Elnady *et al. AAPS Open* (2023) 9:13
https://doi.org/10.1186/s41120-023-00080-x

AAPS Open

REVIEW

Open Access

A review on lipid-based nanocarriers mimicking chylomicron and their potential in drug delivery and targeting infectious and cancerous diseases

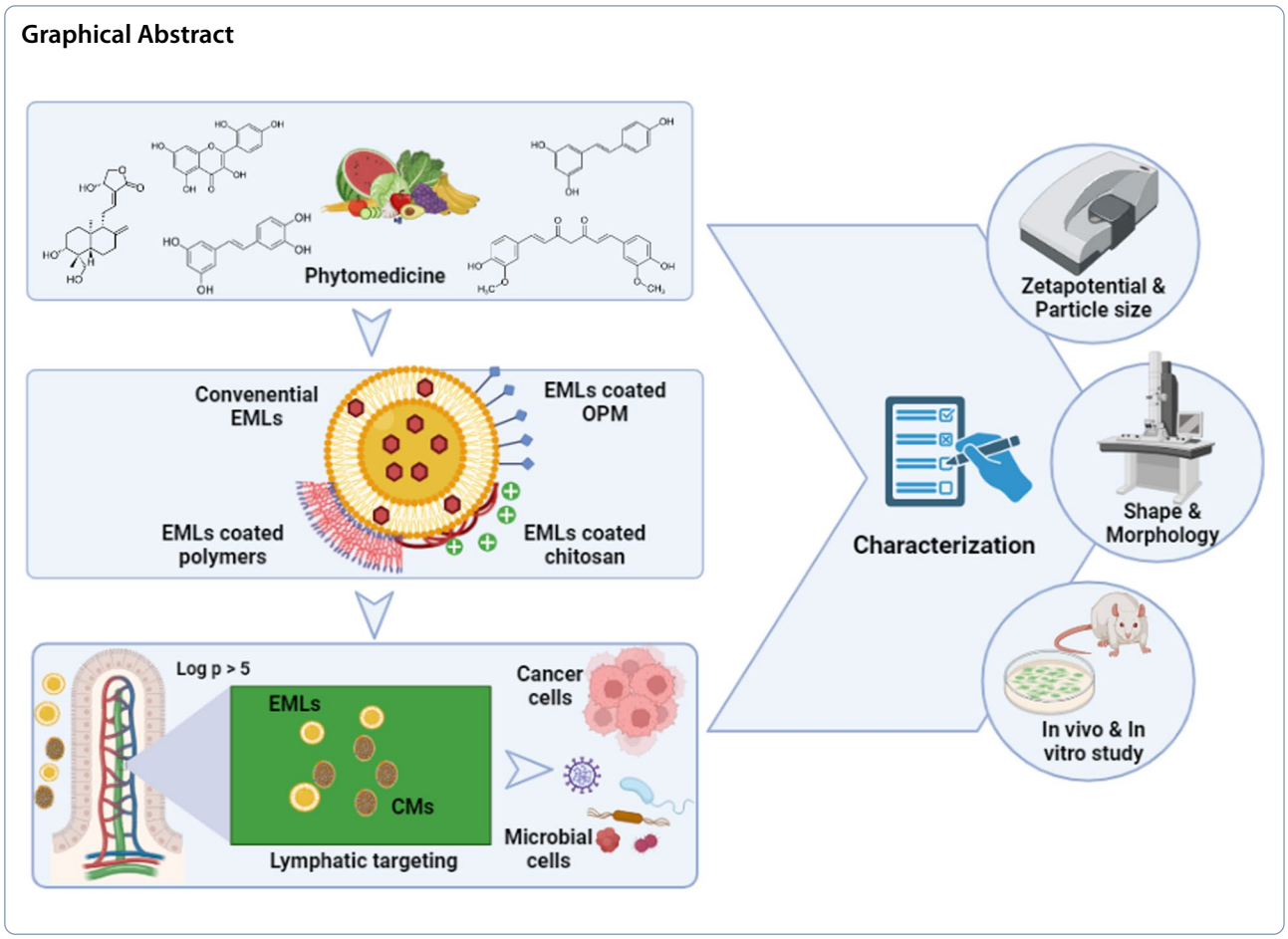
Rana E. Elnady[1*], Maha M. Amin[2] and Mohamed Y. Zakaria[3,4]

Abstract

Infectious and cancerous diseases are tedious to manage. The problem of drug resistance is often associated with anti-microbial and anti-cancer agents and is one of the most significant challenges that restrict their activity. Therefore, it is necessary to increase doses or drug combinations. However, introducing drugs in this way is often ineffective due to poor solubility, low bioavailability, reduced stability, and different drug pharmacokinetic parameters. Vesicular nanocarriers are considered promising for effective drug delivery and overcoming drug resistance. Lipid-based drug delivery systems (LBDDS) such as emulsomes (EMLs) can solve many problems associated with drug physicochemical properties. EMLs share structural similarities with liposomes and solid lipid nanoparticles (SLNs). The main components of emulsomal preparation are triglycerides (TG), phospholipids (PC), and cholesterol (Chol). These systems provide greater stability and pharmacokinetic parameters in vivo compared to liposomes and other lipid-based systems, overcoming their limitations and surpassing their shortcomings. This review offers a broad summary of emulsomal research to date and a comprehensive overview of the formulation materials and their effects on the fabrication, physical characteristics, surface modification, lymphatic targeting, and recent applications of EMLs in infectious and cancerous diseases. EMLs can offer stable and safe lipid-based systems with adequate entrapment and sustained release properties, improving bioavailability and evading multidrug resistance. Furthermore, they hold promise for future clinical applications for anti-microbial and anti-cancer drugs.

Keywords Emulsomes, Lipid-based systems, Entrapment efficiency, Resistance, Lymphatic targeting, Bioavailability

*Correspondence:
Rana E. Elnady
rana.essam@su.edu.eg
Full list of author information is available at the end of the article



Introduction

The urgent need for the discovery of new drugs to treat infectious and cancerous diseases continues to grow due to multidrug resistance. Moreover, increasing the dose of these medications to overcome resistance induces severe side effects. Drug resistance is caused by the inability of bioactive compounds to reach infected cells in adequate concentration (Lee et al. 2013). Additionally, many chemotherapeutic agents with poor solubility and bioavailability have been successfully loaded into nanoparticles (Hu and Zhang 2009). Nanoparticle-based drug delivery systems are critical in delivering many drugs to different body organs. These systems are advantageous for minimizing adverse effects, enhancing bioavailability, and enhancing drugs' physical and chemical properties. LBDDS are one of the most promising drug delivery options and highly researched nanocarriers (Puri et al. 2009). They are an attractive way to deliver drugs with poor solubility and low bioavailability, especially biopharmaceutical classification system (BCS) class II and IV drugs (Alqahtani et al. 2021). According to Chuang et al. (2018), LBDDS is composed of easily tolerated physiological lipids that are typically nontoxic and have safe degradation residuals.

Emulsomes (EMLs) are vesicular lipid-based drug delivery systems considered a modified generation of liposomes (Singh et al. 2013; Alhakamy et al. 2020). Recently, EMLs have been assumed to be chylomicron-mimicking nanocarriers of synthetic lipoprotein-based vehicles that make EMLs circumvent oral obstacles related to drugs with low solubility and low permeability through lymphatic targeting pathways (Rizk and Elsheikh 2021). Compared to liposomes, EMLs are more stable (Sawant et al. 2016), whereas liposomes' tendency to hydrolysis, oxidation, fusion, low drug content, short shelf-life, and sterilization issues limit their use (Akbarzadeh et al. 2013; Lowell et al. 1997). Furthermore, EMLs can overcome some limitations of SLNs, like low encapsulation of bioactive substances, gelation tendency, storage instability, and polymorphic transition (Shidhaye et al. 2008; Vimal Kumar Varma and Amareshwar 2011; Qian et al. 2013). SLNs have low circulation in the body because the reticuloendothelial system (RES) can easily recognize them before reaching

the target tissue (Geszke-Moritz and Moritz 2016). Particle size growth and aggregation also limit the utility of SLNs (Utreja et al. 2010). EMLs are novel, stable, and surfactant-free LBDDS alternatives (Bolat et al. 2020). EMLs have been reported for anti-microbial and anti-cancer in various routes of application: parenteral (silybin and zidovudine) (Vyas et al. 2006; Zhou and Chen 2015), ocular (Sparfloxacin) (Sawant et al. 2016), intraperitoneal (amphotericin B (AmB)) (Pal et al. 2012) and oral (methotrexate) (Paliwal et al. 2009a). Consequently, this review focuses on the ability of EMLs to efficiently deliver anti-microbial and anti-cancer agents to their site of action with minimum resistance and side effects. EMLs, as typical oil-in-water emulsions, have a hydrophobic core (consisting of solid fats rather than oils). Like liposomes, this core is encapsulated and stabilized by phospholipid bilayer coats (Lowell et al. 1997). The aqueous portion of their outer phospholipid membranes can encapsulate water-soluble pharmaceuticals, whereas sufficient amounts of lipophilic drugs fill their cores (Zhou and Chen 2015). Figure 1 displays the structure and composition of EMLs versus liposomes and SLNs (Bay et al. 2019; Guimar and Cavaco-paulo 2021).

