, solvent emulsification-diffusion, spray drying, and solvent injection technique (Saupe and Rades, 2006, Garud *et al.* 2012).

2.1. High pressure homogenization (HPH) and ultrasonication

HPH is efficient and reliable to prepare SLNs and NLCs at a large scale. It is based on reducing the size of droplets and particles under high-pressure conditions (Duong *et al.* 2020). The advantages include ease of synthesis, short production time, organic solvent-free, and feasibility of expansion. There are two types of HPH - hot and cold homogenisation methods (Duong *et al.* 2020). Hot homogenisation is performed at high temperature above the melting point of the lipid (Garud *et al.* 2012; Figure 2a). For the preparation of a drug carrier, the process involves mixing the drug-loaded lipid at pre-emulsion stage with an aqueous-phase emulsion using a high-shear mixing device. This results in a hot water emulsion product. When it is cooled and due to lower viscosity, the lipids crystallise, leading to the SLNs with smaller particle sizes (Garud *et al.* 2012). For temperature-sensitive compounds such as hydrophilic drugs, cold homogenisation is widely used (Figure 2a). The process involves dissolving a compound-containing lipid and reducing the long lipid

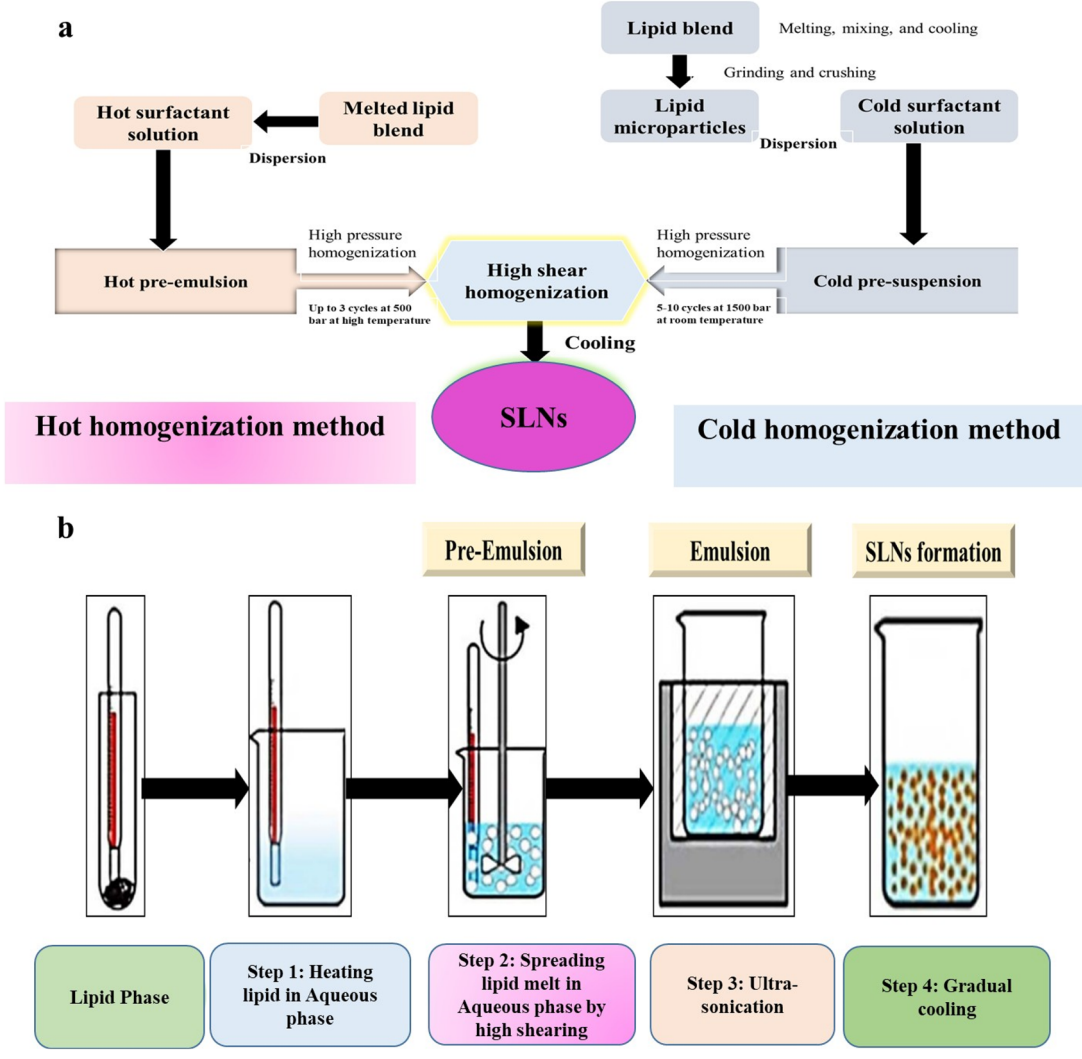


Figure 2. (a) Hot and Cold high pressure homogenisation methods; (b) Ultra-sonication method for the production of the SLN (modified from Pragati *et al.* 2009 and Ganesan and Narayanasamy 2017).

layer into microlipid particles. The lipid melt is cooled rapidly using dry ice or liquid nitrogen and then dispersed in a surfactant, forming a pre-suspension. The pre-suspension is then homogenised at room temperature, where the cavitation forces are high enough to break up the fine lipid particles. This leads to a stable and uniform lipid suspension, which is ideal for the production of lipid-based DDS (Alsaad *et al.* 2020). HPH and ultrasound can reduce the particle sizes of the SLNs to 80–800 nm (Duan *et al.* 2020).

2.2. Microemulsion

During microemulsion, water-immiscible chloroform, cyclohexane, or toluene is commonly used to dissolve the solid lipid. The lipid material can be dissolved in cyclohexane which is emulsified in an aqueous phase by gentle stirring of the lipid and separating it into lipid phase in a water phase containing a surfactant. The solvent is then evaporated at low pressure (Qushawy and Nasr 2019). The SLNs are formed in a high volume of cold water (around 2–3 °C) under moderate stirring. Lipids will precipitate out in the water medium using water phase lipid deposition technique and when the solvent evaporates (Bhattacharjee *et al.* 2020, Sastri *et al.* 2020). The aqueous phase, however, may still contain large amount of surfactant which is scattered together with the lipid phase (Figure 2b). The disadvantages are in the use of organic solvents, varied particle sizes, and a high concentration of surfactants/co-surfactants (Ganesan and Narayanasamy 2017, Qushawy and Nasr 2019). Large amount of surfactants may not produce small-sized NPs and can cause instability during storage.

2.3. Spray drying and solvent injection

Spray drying is cost effective, as compared to lyophilisation and freeze drying. This requires high temperature and shear power which leads to aggregation of molecules. Lipids having melting point of more than 70 °C will be suitable with this method (Naseri *et al.* 2015). During drying, ethanol and carbohydrate mixtures, rather than pure water, are used to improve the properties of the powder after re-dispersion (Pragati *et al.* 2009). This allows modification of properties including the morphology, density, size distribution, and shape of the NPs, as well as the dispersion, bulk density, powder flow ability, and tap density. The disadvantages include instability, unpredictable gelation, removal of active ingredients upon storage, and unpredictable polymorphic dynamic changes of the lipid NPs (Khairnar *et al.* 2022).

For solvent injections, lipid and active components are dissolved in water-soluble isopropanol and ethanol to produce the NPs. The resulting solution is then injected into the water using a syringe needle while continuously stirring at 1000 rpm. Upon contact with water, the lipids are transformed into NPs, entrapping the active components. The size of the NPs is influenced by the type of surfactant, lipid, solvent, and the viscosity of the external phase (Qushawy and Nasr 2019). The technique allows ease of handling and rapid production without complex instrumentation (Duong *et al.* 2020).

2.4. Microwave-assisted and supercritical fluid technology (SFT)

The SLNs can be prepared using microwave-assisted microemulsion technology, utilising a lipid such as stearic acid and a surfactant such as Tween®20. Different components can be tested out for stability and absorption with the SLNs (Shah 2016). The system may include a variable single-mode cavity that holds a reactor tube, and a circular rod to deliver continuous microwave power. To facilitate continuous movement of the components in the reactor tube, a rotating magnetic plate is placed under the floor of the cavity. A sensor is used to measure the temperature at the bottom of the reactor tube where the reaction is set between 25 and 250 °C. The temperature is controlled by an external source of refrigerant, such as clean air or nitrogen, at the pressure between 0 and 21 bar (Shah 2016).

SFT is the eco-friendlier method to produce the NPs. The different types of SFT include Particles from Gas-Saturated Solution (PGSS), Rapid Expansion of Supercritical Solution (RESS), Supercritical Fluid Extraction for Emulsions (SFEE), and Aerosol Solvent Extraction System (ASES) (Khairnar *et al.* 2022). To extract drugs from oil/water emulsion, carbon dioxide as a supercritical fluid is used at moderate temperature (35 °C) and pressure. The advantages are the use of solvent-free system, and the molecules in dry powder form, instead of in suspensions. The limitation is that not all drugs can be dissolved in carbon dioxide (Chattopadhyay *et al.* 2007, Garud *et al.* 2012, Khairnar *et al.* 2022).

3. Types, composition and characterization of SLNs

3.1. Types

Based on drug delivery model, there are three different types of SLNs—SLN Type I, II, and III. For Type I (homogeneous matrix model), the drug is spread

within the lipid core, but with strong interaction between the drug and the lipid. The matrix exhibits controlled release properties. This SLN type can be synthesised by cold homogenisation method, without any solubilising agent. The SLN Type II (drug-enriched model) is where the lipid NP contains both drugs and lipids in the outer solid shell, while the core is drug-free. This is ideal to achieve sustained release. For synthesis, hot homogenisation method is applied where the lipid core is formulated at the recrystallization temperature of the lipid. The drug is then dispersed throughout the lipid matrix, forming strong interaction between the drug and the lipid. Upon cooling, the drug is partitioned into lipid phase in the outer shell. The SLN Type III (drug-enriched basic form) is where drug concentration is close to lipid solubility, causing it to precipitate into the pulp and form lipid enclosure (Borges *et al.* 2020). It is synthesised by cold diffusion which allows supersaturation of the drug and later dissolved in the lipid. The precipitation of the drug is in the liquid lipids and the recrystallization of the lipid is by further cooling where the drug is found in the core (Qushawy and Nasr 2019).

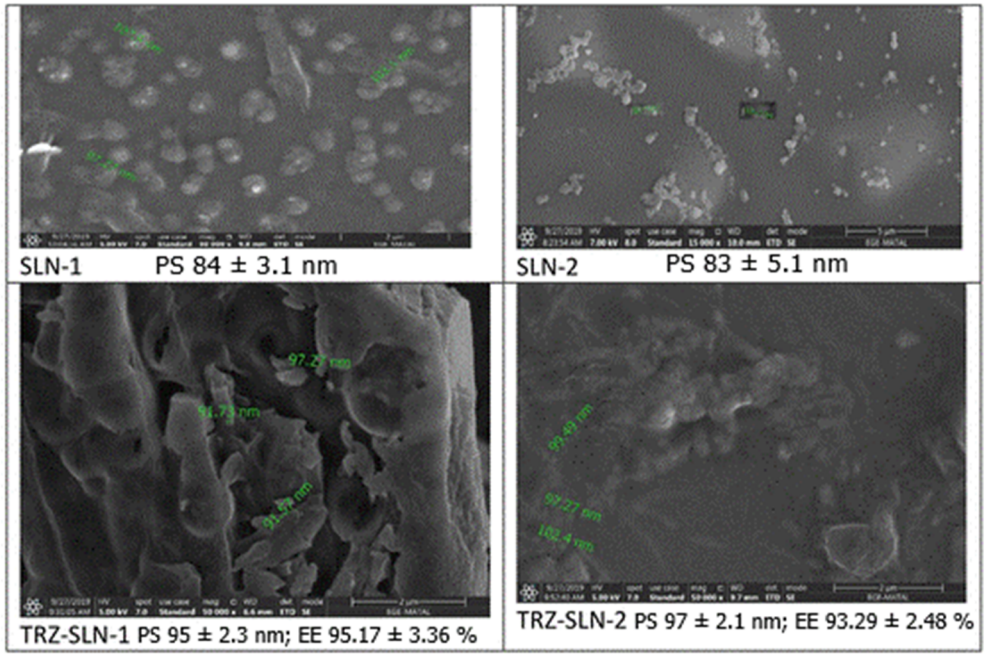
3.2. Composition

The concentrations and properties of lipids and surfactants greatly affect the efficacy and quality of NLCs and lipid NPs (Seo *et al.* 2023). Lipid concentrations eventually determine the stability of the NPs. Triglyceride-based SLN formulations are more stable with larger particle sizes than the SLNs with mono- and diglycerides. Over two years of storage, the larger particle SLNs exhibit lipid degradation of only around 10%. A high melting point lipid synthesised via hot homogenisation method may form SLNs of large volume due to the high viscosity of the diffusion phase. In water scarce environment, crystallisation of lipids could attain fast growing NP sizes, but the long-term stability of the aqueous SLN diffusion may be reduced (Jaiswal *et al.* 2016, Duan *et al.* 2020). Lipids that are not hydrolysed by the aqueous phase are ideal for preparing the SLNs. Furthermore, the natural lipid component in the SLNs requires preservatives to prevent bacterial contamination (Duan *et al.* 2020).

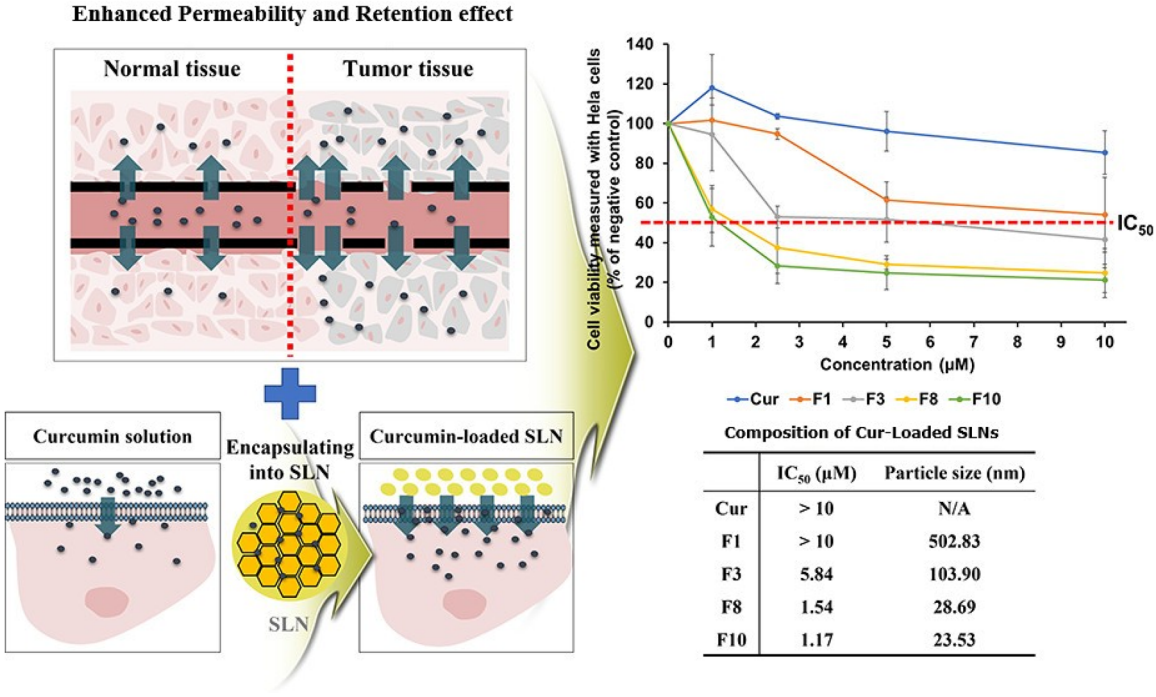
In the development of DDS, supporting agents such as lipids, surfactants, and modifiers are vital in determining product efficacy and standards (Kakkar Thukral *et al.* 2014). The surfactants and modifiers for the preparation of lipid nano-carriers include phospholipids, ethylene oxide/propylene oxide copolymers, sorbitan ethylene oxide/propylene oxide copolymers, alkyl aryl polyether alcohol polymers, bile salts, and alcohol (Jaiswal *et al.* 2016). Capitalising on their amphiphilic nature, surfactants reduce the surface tension between water and lipid phases. The use of combined surfactants may yield smaller NP sizes. Additionally, the structure of the surfactant and lipid molecules can also affect lipid crystallisation. Surfactants of low molecular weight take less time to redistribute, while surfactants of higher molecular weight take longer time and affect efficiency (Jaiswal *et al.* 2016, Duan *et al.* 2020). Different types of aggregates and particle surface charges can be formed and controlled depending on the ratio of macrocyclic compounds to the surfactant. This could create molecular-scale porous materials that react selectively with different types of substrates or biopolymers (Nazarova *et al.* 2022). Modifiers (such as PEGylation, chitosan, and surfactant protein coating) confer high functionality to the NPs for cell membrane penetration, drug release control, and targeting ability (Seo *et al.* 2023). The zeta potential of the SLN changes significantly from −6.54 to +23.0 mV when loaded with positively charged chitosan as a surface modifier (Bhardwaj 2017). This can be tuned to meet the requirements of specific drugs, penetration ability, time of release, and specific target.

3.3. Physico-chemical characterization

Differences in micro and nanostructures of particles are influenced by the synthesis methods. Nanopores act as templates for the formation of anisotropic NPs. Micelles and emulsifiers control the chemical interactions to suit specific intended properties. The characteristic of critical nanoscale shows significant deviations from macroscopic materials. Firstly, the energy transport mechanism changes from electron-transport control to a phonon-control mechanism. Secondly, the material surface-to-volume ratio is significantly increased and the NP interactions are controlled by the surface and interfacial properties, instead of gravity (Otto and De Villiers 2013, Stavis *et al.* 2018, Ahadian *et al.* 2020). These physico-chemical characteristics of the SLNs can be determined and measured. Cryo-field emission scanning electron microscopy (SEM), for instance, can provide information on the surface morphology of the NPs (Saupe *et al.* 2006), while Transmission Electron Microscopy (TEM) describes the internal structure, size, and shape. Imaging techniques offer insights into the morphology and surface properties of the carriers, ensuring their structural integrity and uniformity (Roldán-Matilla *et al.*, 2025). Figure 3a illustrates the SEM images of radiolabeled Trastuzumab (TRZ) encapsulated in the SLN. The release profile exhibits no initial burst release, followed by a



a)



Composition of Cur-Loaded SLNs

	IC_{50} (μM)	Particle size (nm)
Cur	> 10	N/A
F1	> 10	502.83
F3	5.84	103.90
F8	1.54	28.69
F10	1.17	23.53

b)

Figure 3. (a) SEM images of SLN and TRZ-SLN formulations (PS = Mean particle size, EE = Entrapment efficiency) (Adapted from Ozgenc *et al*. 2022, Under CC-BY 4.0 licence); (b) Effects of CUR-loaded SLNs on HeLa cells (Ratios of Cur:LA/SA:PX188 (mg) - F1: Cur 100, LA 100, PX188 200; F3: Cur 100, SA 100, PX188 200; F8: Cur 100, SA 300, PX188 200; F10: Cur 100, SA 500, PX188 200; (Cur, curcumin; LA, lauric acid; SA, stearic acid; PX 188, Poloxamer 188 surfactant) (Adapted from Yeo *et al.* 2022, Under the Creative Commons Attribution 4.0 International licence CC-BY-NC-ND 4.0).

slow-release period. This can be described by a drug-enriched shell model where the area under the curve (AUC_0-24) represents the amount of drug absorbed into the bloodstream. The TRZ-SLN-1 formulation, attaining the TRZ-to-lipid phase mass ratio of 1:5, a negative surface charge (−28 ± 2.2 mV) and a smaller particle size (95 ± 2.3 nm), has resulted in higher plasma concentration (1.48 μg/mL) and more than

2–4-fold higher drug in the bloodstream (13.94 ± 6.03 µg/mL h) than the other formulation or TRZ solution. This formulation indicates that the lipid ratio clearly enhances the TRZ concentration encapsulation and influences the drug release (Ozgenc *et al*. 2022). Figure 3b shows the effects of curcumin (Cur)-loaded SLNs on HeLa cells. Cur has poor aqueous solubility, bioavailability and photostability although it exhibits anticancer activities. The Cur-SLN is developed at different ratios of Cur with lipid-based stearic, lauric and palmitic acid, and different types of surfactants such as Poloxamer 188, Poloxamer 407, Tween 20 and Tween 80, to improve delivery to cancer cells. The mean particle sizes of the stearic acid-based, lauric acid-based, and palmitic acid-based SLNs are 14.70–149.30, 502.83, and 469.53 nm, respectively The Cur-SLN formulations successfully show higher cytotoxic activities against HeLa, A549 and CT-26 cells, than the pure Cur, depending on particle sizes and cancer cell-lines (Yeo *et al*. 2022). For *in vitro* drug release studies, dialysis or Franz diffusion cells are useful to monitor the drug release profiles from the carriers. Determination of release kinetics are essential to optimise the release rates for controlled drug delivery (Gómez-Lázaro *et al*. 2024).

High-performance liquid chromatography (HPLC) and UV–visible spectrophotometry are commonly used to quantify drug encapsulation within the carriers, ensuring that the drug-loading capacity meets the necessary therapeutic requirements (Kako *et al*. 2024). Fourier transform infra-red spectroscopy (FTIR) determines the chemical composition and the interactions between the carrier material and the encapsulated drug (Kumari *et al*. 2010). Differential scanning calorimetry (DSC) is a thermoanalytical technique that determines the crystallinity degree of a lipid based on the enthalpy and stability of the carriers. Powder X-ray diffraction (PXRD) is a non-destructive method to characterise crystal structure, crystallinity, and release rate of drug carriers (Jenning *et al*. 2000, Mishra *et al*. 2018). Particle size and zeta potential are important to determine the physical stability of the NPs. Zeta potential provides information about colloidal stability and the duration of the dispersions. A high zeta potential of more than 30 mV can stabilise colloidal dispersions by creating electrostatic repulsion under specific conditions. This causes the NPs to repel each other, preventing aggregation. The NPs with zeta potential close to zero can be stabilised during storage with a hydrophilic polymer such as Polyethylene glycol (PEG) coating to establish a physical barrier against aggregation, thus ensuring static stability (Mishra *et al*. 2018).

Dynamic light scattering (DLS) measures the fluctuations in scattered light caused by the Brownian motion of the NPs to give an average particle size (*z*-average) and polydispersity of the nanosystem for particle size distribution. These factors are essential for optimising the stability, cellular uptake, and release profile of the carriers. Light diffraction (LD) uses Fraunhofer theory to depict particle shape and size in the diffraction pattern. Polydispersity Index (PDI) indicates the wideness of the size distribution of an NP population, with a value between 0 and 1. A low PDI is desirable, indicating a narrow size distribution of the NPs (Danaei *et al*. 2018). The shape, size, surface coating, and charge directly impact the NP distribution and activity (Mitchell *et al*. 2021). In drug delivery, these influence drug circulation and clearance, and interaction with local barriers such as the tumour mucus layers or microenvironment. Spherical and larger NPs peripheral are more easily circulated, while rod-shaped NPs percolate more easily. Uncoated or positively charged NPs are more rapidly cleared by the macrophages. For local distribution, neutral, rod-shaped, tumour-targeted NPs penetrate more readily, while smaller, positively charged coated NPs could more readily cross mucosal barriers as illustrated in Figure 4a (Mitchell *et al*. 2021). NPs can enter cells through endocytosis or pinocytosis, depending on their size, shape, surface properties, and charge. They may enter via general interactions, like membrane wrapping, or through specific cell surface receptors. Once inside, NPs are contained in compartments called vesicles, like endosomes, which can help release drugs at targeted sites (Figure 4b) (Duan *et al*. 2020).

4. Factors influencing sustained-release and targeted delivery

The colloidal DDS may be in the form of NPs, liposomes, and micelles. The NPs should exhibit high loading capacity and bioavailability of the amphiphiles, biomolecules, and lipophiles, for targeted delivery to specific tissue, with acceptable kinetics of controlled release, lower immune response, and good patient compliance (Duan *et al*. 2020). These are largely influenced by bulk-flow transport, electrostatics interaction, and stearic effects. Bulk-flow transport is associated with mechanical pumping within a circulatory system to allow blood flow in the whole body for rapid distribution of the NP drug conjugates. The relative size and hydrodynamic diameter of the NPs determine the efficiency of the delivery where smaller NPs result in better diffusion and transport in targeted tissue. The interaction between the NPs and the local matrix is controlled by the steric forces, which are affected by the thickness of the polymer coating and the size of

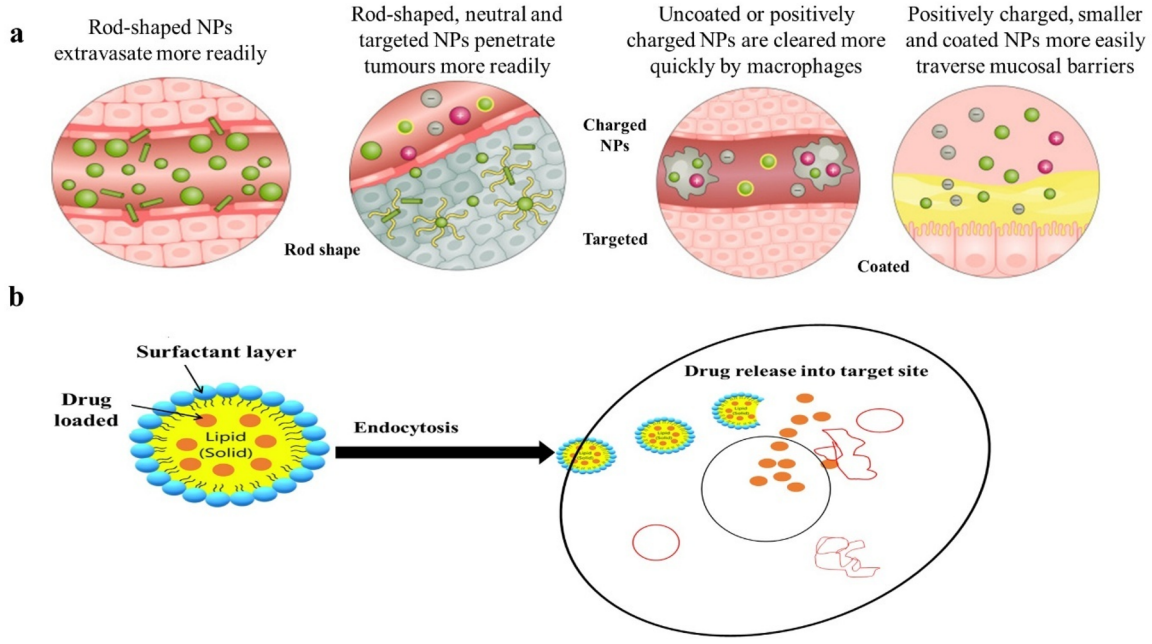


Figure 4. (a) Characteristics and distribution of engineered NPs; (b) SLNs as drug delivery system (Modified from Mitchell *et al.* 2021 and Duan *et al.* 2020).

the NP core. The ratio of ligand thickness to the core radius, and the local environment, also play a role in this interaction. When the NPs are transported to the tissue, the flexibility of the ligand corona determines the interaction with cellular proteins, and this eventually directly impacts the rate of NP transport in the extracellular fluid (Doane and Burda 2013, Si *et al.* 2018, Mitchell *et al.* 2021).

Table 1 summarises the delivery system of SLNs-loaded drugs or bioactive compounds for different disease treatments. Different preparation methods have been reported to improve cargo loading. To attain high loading capacity of astaxanthin-encapsulated SLNs, double emulsion solvent displacement method is used. The enhanced antioxidant activities protect against oxidative stress in neurological disorders (Chandra Bhatt *et al.* 2016, Tang *et al.* 2023). For oral delivery, the core-shell microcapsules containing curcumin (MC-CUR) is designed by firstly incorporating CUR into the SLNs, which are then mineralised with TMOS to create the MC-CUR. This is easily absorbed by the Caco-2 cell line, for intended drug solubility and intestinal permeability (Diab *et al.* 2017). The SLN-loaded CUR exhibits 16.4 times higher bioavailability in the rat brain ischaemic model compared to CUR alone (Kakkar Thukral *et al.* 2014). Sesamol-loaded SLN at 120 nm size also results in improved oral delivery against carbon tetrachloride-induced hepatotoxicity in animal model. The SLN-loaded-sesamol attains stronger protective effect than sesamol alone, with no toxic effect (Ganesan *et al.* 2018). The magnetic SLN based on cetyl palmitate, magnetic surfactant, and plauronic acid P123 can be developed as DDS and then directed under magnetic field to the targeted site (Kim 2018; Figure 1).

SLNs could enhance the ability of the drug to penetrate the blood–brain barrier (BBB). Clonazepam is delivered to the brain through intranasal olfactory mucosa using nano-lipid carriers-loaded-super magnetic iron oxide NPs (SPIONs). The aims are both to apply external magnetic field and direct the nano-carrier to the targeted site. In situ lipid nano-carriers in combination with thermo-sensitive mucosal adhesive gels, enhance clonazepam delivery for intranasal epilepsy whilst reducing the peripheral adverse effects (Abbas *et al.* 2018). Surface-modified SLNs (SMSLNs) for enhanced deliveries of active compounds for the treatment of cancers, diabetes, inflammation, and neurodegenerative diseases, are feasible for long-term storage and suitable for large-scale production (Ramalingam *et al.* 2016, Ganesan *et al.* 2018). SMSLNs such as chitosan can be cost-effective for efficiency of delivery under low pH microenvironment. The SMSLNs produced using heparin, albumin, PEG, and polysaccharides could overcome the limitation of oral delivery and improve the uptake of bioactive compounds such as CUR in the brain for the treatment of neuro-inflammatory diseases (Ganesan *et al.* 2018). Some amounts of coated NPs can be transported *via* ileum absorption. Trimethyl chitosan (TMC) as an SMSLN delivery system exhibits improved delivery of drugs to the mouse model brain with Alzheimer's disease (Ganesan *et al.* 2018).

Table 1. SLN-based systems for delivery of active ingredients.

Active ingredient	SLN-based system	Preparation method	Major findings	Surface modification	Reference
β-carotene	β-carotene-SLNs	High shear homogenisation	β -carotene significantly affects the formulation and process conditions, achieving 40 % entrapment efficiency (EE); the compound remains in the SLNs for 1 month, confirming its stability.	Lipid: Stearic acid; Co-surfactant: Sodium taurocholate	Triplett and Rathman (2009)
Gliclazide		High shear homogenisation, freeze drying	Absorption efficiency of 75.3 %; efficient incorporation of gliclazide into the SLNs	Lipid: Stearic acid; Surfactant: PEG 400 and Tween® 80	Amalia *et al.* (2014)
Buparvaquone (BPQ)	BPQ-SLN	Ultraturrax and high pressure homogeniser	The macrophage cell line attains 52 % uptake of BPQ-SLNs within 1h; potential for targeted delivery to reticuloendothelial system (RES) organs; biodistribution studies in Holtzman rats confirm effective absorption of BPQ-SLNs by RES organs (liver, lung, and spleen) with 75 % uptake	Lutrol F68	Soni *et al.* (2014)
Garlic oil	Garlic oil-SLN	High-pressure homogenisation, ultrasound	Increased drug loading capacity; > 90 % EE; relatively long-term physical stability; faster elimination of garlic oil-SLN complex compared to garlic oil alone	3:1 (w/w) mixture of poloxamer188: lecithin	Wencui *et al.* (2015)
Oxyresveratrol (OXY)	OXY-SLN	High shear homogenisation	EE of 89 ± 0.1 %; greater loading capacity to encapsulate OXY; SLN increases relative oral bioavailability of OXY (177 %) compared to OXY alone (100%)	Lipid: C888 Surfactant: Tween® 80 and soy lecithin	Sangsen *et al.* (2015)
Loperamide (LPM)	LPM-SLN-1	Modified solvent evaporation	Controlled delivery with continuous LPM release and no burst effect; LPM-SLN-1 enhances oral bioavailability (227 %) compared to LPM-SLN-2 (153 %) and LPM tablet (100 %).	High ratio of lipid to drug	Wei *et al.* (2016)
Carvedilol (CL)	CL-SLNs	Hot homogenisation, ultrasonication	In vitro cumulative, controlled drug release from SLNs (96.57 ± 0.40 %) after 24 h; the SLNs remain stable up to three months, indicating a safe and effective delivery system.	Lipid: Trimyristin; Surfactant: Polyethylene glycol sorbitan monooleate	Kipriye *et al.* (2017)
Hydrochlorothiazide (HCT)	HCT-SLN	Hot high-shear homogenisation, ultrasonication	About 65 % EE; SLNs with coground product (GR) systems show better drug release rates compared to free drug-loaded SLNs and simple suspensions; In vivo studies confirm improved diuretic effects and oral bioavailability of HCT; effective for sustained delivery.	Surfactant: Precirol®ATO5, with Tween® 80 and Pluronic F68	Cirri *et al.* (2017)

(*Continued*)

Table 1. Continued.

Active ingredient	SLN-based system	Preparation method	Major findings	Surface modification	Reference
Clarithromycin (CLR)	CLR-SLN	High-speed homogenisation	In vitro sustained release of CLR over 48 h, starting with an initial burst followed by sustained release.	Lipid: Stearic acid, tripalmitin, and glyceryl behenate Surfactant: Tween® 80	Öztürk *et al.* (2019)
Amphotericin B (AmB) and Paromomycin (PM)	m-DDSLNs	Emulsion/solvent evaporation	High EE, with 96 % for AmB and 90 % for PM; 57 % of AmB and 21.5 % of PM released over 72 h, indicating controlled release for therapeutic use; the formulations remain stable at 4 °C and 25 °C over two months of stability studies.	2-hydroxypropyl-β-cyclodextrin (HPCD)	Parvez *et al.* (2020)
Deferoxamine (DFOA)	DFOA-loaded SLNs	Cold homogenisation	60 % EE of DFOA in SLNs; effective encapsulation for hydrophilic drug; release profile shows an initial burst followed by prolonged release, for sustained topical delivery.	Lipid: Compritol® and oleic acid; Surfactant: Tween® 80 and lecithin	Karami *et al.* (2021)
Noscapine (NOS)	SLN-NOS	High-shear homogenisation, ultrasound	High EE of 89.8 %; SLN-NOS 1% releases 83.2 % and 58.5 % of NOS at pH 5.8 and 7.4, respectively, after 72 h	Surfactant: Tween® 80 and Poloxamer® 188	Rahmanian-Devin *et al.* (2023)
Troxerutin (TXR)	TXR-SLN	High-shear homogenisation, ultrasonication.	83.6 % EE; improved drug-loading capacity and extended release	Surfactant: Tween® 80 and lecithin	Jamous *et al.* (2023)
Nevirapine (NVP)	NVP-SLN	Hot homogenisation	NVP-SLN enters the lymphatic system; will not undergo metabolism, less degradation	Tween® 80 and Poloxamer 188	Shinde *et al.* (2023)

NB (Adapted from Hashem *et al.* 2014)
Solid lipid nanoparticles (SLNs) are designed for controlled delivery of active ingredients, with improved stability, solubility, and bioavailability.
Entrapment efficiency (EE %) represents the percentage of active ingredients successfully incorporated into the SLNs compared to the initial amount of substances used.
Bioavailability (%) indicates the percentage of administered drug that reaches the systemic circulation, compared to free drug.
pH-dependent release may involve formulations for release of drugs differently under acidic condition (pH 5.8), as compared to neutral condition (pH 7.4) which mimics human physiological environments.

Lipid-polymer hybrid nanoparticles (LPHNPs) have a large capacity and gradual release of contents, making them effective for hydrophobic compounds. LPHNPs take advantage of physical characteristics of the polymers for controlled release, and the cell membrane permeability and drug loading features of the lipids. This unique composition allows for increased structural integration and encapsulation, stability in serum with sustained release profile and targeting capabilities, making it feasible for co-delivery of amphiphilic molecules, bioactive substances, phytochemicals and chemotherapeutics to the targeted sites (Zhang *et al.* 2008a, Mohammed *et al.* 2016, Parveen *et al.* 2023). The major components consist of a lipid monolayer surrounding the core polymer, with a second lipid-polymer layer to confer stability and to attain sustained release and prevent immune breakdown. The third lipid monolayer in the middle provides a barrier to prevent water from entering the inner core, thus preserving the entrapped substances for a prolonged period. The lipid components are benign and therefore reduce the possibility of toxicity, while the polymer must be biodegradable and safe for human use such as PEG, polylactic acid, poly(lactic-co-glycolic acid), polycaprolactone, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, alginates and chitosan (Zhang *et al.* 2008b, Wakaskar 2018, Parveen *et al.* 2023).

The loading of several drugs in a single nano-complex carrier improves the synergistic anticancer effects. A new protein-lipid nano-complex is developed as a regulated DDS for two anticancer drugs, mitoxantrone (MTO) and doxorubicin (DOX) (Amer Ridha *et al.* 2021). The protein nano-complexes use apoferritin (AFr) loaded with folic acid (FA) to encapsulate DOX, while MTO is loaded into cationic SLN (cSLN) to create liposomal-drug nano-complex NPs (MTO-cSLNs). The two complexes are combined through ionic interactions to create dual-targeted protein-lipid nano-complexes (DTPLNs) with more potent anti-cancer activity than the free DOX

and MTO (Amer Ridha *et al.* 2021, Kargari Aghmiouni and Khoee 2023). Drug solubility, drug-polymer interaction, polymer degradation rate, and particle sizes influence the release properties. While drug diffusion and polymer disintegration facilitate easier release, the hydrolysis of bonds between drugs and polymer chains controls the release of chemically conjugated drugs (Kundu *et al.* 2010). For high surface area-to-volume ratio and fast release of diffusive drug, systemic distribution of NP sizes within the range of 50–150 nm is considered ideal. In the case of cell surface antigens that are upregulated, heterogeneity in expression limits conventional targeting strategy. To accomplish spatial control, the delivery systems should target common vascular antigens already identified for the disease by phage library (Chan *et al.* 2010).

5. Applications

SLNs are more stable than liposomes, and production can be scaled up to meet increasing demand in agriculture and environment, cosmetics, medical, and biomedical applications. As DDS, SLNs have great potentials to treat cancer and parasitic diseases (malaria, leishmaniasis, tuberculosis, and human African trypanosomiasis) (Singh *et al.* 2020). SLNs have been used as colloidal nano-carriers of hydrophilic and hydrophobic drugs including as anti-parasitic, antibacterial, antioxidant, antiviral, anticancer, anti-androgenic, antihypertensive, anti-degenerative, anti-migraine, antipsychotic, and anti-inflammatory agents. SLNs are also effective carriers of gene, vitamins, hormone, plant extracts, and bioactive compounds such as flavonoids, polyphenols, food bioactive ingredients, and carotenoids (Geszke-Moritz and Moritz 2016). SLNs can remain stable for over a year when stored at 4 °C as compared to when kept at room temperature. Both light exposure and temperature affect the stability (Geszke-Moritz and Moritz 2016). These factors must therefore be effectively controlled for the SLNs to function in a wide range of applications.

5.1. Agriculture and environment

SLN is a promising carrier for pesticides with controlled-release profiles for increased efficacy and effectiveness as pest and environmental control (Geszke-Moritz and Moritz 2016). Non-polar materials can be confined and have mobility restricted by the lipids, leading to modified release profiles (Severino *et al.* 2011). As lipids are found in most living organisms, the advantages of lipid-based pesticides include low toxicity, reduced impacts on the environment and humans, smaller amounts of active agents used, and decreased losses due to leaching, volatilisation, and degradation (Wanyika *et al.* 2012).