Emulsomal structure and composition make them more bioavailable and more efficient in delivering poorly soluble drugs. Due to the high encapsulation of drugs in emulsomal formulations, a relatively slow sustained drug release profile was observed (70% after 24 h and almost 100% after 48 h), resolving toxicity issues with certain drugs, such as silybin, that favor localization in liver cells and rapid elimination problems that require frequent administration. (Zhou and Chen 2015).

Materials used in the fabrication of EMLs

Emulsomes are usually prepared using primary structural components. Solid lipids like monoglycerides or TG which form the core structure of EMLs, protect the entrapped drug from the gastric environment, provide high loading capacity of lipophilic drugs and prolong the release of drugs (Rizk and Elsheikh 2021; Sawant et al. 2016; Yilmaz et al. 2020; Islek et al. 2022). PC stabilize the core of EMLs, improve lymphatic transport and enhance the entrapment efficiency (Rizk and Elsheikh 2021; El-Zaafarany et al. 2016; Kamel et al. 2022). Secondary components could be added to enhance the physical characteristics and provide more stability to emulsomal structure. Steroids are incorporated to stabilize the outer

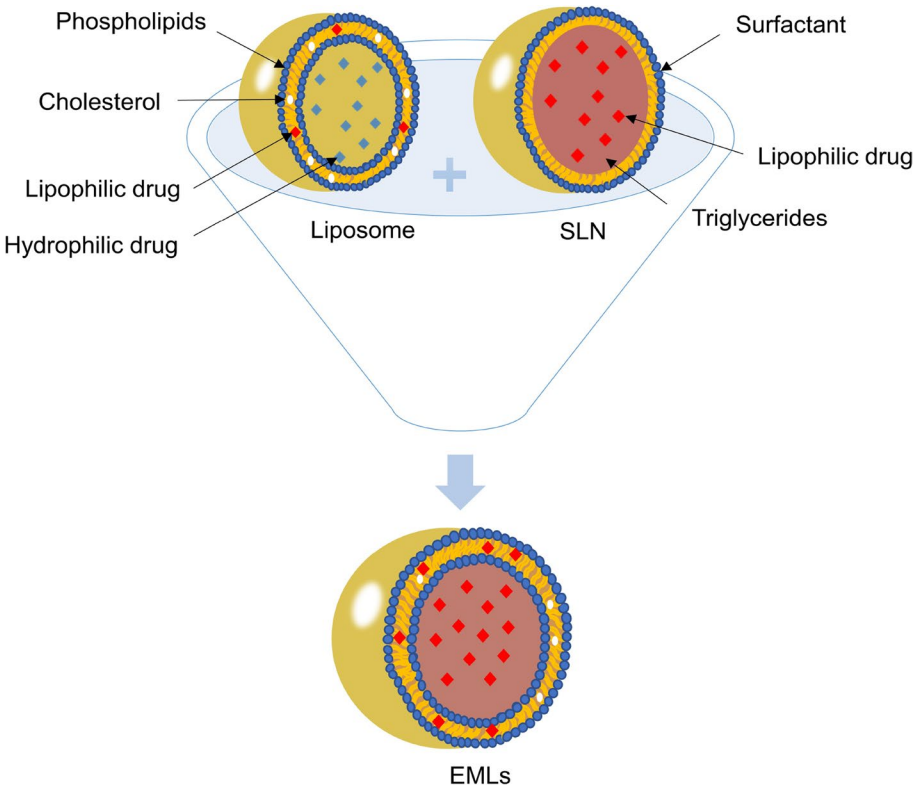


Fig. 1 Emulsomal matrix structure and composition compared to liposomes and SLNs. Schematic adapted from (Bay et al. 2019; Guimar and Cavaco-paulo 2021)

shell of the PC, increasing the entrapment and decreasing the drug's leakage (Rizk and Elsheikh 2021; Zhou and Chen 2015). Surfactants also can be added to minimize particle size of EMLs (Zakaria et al. 2022a). The stability of EMLs can be improved by adding charge inducer to emulsomal surface which increase zeta potential value, make repulsions between phospholipid bilayers, improve the mucoadhesive properties and prolong drug release (Varshosaz et al. 2019; Malviya 2021; Abo El-Enin et al. 2022). Antioxidants are added to prevent or delay lipid oxidation. Table 1 lists examples used as primary and secondary components.

Formulation techniques of EMLs

Methods for preparing EMLs are similar to liposomal techniques. The thin film hydration (TFH) method, lipid film formation method (hand-shaking), cast film method, high-pressure extrusion technique, reverse phase evaporation method, microfluidization, ethanol injection method, and detergent removal technique are considered the most common methods for preparing EMLs (Gill et al. 2012). Frequently used methods are TFH, ethanol injection, and high-pressure extrusion. Figure 2 demonstrates emulsomal fabrication techniques.

Thin film hydration method

The TFH method is a simple and commonly used method for preparing EMLs (Bolat et al. 2020). In a round-bottom flask (RBF), various molar ratios of solid lipids are dissolved in an organic solvent such as chloroform mixed with ethanol or methanol (in various ratios). The drug is added to the solution, and the organic solvents evaporate under high pressure leaving a thin film layer on the flask wall, which is then hydrated with the aqueous solution for a predetermined period at a predetermined temperature (Alhakamy et al. 2020; Sawant et al. 2016; Vyas et al. 2006; Bay et al. 2019; Zakaria et al. 2022a; Abo El-Enin et al. 2022). The hydrated solution is sonicated by a probe or water-bath sonicator to form nano-sized EMLs (Alhakamy et al. 2020; Vyas et al. 2006). For further size reduction, sonication can be followed by high-shear pressure homogenization; moreover, controlling the speed and time of homogenization are essential factors in producing an optimum formula (Rizk and Elsheikh 2021).

Ethanol injection method

In this method, lipids are dissolved in absolute ethanol, and then the solution is injected immediately into a magnetically stirred buffer solution (Sujitha and Muzib 2020). Drugs are added according to their

Table 1 Commonly used primary and secondary components for preparing EMLs

Structural components		Ref
Primary components	Triglycerides	Alhakamy et al. 2020; Vyas et al. 2006; El-Zaafarany et al. 2016; Zakaria et al. 2022a; Malviya 2021; Sahu and Kori 2022)
	Tristearin	Bolat et al. 2020; Pal et al. 2012; Yilmaz et al. 2020; El-Zaafarany et al. 2016; Abo El-Enin et al. 2022; Ucisik et al. 2015a; Fahmy et al. 2020; Awan et al. 2020; Alhakamy et al. 2021)
	Tripalmitin	Vyas et al. 2006; Zhou and Chen 2015; Abo El-Enin et al. 2022)
	Trilaurin	El-Zaafarany et al. 2016; Zakaria et al. 2022a; El-Zaafarany et al. 2018)
	Triolein	Paliwal et al. 2009a; El-Zaafarany et al. 2016; Zakaria et al. 2022a; Abo El-Enin et al. 2022; Chandrika and Babu 2014; Aldawsari et al. 2021)
	Hard fats	Sujitha and Muzib 2020)
	Compritol 888 ATO (CA)	Kamel et al. 2022; Kapadia et al. 2020)
	Stearic acid	Abo El-Enin et al. 2022; Rabaan et al. 2022)
	Glyceryl monostearate (GMS)	Bolat et al. 2020; Yilmaz et al. 2020; Kapadia et al. 2020)
	Phospholipids	Sawant et al. 2016)
	Soybean phosphatidylcholine (Soya PC)	Kamel et al. 2022)
	Dipalmitoyl phosphatidylcholine (DPPC)	Fahmy et al. 2020; Awan et al. 2020; Alhakamy et al. 2021)
	Phospholipon 90G (P90G)	Alhakamy et al. 2020)
	Phospholipon 80H (P80H)	
	Phospholipon 90H (P90H)	
	Lipoid S100	
Secondary components	Steroids	Zhou and Chen 2015; Fahmy et al. 2020; Sujitha and Muzib 2020; Kommana and Babu 2016; Gill and Nanda 2020)
	Cholesterol	Zhou and Chen 2015; El-Zaafarany et al. 2016; Abo El-Enin et al. 2022; El-Zaafarany et al. 2018; Chandrika and Babu 2014; Raza et al. 2013)
	Surfactants	Zakaria et al. 2022a)
	Tween 80	Ucisik et al. 2013a)
	Brij52 (polyoxyethylene (2) cetyl ether)	Kommana and Babu 2016)
	Hexa-decylamine	Malviya 2021; Gill and Nanda 2020)
	Sodium Deoxycholate	El-Zaafarany et al. 2016)
	Charge inducers	Abo El-Enin et al. 2022)
	Stearylamine	Kommana and Babu 2016)
	Chitosan	
	Trimethylchitosan (TMC)	
	Antioxidant	
	Butylated hydroxy toluene	

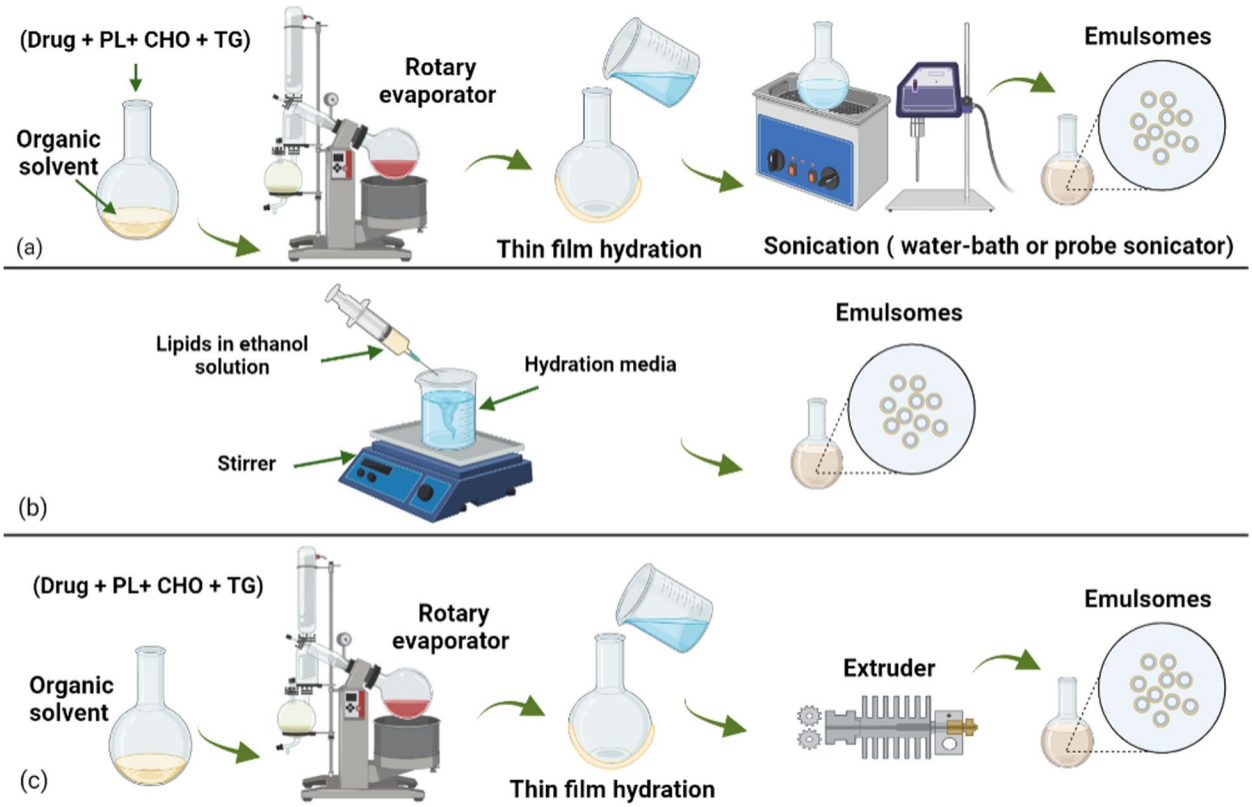


Fig. 2 Preparing EMLs by **a** TFH, **b** ethanol injection method, **c** high-pressure extrusion method

solubility in ethanol or buffer solution, and the appearance of the opalescence of colloidal dispersion indicates the formation of vesicles.

High-pressure extrusion method

Lipids dissolved in an organic solvent are then subjected to a rotary evaporator to eliminate the solvent, hydration of the formed thin film takes place, and the hydrated product is introduced to a high-pressure extrusion system once or more (Ucisik et al. 2013a). Table 2 depicts a comparison of emulsomal techniques.

Effect of formulation variables on EMLs characteristics

Effect of triglyceride type

The particle size of EMLs can vary depending on the type of TG used. Due to tristearin molecules' longer fatty acid chain, tristearin EMLs have larger particle sizes than trilaurin EMLs (Vyas et al. 2006). Similarly, the vesicle size increased in the sequence of tripalmitin < tristearin < Compritol (Kalepu et al. 2013). Contrarily, the use of triolein has been found to produce smaller particle size EMLs with lower polydispersity index than Compritol (El-Zaafarany et al. 2016). Possibly due to the shorter chain length of tripalmitin, Raloxifene

Table 2 Advantages and disadvantages of different emulsomal technique

Technique	Benefits	Shortages	Ref
Thin film hydration method	• Higher entrapment of drug due to its ability to form multilamellar vesicles	• Produce large vesicles	Varshosaz et al. 2019)
Ethanol injection method	• Easy and reproducible • Small particle size was obtained	• Ethanol removal is very difficult	Gouda et al. 2021)
High-pressure extrusion method	• Rapid • Reproducible • Variety of size range	• This technique is unsuitable for heat sensitive materials and large-scale preparations, so the process must be heat controlled	Ucisik et al. 2013a)

Hydrochloride-EMLs containing tripalmitin were significantly smaller than those containing tristearin and Compritol (Aldawsari et al. 2021). Compritol 888 ATO (glyceryl behenate) has also been found to be a promising carrier for the intestinal lymphatic system (Paliwal et al. 2009b). This finding could be attributed to the higher length of Compritol induced higher lipophilicity which could entrap higher amounts of lipophilic drugs into their core than other TG (Zakaria et al. 2022a). Additionally, Compritol is considered a lymphotropic agent and photo stabilizer for bioactive compounds (Rizk and Elsheikh 2021). By comparing the effect of different fatty acid chain lengths, it was found that Compritol (C22), tripalmitin (C16), tristearin (C18), and the unsaturated chain triolein (C18) all had varying effects on the entrapment at the same ratios of PC: TG. At a ratio of 0.5:1, the highest EE% was 23.9% obtained, with Compritol. The ratios 1:1 and 1:2 gave 88% and 91.04% with tripalmitin, while at 3:1 ratio, Compritol, tristearin, and tripalmitin produced the highest entrapment 96.8%, 93.1%, and 95.3% respectively (El-Zaafarany et al. 2016). This result can be attributed to the longer fatty acid chain length of Compritol (C22) and the imperfections in its crystalline lattice that create hollows, allowing for increased drug loading (Aldawsari et al. 2021).

Effect of triglyceride: phospholipid concentration ratio

Increasing the ratio of TG: PC leads to an increase in particle size and entrapment efficiency (Ucisik et al. 2015b). For example, in Etodolac EMLs, when the ratio of tristearin: phospholipid increased from 50 to 150%, the entrapment efficiency increased from 76.46 to 88.46% (Gill and Nanda 2020). Increasing the PC concentration forms multilamellar vesicles that can hold higher amounts of drug (Pal et al. 2012; Ucisik et al. 2015a). A maximum increase in entrapment efficiency reaching 78.1 ± 2.29% using PC: TG w/w 1:1 ratio instead of 0.6:1, and increasing PC concentration beyond 1.2:1 and 1.4:1 ratios led to a decline in entrapment efficiency of about 70.8 ± 1.67 and 64.5 ± 2.58%, respectively. This might be due to the formation of unstable particles with a high tendency for leakage (Zhou and Chen 2015; Pal et al. 2012).

Effect of pH of hydration media

The majority of studies used a 7.4 pH hydration medium during the preparation of EMLs. Increasing the pH of the hydration medium from 5 to 9 increased the entrapment efficiency of Fluvastatin (FLV) loaded EMLs. This increase is attributed to the increasing negative charge on the phospholipid polar head, allowing FLV to align on the phospholipid polar head (Alhakamy et al. 2021).

Effect of sonication time

Sonication time may affect the particle size of EMLs. The particle size of methotrexate-EMLs decreased from 352.7 ± 15.6 to 160.3 ± 10.2 nm when the sonication time was increased from 5 to 10 min (Paliwal et al. 2009b). A significant decrease in the particle size of Febuxostat-EMLs from 183.80 ± 3.11 nm to 90.70 ± 1.19 nm by increasing ultrasonication time from 1 to 5 min (Fahmy et al. 2020). Increasing sonication time from 3 to 9 min resulted in a significant decrease in the particle size of triamcinolone acetonide-EMLs (Kapadia et al. 2020). This reduction in particle size is believed to be due to the high amount of energy input during sonication (Fahmy et al. 2020; Paliwal et al. 2009b).

Effect of drug nature

Hydrophilic and amphiphilic drugs can be entrapped in phospholipid bilayers (Ucisik et al. 2015a). However, the lipophilic nature of Sparfloxacin, Etodolac, and Simvastatin made them particularly well-suited to be entrapped in the solid lipid core and phospholipid bilayers of EMLs, which allowed for a decrease in dosage and reduced cytotoxicity (Qian et al. 2013; Gill and Nanda 2020; Shringarpure et al. 2021).

Effect of surfactant

Emulsomes can contain small quantities of surfactants, such as tween 80 (Zhou and Chen 2015). Combining PC and tween 80 allowed for the emulsification of Compritol, resulting in the formation of smaller particles (Raza et al. 2013). Using tween 80 at 1% v/v enhanced bilayer formation and lipid loading capacity (Abo El-Enin et al. 2022). Brij52 (polyoxyethylene (2) cetyl ether) is a non-ionic surfactant incorporated in a concentration of (10: 30) mg. Increasing Brij concentration resulted in a significant decrease in particle size as it decreased the interfacial tension, a significant decrease in zeta potential due to shielding the surface charge, and a decrease in entrapment efficiency due to the highly porous bilayer vesicles, which increased drug leakage (Zakaria et al. 2022a).

Characterization technique of EMLs

In vitro characterization of EMLs determines the shape and morphology of vesicles, entrapment efficiency, and in vitro release. Table 3 summarizes all characterization techniques.