Tebuconazole (TBZ) (RS-1–(4-chlorophenyl)-(4,4-dimethyl-3)-(1H-1,2,4-triazol-1-ylmethyl)-pentan-3-ol) and carbendazim (MBC) (methyl-2-benzimidazole carbamate) are common fungicides to control fungal diseases. Lipid-based nanocapsules are excellent carrier and release systems for TBZ and MBC, with potent effects on dominant fungi, and reduced impacts on the host crops and the environment (Campos *et al.* 2015). The SLN can be synthesised using Compritol® 888 ATO as lipid excipient and miranol ultra C32, or poloxamer 188 as surfactant (Stavis *et al.* 2018). Essential oil isolated from *Artemisia arborescens* L. encapsulated in the SLN serves as an environmentally safe delivery system for pesticide, with much reduced rapid evaporation, as compared to the use of emulsions (Lai *et al.* 2006).

5.2. Cosmetics

SLNs are suitable to retain and prevent labile compounds such as tocopherol and retinol from degradation, which is a prerequisite in cosmetic applications. SLN could act as an occlusal, and increase skin water content as active carrier for molecular UV blockers and sunscreens (Wissing and Müller 2003, Alsaad *et al.* 2020), or as anti-aging agent (Sanad 2014). Based on the types of SLNs, loading capacity, and release profile, penetration of bioactive compounds through the skin can be enhanced and controlled (Ahmad 2021). The SLN-drug-enriched shell exhibits fast-releasing characteristics, while the SLN loaded-drug-enriched core could attain sustained release. As compared to traditional approach, SLN formulations achieve novel occlusive topical release, with better localisation of vitamin A in the top layers of the skin. The SLN-incorporated sunscreens therefore exhibit good UV-blocking activity and high photoprotection. An in vivo study suggests that the addition of 4% SLN to the traditional cream could increase the skin hydration by 31% after 4 weeks (Wissing and Müller 2003). The occlusion with lipid nano-based systems can be achieved without the use of paraffin or other greasy oils. The film formed is also smoother than the inflexible films formed by paraffin (Jose and Netto 2019). The NPs containing Precirol® ATO 5 with Tween® 80 (SLN 2) and the NPs containing Precirol® ATO 5 with Tween® 80 and Capryol® 90 (NLC 2) have excellent physicochemical properties which are biocompatible for skin applications, with good activities retained and long-term stability for at least one month (Pereira-Leite *et al.* 2023).

5.3. Wound healing

A promising solution for topical treatment of *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) wound infections is to apply lacticin 3147 SLNs gel. The gel demonstrates an increased activity against *S. aureus*-infected pig skin ex vivo for slightly longer duration (11 days) than the free lacticin gel (9 days), with significant bacterial eradication (>75%) after just 1 h. This suggests a prolonged-acting and potent lacticin 3147 SLN gel, exhibiting physicochemical properties for topical delivery of lacticin 3147 for the treatment of *S. aureus*-infected chronic wound (Ryan *et al.* 2023).

5.4. Malarial treatment

For malarial treatment, nanocarriers enhance drug efficacy and improve bioavailability (Nasikkar *et al.* 2019). The characteristics of malaria parasites have placed importance on the use of lipids (SLNs, liposomes, nano- and micro-emulsions) and polymer-based nano-carriers (nanospheres and nanocapsules) (Sarangi and Padhi 2016). The delivery of antimalarial agents through nanovectors should target *Plasmodium* spp.-infected cells. Primaquine-loaded SLNs, for example, effectively treat *Plasmodium berghei*-infected Swiss albino mice without any side-effects (Gujjari *et al.* 2022). The SLNs modified with heparin-coated chloroquine exhibit significant antimalarial activity against *P. falciparum* (chloroquine-susceptible (D6) strains), better than free chloroquine (Muga *et al.* 2018). Artemether and Lumefantrine-loaded-SLNs also exhibit high efficacy against blood parasites (Attama *et al.* 2016). In vivo study of artemether loaded-NPs shows antimalarial effect against *P. berghei* strain, with significant suppression of *Plasmodium* parasite, resulting in increased lifespan of mice as compared to the treatment with the drug alone (Attama *et al.* 2016).

5.5. Gene therapy and nanovaccines

Gene therapy involves altering a mutant gene in its original place or replacing a damaged gene with foreign DNA. The delivery of DNA, *p*-DNA (plasmid deoxyribonucleic acid), and other nucleic acids using SLNs, is feasible as lipids are the essential components of cell membranes. SLNs are safe carriers to penetrate biological membranes via a receptor-mediated pathway to treat both genetic and non-genetic diseases. Modified SLNs could deliver DNA to the targeted sites for treatment of infectious diseases, lysosomal storage problems, and eye and corneal disease (Vicente-Pascual *et al.* 2018, Duan *et al.* 2020). Small interfering RNA (siRNA) and microRNAs (miRNAs) are used in gene silencing and to regulate molecules to overcome drug resistance in cancer cells (Liu *et al.* 2016). Lipid-based NPs (LNPs) can be an efficient delivery system for siRNA. The ionisable lipid begins to protonate as endosomes are taken up and the pH drops. The specific absorption mechanism is still unknown but altering the electrostatic interactions between the NPs and the negative membrane of the endosome could change the surface charges of the NPs from negative to positive. This promotes endosomal escape and the release of siRNA which can be integrated into the RNA-induced silencing complex (RISC) (Yonezawa *et al.* 2020).

Nanovaccine has been an effective immunogenic agent that incites humoral immunological reaction and generation of antibodies in animal models. SLNs are advantageous in transferring antigens to elicit desired immune response. The NPs may target specific sites, regulate the release, hold on the antigens, and disperse uniformly throughout the bloodstream. To overcome the limitations of current lipid-based and polymeric NPs, the cSLNs have been developed for antigen transfer, as cSLNs are biocompatible with enhanced flexibility but reduced cytotoxicity (Assefi *et al.* 2023). The positively charged SLNs interact with the negatively charged nucleic acids and cell membrane and can be catalysed with appropriate cationic surfactants. The cSLNs with protamine especially are promising transfection inducers (Pragati *et al.* 2009). With cSLNs (Genospheres) as intact non-viral gene delivery carriers, the SLNs bind directly to the DNA for the transfection of genes (Naseri *et al.* 2015). However, despite the known properties of SLNs as effective antigen delivery system to boost immune responses against a range of diseases, the development of SLN-based human vaccination requires more research and development.

5.6. Cancer therapy

Chemotherapy remains at present the main cancer treatment (Bayón-Cordero *et al.* 2019, Mohammed *et al.* 2023). The currently administered conventional drugs are replete with challenges related to low specificity, solubility, and efficacy, but high toxicity. There is also a growing concern about multidrug resistance (MDR) of cancer cells. The drugs introduced via injection or intravenously, rather than orally, cause inconvenience to some patients, not to mention the associated side effects including hair loss, fatigue, or loss of appetite (Patel *et al*. 2019). The application of custom-made SLNs could overcome many biological barriers to enhance drug therapy and control the MDR

mechanisms with lower side effects (Geszke-Moritz and Moritz 2016). Table 2 summarises different types of anticancer drugs loaded into SLNs and their ability to enhance *in vitro* and in vivo anticancer activities. These drugs include Tamoxifen (TMX) (Pedersen *et al.* 2006), methotrexate (Mei *et al.* 2005), camptothecin (Chen *et al.* 2006), and DOX (Liu *et al.* 2007). The drug can be loaded through lipid matrix homogeneously, or loaded into the envelope surrounding the matrix, or spread into the outer shell of the SLNs (Bayón-Cordero *et al.* 2019). Upon IV administration, many of these drugs attain slow or controlled release from the SLNs. The drugs may be delivered to the liver *in vitro* and *in vivo*, later taken up by active phagocytes, and are completely biodegradable. The SLN formulations as DDS, target the lymphatic system and tissue distribution via chylomicron uptake, and are especially effective for high-incidence cancers like breast, lung, gastrointestinal, and prostate cancers. There has been improved drug delivery to the brain cells using SLNs. The SLN system also enhances corneal permeability and pre-corneal retention, reducing toxicity while increasing bioavailability and stability in the aqueous humour of the eye (Mohammed *et al.* 2023). The different mechanisms and modes of actions of drug delivery and cancer therapy will greatly benefit from the tuneable properties of the SLNs (Geszke-Moritz and Moritz 2016).

5.6.1. Mechanisms

The major aim of cancer therapy is to achieve selective delivery of drugs to the target sites, with enhanced therapeutic efficacy and minimal side effects. This will be determined largely by the mechanisms of drug delivery and biodistribution in different cells and tissues as illustrated in Figure 5 (Mohammed *et al.* 2023). The three major drug delivery mechanisms are passive, active, and co-delivery mechanisms. Accumulation of drugs at the target sites can be achieved by local injection of drugs at identified areas. However, this can be complex and not always possible in the case of cancer, as identifying pre-cancerous masses can be difficult (Moon *et al.* 2015). The SLNs via passive mechanism allow targeting of cancer tissues with Enhanced Permeability and Retention (EPR) effect where the NPs leak out of the blood vessels, diffuse through tumour tissues, and interact with extracellular or intracellular targets in the tumour microenvironment (Bertrand *et al.* 2014). At the tumour site, angiogenesis causes irregular growth of blood vessels with patchy epithelium. This allows the NPs to move through the interstitial spaces and accumulate in the tumour tissues due to insufficient lymphatic discharge (Bertrand *et al.* 2014, Bayón-Cordero *et al.* 2019).

Active mechanism makes use of identified overexpressed receptors on the surface of tumour cells. Tumour tissue has higher cell proliferation, and therefore higher demand for nutrients. This inadvertently leads to increased expression of transporters or receptors in tumour cells (Kou *et al.* 2018). The DDS can be selectively designed to target cancer cells by modifying the NP surface to enhance specificity and minimise damage and side effects on the normal cells (Sun *et al.* 2014). For ligand-target interaction, the designed nanocarriers should be able to get close to the intended target with high circulation times (Bertrand *et al.* 2014). Certain types of ligands can achieve SLNs-mediated active drug delivery such as hyaluronic acid (HA), tetraiodothyroacetic acid, and pluronic acid. HA, the glycosaminoglycan hyaluronan which is the component of extracellular matrices, and CD44 and receptor for HA-mediated motility (RHAMM), the cell surface receptors of HA, play important roles in inflammation and cancer cell growth, migration and progression. Increased level of high-molecular weight HA (HMWHA) and overexpression of CD44 and RHAMM are associated with cancer development (Misra *et al*. 2015). CD44 receptor is overexpressed in colorectal cancer, lung cancer, melanoma, lymphoma, and breast cancer (Cain *et al*. 2011), but expressed at low levels in normal cells. CD44 also plays an important role in multidrug resistance by protecting P-glycoprotein. The HA-decorated SLNs have resulted in higher drug concentration and efficacy in tumour tissues of mice, than the SLNs without hyaluronic acid and free drug (Bertrand *et al.* 2014). The application of HA in DDS enables targeted approaches to overcome drug-resistant tumours during chemotherapy (Prochazka *et al*. 2014). By interfering with HMWHA-CD44 signalling pathways, the antagonist or the drugs could inhibit cancer or tumour growth (Misra e*t al*. 2015).

Co-delivery mechanism tackles the treatment at diseased sites via multi-pronged strategies such as the use of multiple drugs, or genetic manipulation to alter pathways and responses. Pluronic polymers are effective against resistance mechanisms by inhibiting efflux transporters that are overexpressed in the membrane of cancer cells. The combination of paclitaxel (PTX) and heat shock protein 90 (Hsp90) inhibitor (tanespimycin) in the SLN inhibits Hsp90 and suppresses the receptor expression to reduce gastric cell viability, and the size and weight of gastric tumours in mice (Ma *et al.* 2018). Modification of the SLN with polyethyleneglycol-distearoyl-phosphatidylethanol-amine and functionalization with the trans-activating transcriptional activator or TAT

Table 2. *In vitro* and *in vivo* evaluations of SLNs as delivery systems for anticancer agents.

Drug-SLN	Cancer cell/animal model	Major findings	References
1. In vitro model			
Distearoyl-floxuridine-SLN	M14, HT-29 and MDA-MB231	Distearoyl-floxuridine-SLN; Spherical, mean diameter <300 nm, 70.8–82.8% EE; Significantly higher efficacy than floxuridine alone; 100-fold increase in cancer cell growth inhibition.	Chirio *et al.* (2018)
Epigallocatechingallate (EGCG), EGCG-loaded SLNs	MCF-7, Caco-2 cells	EGCG-SLN; 144 nm size, PDI[a] = 0.160, ZP[b] = +26mV; Intrinsic toxicity with IC_{50}=58.60 ± 3.29 µg/mL against MCF-7, and IC_{50}>500.00 µg/mL against Caco-2.	Silva *et al.* (2019)
Paclitaxel (PTX-SLNs)	Breast cancer cell-line MCF7 and MCF7/ADR variant	PTX-SLNs; Spherical, 210.5 ± 86.3 nm, PDI = 1.23; Enhanced anticancer and significant increase in intracellular uptake of PTX; IC_{50} of 15.5 ± 5.1 and 127.8 ± 19.1 nM, respectively, against MCF7 and MCF7/ADR; Enhanced activity from increased uptake of PTX-SLNs (2.8-fold) in MDR cells, bypassing the efflux pumps that cause drug resistance via caveola-mediated endocytosis; drug-sensitive MCF7 cells may have used different mechanism.	Xu *et al.* (2018)
Cisplatin-loaded SLNs	MCF-7 cells	Cisplatin-loaded SLNs; Spherical, 74.85 nm, PDI = 0.311, ZP= −20.8 mV, 71.8 5% EE; Increased sustainability in breast cancer therapy; IC_{50} of 6.51 ± 0.39 µg/mL and superior biocompatibility.	Aldawsari and Singh (2020)
4-Hexylresorcinol loaded SLNs	HeLa, A549, and CT-26 (colon carcinoma in mice) cell lines	4-HR-loaded SLNs; 169.4–644.8 nm sizes, ZP= −19.8 to −40.3 mV, 75.0–96.5% EE; Enhanced anti-cancer effects as compared to 4-HR alone, attributable to reduced particle sizes and higher cellular uptake; IC_{50} of 88.5 µM (HeLa cells), 70.0 µM (A549 cells), and 97.2 µM (CT-26 cells).	Yeo *et al.* (2024)
Allicin (AC)-SLN decorated with chitosan (CS)-conjugated folic acid (FA)	MCF-7 and HFF cell lines	AC-SLN-CS-FA; Spherical, 86.7 ± 9.4 nm, PDI = 0.31 with uniform distribution, ZP= +21.3 ± 13.3 mV, 86.3% EE, folate binding of 63%; Significant activity in preventing free radicals and triggering apoptosis via intrinsic pathway in MCF-7 cells; IC_{50} of ~20 µg/mL.	Alyasiri *et al.* (2023)
Tamoxifen citrate (TC-SLN)	MCF-7 cells	TC-loaded SLN; 130.40 ± 9.45 and 243.80 ± 12.33 nm, and 86.07 ± 1.74 and 90.40 ± 1.22% EE, respectively; Exhibits in vitro anticancer activity; An initial burst effect followed by sustained drug release; Promising to improve bioavailability and therapeutic efficacy of poorly water-soluble drug such as TC.	Duong *et al.* (2020), Hashem *et al.* (2014)
5-Fluorouracil (5-FU)-SLN	Colorectal cancer HCT-116 cells	5FU-SLN4; 263 ± 3 nm, ZP = 0.1 ± 0.02, 81 ± 10% EE; Higher cellular uptake and cytotoxic effect against HCT-116 cells (IC_{50} of 7.4 µM) as compared to 5-FU alone (17.7 µM).	Smith *et al.* (2020)
Myricetin-loaded SLNs decorated with folic acid-bound chitosan	MCF-7 and human foreskin fibroblast (HFF) cell lines	Myricetin-SLN-CS-FA; 310 nm, ZP= +30 mV; Suitable for oral use; drug release follows Michaelis–Menten model with 144 h lag phase; Significant cytotoxicity, inducing apoptosis in cancer cells in dose-dependent manner, with the highest apoptotic level at 45 µg/ml formulation	Khatamian *et al.* (2023)
2. In vivo model			
Mitoxantrone (MTO-SLN)	MCF-7 and animal model of P388 lymph node	MTO-SLN; 61nm, 4.18 ± 0.10% drug content, 87.23 ± 2.16% EE; In vitro release study shows sustained release of MTO from MTO-SLN without burst effect; cumulative release rate Q_{24h}=25.86 ± 0.82%, t_{50}=(5.25 ± 1.10) d and t_{90}=(28.38 ± 4.50) d); MTO-SLN shows comparable efficacy to MTO solution (Soln) in inhibiting breast cancer growth at 81.81% inhibition rate; significantly reduces lymph node metastasis size to 41.85 mm^3 with minimal toxicity to major organs, compared to 119.32 mm^3 for MTO-Soln with moderate to severe liver and lung toxicity.	Lu *et al.* (2006)
Epirubicin-loaded SLNs (EPI-SLNs)	Male Sprague-Dawley rats	EPI-SLNs; 223.7 nm size, size increases slightly after nebulisation, no significant change in EE/ZP before and after nebulisation, 78.9%/−30.6mV and 77.6%/−28.4mV, respectively; Inhalation of EPI-SLNs leads to significantly higher drug concentrations in the lungs compared to the EPI soln, with much greater levels in the lungs than in the plasma; EPI-SLNs are promising as inhaling delivery system for lung cancer therapy.	Hu *et al.* (2010)

(*Continued*)

Table 2. Continued.