Shape and morphology of EMLs

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are optimal techniques for

Table 3 Therapeutic applications of EMLs in infectious diseases

S. No	Drug	Indication	Components	Method	PS	EE%	Animal or cell line model	Purpose of study	Outcomes	Ref
1	Sparfloxacin	Ophthalmic antibacterial	CA, P90G	TFH	217 ± 3.78 nm	72.83 ± 2.56%	Male albino rabbits Organism (S. aureus)	Determination of the biological activity of EMLs–gel system compared with pure drug solution against microorganisms	• Sustained drug release, formulation with non-irritant and promising antibacterial action both in vitro and in vivo • The infection disappeared within (4–5 days)	Sawant et al. 2016)
2	Silybin	Hepatitis and cirrhosis	Trilaurin, Soybean PC (> 94%). Chol, tween80	TFH	364.1 ± 20 nm	> 80%	Male Wistar rats	Comparing pharmacokinetic parameters between silybin-EMLs and pure drug solution	• Improved bioavailability, sustained release profile, increased mean residence time by 2.5-folds • Targeting the drug to liver increasing its rate and extent	Zhou and Chen 2015)
3	Zidovudine	Hepatitis	Tristearin, trilaurin, soya PC, Chol, stearylamine	TFH	130 ± 18 to 142 ± 22 nm	57.8 ± 6.2% (Tristearin) and 59.7 ± 6.1% (Trilaurin)	Albino rats	Comparing organ distribution of zidovudine-EMLs and free drug	• Reduced toxicity with liver targeting and prolonged action	Vyas et al. 2006)
4	Amphotericin B (AMB)	Visceral leishmaniasis	Soya PC, stearylamine, Chol, tripalmitin	TFH	plain EMLs (0.529 ± 0.016 µm) and coated EMLs (0.646 ± 0.015 µm)	Plain EMLs (78.1 ± 2.29) and coated EMLs (77.5 ± 2.95) %	Albino rats	Comparing organ distribution of amphotericin B-EMLs and free drug	• AMB-loaded OPM-EMLs showed (62.76 ± 3.54) % higher parasitic inhibition than the AMB-EMLs (42.68 ± 2.36) % and free AmB (25.87 ± 3.87) % • Higher drug EMLs concentration in macrophage-rich organs than plain AMB	Pal et al. 2012)

Table 3 (continued)

S. No	Drug	Indication	Components	Method	PS	EE%	Animal or cell line model	Purpose of study	Outcomes	Ref
5	Bifonazole	Anti-fungal for skin or mucosal mycoses	Lecithin, Tristearin, Chol, Stearylamine (Octadecyl amine)	TFH	390.394 nm	81.642%	-	Optimization of emulsomal formulation using Box-Behnken design	• The optimized formulation achieved higher EE%, ZP, and minimum PS	Malviya 2021)
6	Bisnapthalimidopr-opyl derivatives (BNIPDaoct and BNIPDanon)	Anti-leishmanial therapy	Tripalmitin ≥ 99%, DPPC, ~ 99%, Chol	TFH	363.1 ± 51.7 nm	-	Macrophages infected with Leishmania infantum parasites	Comparing the IC50 of drugs-EMLs and free drugs	• Drug-EMLs demonstrated higher cytotoxic activity by two folds	Islek et al. 2022)
7	Morin hydrate (MH)	Anti-MERS-CoV	PC (lecithin), triolein, Brij52 (polyoxyethylene (2) cetyl ether), CA	TFH	177.3 ± 18.9 nm	79.1 ± 2.2%	Vero E6 cells Respiratory tract of the infected mice	Determination of the anti-viral activity against MERS-CoV	• MH-EMLs increased permeation by four times more than free MH • Suppressed MERS-CoV-induced histopathological alterations in lung tissue • Reduce the levels of oxidative and inflammatory biomarkers	Zakaria et al. 2022a)
8	Resveratrol (RSV)	Anti-MERS-CoV	CA or tristearin, (DSPE-mPEG 2000), Chol	TFH	172.1 ± 19.5 nm	75.8 ± 3.7%	Vero E6 cells Respiratory tract of the infected mice	Determination of the anti-viral activity against MERS-CoV	• Suppress the inflammatory response and oxidative stress resulting from MERS-CoV 26 times more than RSV dispersion	Zakaria et al. 2022b)

examining the morphological structure of EMLs on a nanoscale. For TEM analysis, the emulsomal formulation was diluted with deionized water and added to the copper grid until dried for examination (Rizk and Elsheikh 2021). TEM images demonstrated the spherical shape of EMLs (Zhou and Chen 2015). All vesicles were mono-dispersed, and no signs of aggregated vesicles were observed (Gill and Nanda 2020). Multilamellar EMLs can be observed under TEM examination (Awan et al. 2020). These multilayers of phospholipids distinguish EMLs from SLNs (Paliwal et al. 2009b). The SEM images revealed that almost every particle in the formulation has the same rough, spherical surface morphology, offering homology in its characteristic structure, where phospholipid bilayers stabilize the outer surface (Bolat et al. 2020). SEM images show that EMLs have surface features similar to liposomes (Yilmaz et al. 2020).

Particle size and zeta potential

Particle size and zeta potential are good indicators of emulsomal stability. Sonication or high-pressure homogenization can be used to maintain size reduction and homogenization after hydration. Homogenization lasting longer than 10 min results in larger particles due to the increased energy procured (Rizk and Elsheikh 2021). The particle size of EMLs could be in a range of 10:250 nm, allowing for intravenous administration (Kommana and Babu 2016). Nano-sized emulsomal formulations are promising candidates for tumor targeting (Aldawsari et al. 2021). Formulations containing ß-sitosterol observed smaller particle sizes due to increasing the phospholipid bilayer's hydrophilic nature with decreasing the interfacial tension (Kamel et al. 2022). Zeta potential has a significant effect on cellular drug uptake, as cationic charge enhances drug internalization through cells more than negative or neutral-charged vesicles (Bolat et al. 2020). The distribution of negatively charged phospholipids in the outer layer influences the electronegativity charges of the vesicles (El-Zaafarany et al. 2016; Aldawsari et al. 2021). Due to the negative charge of phospholipids, a rise in the ratio of PC to TG increased the zeta value. In contrast, the TG type had no effect on the zeta potential value (Aldawsari et al. 2021).

Entrapment efficiency

The entrapped drug is determined by analyzing the drug content in EMLs compared to the total amount added (Alhakamy et al. 2020). A definite amount of emulsomal formulation was taken in the Eppendorf tube, centrifuged to separate the unentrapped drug, and measured by a UV spectrophotometer (Paliwal et al. 2009b), or HPLC (Awan et al. 2020). The following equation can be used to illustrate entrapment efficiency (Varshosaz et al. 2019).

$$\begin{aligned} EE\% &= (\text{Total drug} - \text{Free drug}) \\ &\quad / (\text{Total drug added to emulsomal formulation}) \\ &\quad \times 100 \end{aligned}$$

In vitro release study

In vitro release study is a critical indicator for in vivo efficacy. The study was performed using the dialysis method (Sawant et al. 2016). A specific amount of formulation in the dialysis bag was retained in a thermostable shaker at physiological temperature and suitable rpm, and then, samples were collected at different time intervals to be analyzed for drug content using the validated method (Sawant et al. 2016; Awan et al. 2020). Drugs spread from EMLs and across the phospholipid bilayer membrane barrier as lipophilic components must diffuse from the lipidic core before the release, and the phospholipid bilayer may slow down this process, resulting in sustained release (Zhou and Chen 2015). Most formulations have slow drug release due to the high entrapment of lipophilic drugs (Aldawsari et al. 2021).

Stability

Emulsomes as vesicular lipid-based nanoparticles demonstrated higher stability compared with conferential liposomes or other lipid-based systems. Problems such as oxidation, hydrolysis, or aggregation can be avoided by loading drugs into EMLs (Sawant et al. 2016). Stability studies provide data about storage-related issues, such as studies that consider the efficacy of emulsomal formulation for a certain period of time, entrapment efficiency, particle size, and possibility of aggregation. Additionally, they do not necessitate the incorporation of surfactants or cosolvents (El-Zaafarany et al. 2016). Emulsomal structure and components impose their stability. TG such as Compritol, could protect dithranol from photodegradation, enhancing drug stability (Raza et al. 2013). Moreover, Compritol provides a cationic charge around the emulsomal surface, inducing repulsion forces between particles and preventing their aggregation (Abo El-Enin et al. 2022), whereas the phospholipid bilayer stabilizes the outer layer of EMLs (Kamel et al. 2022). Tripalmitin demonstrated a higher melting point, biocompatibility and physicochemical stability (Ucisik et al. 2013b). In emulsomal formulations, characteristic parameters such as entrapment efficiency, zeta potential, and particle size showed no significant change. Curcumin-loaded EMLs could withstand stability for 11 months at refrigerated conditions (4 °C) without any significant change in particle size, charge, or polydispersity index (PDI) (Yilmaz

et al. 2020). The change in pH could affect the stability of EMLs. Methotrexate-loaded EMLs exhibited a significant increase in particle size by decreasing pH to 1.2, affecting the stability of EMLs, such increase could be due to aggregation of the formation (Paliwal et al. 2009a).