Drug-SLN	Cancer cell/animal model	Major findings	References
Paclitaxel (PTX)	KB cell xenografted Female BALB/c nu/nu mice	Mean diameters of 180.9 ± 14.9 nm for empty cSLN, 183.1 ± 12.0 nm for PTX-cSLN; PTX is continuously released over 12 h of incubation, 5.3% after 1 h, 96.7% released after 12 h; The PTX-cSLN (PTX-loaded cSLN complex with human MCL1-specific siRNA (siMCL1)) significantly inhibits tumour growth in mice with KB cell xenografts.	Yu *et al*. (2012)
Gambogenic acid (GNA)	White New Zealand	SLN mean diameter of 163.3 nm, PDI = 0.203, ZP= −16.9 mV; GNA–SLNs mean particle sizes of 173 nm, PI = 0.253, with no significant change in ZP, 61.2% EE; SLN encapsulation increases bioavailability of GNA; 3.1-fold increase in area under the curve, $AUC_{(0-t)}$ and 3.03-fold decrease in clearance compared to free GNA	Huang *et al.* (2013)
Noscapine (Nos)	Swiss male albino mice	Nos-SLN of 61.3 ± 9.3 nm and Nos-PEG-SLN of 80.5 ± 8.9 nm sizes, with EE/ZP of 80.4 ± 3.2%/−35.1 ± 0.1 mV and 83.6 ± 1.2%/−42.4 ± 0.2 mV, respectively; Nos-PEG-SLN and Nos-SLN increase the plasma half-life by 11-fold and 5-fold, respectively, compared to the free drug; more sustained release following first-order kinetics and Higuchi model.	Madan *et al.* (2013)
Docetaxel (D), Ketoconazole (K)	Male Wistar rats	Blank SLNs = 55.57 ± 3.51 nm, D-SLNPs =76.43 ± 6.05, DK-SLNPs = 80.77 ± 2.50 nm; EE of D-SLNs = 99.8%, EE of D in DK-SLNPs decreases to 95.4% due to the addition of K; Drug release = 16.8 ± 1.01% of D from D-SLNs in 24 h, 18.8 ± 1.16% of D and 29.21 ± 1.66% of K from DK-SLNs; SLNs co-loaded with D and K significantly improve the brain uptake of D; 44-fold increase compared to the free drug; enhancement due to K which inhibits p-glycoprotein (p-gp) efflux and facilitates better delivery of D across the BBB.	Venishetty *et al.* (2013)
Luteolin-loaded SLNs (Lu-SLNs)	Male Sprague–Dawley rats	Lu-SLN; Round-shaped, 47–118 nm sizes, PI = 0.247, ZP=-9.2 mV, EE = 74.80%; The half-life of Lu-SLNs increases by about 2 h; drug distribution and clearance significantly reduced by 2.16 to 10.57-fold, respectively.	Dang *et al*. (2014)
Chitosan-SLN- encapsulating Ferulic acid (FA), aspirin (ASP), c-SLN-FA-ASP	Pancreatic cancer cells (MIA PaCa-2 and Panc-1), and MIA PaCa-2 pancreatic tumour xenograft mice model	c-SLNs-FA and c-SLNs-ASP; 183 ± 46 and 229 ± 67 nm sizes, ZP = 39.1 and 50.3 mV, 80 and 78% EE, respectively; Oral administration of 75 and 25 mg/kg of FA and ASP c-SLNs to MIA PaCa-2 pancreatic tumour xenograft mice model reduces tumour growth by 45% compared to control; Tumour tissue analysis shows decreased proliferation markers (PCNA and MKI67) and increased apoptotic markers (p-RB, p21, and p-ERK1/2), indicating pro-apoptotic effects.	Thakkar *et al.* (2015)
Chitosan-SLN- encapsulated aspirin (ASP), curcumin (CUR), and free sulforaphane (SFN) combination (ACS) ACS-c-SLNs	BALB/c mice pancreatic cancer	ASP SLN = 361 nm, ASP-c-SLNs = 430 nm, CUR SLN = 400 nm, CUR-c-SLNs = 440 nm; EE/ZP/PDI of ASP-c-SLN = 65%/16 mV/0.2, CUR-c-SLNs = 72%/17 mV/0.2, as compared to ASP-SLN=-/-10.6 mV/0.4, CUR-SLNs=-/-13.3 mV/0.5; Cumulative drug release of ASP ~98%, CUR 94% within 72 h; No animal deaths during the three treatment periods: acute (3 days), subacute (28 d), and subchronic (90 d); The ACS-c-SLNs treatment shows no significant change in body weight, blood counts, or blood chemistry; tissues of different organs (pancreas, heart, liver, kidneys, and brain) show normal appearance, no organ damage or toxicity.	Thakkar *et al*. (2016)
Methotrexate-loaded fucose (Fu-MTX-SLNs)	Female Sprague Dawley strain	Fu-MTX-SLNs = 174.51 ± 5.1 nm, PDI = 0.33, ZP = 7.27 ± 0.54 mV, EE = 84.2%, Drug loading = 15.2%; MTX-SLNs = 163.8 ± 3.2 nm, PDI = 0.27, ZP = 10.21 ± 0.38 mV, EE = 87.8%, Drug loading = 16.5%, with positively charged amine group surfaces; Cumulative MTX release ~ 90.38 ± 2.19% from MTX-SLNs, 84.9 ± 2.32% from Fu-MTX-SLNs after 96 h; Fu-MTX-SLNs improve cellular uptake at 39.81 ± 2.51%; lower IC_{50} of MTX against MCF-7; increased apoptosis with changes in the permeability of lysosomal membranes.	Garg *et al*. (2016)

(*Continued*)

Table 2. Continued.

Drug-SLN	Cancer cell/animal model	Major findings	References
Paclitaxel (PTX) and α-tocopherol succinate-cisplatin prodrug (TOS-CDDP) (TAT PTX/ TOS-CDDP SLNs)	Cervical cancer cells	SLNs with 83 nm size, ZP=−12 mV, TAT PTX/ TOS-CDDP SLNs with 109 nm, ZP=−31 mV, EE of PTX and CDDP of all formulations ~ 90%; Drug release of PTX between 3.5 and 5.9%, CDDP between 2.3 and 4.4%, more than 70% of the drugs remain encapsulated after 24 h; The drug-loaded SLNs accumulate well in tumour tissues; improved ability to target and treat cancer effectively; Co-delivery system is superior against tumours compared to other treatments, leading to significant tumour reduction; the TAT PTX/TOS-CDDP SLNs exhibit much lower toxicity in vivo, safer than conventional therapies.	Liu *et al*. (2017)
PTX folate receptor (FR)-PEG-N-[(2-hydrox y-3-trimethylammonium)propyl] chitosan chloride (HTCC)-PTX-SLN	M109 tumours	Folate-PEG-HTCC-coated SLNs of 249 nm mean size, PDI = 0.31, ZP=+32 mV, 99% EE, Drug loading = 4.6%; Folate-coated SLNs improve PTX delivery through inhalation, enhancing tumour selectivity, extending lung residence to 6 h; superior pharmacokinetic profiles; a promising strategy for lung cancer treatment.	Rosière *et al*. (2018)
Myricetin-loaded SLNs decorated with folic acid-bound chitosan	Mice model	Myricetin-SLN-CS-FA; 310 nm size, ZP=+30 mV, suitable for oral use, drug release follows Michaelis–Menten model with 144 h lag phase; Cumulative drug release of 88.7% after 144 h; Myricetin-SLN-CS-FA significantly reduces tumour volume, showing statistically significant effects (*$p < 0.05$, ***$p < 0.001$); Histological analysis of liver tissue and monitoring of animal weight suggests the formulation is safe.	Khatamian *et al*. (2023)

NB (Adapted from Liu et al. 2017; Aldawsari and Singh 2020)
[a]Polydispersity Index (PDI) measures the heterogeneity of a sample based on size, distribution, or aggregation.
[b]Zeta potential (ζ potential, ZP) measures the level of electrostatic attraction or repulsion between particles, impacting system stability where high ZP (negative or positive) is electrically stable, and low ZP tends to coagulate.

peptide, ease the penetration of the nano-carriers and enhance the uptake into the lung cancer cells (Liu *et al.* 2017).

5.6.2. In vitro study

Using a polymer core loaded with PTX conjugates that elute slowly, hybrid NPs of 60 nm sizes have been developed to regulate drug release and ester hydrolysis over a period of around 12 days, giving ways for temporal control (Chan *et al.* 2010). LNPs take advantages of the phospholipids on their surface and the structure of the LNPs which mimic cell membrane to assist in endocytosis (Yonezawa *et al.* 2020). The content of the LNPs should be released into the cytosol rather than into lysosomes or the endocytic recycling process. For ionisable lipids to readily protonate and escape from the lysosomes, its pKa value should not be too low. In a pancreatic cancer model, a pKa value of 6 has resulted in increased endosomal escape with enhanced efficacy of siRNA-LNPs (Patel *et al.* 2022). The DOX-oleic acid (OA) incorporation into NLCs has been achieved with HPH method, resulting in drug loading of about 4.1%, and entrapment efficiency of 97.8%. Fast drug release is exhibited at pH 3.8 and 5.7, and sustained release at pH 7.4, with comparable cytotoxicity of DOX-OA/NLCs with pure DOX against human colorectal carcinoma HCT 116 cells (Zhao *et al*. 2016). DOX complexes with an anionic polymer based on soybean oil and dispersed with lipid in water to form SLN-loaded-DOX to attain 80–350 nm sizes and encapsulation efficiency of 60–80%. The SLN-loaded-DOX achieves more than 8-fold increase in the killing of multi-drug-resistant breast cancer cells as compared to the free DOX (Wong *et al*. 2006). A tween 80-coated-SLNs-loaded with folic acid-DOX (FAD) for DOX delivery to specific sites in brain cancer cells (U87 MG), attains high cytotoxicity against U87 MG cell lines with IC_{50} of 2.5 µg/ml (Jain *et al*. 2022). This suggests the potential of the SLNs to deliver DOX selectively to U87 MG brain cancer cells.

Distearoylphosphatidylethanolamine-poly(ethylene glycol)-folic acid (DSPE-PEG-FA) ligand can functionalise Mitoxantrone (Mito)-loaded SLN. The NPs are hemocompatible, of the right sizes with intravenous size distribution delivery, and could remain stable for at least six months, for enhanced blood circulation but decreased systemic side-effects. The functionalised NPs promote anti-cancer activity through apoptosis where the absorption of the SLN is caused by endocytosis mediated by clathrin and macropinocytosis, via folate receptor (FR) (Granja *et al.* 2022). The Quality by Design (QbD) approach is used to synthesise Palbociclib-loaded

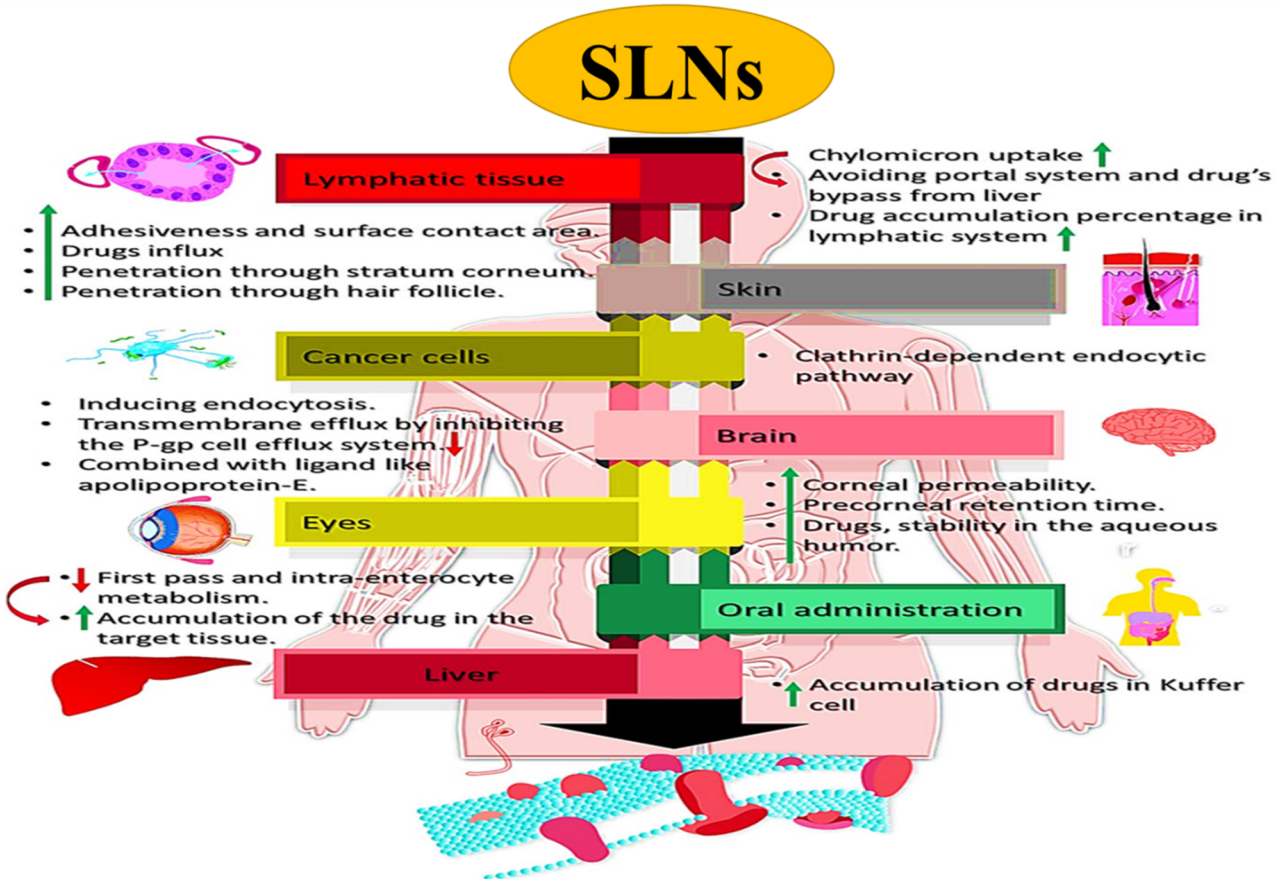


Figure 5. Mechanisms of SLN based on delivery of drugs and biodistribution in different organs and tissue sites with their bioactivities (Mohammed *et al*. 2023) (Under the Creative Commons Attribution 4.0 International licence).

FA-adorned lipid-polymer hybrid NPs (FA-PLPHNPs) for anti-cancer effects on FR-positive breast cancer cell lines. After 48 h treatment, FA-PLPHNPs exhibit 9–11 times higher cytotoxicity than the free Palbociclib against MDA-MB-231 and MCF-7 cells. The FA-PLPHNPs are suggested to be taken up by the FR-mediated endocytosis which elevate the reactive oxygen species (ROS), and induce apoptosis in the MDA-MB-231 and MCF-7 cells (Rajana *et al.* 2024). The anticancer activity of diallyl trisulphide (DATS) mixed with FA and loaded into SLNs (FA-DATS-SLNs) against negative breast cancer, overcome the limitations of DATS such as limited bioavailability and short half-life. FA is a well-known receptor where the overexpression of Folate receptor on the surface of negative breast cancer could overcome non-targeted delivery. With the NP sizes of 168.2 ± 3.78 nm and a DATS entrapment of 71.91 ± 6.27%, the FA-DATS-SLNs show potent cytotoxic activity against MCF-7, MDA-MB-231, and MCF-10A with IC_{50} of 10.8, 7.1, and 93.3, respectively, far superior to DATS alone and DATS with SLNs (De *et al.* 2023).

HA-SLN is a promising DDS for docetaxel (DTX) delivery and in targeting drug-resistant tumours. HA-coated, DTX-loaded SLN (HA-DTX-SLN) is aimed at targeting and overcoming drug-resistant MCF7, MDA-MB-231, and MCF7/ADR cells. Using CTAB, stearic acid (SA), soy phosphatidylcholine (PC), and DTX, the SLNs are prepared via lipid film method. The SLNs are then coated with HA through electrostatic attraction. The HA-SLN exhibits particle sizes of 224.3 ± 15.9 nm, and a negative surface charge (−17.1 ± 0.7 mV), as compared to the smaller SLN sizes (109.5 ± 8.2 nm) with a positive surface charge (32.5 ± 3.7 mV). The HA-SLN demonstrates higher levels of cellular uptake and cytotoxicity in MCF7/ADR cells where more significant CD44 expressions than other cells, is detected (Lee *et al.* 2019). HA-coated, cabazitaxel-loaded SLNs (HA-CZ-SLNs), prepared using homogenisation method, is designed to attain prolonged circulation, slow release, and efficient internalisation for breast cancer treatment. The spherical NPs of around 210 nm in diameter contain HA shell components. The HA-CZ-SLNs demonstrate a biphasic *in vitro* drug release profile and sustained release, with higher cytotoxicity against MCF-7 cells than the drug CZ alone. It is suggested that HA coating could have interacted with CD44 receptors, resulting in enhanced cell internalisation from receptor-mediated endocytosis, facilitating effective drug delivery to target cells (Zhu and An 2017).

5.6.3. In vivo study

Figure 6 exhibits biodistribution and absorption in different organs of a rat model. The functionalised/modified SLNs (MSLN) are loaded with the drug and subsequently administered to the rats, resulting in enhanced intestinal absorption. This is followed by the transport of the drug into systemic circulation and its distribution across various organs (Ganesan *et al.* 2018). A novel high payload of SLN-loaded 5-Fluorouracil (5-FU) developed to treat colorectal cancer (CRC) has shown significant uptake of 5FU-SLN4 by the HCT-116 cells. The 5FU-SLN4 formulation significantly inhibits subcutaneous tumour growth in mice in comparison to the free 5-FU, suggesting delivery efficiency of cancer drugs to the tumours (Smith *et al.* 2020). Genistein, a phytoestrogen widely used in hormone-related cancers, has limited bioavailability. However, Genistein-loaded solid lipid microparticles (SLMs, 6 µm) have been demonstrated to exhibit improved bioavailability, with higher anticancer effects as compared to the SLNs (120 nm). When orally delivered, the higher activities are attributed to slow degradation in the intestine and the ability of the molecules to reach the colon (Kim *et al.* 2017, Ganesan *et al.* 2018). The DOX-SLN encapsulation changes DOX partition coefficient and enhances distribution in the lipid matrix of the stratum corneum, with high drug concentration in the skin follicles of squamous cell carcinoma induced nude BALB/c mice. The iontophoresis of cSLN-DOX elevates DOX penetration in the viable epidermis by almost 50-fold, as compared to only 4-fold increase with the iontophoresis of just a DOX solution (Huber *et al.* 2015).

Co-loading of DOX and mitomycin C (MMC) in LPHNPs and delivery to the breast tumour induced Balb/c mice, has shown sustained circulation, accumulation at tumour site and release upto 24 h, before being destroyed in the liver, and eliminated from the body within 72 h period. At enhanced DOX-MMC doses in LPHNP, increased apoptosis with low organ damage is observed, suggesting the efficacy and safety aspects of LPHNPs as carriers (Zhang *et al.* 2016). TRZ-loaded SLNs, synthesised using sonication and high-shear homogenisation methods, are highly effective in inducing apoptosis in MCF-7 cells. The TRZ-99mTc-labeled SLNs, designed as nanotheranostic agents for the diagnosis and treatment of breast cancer, exhibit stability up to 90 days, even at 40 °C. A controlled release profile of the TRZ-SLNs in blood circulation of in vivo model has established that the TRZ-SLN formulations have induced apoptosis, suggesting big potential as a therapy for breast cancer (Ozgenc *et al.* 2022).

Lung cancer which is one of the major global causes of death, has been tested with the SLNs co-loaded with PTX and Curcumin (CUR) (PTX-CUR-SLNs). As roughly 85% of instances of lung cancer are non-small cell lung cancer (NSCLC), nano-based co-delivery of PTX and CUR via the SLNs provides synergistic impact during treatment with controlled-release of PTX and CUR. The PTX-CUR-SLNs are synthesised via HPH and evaluated against Alveolar basal epithelial cells (A549) cell lines from human adenocarcinoma, and BALB/c mice for antitumor efficacy and any adverse effects. The combos of 190 nm sizes are uniformly distributed with encapsulation efficiency greater than 94% for both PTX and CUR, and higher cytotoxicity than pure PTX or PTX-loaded SLNs. The PTX-CUR-SLNs exhibit 12-fold reduction in tumour volume, reaching 82.7% tumour inhibition on day 28, with almost no change in the body weight of BALB/c mice (Li *et al.* 2024). Co-encapsulation of drugs with natural anticancer product in SLNs may improve tumour targeting. The HA-decorated SLNs have achieved higher drug concentration and efficacy in tumour tissues of mice, than the SLNs without HA and free drug (Bertrand *et al.* 2014). The formulation of SLN-HA-Bovine serum albumin (BSA)-chitosan loaded with irinotecan (IRN) and daidzein (DZN) for oral delivery has shown great potential to treat colon cancer cells. Cytotoxicity against HT-29 cell lines at 75 µg/ml is attributable to induction of apoptosis, and growth arrest at G0/G1 phase, and proposed to proceed via receptor-mediated endocytosis. Analyses suggest restoration of normal colon mucosa and downregulation of carcinoembryonic antigen (CEA) but with the tumour necrosis factor-α (TNF-α) upregulated (Ahmed *et al.* 2024).

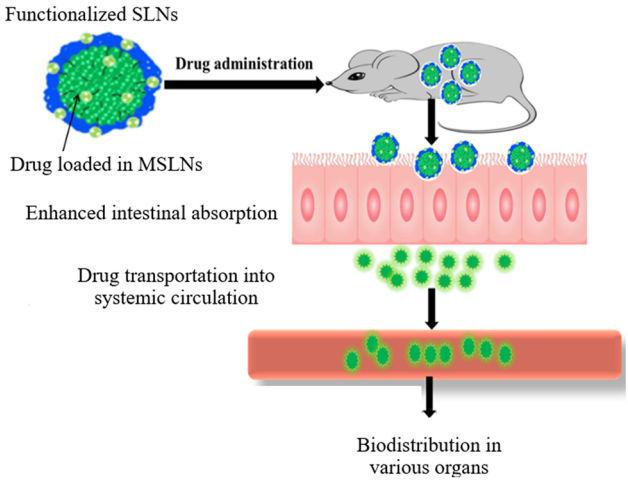


Figure 6. Bio-distribution of drug-loaded functionalised MSLN (Modified from Ganesan *et al.* 2018).

6. Issues, challenges, and the way forward

Poorly soluble compounds in water present significant challenges for formulation, and for pharmacokinetic, pharmacological, and toxicological studies. There are concerns on toxicity and how the body will process and respond during drug development, optimisation, and design. The SLNs as DDS assist in enhancing drug absorption into systemic circulation via lymphatic-enteric pathway for a more effective treatment (Ganesan and Narayanasamy 2017). Lipid NPs, which are composed of lipids, surfactants, and co-solvents, serve as bio-membranes (phospholipids), and energy storage (lipids), with significant metabolic function (bile acids). They are biocompatible, biodegradable and under GRAS class for Food and Drug Administration (FDA)-approval. As a "Safe Nano Carrier" with no known toxic effects, SLNs can minimise the side effects normally associated with polymeric or metallic DDS. Lipid NPs are much easier to synthesise than biopolymer NPs, and are feasible for industrial scale production for practical and clinical use (Ganesan and Narayanasamy 2017).

While the SLNs have shown promising advancements as DDS, the lack of adequate clinical studies and data impedes rapid development in clinical settings. More research is needed for transition from the laboratory to the market, in assessing the toxicity profiles, and in addressing problems associated with complexities in formulation and characterisation of nanomedicines (Bukke *et al*. 2024). In the treatment of brain tumour which is the Central Nervous System (CNS) disorder, the challenge is in overcoming the blocking of medication by the BBB. Nanolipid-based systems can be effective for nose to brain delivery systems that could bypass the BBB and hepatic metabolism. The drug-nanolipid formulation enters the brain through blood circulation, olfactory and trigeminal nerve pathways and acts on target neurons at minimal dosage and optimal bioavailability, but with reduced adverse effects (Hameed *et al*., 2024). In cancer immunotherapy, mRNA structure instability and degradation by lysosomes are major concerns for effective delivery of mRNA. *In vivo* imaging is crucial to speed up the drug development pathways of LNP-based RNA. It could identify drug targets, determine drug pharmacokinetics and pharmacodynamics, and select the most suitable drug candidates. The imaging biomarkers assist in selecting patients for clinical trials, and predictive biomarkers will become indispensable in clinical settings (Jung *et al.* 2022). The future direction may involve the delivery of genes, ionisable lipids, and drugs and bioactive substances in core treatment or adjuvant therapy.

6.1. mRNA and siRNA delivery

In the 1960s, sealed lipid bilayer vesicles, or liposomes, have been demonstrated to spontaneously grow in water. This earlier development of liposomes has inspired the development of LNPs. Liposomes (sizes of 200–600 nm) are however simpler lipid vesicles based on cholesterol and phospholipids, and of greater sizes than the LNPs (less than 100 nm) (Pattni *et al.* 2015, Mashima and Takada 2022). Later phase polymers carrying proteins and nucleic acids (DNA and RNA), or both, are among innovative pharmaceutical formulation, making use of spherical vesicles or LNPs. Between August 1998 and August 2019, licences for 22 gene treatments, including CRISPR-Cas9 technology, have been granted for the treatment of human diseases (Ma *et al.* 2020). Based on animal models, the HIV-1 genome could be totally removed using CRISPR-Cas9 to completely halt HIV-1 replication and remove the virus from infected cells (Liu *et al.* 2017).

As shown in Figure 7, LNPs offer protection to the mRNA and improve intracellular delivery efficiency and bioavailability for antigen receptors, and for adjuvant, and protein (Jung *et al.* 2022, Hajiaghapour Asr *et al.* 2023, Han *et al.* 2023). LNP can effectively deliver mRNA vaccines and trigger immune responses against tumours in mice (Sáez-Llorens *et al*. 2022, Li *et al.* 2023). Some mRNA vaccines target specific tumour proteins, and when delivered using LNP, can produce high levels of antibodies and activate immune cells, which slow down tumour growth and lengthen the survival in mice. Additionally, LNP-assisted mRNA vaccines activate $CD8^+$ T cells and improve the ability of immune system to recognise and attack tumours (Sáez-Llorens *et al*. 2022, Zhang *et al*. 2023). This is important for controlling tumour growth. LNP carriers can enhance the stability and uptake of mRNA vaccines inside the cells, making them effective in cancer treatment (Sáez-Llorens *et al.* 2023).

Based on the European Medicines Agency (EMA) assessment report for mRNA-LNP, the intramuscularly administered RNA vaccines prepared with LNP induce transient local inflammation that attracts neutrophils and antigen-presenting cells (APCs) to the site of administration. APCs produce proteins (such as in the case of an increase in SARS-CoV-2) and absorb LNPs, which then move to the draining lymph nodes in the area where T cell priming takes place (Xu and Xia 2023). For it to be successful, the LNPs must be transferred into an internal environment from an extracellular environment. For nucleic acid therapy, getting RNA into the cytoplasm, which possesses all the natural machinery for RNA interference and protein translation,

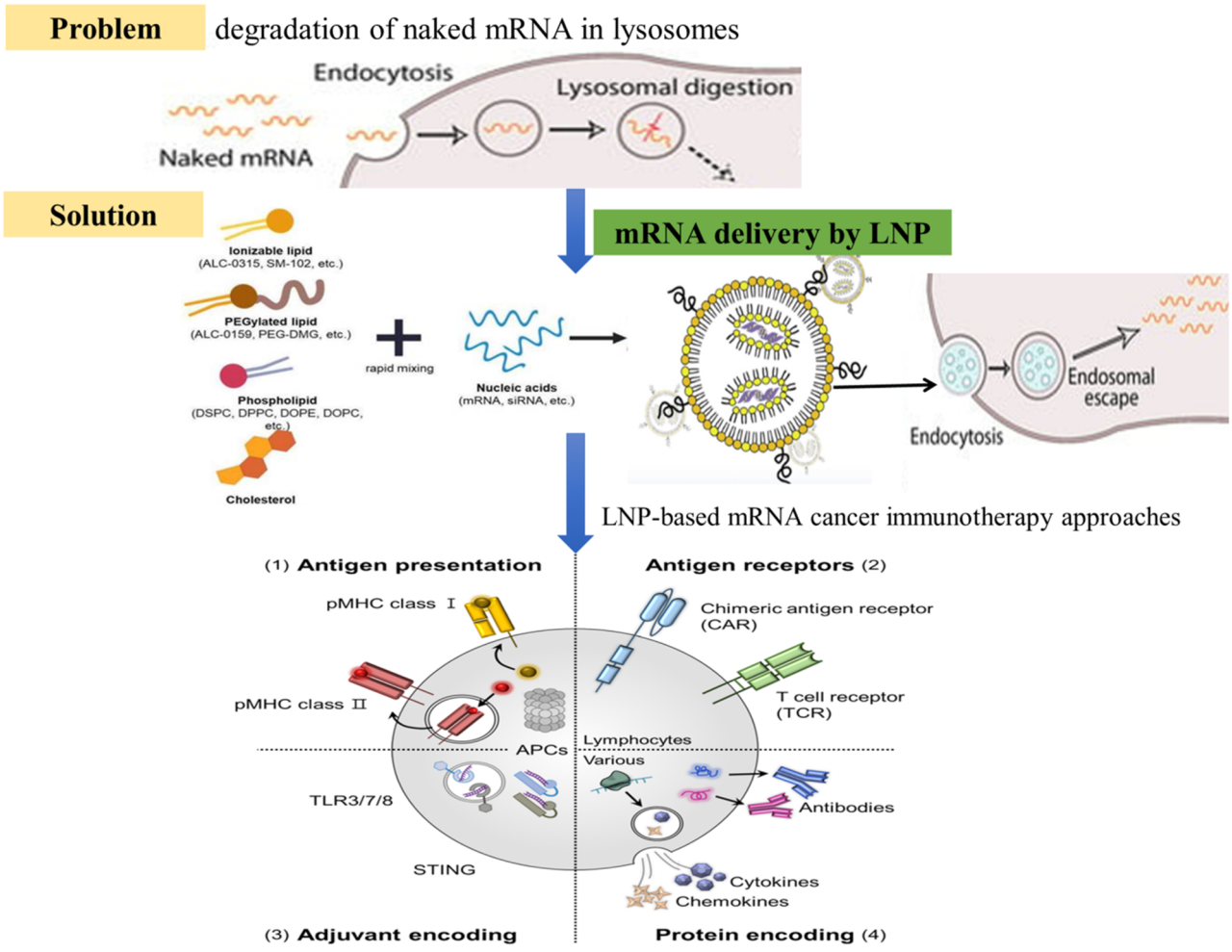


Figure 7. Lipid nanoparticle-loaded mRNA DDS for cancer immunotherapy (Modified from Jung *et al*. 2022, Hajiaghapour Asr *et al*. 2023, Han *et al*. 2023).

will be the biggest challenge. The LNP-based delivery strategies for mRNA (Maugeri *et al.* 2019) and siRNA (Suzuki and Ishihara 2016) involve three primary steps—LNP encapsulation of RNA; cellular internalisation of LNP-RNA; and absorption of RNA. To prevent nuclease digestion, LNP must first completely encapsulate the RNA. With the use of ionisable lipid and PEG-lipid, the LNPs have neutral physiological pH, which reduces their non-specific interactions with serum proteins (Akinc *et al*. 2010). Secondly, once the PEG-lipid system dissociates, cells internalise LNPs via either Apolipoprotein E (ApoE)-dependent or ApoE-independent pathway. Finally, as the LNPs become acidified in the endosome and protonated, the LNPs form hexagonal phase structures which disrupt the endosomal membranes. The RNA molecules are finally released into the cytoplasm (Akinc *et al*. 2010, Suzuki and Ishihara 2021). The released RNA molecules either cause the target protein expression to be up-regulated (by the mRNA) or down-regulated (by siRNA). The LNP absorption into the hepatocytes and the internalisation however have been demonstrated via low density lipoprotein (LDL) receptors through the ApoE-dependent pathway (Akinc *et al.* 2019). Effective localisation of nucleic acids in the cytoplasm has been reported but the mechanisms underlying their uptake into the APCs need further investigation (Basha *et al.* 2011).

One of the success stories in overcoming the COVID-19 pandemic has been attributed to the Pfizer/BioNTech's BNT162 and Moderna's mRNA-1273 (Wilson and Geetha 2022), through the application of LNP-nCoVsaRNA (Szubert *et al.* 2023), and DS-5670 as mRNA vaccine (Toyama *et al.* 2023). Although vaccines alone may not hamper the progression of SARS-CoV-2 (Van Egeren *et al.* 2023), the properties of mRNA molecules in in vivo translation can be enhanced by RNA engineering, while the LNP-mRNA formulations ensure stable, safe, and efficient control of cellular release, mRNA uptake and protection from DNA degradation. Self-amplifying RNA SARS-CoV-2 LNP vaccine candidate has the capability of inducing high neutralising antibody titres in mice model (McKay *et al.* 2020). The

design of noninflammatory synthetic siRNA mediating potent gene silencing in vivo (Judge *et al.* 2006), optimisation of LNP-mRNA vaccine candidate targeting SARS-CoV-2 receptor-binding domain (Kobiyama *et al.* 2021), and the clinical precedent in the delivery of SLNs-mRNA vaccines against COVID-19 represents great milestone in mRNA therapies (Hou *et al.* 2021).

LNPs have made it possible to deliver RNA, with the LNP-based siRNA medication patisiran (Onpattro), first approved in 2018 (Akinc *et al.* 2019). The two LNPs-based SARS-CoV-2 mRNA vaccines, Tozinameran (known as Comirnaty or the Pfizer-BioNTech COVID-19 vaccine) and Elasomeran (known as Spikevax or the COVID-19 vaccine Moderna) receive conditional approval to treat the 2020 coronavirus outbreak (Suzuki and Ishihara 2021). Unlike the two vaccinations which are lengthy, patisiran's siRNA is a short, double-stranded RNA (dsRNA) with 21 bases in each strand, while single-stranded mRNA has nearly 4000 bases (Akinc *et al.* 2019). The body identifies RNA as a harmful virus, rather than a prescription drug, by triggering biological defence systems against invasive infections. TLRs (Toll-like receptors) and RIG-I (retinoic acid-inducible gene I receptors) are examples of pattern recognition receptors (PRRs) that can elicit reactions for the RNA to avoid (Thompson and Locarnini 2007). In siRNA, 2^{i}-O-methyl uridine and cytosine partially substitute uridine and cytosine. In mRNA, N1-methyl pseudouridine completely replaces uridine which elevates protein synthesis and boosts immunogenicity (Svitkin *et al.* 2017). Innate immune responses normally suppress mRNA translation when the eIF2A (Eukaryotic translation initiation factor 2 A) is activated by the dsRNA-dependent protein kinase. This eIF2 therefore plays important role in maintaining rate-limiting step in the translation of mRNA (García *et al.* 2007). In the delivery into the liver via intravenous injection, the formulated siRNA-LNP accumulates in the liver, the organ responsible for producing transthyretin (TTR). TTR is a protein that transports thyroxine (thyroid hormone) and retinol to the liver. Once the LNPs are taken up by the hepatocytes in the liver, the siRNA utilises the body's built-in RNA interference mechanism to degrade the TTR mRNA and reduce the production of TTR (Suzuki and Ishihara 2021).

SLNPs have been synthesised using sphingomyelin and cholesterol, containing *Ginkgo biloba* leaf extract (GBE) to improve compatibility, and protect nerve cells, with the aim to meet the medical needs of patients with neurological disorders. Poly-L-lysine (PLL) helps the SLNPs bind to siRNA, safely transport it, and shield it from enzyme degradation. The GBE-PLL-SLNPs of 93.2 nm average sizes show better siRNA binding and protection from enzyme breakdown, with very low cytotoxicity in embryonic kidney cells (<10%) and human neuroblastoma (SH-SY5Y) cells (<15%). The caspase 3/7 activities are significantly low in both cell types while the cellular uptake is efficient (Jagaran *et al.* 2024). A non-cationic thiourea LNPs (NC-TNP) system for mRNA delivery has been developed, utilising strong hydrogen bond interactions between thiourea groups in NC-TNP and the phosphate groups of mRNAs, instead of relying on electrostatic forces. The preparation method of NC-TNP system is convenient, with negligible inflammatory and cytotoxic side effects. Both the NC-TNPs and LNPs are taken up via the micropinocytosis pathway but the NC-TNP exhibits enhanced targeting capabilities to the spleen, with higher intracellular accumulation than the LNPs, and induces strong immune responses by promoting the expression of mRNA-encoded antigens in the targeted spleen. Intracellular trafficking studies suggest that the LNPs are primarily trapped in early endosomes, while the NC-TNPs are found in late endosomes and the cytoplasm. As a result, the LNPs undergo a greater degree of recycling through the endocytic pathway, which leads to their exocytosis, while the NC-TNPs bypasses this recycling process, facilitating more effective mRNA release, and promotes better gene transfection efficiency both *in vitro* and *in vivo*. Endosomal escape assays demonstrate that the LNPs could destabilise endosome/lysosome membranes more effectively, but it is the intact nanostructure of the NC-TNPs that allow them to escape endosomes without membrane disruption, resulting in more stable mRNA delivery into the cytoplasm. The unique hydrogen-bond interaction mechanism of the NC-TNPs offers superior mRNA delivery efficiency, minimal cytotoxicity, and enhanced immune response, as compared to the traditional LNPs (Wanga *et al.* 2023).

6.2. Ionisable LNPs

LNPs can be synthesised with an ionisable lipid (a helper lipid, PEG-lipid, and cholesterol) consisting of hydrophobic alkyl tails and one or several amino head groups with an acid dissociation constant (*pKa*) of less than 7. Ionisable lipids in LNPs have a positive charge in acidic environments, allowing them to interact with the negatively charged mRNA. At physiological pH, the LNPs become uncharged to avoid rapid clearance in the bloodstream. Finally, in the endosome of cells, they become positively charged again, facilitating the release of mRNA. Ionisable lipids help to reduce toxicity and unwanted interactions with cellular components encountered by the cationic lipids (Huo *et al.*

2023). Several ionisable lipids have been developed and are effective in delivering mRNA. However, there is still a need for new formulation and design to improve further delivery efficiency and reduce toxicity and immunogenicity associated with the mRNA and LNPs (Huo *et al.* 2023, Young *et al.* 2024). There are numerous encouraging reports on the ability of ionisable LNPs to positively affect the tumour environment. The siRNA molecules mixed with PEG and loaded onto the SLNs (SLN-siRNA-PEG formulation) significantly reduce the growth of brain tumour with no systemic toxicity (Jin *et al.* 2011). Strong immune response has been demonstrated in a Lewis lung carcinoma model by ionisable LNPs loaded with circular RNA (circRNA) encoding interleukin-12 (IL-12). The high delivery efficiency of circRNA has resulted in significant tumour shrinkage. The treated tumours exhibit noticeable increase in $CD45^+$ leukocytes with enhanced infiltration of $CD8^+$ T cells. There is a big potential for improved RNA drug delivery for cancer treatment, and expand the possibilities of RNA-based immunotherapies using ionisable LNPs (Xu *et al.* 2024). Modification of the linker component in ionisable lipids could significantly improve the biodistribution of LNPs. Lipids containing amide and urea linkers have remarkable ability to target the lungs more effectively, which is crucial for enhanced transfection efficiency of mRNA to lung epithelial and endothelial cells. When the LNPs are loaded with mRNA encoding *Pseudomonas exotoxin* A (mmPE) formulated with lipid 35, the lipid that results in much higher transfection efficiency, significant reduction of lung tumour burden is observed. Mice treated with lipid 35 LNPs exhibit better outcomes with only transient immune response which is resolved within 24 h, increased survival rates, and no significant liver or organ damage, even with repeated dosing. The amide/urea-based lipid exhibits chemical stability and the LNPs maintain their sizes, charges and encapsulation efficiencies over 2 months of storage, suggesting great potential for practical application and for large-scale development of mRNA therapeutics. The lung-targeting DDS based on LNPs paves the way for effective treatments of lung diseases (Somu Naidu *et al*. 2025).

The LNPs can be viable platform for RAS proteases delivery for future cancer therapies (Atsavapranee *et al*. 2024). *RAS* proteins are important in cellular growth, proliferation and signalling. The *KRAS*, *HRAS*, and *NRAS* genes are the main members of the *RAS* gene family, and any mutations of the *RAS* genes could lead to the cells becoming cancerous (National Cancer Institute, 2024). The mutations have been suggested to be responsible for pancreatic, colorectal, and lung cancer. Therapies are being developed to effectively halt RAS-induced tumour growth through engineered protease that targets active *RAS* as a new approach in treating cancers. However, intracellular protein-based therapies such as proteases require a vector to deliver to the specific site (Narváez-Narváez *et al.* 2023, Atsavapranee *et al.* 2024). The incorporation of cationic lipids into ionisable LNPs to create a delivery platform for RAS protease has been evaluated for inhibition of colorectal cancer cell proliferation both *in vitro* and in vivo. A set of 13 LNPs containing RAS protease with different formulations is assessed for delivery efficiency and toxicity *in vitro*. The formulation generally affects the proliferation of cancer cells with mutated KRAS, and the most effective formulation successfully delivers RAS proteases intracellularly *in vivo*. Cancer cell proliferation and tumour growth and size in a xenograft animal model are greatly reduced (Atsavapranee *et al.* 2024). The FDA has approved the treatment which targets KRAS G12C mutation for non-small-cell lung cancer patients. Efforts are being made to develop combinatorial therapy with RAS-targeted drugs, and to identify molecules that could bind the mutated KRAS proteins (National Cancer Institute, 2024). K27, which is a modified protein from a Designed Ankyrin Repeat Protein (DARPin) to block RAS, has been developed with LNPs to effectively deliver functional K27-D30 into both *in vitro* and *in vivo* cells. The formulation results in increased delivery to 90% of the cells *in vitro* for 45 days of storage. In HTVI-induced mouse model of hepatocellular carcinoma, the LNPs deliver K27-D30 to the cytosol of liver cells, which inhibits RAS-driven growth and reduces tumour size (Haley *et al.* 2023).