Surface engineering and targeting strategies of EMLs

Surface modification of nanoparticles is a crucial technique for the development of biocompatible EMLs with specific properties. Due to the presence of phospholipid layers on the surfaces of both EMLs and liposomes, all surface modifications that are possible for liposomes may also be possible for EMLs (Ucisik et al. 2013b). By coating their surface with the macrophage-specific ligand O-palmitoyl mannan (OPM), emulsomal modification renders them macrophage-targeting. OPM-coated EMLs could target AmB to lung tissues in pulmonary fungal infections and other infectious diseases of the respiratory tract (Vyas et al. 2006; Gupta and Kumar 2012). Moreover, OPM-coated tripalmitin EMLs were more effective at inhibiting parasitic infection in the spleen, indicating that mannose receptors are expressed on the membranes of the liver and splenic macrophages, resulting in ligand-receptor interaction (Pal et al. 2012). The crystalline bacterial cell surface layer (S-layer) fusion protein forms a homogeneous monomolecular lattice on the emulsomal surface (Ucisik et al. 2013b). S-layer altered the surface properties of the lipidic nanocarrier and conferred IgG functional adhesion on its surface, exhibiting antibody targeting (Ucisik et al. 2015a), whereas S-layer EMLs have more biocompatibility, less toxicity, and oxidative stress protection than bare EMLs (Ucisik et al. 2015a; Gerrard and Editors 2020). Sorafenib characterized by low bioavailability, poor solubility, rapid metabolism, and liver cancer resistance. PEGylated trimethyl chitosan (TMC)-EMLs conjugated with octreotide targeting sorafenib to hepatocellular carcinoma could reduce free sorafenib IC50 of HepG2 cells more than non-targeted EMLs (Varshosaz et al. 2019). Furthermore, this conjugation enhanced drug release in pH-acidic lysosomal media increased the permeability to tumor cells, and imparted a positive charge to EMLs, which improves vesicle stability (Varshosaz et al. 2019). A thermosensitive tri-copolymer (PLGA-PEG-PLGA) is commonly used in nanoparticles due to its biocompatibility, biodegradability, and nontoxic properties; moreover, it offers a more efficient and controlled release (Rahmani et al. 2023). The tri-copolymer was added to EMLs to form thermosensitive gels exhibiting a higher residence time in the nasal cavity and extending the action of the drug in the brain (El-Zaafarany et al. 2018). Stearylamine as a solid lipid charge inducer was added to the system to give it a cationic charge, protect EMLs from lysosomal degradation, provide intracellular localization with a gradual slow release of zidovudine from its lipidic core, and potentially prevent multidrug resistance (Vyas et al. 2006). It is an electrostatic stabilizer that maintains the optimal emulsomal zeta potential. Increasing the stearylamine percentage increases the zeta potential value, making repulsion between phospholipid bilayers, causing an increase in particle size and a subsequent increase in the capturing volume of the entrapped drug (Vyas et al. 2006; Malviya 2021; Pardeshi et al. 2013). Chitosan and its derivatives are polymers offering a positive charge that can impart mucoadhesive properties. In addition, low molecular weight Chitosan prevents particle size growth (El-Zaafarany et al. 2016). Chitosan-coated EMLs regulated the release of Eletriptan Hydrobromide, reduced toxicity, and increased therapeutic efficacy (Abo El-Enin et al. 2022). 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000] (DSPE-mPEG 2000) is used as a coat forming material which induces a higher electronegativity to emulsomal surface providing greater stability to the system than the uncoated (Zakaria et al. 2022b). All surface modifications that have been developed are illustrated in Fig. 3.

Lymphatic targeting ability of emulsomal formulations

The lymphatic pathway is essential for the delivery of drugs with decreased bioavailability, and it can circumvent first-pass metabolism by serving as a bypass route for those undergoing extensive hepatic metabolism (Khan et al. 2013). In addition to enhancing bioavailability, lymphatic delivery contributes to targeting drugs to lymphatic organs. Lipid-based nanoparticles are considered one of the most promising methods to enhance drug permeability, solubility, and bioavailability through the lymphatic system. Lymphatic drug transport depends on many factors, the most important of which are the size of nanoparticles (10:100 nm), triglyceride solubility > 50 mg/ml, log $p > 5$, surface charge (negative > positive > neutral), and lipid type (long-chain fatty acid has the highest lymphatic uptake) (Khan et al. 2013; Vishwakarma et al. 2019). The similarity in behavior is due to the structural resemblance between EMLs and endogenous chylomicrons. Methotrexate-EMLs showed higher fold drug uptake in the lymphatic region than the free drug (Paliwal et al. 2009a). A 33% decrease in baicalin absorption by the chylomicron flow blockage assay confirmed that baicalin-EMLs have potential lymphatic targeting properties (Rizk and Elsheikh 2021).

Recent applications of EMLs in infectious and cancerous diseases

The widespread use of EMLs in medical applications can be attributed to their ease of fabrication and versatility. Since EMLs are considered LBDDS, which have

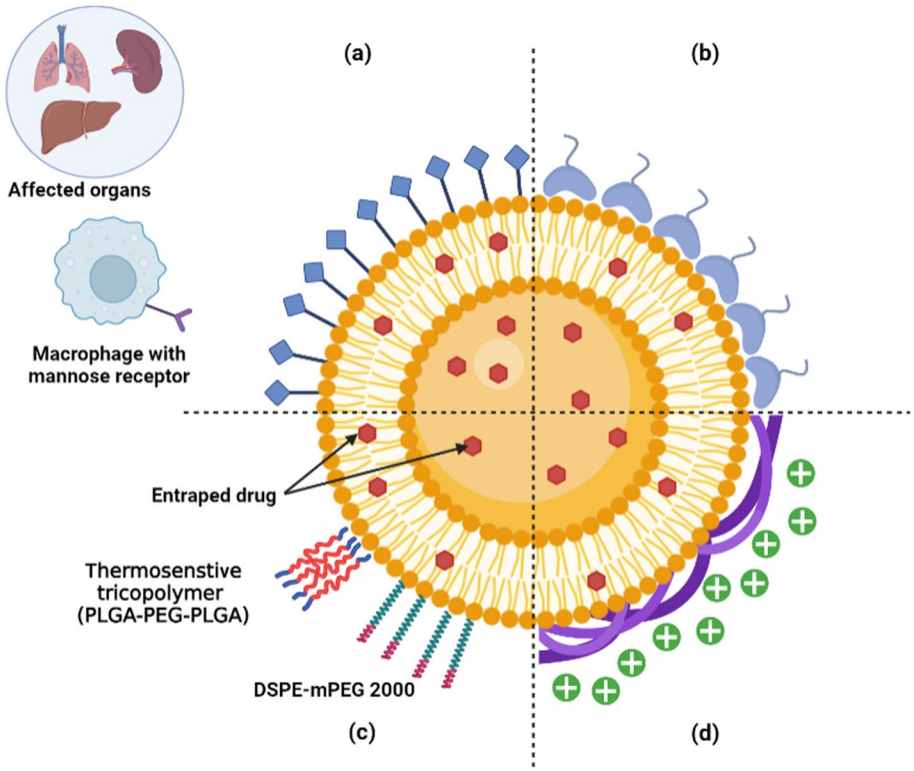


Fig. 3 Different surface modification of EMLs. **a** EMLs coated with O-Palmitoyl manne (OPM), **b** S-layer coated-EMLs, **c** EMLs coated polymers, **d** Chitosan coated-EMLs. Created with BioRender.com

properties close to natural biological components, they can interact easily with cells and tissues, are non-toxic and biodegradable and can be administrated orally (Pinilla et al. 2021). Due to these characteristics, they are highly desirable for anti-microbial delivery. In contrast to the anti-leishmaniasis drugs loaded into polymeric nanoparticles, which were less able to interact with macrophages, EMLs of lipidic based origin were able to easily penetrate the macrophages and accumulate inside the RES in a way that exceeded the polymeric nanoparticles (Islek et al. 2022). Moreover, Sparfloxacin as anti-bacterial agent suffers from poor solubility, short residence time, drug drainage, multiple administration, and poor corneal permeability (Gupta et al. 2010). Loading Sparfloxacin into EMLs in situ gel provided slower diffusion of drug from solid core and prolonged its release with higher corneal permeation (Sawant et al. 2016). They have also been extensively studied in cancer therapy, both in vitro and in vivo, with promising outcomes in clinical trials (Garc et al. 2019). Tables 3 and 4 summarize all anti-infectious and anti-cancer chemotherapy loaded into EMLs with their characterizations and benefits.

Potential of EMLs in loading anti-microbial and anti-cancer phytomedicinal compounds

Phytomedicines have proven to have many therapeutic utilities in various diseases, especially infectious diseases and cancers, due to the diversity of their structures. However, herbal compounds are characterized by their insolubility, low absorption, and toxicity in large quantities, resulting in low bioavailability and activity (Kaplan 2022). Loading phytomedicines into EMLs showed efficacy in the treatment of microbial and cancerous diseases and may be a promising alternative to traditional therapies.

Phyto-emulsomal potential in microbial diseases

Morin hydrate (MH) is a bioflavonoid that exhibits anti-bacterial and anti-viral activities (Rajput et al. 2021). The low solubility and bioavailability of MH rendered its pharmacological use (Karamchedu et al. 2020). Plaque assay for infected lung demonstrated 51% and 82% viral inhibition for MH-loaded EMLs, while 27.1% and 44.8% inhibition for MH suspension after 3 and 6 days, respectively (Zakaria et al. 2022a). Moreover, MH-EMLs significantly suppressed protein expression of MERS-CoV

Table 4 Therapeutic applications of EMLs in cancer

S. No	Drug	Indication	Components	Method	PS	EE%	Animal or cell line model	Purpose of study	Outcomes	Ref
1	Piceatannol (PIC)	Colorectal cancer	Chol, tristearin, Lipoid ®S100 (hydrogenated soybean lecithin),	TFH	125.45 nm	93.14%	Colorectal cancer cells HCT 116	Development of EMLs and assessment of anti-tumor activity	• PIC-EMLs exhibited higher cell death against colon cancer cells than the raw PIC • PIC-EMLs decreased the IC50 by one-half than raw PIC	Alhakamy et al. 2020)
2	Baicalin	Lymphoma	CA, Lipoid S100 (l-α-PC), Chol	TFH	240.1 ± 1.07 nm	98.44 ± 0.06%	Male Sprague–Dawley rats	Lymphatic targeting ability of EMLs by chylomicron flow blockage assay	• Improved the bioavailability twofold compared with free drug	Rizk and Elsheikh 2021)
3	Methotrexate	Intestine lymphatic carcinoma	Soya lecithin, CA	TFH	160.3 ± 10.2 nm	72.8 ± 6.5%	Albino rats	Comparing pharmacokinetic parameters between plain and emulsomal methotrexate	• Relative bioavailability is enhanced by 5.7 times than free drug, with better absorption and longer residence duration in lymphatics	Paliwal et al. 2009a)
4	Sorafenib	Hepatocellular carcinoma	Lecithin, GMS	TFH	127 nm	95%	Hepatocellular carcinoma cells of HepG2	Cell cycle analysis comparing sorafenib-targeting EMLs, non-targeting EMLs, and free sorafenib	• Octreotide-PEGylated TMC-EMLs reduced the IC50 of free sorafenib from 6.265 µg/ml to 0.256 µg/ml on HepG2 cells	Varshosaz et al. 2019)
5	Raloxifene HCl (RLX)	Breast cancer	Chol, Tripalmitin, Tristearin,), CA, PC (Lipoid 90H)	TFH	97.2 ± 1.8 to 247.1 ± 9.8 nm	98.9 ± 4.9%	Human breast cancer (MCF-7) cells	Development of EMLs and assessment of anti-tumor activity	• Controlled release profile, enhanced anti-proliferative and apoptotic activity against cancer cells more than free RLX	Aldawsari et al. 2021)

Table 4 (continued)

S. No	Drug	Indication	Components	Method	PS	EE%	Animal or cell line model	Purpose of study	Outcomes	Ref
6	Febuxostat (FBX)	Colon cancer	PC (P90H), Chol, Tripalmitin	TFH	79.97 ± 0.98 to 200.17 ± 3.98 nm	-	Human colorectal carcinoma (HCT 116) cells	Development of EMLs and assessment of anti-tumor activity	• Enhanced all parameters related to the toxic potential of the FBX towards colon cancer	Fahmy et al. 2020)
7	Fluvastatin	Prostate cancer	PC (P90H), Chol, Tripalmitin	TFH	85.12 nm	93.74%	PC3 prostate cancer cells	Development of EMLs and assessment of anti-tumor activity	• Compared to the free drug, significant anti-proliferative activity was explained by cell cycle arrest action	Alhakamy et al. 2021)
8	Simvastatin	Breast cancer	PC (P90H), Chol, Tripalmitin	TFH	112.42 ± 2.1 nm	94.34 ± 1.11%	MCF-7 breast cancer cells	Assessment of cytotoxic activities of simvastatin	• Slow drug release with significant cell death-inducing activity against MCF-7 cancer cells compared to pure SMV	Awan et al. 2020)
9	Curcumin	Hepatocellular carcinoma	Tripalmitin, Chol, DPPC	High-pressure extrusion	286 nm	-	HepG2 human liver carcinoma cell line	Assessment of cell viability, apoptosis, and cell cycle	• Prolongation of biological activity and demonstrated therapeutic efficacy compared to free curcumin against HepG2 in vitro	Ucisik et al. 2013a)
10		Human cancers	Tripalmitin, DPPC human IgG-Reagent Grade, anti-human IgG chain, Chol	High-pressure extrusion	291 ± 48 nm	-	-	Confirming selective targeting of tumor cells	• Exhibited a selective binding affinity for IgG which serves as a potential target in cancer therapy	Ucisik et al. 2015b)

Table 4 (continued)

S. No	Drug	Indication	Components	Method	PS	EE%	Animal or cell line model	Purpose of study	Outcomes	Ref
11	Curcumin and Piperine	Colorectal Cancer	Tripalmitin, DPPC, Chol	TFH	184.21 and 248.76 nm, respectively	4.4 and 3.6%, respectively	HCT116 Colorectal Cancer	Anti-tumor activity assessment	• Combination of 7 μM Piperine EMLs and 25 μM Curcumin EMLs • Effectively inhibited cell proliferation • Achieved a fourfold increase in Caspase 3 level, with a sixfold increase in the level of apoptotic marker	Bolat et al. 2020)
12	Andrographolide	Non-Hodgkin's lymphoma	PC (Lipoid® S100), Chol, CA	TFH	281.62 ± 1.73 nm	96.55% ± 0.25%	Sprague–Dawley male rats	Pharmacokinetics and Lymphatic Targeting Assessments	• Targeted delivery to the lymphatic system at a lower dose with fewer side effects • More than a sixfold increase in the rate and extent of absorption than the free drug	Elsheikh et al. 2021)
13	Morin hydrate	Leukemia	PC (P80H), GMS	TFH	271.7 ± 4.86 nm	79.95 ± 0.63%	Adult male Wistar rats Acute monocytic leukemia (AML) cell line (Kasumi-1)	Pharmacokinetics and anti-tumor activity assessments	• A significant increase in all pharmacokinetic parameters compared to the free drug suspension • A significant decrease in cancer cell viability in MH-EMLs compared to the unmedicated one	Kamel et al. 2022)

infection and bronchial alveolar lavage fluid levels than free MH (Zakaria et al. 2022a).

Resveratrol (RSV) is a natural polyphenolic compound having different anti-microbial properties (Abedini et al. 2021). Unfortunately, resveratrol's medicinal applications are limited due to its low bioavailability, which can be improved using nanocarriers (Talita et al. 2021). Plaque assay revealed 57.6% and 82% viral inhibition for resveratrol-loaded EMLs, and 30.5% and 45.6% inhibition for resveratrol suspension after 3 and 6 days, respectively (Zakaria et al. 2022b). Moreover, resveratrol-EMLs significantly suppressed bronchial alveolar lavage fluid levels more than free resveratrol.

Phyto-emulsomal potential in cancers

Piceatannol (PIC) is a polyphenolic stilbene present in many herbal plants (Regulation 2020). Polyphenolic compounds have poor solubility, and reduced bioavailability. PIC exerts anti-cancer and anti-inflammatory activities suggesting a superior cell death activity against HCT 116 colon cancer cells (Alhakamy et al. 2020).

Andrographolide (AG) is extracted from a natural herb. Despite the fact that AG is effective against numerous cancer cell lines, its poor solubility and low bioavailability limit its biological applications (Li et al. 2022). EMLs as a lipoprotein stimulating system showed a significant enhancement in drug rate and extent of absorption by 6-folds more than free AG (Elsheikh et al. 2021).

Curcumin is a natural compound found in turmeric plants with good anti-cancer activity against different cell lines (Dinesh Kumar Agrawal and Pushpesh Kumar Mishra 2009). Curcumin's applications have been reduced due to its low solubility, poor stability, and rapid metabolism (Yavarpour-Bali et al. 2019). The solubility of curcumin-loaded EMLs significantly increased by 2700 times. Moreover, the S-layer fusion to curcumin's surface enhanced the binding affinity of IgG secreted by human cancer cells (Ucisik et al. 2015b). Curcumin loaded-EMLs exhibited a significant in vitro prolonged activity and therapeutic efficacy against HepG2 human liver cancer cell line as measured by cell viability, apoptosis, and cell cycle studies (Ucisik et al. 2013a). The prolonged release of curcumin from EMLs is suggested to be due to the solid nature of the nanocarrier (Ucisik et al. 2013a). In cancer therapy, drug combinations have become popular due to the fact that different mechanisms are used to administer treatment. The EMLs containing curcumin and piperine is one of these combinations (Bolat et al. 2020). This combination added a lot to cancer treatment leading to a sixfold increase in apoptotic markers in colorectal cancer HCT116 cells (Bolat et al. 2020).

Baicalin is a bioactive flavone with a wide range of applications in nutraceuticals and pharmaceuticals, and it has demonstrated significant potential for treating and preventing cancer without significant side effects (Gaoa et al. 2016). Baicalein has been found to inhibit various types of cancer by binding to multiple molecular targets (Chen and Huang 2016). Baicalin-loaded EMLs showed a significant lymphatic targeting activity than the free drug, promising lymphoma treatment (Rizk and Elsheikh 2021).

Morin hydrate-loaded EMLs can be viewed as a potential delivery method for oral administration of MH, as they induce significant improvement to the solubility, bioavailability when taken orally, and the drug efficacy against tumors (Kamel et al. 2022). MH-EML treatment significantly decreased in the survival rate of cancer cells when compared to a drug suspension and the untreated cells at different concentrations of up to 300 μg/ml (Kamel et al. 2022).