6.3. Delivery of bioactive compounds

Antioxidant nutraceutical-loaded LNPs and NLCs will have improved loading capacity, stability, and bioavailability, in addition to low cost, and ease of production scaling-up (Khairnar *et al.* 2022). Although lipid-based nano-delivery platforms are suitable and feasible to meet regulatory requirements for clinical use approval, the market for commercial antioxidant nutraceuticals is still limited (Tounsi *et al.* 2022). NLC is made of liquid lipids to overcome some of the drawbacks of the SLN. Rice bran, sunflower, pomegranate, grapeseed, and naturally occurring vegetable oils containing high antioxidant components can be formulated with liquid lipids (Manea *et al.* 2014; Soleimanian *et al.* 2018). Natural oils are also biocompatible and biodegradable, and the use of NLC matrix system will enhance the delivery of antioxidant nutraceuticals and promote antioxidant effects for the prevention of specific diseases. Natural

antioxidants such as quercetin (QUE) and luteolin (LUE) from *Carthamus tinctorius* L. (Safflower) can assist in protecting the skin from UV-induced damage. SLN-based hydrogel formulations could improve the issues on poor solubility and limited skin penetration through the skin to enhance efficacy. In a study, the SLNs are synthesised using ultrasonic hot emulsification method, and 100% ethanol is used as extracting solvent to maximise the antioxidant activity. More than 80% of both QUE and LUE are successfully encapsulated where the compounds are uniformly distributed in the lipid matrix with enhanced solubility. The SLN-hydrogel formulations successfully release the bioactive compounds over 24 h and improve skin penetration and retention by up to 19 times. *In vitro* biocompatibility tests exhibit no haemolytic toxicity at concentrations below 500 µg/ml, confirming the safety aspect of the formulation (Aanisah *et al.* 2023).

If the cost of production and complexity of DDS synthesis and formulation are the major challenges, the development of functional food and healthy eating habits are viable alternatives or integral to any treatment regime. With issues related to systemic drug distribution within patient, the lack of target specificity, drug resistance, and all the associated side-effects, safer natural agents should be the way forward to improve efficiency, safety and efficacy of treatment, reduce the high cost, and alleviate the pain in patients (Baliga and Dsouza 2011, Zingue *et al*. 2018, Pereira 2018, Abdullah 2024). Marine resources are rich in lipids, PUFAs, polysaccharides, proteins/peptides/protein hydrolysates/enzymes, natural pigments, carotenoids, phenolic compounds, saponins, vitamins, and essential minerals, with diverse bioactivities such as antimicrobial, anticancer/antiproliferative, anti-inflammatory, antithrombotic, anticoagulant, antidiabetic, anti-allergic, hypocholesterolemic and hypoglycaemic, and cardioprotective effects. The functional properties such as stabilising, emulsifying, gelling, thickening and foaming agents could improve the qualities of nutraceutical, pharmaceutical, functional food, and dietary supplement products (Rioux *et al*. 2017, Pereira 2018, Senadheera *et al*. 2023).

For centuries, algae are used in folk remedies, herbal medicines, and health care and food products (Pereira 2018). Some algal species are classified as GRAS that the utilisation in clinical setting must be explored and implemented. The application of algal bioactive compounds with nanoparticles and approved drugs such as tamoxifen (TMX) could improve cancer diagnosis and treatment. The synergistic application of microalgal extracts with silver nanoparticles (AgNP) and TMX have shown high *in vitro* cytoxicity against MCF-7 and 4T1 breast cancer cells (IC_{50} of 6–28 µg/mL), after 48 and 72 h, comparable to single AgNP (5–24 µg/mL) and TMX (5–12 µg/mL), but with no or low toxicity against the non-cancerous Vero cells (IC_{50} of 24–100 µg/mL) (Hussein *et al*. 2020, 2022, Abdullah 2024). The chitosan-alginate nanoparticles encapsulating Amoxicillin-DHA have resulted in enhanced biocidal activities against *Helicobacter pylori* infection in rat model (Khoshnood *et al*. 2023). *Spirulina* products have been commercialised in cosmetics, nutraceuticals, human food and beverages and animal feed (Amin *et al*. 2024). Marine-based/Algal-based solution therefore can be developed to reduce conflict with land-based cultivation to produce SLN for general, specific or targeted deliveries, for health promotion, to reduce risk of chronic diseases and as preventive/neo-adjuvant/adjunct/adjuvant strategies during cancer therapeutics (Abdullah 2024).

7. Conclusion

This review highlights the synthesis, structural characteristics, and various applications of solid lipid nanoparticles. Lipid nano-carriers are versatile for environmental and agro-applications and suitable for nano-based biomedical applications, attributable to their unique properties such as low toxicity, bioavailability, and ease of preparation. SLN in combination with a variety of drugs is promising as a drug delivery system especially for cancer treatment to overcome the resistance mechanisms in cancer cells. SLNs facilitate cellular absorption of combined drugs by modulating passive, active, and co-transport mechanisms to overcome biological barriers. Surface-modified SLNs for topical cosmetic application or wound healing; or for delivery to different types of tumours, or disease types such as malaria with different associated resistance mechanisms; or for gene and nanovaccines therapy, can be advantageous for highly specific treatments. Future developments may lie in ionisable lipids and LPHNPs for bioactive compounds and RNA deliveries, and RAS-based therapy, with potentials for integration with nature/bio-based solutions.

Acknowledgements

The authors thank the respective institutions for research opportunities and facilities.

Disclosure statement

The authors declare no competing interests.

Funding

The authors have no external funding and financial support

Data availability

Data based on published data from literature are duly cited, and personal data will be made available upon request.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

ORCID

Hanaa Ali Hussein http://orcid.org/0000-0003-2848-5540
Fatin L. Khaphi http://orcid.org/0000-0002-2107-7192
Ramachandran Sivaramakrishnan http://orcid.org/0000-0003-4912-2175
Sivamani Poornima http://orcid.org/0000-0002-2973-7319
Mohd Azmuddin Abdullah http://orcid.org/0000-0001-8755-5444

References

Aanisah, N., *et al.*, 2023. Development of solid lipid nanoparticle-loaded polymeric hydrogels containing antioxidant and photoprotective bioactive compounds of safflower (*Carthamus tinctorius* L.) for improved skin delivery. *Langmuir: the ACS journal of surfaces and colloids*, 39 (5), 1838–1851. doi: 10.1021/acs.langmuir.2c02754.

Abbas, H., Refai, H., and El Sayed, N., 2018. Superparamagnetic iron oxide–loaded lipid nanocarriers incorporated in thermosensitive in situ gel for magnetic brain targeting of clonazepam. *Journal of pharmaceutical sciences*, 107 (8), 2119–2127. doi: 10.1016/j.xphs.2018.04.007.

Abdullah M.A., 2024. Algae as sources of functional food and adjuvant for cancer therapeutics. *In*: *Proceeding of conference on traditional medicine, immunology, biochemistry and food technology*, 25–26 November 2024, Zurich, Switzerland.

Abdullah, M.A., *et al.*, 2024. New perspectives on biomass conversion and circular economy based on integrated algal-oil palm biorefinery framework for sustainable energy and bioproducts co-generation. *Industrial crops and products*, 213, 118452. doi: 10.1016/j.indcrop.2024.118452.

Ahadian, S., *et al.*, 2020. Micro and nanoscale technologies in oral drug delivery. *Advanced drug delivery reviews*, 157, 37–62. doi: 10.1016/j.addr.2020.07.012.

Ahmad, J., 2021. Lipid nanoparticles based cosmetics with potential application in alleviating skin disorders. *Cosmetics*, 8 (3), 84. doi: 10.3390/cosmetics8030084.

Ahmed, S.S., *et al.*, 2024. Oral delivery of solid lipid nanoparticles surface decorated with hyaluronic acid and bovine serum albumin: A novel approach to treat colon cancer through active targeting. *International journal of biological macromolecules*, 279 (Pt 1), 135487. doi: 10.1016/j.ijbiomac.2024.135487.

Akinc, A., *et al.*, 2010. Targeted delivery of RNAi therapeutics with endogenous and exogenous ligand-based mechanisms. *Molecular therapy: the journal of the American society of gene therapy*, 18 (7), 1357–1364. doi: 10.1038/mt.2010.85.

Akinc, A., *et al.*, 2019. The Onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. *Nature nanotechnology*, 14 (12), 1084–1087. doi: 10.1038/s41565-019-0591-y.

Aldawsari, H.M., and Singh, S., 2020. Rapid microwave-assisted cisplatin-loaded solid lipid nanoparticles: Synthesis, characterization and anticancer study. *Nanomaterials*, 10 (3), 510. doi: 10.3390/nano10030510.

Alsaad, A.A.A., Hussien, A.A., and Gareeb, M.M., 2020. Solid lipid nanoparticles (SLN) as a novel drug delivery system: a theoretical review. *Systematic review pharmacy*, 11, 259–273.

Alyasiri, F.J., Ghobeh, M., and Tabrizi, M.H., 2023. Preparation and characterization of allicin-loaded solid lipid nanoparticles surface-functionalized with folic acid-bonded chitosan: in vitro anticancer and antioxidant activities. *Frontiers in bioscience - landmark*, 28, 135.

Amalia, A., Jufri, M., and Anwar, E., 2014. Preparasi dan Karakterisasi Sediaan solid lipid nanoparticle (SLN) Gliklazid (Preparation and characterization of solid lipid nanoparticle (SLN) of gliclazide). *Jurnal ilmu kefarmasian Indonesia*, 13, 108–114.

Amer Ridha, A., *et al.*, 2021. A promising dual-drug targeted delivery system in cancer therapy: nanocomplexes of folate–apoferritin-conjugated cationic solid lipid nanoparticles. *Pharmaceutical development and technology*, 26 (6), 673–681. doi: 10.1080/10837450.2021.1920037.

Amin, A. M., *et al.*, 2024. *Spirulina* as a food of the future, In: M.A. Mehmood, P. Verma, M.P. Shah, and M.J. Betenbaugh, eds., *Pharmaceutical and nutraceutical potential of cyanobacteria*, Springer Nature, Switzerland AG. doi: 10.1007/978-3-031-45523-0_3.

Assefi, M., *et al.*, 2023. A state-of-the-art review on solid lipid nanoparticles as a nanovaccines delivery system. *Journal of drug delivery science and technology*, 86, 104623. doi: 10.1016/j.jddst.2023.104623.

Atsavapranee, E., *et al.*, 2024. Ionizable lipid nanoparticles for RAS protease delivery to inhibit cancer cell proliferation. *Journal of controlled release: official journal of the controlled release society*, 370, 614–625. doi: 10.1016/j.jconrel.2024.05.015.

Attama, A.A., *et al.*, 2016. Solid lipid nanoparticles encapsulating a fluorescent marker (coumarin 6) and antimalarials - Artemether and lumefantrine: evaluation of cellular uptake and antimalarial activity. *European journal of nanomedicine*, 8 (3), 129–138. doi: 10.1515/ejnm-2016-0009.

Baliga, M.S., and Dsouza, J.J., 2011. Amla (*Emblica officinalis* Gaertn), a wonder berry in the treatment and prevention of cancer. *European journal of cancer prevention: the official journal of the European cancer prevention organisation (ECP)*, 20 (3), 225–239. doi: 10.1097/CEJ.0b013e32834473f4.

Barba, A.A., *et al.*, 2015. Novel lipid and polymeric materials as delivery systems for nucleic acid based drugs. *Current drug metabolism*, 16 (6), 427–452. doi: 10.2174/1389200216666150812142557.

Basha, G., *et al.*, 2011. Influence of cationic lipid composition on gene silencing properties of lipid nanoparticle formulations of siRNA in antigen-presenting cells. *Molecular therapy: the journal of the American society of gene therapy*, 19 (12), 2186–2200. doi: 10.1038/mt.2011.190.

Bayón-Cordero, L., Alkorta, I., and Arana, L., 2019. Application of solid lipid nanoparticles to improve the efficiency of anticancer drugs. *Nanomaterials*, 9 (3), 474. doi: 10.3390/nano9030474.

Bertrand, N., *et al.*, 2014. Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. *Advanced drug delivery reviews*, 66, 2–25. doi: 10.1016/j.addr.2013.11.009.

Bhardwaj, K., 2017. *Formulation and evaluation of solid lipid nanoparticles loaded with orlistat for oral drug delivery*. Phagwara, Punjab, India: Lovely Professional University.

Bhattacharjee, S., *et al.*, 2020. A technical review: solid- lipid nanoparticle (SLN), their characteristics and their preparation. *Asian journal of pharmaceutical research and development*, 8 (3), 185–189. doi: 10.22270/ajprd.v8i3.764.

Borges, A., *et al.*, 2020. Solid lipid nanoparticles as carriers of natural phenolic compounds. *Antioxidants*, 9 (10), 998. doi: 10.3390/antiox9100998.

Bukke, S.P.N., *et al.*, 2024. Solid lipid nanocarriers for drug delivery: design innovations and characterization strategies—a comprehensive review. *Discover applied sciences*, 6 (6), 279. doi: 10.1007/s42452-024-05897-z.

Cain, J.W., *et al.*, 2011. Identification of CD44 as a surface biomarker for drug resistance by surface proteome signature technology. *Molecular cancer research: MCR*, 9 (5), 637–647. doi: 10.1158/1541-7786.MCR-09-0237.

Campos, E.V.R., *et al.*, 2015. Polymeric and solid lipid nanoparticles for sustained release of carbendazim and tebuconazole in agricultural applications. *Scientific reports*, 5 (1), 13809. doi: 10.1038/srep13809.

Cerone, M., and Smith, T.K., 2021. A brief journey into the history of and future sources and uses of fatty acids. *Frontiers in nutrition*, 8, 570401. doi: 10.3389/fnut.2021.570401.

Chan, J.M., *et al.*, 2010. Spatiotemporal controlled delivery of nanoparticles to injured vasculature. *Proceedings of the national academy of sciences of the united states of America*, 107 (5), 2213–2218. doi: 10.1073/pnas.0914585107.

Chandra Bhatt, P., *et al.*, 2016. Nose to brain delivery of astaxanthin-loaded solid lipid nanoparticles: fabrication, radio labeling, optimization and biological studies. *RSC advances*, 6 (12), 10001–10010. doi: 10.1039/C5RA19113K.

Chattopadhyay, P., *et al.*, 2007. Production of solid lipid nanoparticle suspensions using supercritical fluid extraction of emulsions (SFEE) for pulmonary delivery using the AERx system. *Advanced drug delivery reviews*, 59 (6), 444–453. doi: 10.1016/j.addr.2007.04.010.

Chen, H., *et al.*, 2006. Podophyllotoxin-loaded solid lipid nanoparticles for epidermal targeting. *Journal of controlled release: official journal of the controlled release society*, 110 (2), 296–306. doi: 10.1016/j.jconrel.2005.09.052.

Chirio, D., *et al.*, 2018. Lipophilic prodrug of floxuridine loaded into solid lipid nanoparticles: In vitro cytotoxicity studies on different human cancer cell lines. *Journal of nanoscience and nanotechnology*, 18 (1), 556–563. doi: 10.1166/jnn.2018.13964.

Cirri, M., *et al.*, 2017. Development and in vivo evaluation of an innovative "Hydrochlorothiazide-in Cyclodextrins-in Solid Lipid Nanoparticles" formulation with sustained release and enhanced oral bioavailability for the hypertension treatment in pediatrics. *International journal of pharmaceutics*, 521 (1-2), 73–83. doi: 10.1016/j.ijpharm.2017.02.022.

Danaei, M., *et al.*, 2018. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. *Pharmaceutics*, 10 (2), 57. doi: 10.3390/pharmaceutics10020057.

Dang, H., *et al.*, 2014. Luteolin-loaded solid lipid nanoparticles synthesis, characterization, & improvement of bioavailability, pharmacokinetics in vitro and vivo studies. *Journal of nanoparticle research*, 16 (4), 1–10. doi: 10.1007/s11051-014-2347-9.

De, A., *et al.*, 2023. Folic acid functionalized diallyl trisulfide–solid lipid nanoparticles for targeting triple negative breast cancer. *Molecules (Basel, Switzerland)*, 28 (3), 1393. doi: 10.3390/molecules28031393.

Diab, R., *et al.*, 2017. Silica-based systems for oral delivery of drugs, macromolecules and cells. *Advances in colloid and interface science*, 249, 346–362. doi: 10.1016/j.cis.2017.04.005.

Doane, T., and Burda, C., 2013. Nanoparticle mediated non-covalent drug delivery. *Advanced drug delivery reviews*, 65 (5), 607–621. doi: 10.1016/j.addr.2012.05.012.

Duan, Y., *et al.*, 2020. A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. *RSC advances*, 10 (45), 26777–26791. doi: 10.1039/d0ra03491f.

Duong, V.A., Nguyen, T.T.L., and Maeng, H.J., 2020. Preparation of solid lipid nanoparticles and nanostructured lipid carriers for drug delivery and the effects of preparation parameters of solvent injection method. *Molecules (Basel, Switzerland)*, 25 (20), 4781. doi: 10.3390/molecules25204781.

Ekambaram, P., Sathali, A.A.H., and Priyanka, K., 2012. Solid lipid nanoparticles: a review. *Scientific review & chemical communication*, 2, 80–102.

Ganesan, P., *et al.*, 2018. Recent developments in solid lipid nanoparticle and surface-modified solid lipid nanoparticle delivery systems for oral delivery of phyto-bioactive compounds in various chronic diseases. *International journal of nanomedicine*, 13, 1569–1583. doi: 10.2147/IJN.S155593.

Ganesan, P., and Narayanasamy, D., 2017. Lipid nanoparticles: different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery. *Sustainable chemistry and pharmacy*, 6, 37–56. doi: 10.1016/j.scp.2017.07.002.

García, M.A., Meurs, E.F., and Esteban, M., 2007. The dsRNA protein kinase PKR: virus and cell control. *Biochimie*, 89 (6–7), 799–811. doi: 10.1016/j.biochi.2007.03.001.

Garg, N.K., *et al.*, 2016. Fucose decorated solid-lipid nanocarriers mediate efficient delivery of methotrexate in breast cancer therapeutics. *Colloids and surfaces. B, biointerfaces*, 146, 114–126. doi: 10.1016/j.colsurfb.2016.05.051.

Garud, A., Singh, D., and Garud, N., 2012. Solid lipid nanoparticles (SLN): method, characterization and applications. *International current pharmaceutical journal*, 1 (11), 384–393. doi: 10.3329/icpj.v1i11.12065.

Geszke-Moritz, M., and Moritz, M., 2016. Solid lipid nanoparticles as attractive drug vehicles: composition, properties and therapeutic strategies. *Materials science & engineering. C, materials for biological applications*, 68, 982–994. doi: 10.1016/j.msec.2016.05.119.

Gómez-Lázaro, L., *et al.*, 2024. Assessment of in vitro release testing methods for colloidal drug carriers: the lack of standardized protocols. *Pharmaceutics*, 16 (1), 103. doi: 10.3390/pharmaceutics16010103.

Granja, A., *et al.*, 2022. Folate receptor-mediated delivery of mitoxantrone-loaded solid lipid nanoparticles to breast cancer cells. *Biomedicine & pharmacotherapy = biomedecine & pharmacotherapie*, 154, 113525. doi: 10.1016/j.biopha.2022.113525.

Gujjari, L., *et al.*, 2022. Current challenges and nanotechnology-based pharmaceutical strategies for the treatment and control of malaria. *Parasite epidemiology and control*, 17, e00244. doi: 10.1016/j.parepi.2022.e00244.

Hajiaghapour Asr, M., *et al.*, 2023. Lipid nanoparticles as promising carriers for mRNA vaccines for viral lung infections. *Pharmaceutics*, 15 (4), 1127. doi: 10.3390/pharmaceutics15041127.

Haley, R.M., *et al.*, 2023. Lipid nanoparticle delivery of small proteins for potent in vivo RAS inhibition. *ACS applied materials & interfaces*, 15 (18), 21877–21892. doi: 10.1021/acsami.3c01501.

Hameed, H., *et al.*, 2024. A comprehensive review on lipid-based nanoparticles via nose to brain targeting as a novel approach. *Journal of microencapsulation*, 41 (8), 681–714. doi: 10.1080/02652048.2024.2404414.

Han, J., *et al.*, 2023. Lipid nanoparticle-based mRNA delivery systems for cancer immunotherapy. *Nano convergence*, 10 (1), 36. doi: 10.1186/s40580-023-00385-3.

Hashem, F.M., Nasr, M., and Khairy, A., 2014. In vitro cytotoxicity and bioavailability of solid lipid nanoparticles containing tamoxifen citrate. *Pharmaceutical development and technology*, 19 (7), 824–832. doi: 10.3109/10837450.2013.836218.

Hou, X., *et al.*, 2021. Lipid nanoparticles for mRNA delivery. *Nature reviews. Materials*, 6 (12), 1078–1094. doi: 10.1038/s41578-021-00358-0.

Hu L.D., Jia Y., and Ding W., 2010. Preparation and characterization of solid lipid nanoparticles loaded with epirubicin for pulmonary delivery. *Die pharmazie*, 8, 65: 585–587.

Huang, X., *et al.*, 2013. Solid lipid nanoparticles as delivery systems for Gambogenic acid. *Colloids and surfaces. B, biointerfaces*, 102, 391–397. doi: 10.1016/j.colsurfb.2012.08.058.

Huber, L.A., *et al.*, 2015. Topical skin cancer therapy using doxorubicin-loaded cationic lipid nanoparticles and iontophoresis. *Journal of biomedical nanotechnology*, 11 (11), 1975–1988. doi: 10.1166/jbn.2015.2139.

Huo, H., *et al.*, 2023. A fluorinated ionizable lipid improves the mRNA delivery efficiency of lipid nanoparticles. *Journal of materials chemistry. B*, 11 (19), 4171–4180. doi: 10.1039/d3tb00516j.

Hussein, H.A., *et al.*, 2022. Cytotoxicity and ^{1}H NMR metabolomics analyses of microalgal extracts for synergistic application with Tamoxifen on breast cancer cells with reduced toxicity against Vero cells. *Heliyon*, 8 (3), e09192. doi: 10.1016/j.heliyon.2022.e09192.

Hussein, H.A., and Abdullah, M.A., 2022. Novel drug delivery systems based on silver nanoparticles, hyaluronic acid, lipid nanoparticles and liposomes for cancer treatment. *Applied nanoscience*, 12 (11), 3071–3096. doi: 10.1007/s13204-021-02018-9.

Hussein, H.A., Maulidiani, M., and Abdullah, M. A., 2020. Microalgal metabolites as anticancer/antioxidant agents reduce cytotoxicity of elevated silver nanoparticle levels against non-cancerous Vero cells. *Heliyon*, 6 (10), e05263. doi: 10.1016/j.heliyon.2020.e05263.

Jagaran, K., Habib, S., and Singh, M., 2024. Bio-inspired polymeric solid lipid nanoparticles for sirna delivery: cytotoxicity and cellular uptake in vitro. *Polymers*, 16 (23), 3265. doi: 10.3390/polym16233265.

Jain, P., Pandey, V., and Soni, V., 2022. Clinical and immunological erythematosus patients characteristics in systemic lupus Maryam. *Indian journal of medical research*, 156, 139–148.

Jaiswal, P., Gidwani, B., and Vyas, A., 2016. Nanostructured lipid carriers and their current application in targeted drug delivery. *Artificial cells, nanomedicine, and biotechnology*, 44 (1), 27–40. doi: 10.3109/21691401.2014.909822.

Jamous, Y.F., *et al.*, 2023. Formulation and characterization of solid lipid nanoparticles. *Processes*, 11 (10), 3039. doi: 10.3390/pr11103039.

Jenning, V., Thünemann, A.F., and Gohla, S.H., 2000. Characterization of a novel solid lipid nanoparticles carrier system based on binary mixtures of liquid and solid lipids. *International journal of pharmaceutics*, 199 (2), 167–177. doi: 10.1016/s0378-5173(00)00378-1.

Jin, J., *et al.*, 2011. In vivo specific delivery of c-Met siRNA to glioblastoma using cationic solid lipid nanoparticles. *Bioconjugate chemistry*, 22 (12), 2568–2572. doi: 10.1021/bc200406n.

Jose, J., and Netto, G., 2019. Role of solid lipid nanoparticles as photoprotective agents in cosmetics. *Journal of cosmetic dermatology*, 18 (1), 315–321. doi: 10.1111/jocd.12504.

Judge, A.D., *et al.*, 2006. Design of noninflammatory synthetic siRNA mediating potent gene silencing in vivo. *Molecular therapy: the journal of the American society of gene therapy*, 13 (3), 494–505. doi: 10.1016/j.ymthe.2005.11.002.

Jung, H.N., *et al.*, 2022. Lipid nanoparticles for delivery of RNA therapeutics: current status and the role of in vivo imaging. *Theranostics*, 12 (17), 7509–7531. doi: 10.7150/thno.77259.

Kakkar Thukral, D., Dumoga, S. K., and Mishra, A., 2014. Solid lipid nanoparticles: promising therapeutic nanocarriers for drug delivery. *Current drug delivery*, 11 (6), 771–791. doi: 10.2174/1567201811061412022233 5.

Kako, D., Ghareeb, M.M., and Al-Lami, M.S., 2024. High-performance liquid chromatography (HPLC) method validation for identifying and quantifying rebamipide in ethosomes. *Cureus*, 16 (3), e56061. doi: 10.7759/cureus.56061.

Karami, M.A., Makhmalzadeh, B.S., and Mosaddegh Rad, N., 2021. Preparation and characterization of topical solid lipid nanoparticles containing deferoxamine. *Ars pharmaceutica (internet)*, 62 (3), 224–234. doi: 10.30827/ars.v62i3.15493.

Kargari Aghmiouni, D., and Khoee, S., 2023. Dual-drug delivery by anisotropic and uniform hybrid nanostructures: a comparative study of the function and substrate–drug interaction properties. *Pharmaceutics*, 15 (4), 1214. doi: 10.3390/pharmaceutics15041214.

Kaur, J., *et al.*, 2012. Innovative growth in developing new methods for formulating solid lipid nanoparticles and microparticles. *Journal of drug delivery and therapeutics*, 2 (5), 146–150. doi: 10.22270/jddt.v2i5.295.

Khairnar, S.V., *et al.*, 2022. Review on the scale-up methods for the preparation of solid lipid nanoparticles. *Pharmaceutics*, 14 (9), 1886. doi: 10.3390/pharmaceutics14091886.

Khan, Y., *et al.*, 2022. Nanoparticles, and their applications in various fields of nanotechnology: a review. *Catalysts*, 12 (11), 1386. doi: 10.3390/catal12111386.

Khatamian, N., *et al.*, 2023. Preparation and characterization of the myricetin-loaded solid lipid nanoparticles decorated with folic acid-bound chitosan and evaluation of its antitumor and anti-angiogenic activities in vitro and in vivo in mice bearing tumor models. *Cancer nanotechnology*, 14 (1), 1–21. doi: 10.1186/s12645-023-00160-3.

Khoshnood, S., *et al.*, 2023. Amoxicillin-docosahexaenoic acid encapsulated chitosan-alginate nanoparticles as a delivery system with enhanced biocidal activities against *Helicobacter pylori* and improved ulcer healing. *Frontiers in microbiology*, 14, 1083330. doi: 10.3389/fmicb.2023.1083330.

Kim, J.T., *et al.*, 2017. Absorption study of genistein using solid lipid microparticles and nanoparticles: Control of oral bioavailability by particle sizes. *Biomolecules & therapeutics*, 25 (4), 452–459. doi: 10.4062/biomolther.2017.095.

Kim S., 2018. *Designing stimuli-responsive porous silica materials using solid lipid nanoparticles (SLN) and magneto-responsive surfactants for delivery of curcumin*. Doctoral dissertation, Université de Lorraine.

Kipriye, Z., Şenel, B., and Yenilmez, E., 2017. Preparation and evaluation of carvedilol-loaded solid lipid nanoparticles for targeted drug delivery. *Tropical journal of pharmaceutical research*, 16 (9), 2057–2068. doi: 10.4314/tjpr.v16i9.4.

Kobiyama, K., *et al.*, 2021. Optimization of an LNP-mRNA vaccine candidate targeting SARS-CoV-2 receptor- binding domain. *BioRxiv*, 03, 433852.

Kou, L., *et al.*, 2018. Transporter-guided delivery of nanoparticles to improve drug permeation across cellular barriers and drug exposure to selective cell types. *Frontiers in pharmacology*, 9, 27. doi: 10.3389/fphar.2018.00027.

Kumar, R., 2019. Lipid-based nanoparticles for drug-delivery systems. In: S.S. Mohapatra, S. Ranjan, N. Dasgupta, R.K. Mishra, and S. Thomas, eds., *Nanocarriers for drug delivery*. Amsterdam, Netherlands: Elsevier. p. 249–284.

Kumari, A., Yadav, S.K., and Yadav, S.C., 2010. Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids and surfaces. B, biointerfaces*, 75 (1), 1–18. doi: 10.1016/j.colsurfb.2009.09.001.

Kundu, J., *et al.*, 2010. Silk fibroin nanoparticles for cellular uptake and control release. *International journal of pharmaceutics*, 388 (1–2), 242–250. doi: 10.1016/j.ijpharm.2009.12.052.

Lai, F., *et al.*, 2006. Artemisia arborescens L. essential oil-loaded solid lipid nanoparticles for potential agricultural application: preparation and characterization. *AAPS PharmSciTech*, 7 (1), E2–E18. doi: 10.1208/pt070102.

Landoni, M., *et al.*, 2023. Opportunities and challenges of castor bean (*Ricinus communis* L.) genetic improvement. *Agronomy*, 13 (8), 2076. doi: 10.3390/agronomy13082076.

Lee, S.-E., *et al.*, 2019. Hyaluronic acid-coated solid lipid nanoparticles to overcome drug-resistance in tumor cells. *Journal of drug delivery science and technology*, 50, 365–371. doi: 10.1016/j.jddst.2019.01.042.

Li, D., *et al.*, 2023. A novel Toxoplasma gondii TGGT1_316290 mRNA-LNP vaccine elicits protective immune response against toxoplasmosis in mice. *Frontiers in microbiology*, 14, 1145114. doi: 10.3389/fmicb.2023.1145114.

Li, M., *et al.*, 2024. Co-delivery of paclitaxel and curcumin loaded solid lipid nanoparticles for improved targeting of lung cancer: In vitro and in vivo investigation. *Heliyon*, 10 (9), e30290. doi: 10.1016/j.heliyon.2024.e30290.

Lingayat, V.J., Zarekar, N.S., and Shendge, R.S., 2017. Solid lipid nanoparticles- a review. *International journal of applied pharmaceutics*, 4, 67–72.

Liu, B., *et al.*, 2017. Co-delivery of paclitaxel and TOS-cisplatin via TAT-targeted solid lipid nanoparticles with synergistic antitumor activity against cervical cancer. *International journal of nanomedicine*, 12, 955–968. doi: 10.2147/IJN.S115136.

Liu, J., *et al.*, 2007. Isotretinoin-loaded solid lipid nanoparticles with skin targeting for topical delivery. *International journal of pharmaceutics*, 328 (2), 191–195. doi: 10.1016/j.ijpharm.2006.08.007.

Liu, J., *et al.*, 2016. MicroRNA-200c delivered by solid lipid nanoparticles enhances the effect of paclitaxel on breast cancer stem cell. *International journal of nanomedicine*, 11, 6713–6725. doi: 10.2147/IJN.S111647.

Liu, Z., *et al.*, 2017. Genome editing of the HIV co-receptors CCR5 and CXCR4 by CRISPR-Cas9 protects CD4+ T cells from HIV-1 infection. *Cell & bioscience*, 7 (1), 47. doi: 10.1186/s13578-017-0174-2.

Lu, B., *et al.*, 2006. Solid lipid nanoparticles of mitoxantrone for local injection against breast cancer and its lymph node metastases. *European journal of pharmaceutical sciences: official journal of the European federation for pharmaceutical sciences*, 28 (1–2), 86–95. doi: 10.1016/j.ejps.2006.01.001.

Ma, C.C., *et al.*, 2020. The approved gene therapy drugs worldwide: from 1998 to 2019. *Biotechnology advances*, 40, 107502. doi: 10.1016/j.biotechadv.2019.107502.

Ma, L., *et al.*, 2018. Co-delivery of paclitaxel and tanespimycin in lipid nanoparticles enhanced anti-gastric-tumor effect in vitro and in vivo. *Artificial cells, nanomedicine, and biotechnology*, 46 (sup2), 904–911. doi: 10.1080/21691401.2018.1472101.

Madan, J., *et al.*, 2013. Poly (ethylene)-glycol conjugated solid lipid nanoparticles of noscapine improve biological half-life, brain delivery and efficacy in glioblastoma cells. *Nanomedicine: nanotechnology, biology, and medicine*, 9 (4), 492–503. doi: 10.1016/j.nano.2012.10.003.

Manea, A.M., Ungureanu, C., and Meghea, A., 2014. Effect of vegetable oils on obtaining lipid nanocarriers for sea buckthorn extract encapsulation. *Comptes rendus. Chimie*, 17 (9), 934–943. doi: 10.1016/j.crci.2013.10.020.

Mashima, R., and Takada, S., 2022. Lipid nanoparticles: a novel gene delivery technique for clinical application. *Current issues in molecular biology*, 44 (10), 5013–5027. doi: 10.3390/cimb44100341.

Maugeri, M., *et al.*, 2019. Linkage between endosomal escape of LNP-mRNA and loading into EVs for transport to other cells. *Nature communications*, 10 (1), 4333. doi: 10.1038/s41467-019-12275-6.

McKay, P.F., *et al.*, 2020. Self-amplifying RNA SARS-CoV-2 lipid nanoparticle vaccine candidate induces high neutralizing

antibody titers in mice. *Nature communications*, 11 (1), 3523. doi: 10.1038/s41467-020-17409-9.

Mei, Z., *et al.*, 2005. Triptolide loaded solid lipid nanoparticle hydrogel for topical application. *Drug development and industrial pharmacy*, 31 (2), 161–168. doi: 10.1081/ddc-200047791.

Mishra, V., *et al.*, 2018. Solid lipid nanoparticles: emerging colloidal nano drug delivery systems. *Pharmaceutics*, 10 (4), 191. doi: 10.3390/pharmaceutics10040191.

Misra, S., *et al.*, 2015. Interactions between hyaluronan and its receptors (CD44, RHAMM) regulate the activities of inflammation and cancer. *Frontiers in immunology*, 6, 201. doi: 10.3389/fimmu.2015.00201.

Mitchell, M.J., *et al.*, 2021. Engineering precision nanoparticles for drug delivery. *Nature reviews. Drug discovery*, 20 (2), 101–124. doi: 10.1038/s41573-020-0090-8.

Mohammed, H.A., *et al.*, 2023. Solid lipid nanoparticles for targeted natural and synthetic drugs delivery in high-incidence cancers, and other diseases: Roles of preparation methods, lipid composition, transitional stability, and release profiles in nanocarriers' development. *Nanotechnology reviews*, 12 (1), 20220517. doi: 10.1515/ntrev-2022-0517.

Mohammed, L., Ragab, D., and Gomaa, H., 2016. Bioactivity of hybrid polymeric magnetic nanoparticles and their applications in drug delivery. *Current pharmaceutical design*, 22 (22), 3332–3352. doi: 10.2174/1381612822666160208143237.

Moon, J.H., *et al.*, 2015. Nanoparticle approaches to combating drug resistance. *Future medicinal chemistry*, 7 (12), 1503–1510. doi: 10.4155/fmc.15.82.

Muga, J.O., *et al.*, 2018. In vitro evaluation of chloroquine-loaded and heparin surface-functionalized solid lipid nanoparticles. *Malaria journal*, 17 (1), 133. 7. doi: 10.1186/s12936-018-2302-9.

Narváez-Narváez, D.A., *et al.*, 2023. Comparative analysis of the physicochemical and biological characteristics of freeze-dried PEGylated cationic solid lipid nanoparticles. *Pharmaceuticals*, 16 (11), 1583. doi: 10.3390/ph16111583.

Naseri, N., Valizadeh, H., and Zakeri-Milani, P., 2015. Solid lipid nanoparticles and nanostructured lipid carriers: Structure preparation and application. *Advanced pharmaceutical bulletin*, 5 (3), 305–313. doi: 10.15171/apb.2015.043.

Nasikkar, Z.T., Khutle, N.M., and Nasikkar, H.T., 2019. Solid lipid nanoparticles: a review. *World journal of pharmaceutical research*, 8, 567–578.

National Cancer Institute - The RAS Initiative, 2024. https://www.cancer.gov/research/key-initiatives/ras. Accessed on 9th September, 2024.

Nazarova, A., *et al.*, 2022. Surfactant effect on the physicochemical characteristics of solid lipid nanoparticles based on Pillar[5]arenes. *International journal of molecular sciences*, 23 (2), 779. doi: 10.3390/ijms23020779.

Otto, D.P., and De Villiers, M.M., 2013. Why is the nanoscale special (or not)? Fundamental properties and how it relates to the design of nano-enabled drug delivery systems. *Nanotechnology reviews*, 2 (2), 171–199. doi: 10.1515/ntrev-2012-0051.

Ozgenc, E., *et al.*, 2022. Radiolabeled trastuzumab solid lipid nanoparticles for breast cancer cell: in vitro and in vivo studies. *ACS omega*, 7 (34), 30015–30027. doi: 10.1021/acsomega.2c03023.

Öztürk, A.A., Aygül, A., and Şenel, B., 2019. Influence of glyceryl behenate, tripalmitin and stearic acid on the properties of clarithromycin incorporated solid lipid nanoparticles (SLNs): formulation, characterization, antibacterial activity and cytotoxicity. *Journal of drug delivery science and technology*, 54, 101240. doi: 10.1016/j.jddst.2019.101240.

Parveen, A., *et al.*, 2023. Lipid polymer hybrid nanoparticles as potent vehicles for drug delivery in cancer therapeutics. *Medicine in drug discovery*, 20, 100165. doi: 10.1016/j.medidd.2023.100165.

Parvez, S., *et al.*, 2020. Modified solid lipid nanoparticles encapsulated with Amphotericin B and Paromomycin: an effective oral combination against experimental murine visceral leishmaniasis. *Scientific reports*, 10 (1), 12243. doi: 10.1038/s41598-020-69276-5.

Patel, P., *et al.*, 2019. *Surface modification of nanoparticles for targeted drug delivery*. Cham, Switzerland: Springer International Publishing. doi: 10.1007/978-3-030-06115-9_2.

Patel, P., *et al.*, 2022. Development of amino acid-modified biodegradable lipid nanoparticles for siRNA delivery. *Acta biomaterialia*, 154, 374–384. doi: 10.1016/j.actbio.2022.09.065.

Pattni, B.S., Chupin, V.V., and Torchilin, V.P., 2015. New developments in liposomal drug delivery. *Chemical reviews*, 115 (19), 10938–10966. doi: 10.1021/acs.chemrev.5b00046.

Pedersen, N., *et al.*, 2006. Solid lipid nanoparticles can effectively bind DNA, streptavidin and biotinylated ligands. *European journal of pharmaceutics and biopharmaceutics: official journal of arbeitsgemeinschaft fur pharmazeutische verfahrenstechnik e.V*, 62 (2), 155–162. doi: 10.1016/j.ejpb.2005.09.003.