Hesperidin and silybin-loaded EMLs showed enhanced pharmacokinetic behavior compared to the free drug (Zhou and Chen 2015; Sujitha and Muzib 2020). Hesperidin and silybin have phytomedicinal activity against many diseases and expected to be boosted when loaded into EMLs.

Future clinical potential of emulsomes for anti-microbial and anti-cancer drugs

The emulsomal system is one of the LBDDS, making its permeability through the skin high and expecting emulsomal advances in other skin diseases. This system will provide a promising solution for class II and IV drug solubility issues within 5 to 10 years. It is challenging to load hydrophilic drugs into nanoparticles, but we predict that they can be conjugated with fatty acids and loaded into emulsomal nanoparticles for further encapsulation. Due to the emulsomal tight configuration, EMLs offer more stability than liposomes or other lipid-based carriers with adequate drug-loading capacity. Bio-response modifiers can also be used to achieve effective macrophage activation, which has a powerful synergistic effect on opportunistic infections and multidrug resistance diseases. EMLs demonstrated advancements in the treatment of numerous diseases and will soon cover our regulatory market.

Conclusions

Emulsomes are considered a linkage between liposomes and SLNs features, where they can encapsulate both lipid and water-soluble drugs. Using biocompatible, environmentally friendly constituents and preparation methods are the significant benefits of EMLs. Due to the decreased particle size and increased drug entrapment, the formulated EMLs are nano-sized with high drug entrapment of

more than 80% and have a spheroidal shape with progressive and complete in vitro release. Due to the high encapsulation in the lipid core and sustained release properties, in vivo studies revealed an improvement in bioavailability. Further research on EMLs is required to develop novel and promising therapeutic methods for a wide variety of diseases. The structural similarity between EMLs and chylomicrons demonstrates a promising method for oral lymphatic targeting to enhance oral bioavailability. In recent years, EMLs have piqued the interest of scientists because they cover numerous important therapeutic areas. They can improve the bioavailability and solubility of anti-microbial agents (anti-bacterial, anti-viral, anti-protozoal, and anti-fungal) and anti-cancer drugs. The primary goals of such systems are to allow more selectivity, targeting, or controlled drug release, resulting in greater therapeutic efficacy with reduced drug dosage and frequency, fewer side effects, and optimal patient compliance.

Being a lipidic system, it achieved more excellent absorption of poorly soluble medications by distinct mechanisms such as prolonged stomach retention, increased solubilization, promotion of gastrointestinal lymphatic transport, and impact on the biochemical and physical barrier of the gastrointestinal tract. Nevertheless, several investigations have demonstrated that they are suitable for delivering hydrophilic moieties.

Emulsomes offer more stability than liposomes or other lipid-based carriers with adequate drug-loading capacity. Emulsomal tight configuration ensures core stabilization and implies that drug leakage is unlikely. Furthermore, the rise in PC content associated with higher PC: TG ratios may create PC multilayers around the lipid core, allowing for additional drug encapsulation through these layers. EMLs mediated synergistic effects on the route and mechanism of either paracellular or transcellular with higher concentrations than the plain drug solution.

In the process of creating anti-microbial EMLs, in vivo and in vitro tests were significantly improved. Conversely, EMLs as pharmaceutical drug carriers, have successfully demonstrated clinical applications in most cancer cases with the ability to improve the cytotoxic and apoptotic potency of drugs on cancer cells, reducing side effects and safety problems.

In addition, targeting the blood–brain barrier (BBB) is very restricted as it prohibits the passage of hydrophilic, charged, or large molecules. EMLs can efficiently incorporate drugs into the BBB through the intranasal route, allowing for treating brain diseases and managing epileptic disorders. Additionally, emulsomal formulations demonstrate a significant lack of multidrug resistance. EMLs will be commercialized immediately since the preparation process is straightforward and inexpensive.

Acknowledgements
Not applicable.

Authors' contributions
Mohamed Y. Zakaria designed the theoretical framework; Rana E. Elnady contributed in drafting the work, results interpretation and collection, graphical illustrations and writing, Mohamed Y. Zakaria and Maha M. Amin were responsible for the revision of the intellectual content and the final approval of the manuscript, conceptualization (review and editing), supervision, validation, international publishing process. All authors read and approved the final manuscript.

Funding
The authors declare that no specific funding, grants, or sponsorship was provided by any financial institution in the public, commercial, or not-for-profit sectors for this research.

Availability of data and materials
Not applicable.

Declarations

Competing interests
The authors declare that they have no conflicts of interest.

Author details
[1]Department of Pharmaceutics and Industrial Pharmacy, Sinai University, Arish 45511, Egypt. [2]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt. [3]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Port Said University, Port Said 42526, Egypt. [4]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, King Salman International University, Ras Sudr 46612, South Sinai, Egypt.

Received: 23 February 2023 Accepted: 22 May 2023
Published online: 03 July 2023

References

Abedini E, Khodadadi E, Zeinalzadeh E, Moaddab SR, Asgharzadeh M, Mehramouz B, Dao S, Kafil HS (2021) A comprehensive study on the antimicrobial properties of resveratrol as an alternative therapy. Hindawi 2021:15

Abo El-Enin HA, Mostafa RE, Ahmed MF, Naguib IA, Abdelgawad MA, Ghoneim MM, Abdou EM (2022) Assessment of nasal-brain-targeting efficiency of new developed mucoadhesive emulsomes encapsulating an anti-migraine drug for effective treatment of one of the major psychiatric disorders symptoms. Pharmaceutics 14:410

Akbarzadeh A, Rezaei-sadabady R, Davaran S, Joo SW, Zarghami N (2013) Liposome : classification, prepNew aspects of liposomesaration, and applications. Nanoscale Res Lett 8:1–9

Aldawsari HM, Ahmed OAA, Alhakamy NA, Neamatallah T, Fahmy UA, Badr-Eldin SM (2021) Lipidic nano-sized emulsomes potentiates the cytotoxic and apoptotic effects of raloxifene hydrochloride in mcf-7 human breast cancer cells: factorial analysis and in vitro anti-tumor activity assessment. Pharmaceutics 13:783

Alhakamy NA, Badr-Eldin SM, Ahmed OAA et al (2020) Piceatannol-loaded emulsomes exhibit enhanced cytostatic and apoptotic activities in colon cancer cells. Antioxidants 9:419

Alhakamy NA, Badr-Eldin SM, Aldawsari HM et al (2021) Fluvastatin-loaded emulsomes exhibit improved cytotoxic and apoptosis in prostate cancer cells. AAPS PharmSciTech 22:177

Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ (2021) Advances in oral drug delivery. Front Pharmacol. https://doi.org/10.3389/fphar.2021.618411

Awan ZA, Fahmy UA, Badr-eldin SM et al (2020) The enhanced cytotoxic and pro-apoptotic effects of optimized simvastatin-loaded emulsomes on MCF-7 breast cancer cells. Pharmaceutics 12:597

Bay L, Alkorta I, Arana L (2019) Application of solid lipid nanoparticles to improve the efficiency of anticancer drugs. Nanomaterials 9:474