Pereira, L., 2018. *Therapeutic and nutritional uses of algae*. Florida: CRC Press Taylor & Francis.

Pereira-Leite, C., *et al.*, 2023. Exploring stearic-acid-based nanoparticles for skin applications—focusing on stability and cosmetic benefits. *Cosmetics*, 10 (4), 99. doi: 10.3390/cosmetics10040099.

Pragati, S., *et al.*, 2009. Solid lipid nanoparticles: a promising drug delivery technology. *International journal of pharmaceutical sciences and nanotechnology*, 2, 509–516.

Prochazka, L., Tesarik, R., and Turanek, J., 2014. Regulation of alternative splicing of CD44 in cancer. *Cellular signalling*, 26 (10), 2234–2239. doi: 10.1016/j.cellsig.2014.07.011.

Qushawy, M., and Nasr, A., 2019. Solid lipid nanoparticles (SLNs) as nano drug delivery carriers: Preparation, characterization and application. *International journal of applied pharmaceutics*, 12, 1–9. doi: 10.22159/ijap.2020v12i1.35312.

Rahmanian-Devin, P., *et al.*, 2023. Preparation and characterization of solid lipid nanoparticles encapsulated noscapine and evaluation of its protective effects against imiquimod-induced psoriasis-like skin lesions. *Biomedicine & pharmacotherapy = biomedecine & pharmacotherapie*, 168, 115823. doi: 10.1016/j.biopha.2023.115823.

Rajana, N., *et al.*, 2024. Targeted delivery and apoptosis induction of CDK-4/6 inhibitor loaded folic acid decorated lipid-polymer hybrid nanoparticles in breast cancer cells. *International journal of pharmaceutics*, 651, 123787. doi: 10.1016/j.ijpharm.2024.123787.

Ramalingam, P., Yoo, S.W., and Ko, Y.T., 2016. Nanodelivery systems based on mucoadhesive polymer coated solid lipid nanoparticles to improve the oral intake of food cur-

cumin. *Food research international*, 84, 113–119. doi: 10.1016/j.foodres.2016.03.031.

Ray, P.C., Yu, H., and Fu, P.P., 2009. Toxicity and environmental risks of nanomaterials: challenges and future needs. *Journal of environmental science and health. Part C, Environmental carcinogenesis & ecotoxicology reviews*, 27 (1), 1–35.

Rioux, L., Beaulieu, L., and Turgeon, S.L., 2017. Seaweeds: a traditional ingredients for new gastronomic sensation. *Food hydrocolloids*, 68, 255–265. doi: 10.1016/j.foodhyd.2017.02.005.

Roldán-Matilla, M., *et al*., 2025. Structural characterisation and dynamic modelling of pegylated graphene oxide with Ag and Cu nanocluster. *Applied surface science*, 688, 162430. doi: 10.1016/j.apsusc.2025.162430.

Rosière, R., *et al.*, 2018. New folate-grafted chitosan derivative to improve delivery of paclitaxel-loaded solid lipid nanoparticles for lung tumor therapy by inhalation. *Molecular pharmaceutics*, 15 (3), 899–910. doi: 10.1021/acs.molpharmaceut.7b00846.

Ryan, A., *et al.*, 2023. The development of a solid lipid nanoparticle (SLN)-based lacticin 3147 hydrogel for the treatment of wound infections. *Drug delivery and translational research*, 13 (9), 2407–2423. doi: 10.1007/s13346-023-01332-9.

Sáez-Llorens, X., *et al.*, 2022. Safety and immunogenicity of mRNA-LNP COVID-19 vaccine CVnCoV in Latin American adults: A phase 2 randomized study. *Vaccine: X*, 11, 100189. doi: 10.1016/j.jvacx.2022.100189.

Sáez-Llorens, X., *et al.*, 2023. Corrigendum to "Safety and immunogenicity of mRNA-LNP COVID-19 vaccine CVnCoV in Latin American adults: A phase 2 randomized study" [Vaccine: X 11 (2022) 100189] (Vaccine: X, 11, (S2590136222000493), doi: 10.1016/j.jvacx.2022.100189)). *Vaccine X* 14: 100307.

Sanad, R.A., 2014. Lipid nanoparticles (SLNs and NLCs): wide range of application from cosmetics to cancer chemotherapy. *Journal of drug research (Egypt)*, 35 (1), 73–78.

Sangsen, Y., *et al*., 2015. Modification of oral absorption of oxyresveratrol using lipid based nanoparticles. *Colloids and surfaces. B, biointerfaces*, 131, 182–190. doi: 10.1016/j.colsurfb.2015.04.055.

Sarangi, M.K., and Padhi, S., 2016. Solid lipid nanoparticles- a review. *International journal of applied pharmaceutics*, 3, 5–12.

Sastri, K.T., *et al.*, 2020. Solid lipid nanoparticles: preparation techniques, their characterization, and an update on recent studies. *Journal of applied pharmaceutical science*, 10, 126–141.

Saupe, A., and Rades, T., 2006. Solid Lipid Nanoparticles. In: Mozafari, M.R. (ed.) Nanocarrier Technologies: Frontiers of Nanotherapy. Springer, Dordrecht, Netherlands, pp. 41-50 10.1007/978-1-4020-5041-1_3.

Saupe, A., Gordon, K.C., and Rades, T., 2006. Structural investigations on nanoemulsions, solid lipid nanoparticles and nanostructured lipid carriers by cryo-field emission scanning electron microscopy and Raman spectroscopy. *International journal of pharmaceutics*, 314 (1), 56–62. doi: 10.1016/j.ijpharm.2006.01.022.

Senadheera, T.R.L., Hossain, A., and Shahidi, F., 2023. Marine bioactives and their application in the food industry: a review. *Applied sciences*, 13 (21), 12088. doi: 10.3390/app132112088.

Seo, Y., *et al.*, 2023. Recent progress of lipid nanoparticles-based lipophilic drug delivery: focus on surface modifications. *Pharmaceutics*, 15 (3), 772. doi: 10.3390/pharmaceutics15030772.

Severino, P., *et al.*, 2011. Polymorphism, crystallinity and hydrophilic-lipophilic balance of stearic acid and stearic acid-capric/caprylic triglyceride matrices for production of stable nanoparticles. *Colloids and surfaces. B, biointerfaces*, 86 (1), 125–130. doi: 10.1016/j.colsurfb.2011.03.029.

Shah R., 2016. *Microwave-assisted production of solid lipid nanoparticles*. Ph.D Thesis, Swinburne University of Technology.

Shinde, R.B., *et al.*, 2023. Preparation, statistical optimization, in-vitro evaluation and characterization of solid lipid nanoparticles of an anti-retroviral drug Nevirapine. *Research journal of pharmacy and technology*, 16, 3899–3908. doi: 10.52711/0974-360X.2023.00642.

Si, K.J., *et al.*, 2018. Nanoparticle superlattices: the roles of soft ligands. *Advanced science*, 5 (1), 1700179. doi: 10.1002/advs.201700179.

Silva, A.M., *et al.*, 2019. Comparison of antiproliferative effect of epigallocatechin gallate when loaded into cationic solid lipid nanoparticles against different cell lines. *Pharmaceutical development and technology*, 24 (10), 1243–1249. doi: 10.1080/10837450.2019.1658774.

Singh, A., *et al.*, 2020. Formulation, characterization and in vitro anti-leishmanial evaluation of amphotericin B loaded solid lipid nanoparticles coated with vitamin B12-stearic acid conjugate. *Materials science & engineering. C, materials for biological applications*, 117, 111279. doi: 10.1016/j.msec.2020.111279.

Smith, T., *et al.*, 2020. Application of smart solid lipid nanoparticles to enhance the efficacy of 5-fluorouracil in the treatment of colorectal cancer. *Scientific reports*, 10 (1), 16989. doi: 10.1038/s41598-020-73218-6.

Soleimanian, Y., *et al.*, 2018. Formulation and characterization of novel nanostructured lipid carriers made from beeswax, propolis wax and pomegranate seed oil. *Food chemistry*, 244, 83–92. doi: 10.1016/j.foodchem.2017.10.010.

Somu Naidu, G., *et al.*, 2025. Ionizable lipids with optimized linkers enable lung-specific, lipid nanoparticle-mediated mRNA delivery for treatment of metastatic lung tumors. *ACS nano*, 19 (6), 6571–6587. doi: 10.1021/acsnano.4c18636.

Soni, M.P., *et al.*, 2014. Buparvaquone loaded solid lipid nanoparticles for targeted delivery in theleriosis. *Journal of pharmacy & bioallied sciences*, 6 (1), 22–30. doi: 10.4103/0975-7406.124309.

Stanisic, D., *et al.*, 2018. Applications of flavonoids, with an emphasis on hesperidin, as anticancer prodrugs: phytotherapy as an alternative to chemotherapy. *Studies in natural products chemistry*, 58, 161–212.

Stavis, S.M., *et al.*, 2018. Nanoparticle manufacturing-heterogeneity through processes to products. *ACS applied nano materials*, 1 (9), 4358–4385. doi: 10.1021/acsanm.8b01239.

Stoyneva-Gärtner, M., Uzunov, B., and Gärtner, G., 2022. Aeroterrestrial and extremophilic microalgae as promising sources for lipids and lipid nanoparticles in dermal cosmetics. *Cosmetics*, 9 (1), 11. doi: 10.3390/cosmetics9010011.

Sun, T., *et al.*, 2014. Engineered nanoparticles for drug delivery in cancer therapy. *Angewandte chemie (international ed.*

in English), 53 (46), 12320–12364. doi: 10.1002/anie.201403036.

Suzuki, Y., and Ishihara, H., 2016. Structure, activity and uptake mechanism of siRNA-lipid nanoparticles with an asymmetric ionizable lipid. *International journal of pharmaceutics*, 510 (1), 350–358. doi: 10.1016/j.ijpharm.2016.06.124.

Suzuki, Y., and Ishihara, H., 2021. Difference in the lipid nanoparticle technology employed in three approved siRNA (Patisiran) and mRNA (COVID-19 vaccine) drugs. *Drug metabolism and pharmacokinetics*, 41, 100424. doi: 10.1016/j.dmpk.2021.100424.

Svitkin, Y.V., *et al.*, 2017. N1-methyl-pseudouridine in mRNA enhances translation through eIF2α-dependent and independent mechanisms by increasing ribosome density. *Nucleic acids research*, 45 (10), 6023–6036. doi: 10.1093/nar/gkx135.

Szubert, A.J., *et al.*, 2023. COVAC1 phase 2a expanded safety and immunogenicity study of a self-amplifying RNA vaccine against SARS-CoV-2. *EClinicalMedicine*, 56, 101823. doi: 10.1016/j.eclinm.2022.101823.

Tang, C.H., Chen, H.L., and Dong, J.R., 2023. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) as food-grade nanovehicles for hydrophobic nutraceuticals or bioactives. *Applied sciences*, 13 (3), 1726. doi: 10.3390/app13031726.

Thakkar, A., *et al.*, 2015. Ferulic acid combined with aspirin demonstrates chemopreventive potential towards pancreatic cancer when delivered using chitosan-coated solid-lipid nanoparticles. *Cell & bioscience*, 5 (1), 46. doi: 10.1186/s13578-015-0041-y.

Thakkar, A., *et al.*, 2016. Preclinical systemic toxicity evaluation of chitosan-solid lipid nanoparticle-encapsulated aspirin and curcumin in combination with free sulforaphane in BALaIB/c mice. *International journal of nanomedicine*, 11, 3265–3276. doi: 10.2147/IJN.S106736.

Thompson, A.J., and Locarnini, S.A., 2007. Toll-like receptors, RIG-I-like RNA helicases and the antiviral innate immune response. *Immunology and cell biology*, 85 (6), 435–445. doi: 10.1038/sj.icb.7100100.

Tounsi, L., *et al.*, 2022. Microalgae as feedstock for bioactive polysaccharides. *International journal of biological macromolecules*, 221, 1238–1250. doi: 10.1016/j.ijbiomac.2022.08.206.

Toyama, K., *et al.*, 2023. DS-5670a, a novel mRNA-encapsulated lipid nanoparticle vaccine against severe acute respiratory syndrome coronavirus 2: Results from a phase 2 clinical study. *Vaccine*, 41 (38), 5525–5534. doi: 10.1016/j.vaccine.2023.07.012.

Triplett, M.D., and Rathman, J.F., 2009. Optimization of β-carotene loaded solid lipid nanoparticles preparation using a high shear homogenization technique. *Journal of nanoparticle research*, 11 (3), 601–614. doi: 10.1007/s11051-008-9402-3.

Van Egeren, D., *et al.*, 2023. Vaccines alone cannot slow the evolution of SARS-CoV-2. *Vaccines*, 11 (4), 853. doi: 10.3390/vaccines11040853.

Venishetty, V.K., *et al.*, 2013. Increased brain uptake of docetaxel and ketoconazole loaded folate-grafted solid lipid nanoparticles. *Nanomedicine: nanotechnology, biology, and medicine*, 9 (1), 111–121. doi: 10.1016/j.nano.2012.03.003.

Vicente-Pascual, M., *et al.*, 2018. Gene delivery in the cornea: In vitro & ex vivo evaluation of solid lipid nanoparticle-based vectors. *Nanomedicine (London, England)*, 13 (15), 1847–1854. doi: 10.2217/nnm-2018-0112.

Wakaskar, R.R., 2018. General overview of lipid-polymer hybrid nanoparticles, dendrimers, micelles, liposomes, spongosomes and cubosomes. *Journal of drug targeting*, 26 (4), 311–318. doi: 10.1080/1061186X.2017.1367006.

Wang, J.-L., *et al.*, 2014. Preparation and characterization of novel lipid carriers containing microalgae oil for food applications. *Journal of food science*, 79 (2), E169–E177. doi: 10.1111/1750-3841.12334.

Wanga, C., *et al.*, 2023. Biomimetic noncationic lipid nanoparticles for mRNA delivery. *Proceedings of the national academy of sciences of the United States of America*, 120, e2311276120.

Wanyika, H., *et al.*, 2012. Mesoporous silica nanoparticles carrier for urea: potential applications in agrochemical delivery systems. *Journal of nanoscience and nanotechnology*, 12 (3), 2221–2228. doi: 10.1166/jnn.2012.5801.

Wei, L., *et al.*, 2016. Preparation and characterization of loperamide-loaded dynasan 114 solid lipid nanoparticles for increased oral absorption in the treatment of diarrhea. *Frontiers in pharmacology*, 7, 332. doi: 10.3389/fphar.2016.00332.

Wencui, Z., *et al.*, 2015. Preparation of solid lipid nanoparticles loaded with garlic oil and evaluation of their in vitro and in vivo characteristics. *European review for medical and pharmacological sciences*, 19, 3742–3750.

Wilson, B., and Geetha, K.M., 2022. Lipid nanoparticles in the development of mRNA vaccines for COVID-19. *Journal of drug delivery science and technology*, 74, 103553. doi: 10.1016/j.jddst.2022.103553.

Wissing, S.A., and Müller, R.H., 2003. Cosmetic applications for solid lipid nanoparticles (SLN). *International journal of pharmaceutics*, 254 (1), 65–68. doi: 10.1016/s0378-5173(02)00684-1.

Wong, H.L., *et al.*, 2006. A new polymer-lipid hybrid nanoparticle system increases cytotoxicity of doxorubicin against multidrug-resistant human breast cancer cells. *Pharmaceutical research*, 23 (7), 1574–1585. doi: 10.1007/s11095-006-0282-x.

Xu, S., *et al.*, 2024. Tumor-tailored ionizable lipid nanoparticles facilitate IL-12 circular RNA delivery for enhanced lung cancer immunotherapy. *Advanced materials*, 36 (29), 2400307. doi: 10.1002/adma.202400307.

Xu, W., Bae, E.J., and Lee, M.K., 2018. Enhanced anticancer activity and intracellular uptake of paclitaxel-containing solid lipid nanoparticles in multidrug-resistant breast cancer cells. *International journal of nanomedicine*, 13, 7549–7563. doi: 10.2147/IJN.S182621.

Xu, X., and Xia, T., 2023. Recent advances in site-specific lipid nanoparticles for mRNA delivery. *ACS nanoscience Au*, 3 (3), 192–203. doi: 10.1021/acsnanoscienceau.2c00062.

Yeo, S., *et al.*, 2022. Solid lipid nanoparticles of curcumin designed for enhanced bioavailability and anticancer efficiency. *ACS omega*, 7 (40), 35875–35884. doi: 10.1021/acsomega.2c04407.

Yeo, S., *et al.*, 2024. 4-Hexylresorcinol loaded solid lipid nanoparticles for enhancing anticancer activity. *Pharmaceuticals*, 17 (10), 1296. doi: 10.3390/ph17101296.

Yonezawa, S., Koide, H., and Asai, T., 2020. Recent advances in siRNA delivery mediated by lipid-based nanoparticles.

Advanced drug delivery reviews, 154–155, 64–78. doi: 10.1016/j.addr.2020.07.022.

Young, R.E., *et al.*, 2024. Systematic development of ionizable lipid nanoparticles for placental mRNA delivery using a design of experiments approach. *Bioactive materials*, 34, 125–137. doi: 10.1016/j.bioactmat.2023.11.014.

Yu, Y.H., *et al.*, 2012. Cationic solid lipid nanoparticles for co-delivery of paclitaxel and siRNA. *European journal of pharmaceutics and biopharmaceutics: official journal of arbeitsgemeinschaft fur pharmazeutische verfahrenstechnik e.V*, 80 (2), 268–273. doi: 10.1016/j.ejpb.2011.11.002.

Zhang, L., *et al.*, 2008a. Nanoparticles in medicine: therapeutic applications and developments. *Clinical pharmacology and therapeutics*, 83 (5), 761–769. doi: 10.1038/sj.clpt.6100400.

Zhang, L., *et al.*, 2008b. Self assembled lipid–polymer hybrid nanoparticles: a robust drug delivery platform. *ACS nano*, 2 (8), 1696–1702. doi: 10.1021/nn800275r.

Zhang, R.X., *et al.*, 2016. Polymer-lipid hybrid nanoparticles synchronize pharmacokinetics of co-encapsulated doxorubicin mitomycin C and enable their spatiotemporal co-delivery and local bioavailability in breast tumor. *Nanomedicine: nanotechnology, biology, and medicine*, 12 (5), 1279–1290. doi: 10.1016/j.nano.2015.12.383.

Zhang, R.X., *et al.*, 2017. Design of nanocarriers for nanoscale drug delivery to enhance cancer treatment using hybrid polymer and lipid building blocks. *Nanoscale*, 9 (4), 1334–1355. doi: 10.1039/c6nr08486a.

Zhang, Y., *et al.*, 2023. Immunization with a novel mRNA vaccine, TGGT1_216200 mRNA-LNP, prolongs survival time in BALB/c mice against acute toxoplasmosis. *Frontiers in immunology*, 14, 1161507. doi: 10.3389/fimmu.2023.1161507.

Zhao, S., *et al.*, 2016. Doxorubicin hydrochloride-oleic acid conjugate loaded nanostructured lipid carriers for tumor specific drug release. *Colloids and surfaces. B, biointerfaces*, 145, 95–103. doi: 10.1016/j.colsurfb.2016.04.027.

Zhu, C.J., and An, C. G., 2017. Enhanced antitumor activity of cabazitaxel targeting CD44+ receptor in breast cancer cell line via surface functionalized lipid nanocarriers. *Tropical journal of pharmaceutical research*, 16 (6), 1383–1390. doi: 10.4314/tjpr.v16i6.24.

Zingue, S., *et al.*, 2018. The hydro-ethanolic extract of *Acacia seyal* (Mimosaceae) stem barks induced death in an ER-negative breast cancer cell line by the intrinsic pathway of apoptosis and inhibited cell migration. *Journal of ethnopharmacology*, 223, 41–50. doi: 10.1016/j.jep.2018.05.021.