Bolat ZB, Islek Z, Demir BN, Yilmaz EN, Sahin F, Ucisik MH (2020) Curcumin- and piperine-loaded emulsomes as combinational treatment approach enhance the anticancer activity of curcumin on HCT116 colorectal cancer model. Front Bioeng Biotechnol 8:1–21
Chandrika MV, Babu MK (2014) Design and development of Candesartan cilexetil emulsomal drug delivery systems for the effective management of cardiovascular diseases. Indian J Res Pharm Biotechnol 5674:1283–1287
Chen A, Huang H (2016) The fascinating effects of baicalein on cancer : a review. Int J Mol Sci 17:1–18
Chuang SY, Lin CH, Huang TH, Fang JY (2018) Lipid-based nanoparticles as a potential delivery approach in the treatment of rheumatoid arthritis. Nanomaterials 8:1–16
Dinesh Kumar Agrawal and Pushpesh Kumar Mishra (2009) Curcumin and its analogues: potential anticancer agents. Med Res Rev 30:818–860
Elsheikh MA, Rizk SA, Elnaggar YSR, Abdallah OY (2021) Nanoemulsomes for enhanced oral bioavailability of the anticancer phytochemical andrographolide: characterization and pharmacokinetics. AAPS PharmSciTech 22:246
El-Zaafarany GM, Soliman ME, Mansour S, Awad GAS (2016) Identifying lipidic emulsomes for improved oxcarbazepine brain targeting: in vitro and rat in vivo studies. Int J Pharm 503:127–140
El-Zaafarany GM, Soliman ME, Mansour S, Cespi M, Palmieri GF, Illum L, Casettari L, Awad GAS (2018) A tailored thermosensitive PLGA-PEG-PLGA/emulsomes composite for enhanced oxcarbazepine brain delivery via the nasal route. Pharmaceutics 10:217
Fahmy UA, Aldawsari HM, Badr-Eldin SM, Ahmed OAA, Alhakamy NA, Alsulimani HH, Caraci F, Caruso G (2020) The encapsulation of febuxostat into emulsomes strongly enhances the cytotoxic potential of the drug on HCT 116 colon cancer cells. Pharmaceutics 12:956
Gaoa Y, Snydera SA, Smitha JN, Chen YC (2016) Anticancer properties of baicalein: a review. Med Chem Res 25:1515–1523
Garc B, Porras-alcal C, Ortega-rodr A (2019) Lipid-based nanoparticles : application and recent advances in cancer treatment. Nanomaterials 9:638
Gerrard JA, Editors LJD (2020) Protein nanotechnology, 3rd edn. https://doi.org/10.1007/978-1-4939-9869-2
Geszke-Moritz M, Moritz M (2016) Solid lipid nanoparticles as attractive drug vehicles: composition, properties and therapeutic strategies. Mater Sci Eng C 68:982–994
Gill V, Nanda A (2020) Preparation and characterization of etodolac bearing emulsomes. Int J Appl Pharm 12:166–172
Gill B, Singh J, Sharma V, Hari Kumar S (2012) Emulsomes: an emerging vesicular drug delivery system. Asian J Pharm 6:87–94
Gouda A, Sakr OS, Nasr M, Sammour O (2021) Ethanol injection technique for liposomes formulation: an insight into development, influencing factors, challenges and applications. J Drug Deliv Sci Technol 61:102174
Guimar D, Cavaco-paulo A (2021) Design of liposomes as drug delivery system for therapeutic applications. Int J Pharm 601:120571
Gupta S, Kumar P (2012) Drug delivery using nanocarriers : Indian perspective. Proc Natl Acad Sci India Sect B Biol Sci 82:167–206
Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G (2010) Sparfloxacin-loaded PLGA nanoparticles for sustained ocular drug delivery. Nanomedicine 6:324–333
Hu CJ, Zhang L (2009) Therapeutic nanoparticles to combat cancer drug resistance therapeutic nanoparticles to combat cancer drug resistance. Curr Drug Metab 10:836–841
Islek Z, Ucisik MH, Keskin E, Sucu BO, Gomes-Alves AG, Tomás AM, Guzel M, Sahin F (2022) Antileishmanial activity of BNIPDaoct- and BNIPDanon-loaded emulsomes on leishmania infantum parasites. Front Nanotechnol 3:773741
Kalepu S, Manthina M, Padavala V (2013) Oral lipid-based drug delivery systems – an overview. Acta Pharm Sin B 3:361–372
Kamel R, Abousamra MM, Afifi SM, Galal AF (2022) Phyto-emulsomes as a novel nano-carrier for morine hydrate to combat leukemia : In vitro and pharmacokinetic study. J Drug Deliv Sci Technol 75:103700
Kapadia R, Parikh K, Jain M, Sawant K (2020) Topical instillation of triamcinolone acetonide-loaded emulsomes for posterior ocular delivery: statistical optimization and in vitro-in vivo studies. Drug Deliv Transl Res 11:984–999
Kaplan A (2022) The nanocomposites designs of phytomolecules from medicinal and aromatic plants: promising anticancer-antiviral applications. Beni-Suef Univ J Basic Appl Sci. https://doi.org/10.1186/s43088-022-00198-z
Karamchedu S, Tunki L, Kulhari H, Pooja D (2020) Morin hydrate loaded solid lipid nanoparticles: characterization, stability, anticancer activity, and bioavailability. Chem Phys Lipids 233:104988
Khan AA, Mudassir J, Mohtar N, Darwis Y (2013) Advanced drug delivery to the lymphatic system: lipid-based nanoformulations. Int J Nanomedicine 8:2733–2744
Kommana N, Babu MK (2016) Formulation and evaluation of soyalecithin based emulsomes for topical administration of Lornoxicam. Indian J Res Pharm Biotechnol 4:28–38
Lee R, Rakesh K, Zhou NVS (2013) Multifunctional and multitargeted nanoparticles for drug delivery to overcome barriers of drug resistance in human cancers. Drug Discov Today. https://doi.org/10.1016/j.drudis.2013.09.009
Li H, Qu X, Qian W, Song Y, Wang C, Liu W (2022) Andrographolide-loaded solid lipid nanoparticles enhance anti-cancer activity against head and neck cancer and precancerous cells. Oral Dis 28:142–149
Lowell GH, Kaminski RW, VanCott TC et al (1997) Proteosomes, emulsomes, and cholera toxin B improve nasal immunogenicity of human immunodeficiency virus gp160 in mice: Induction of serum, intestinal, vaginal, and lung IgA and IgG. J Infect Dis 175:292–301
Malviya V (2021) Preparation and evaluation of emulsomes as a drug delivery system for bifonazole. Indian J Pharm Educ Res 55:86–94
Pal A, Gupta S, Jaiswal A, Dube A, Vyas SP (2012) Development and evaluation of tripalmitin emulsomes for the treatment of experimental visceral leishmaniasis. J Liposome Res 22:62–71
Paliwal R, Paliwal SR, Mishra N, Mehta A, Vyas SP (2009a) Engineered chylomicron mimicking carrier emulsome for lymph targeted oral delivery of methotrexate. Int J Pharm 380:181–188
Paliwal R, Rai S, Vaidya B, Khatri K, Goyal AK, Mishra N, Mehta A, Vyas SP (2009b) Effect of lipid core material on characteristics of solid lipid nanoparticles designed for oral lymphatic delivery. Nanomedicine 5:184–191
Pardeshi CV, Rajput PV, Belgamwar VS, Tekade AR, Surana SJ (2013) Novel surface modified solid lipid nanoparticles as intranasal carriers for ropinirole hydrochloride: application of factorial design approach. Drug Deliv 20:47–56
Pinilla CMB, Lopes NA, Brandelli A (2021) Lipid-based nanostructures for the delivery of natural antimicrobials. Molecules 26:3587
Puri A, Loomis K, Smith B, Lee JH, Yavlovich A, Heldman E, Blumenthal R (2009) Lipid-based nanoparticles as pharmaceutical drug carriers: from concepts to clinic. Crit Rev Ther Drug Carrier Syst 26:523–580
Qian C, Decker EA, Xiao H, McClements DJ (2013) Impact of lipid nanoparticle physical state on particle aggregation and β-carotene degradation: potential limitations of solid lipid nanoparticles. Food Res Int 52:342–349
Rabaan AA, Alhumaid S, Albayat H et al (2022) Promising antimycobacterial activities of flavonoids against Mycobacterium sp. drug targets: a comprehensive review. Molecules 27:1–15
Rahmani F, Atabaki R, Behrouzi S, Mohamadpour F, Kamali H (2023) The recent advancement in the PLGA-based thermo-sensitive hydrogel for smart drug delivery. Int J Pharm 631:122484
Rajput SA, Wang X, Yan H (2021) Biomedicine & Pharmacotherapy Morin hydrate : a comprehensive review on novel natural dietary bioactive compound with versatile biological and pharmacological potential. Biomed Pharmacother 138:111511
Raza K, Katare OP, Setia A, Bhatia A, Singh B (2013) Improved therapeutic performance of dithranol against psoriasis employing systematically optimized nanoemulsomes. J Microencapsul 30:225–236
Regulation D (2020) Albumin nano-encapsulation of piceatannol enhances its anticancer potential in colon cancer via
Rizk SA, Elsheikh MA (2021) Novel bioemulsomes for baicalin oral lymphatic targeting : development, optimization and pharmacokinetics. Nanomedicine (lond) 16:1983–1998
Sahu B, Kori ML (2022) Topical delivery of emulsomal gel for the. Asian J Pharm 16:378–386
Sawant D, Dandagi PM, Gadad AP (2016) Formulation and evaluation of sparfloxacin emulsomes-loaded thermosensitive in situ gel for ophthalmic delivery. J Sol-Gel Sci Technol 77:654–665
Shidhaye S, Vaidya R, Sutar S, Patwardhan A, Kadam V (2008) Solid lipid nanoparticles and nanostructured lipid carriers – innovative generations of solid lipid carriers. Curr Drug Deliv 5:324–331
Shringarpure M, Gharat S, Momin M, Omri A (2021) Management of epileptic disorders using nanotechnology-based strategies for nose-to-brain drug delivery. Expert Opin Drug Deliv 12:169–185

Singh N, Gill V, Gill P, Singh S (2013) International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS) Chronopharmaceutical drug delivery system-a guided therapy. Int Res J Pharm Appl Sci 3:84–87
Sujitha YS, Muzib YI (2020) Preparation of topical nano gel loaded with hesperidin emulsomes : in vitro and in vivo studies. Int J Pharm Investig 10:500–505
Talita M, De OP, Coutinho DDS, Guterres S, Bernardi A (2021) Resveratrol-loaded lipid-core nanocapsules modulate acute lung inflammation and oxidative imbalance induced by LPS in mice. Pharmaceutics 13:1–17
Ucisik MH, Küpcü S, Schuster B, Sleytr UB (2013a) Characterization of CurcuEmulsomes: Nanoformulation for enhanced solubility and delivery of curcumin. J Nanobiotechnology 11:1–13
Ucisik MH, Küpcü S, Debreczeny M, Schuster B, Sleytr UB (2013b) S-layer coated emulsomes as potential nanocarriers. Small 9:2895–2904
Ucisik M, Sleytr U, Schuster B (2015a) Emulsomes meet S-layer proteins: an emerging targeted drug delivery system. Curr Pharm Biotechnol 16:392–405
Ucisik MH, Küpcü S, Breitwieser A, Gelbmann N, Schuster B, Sleytr UB (2015b) S-layer fusion protein as a tool functionalizing emulsomes and CurcuEmulsomes for antibody binding and targeting. Colloids Surfaces B Biointerfaces 128:132–139
Utreja P, Jain S, K. Tiwary A, (2010) Novel drug delivery systems for sustained and targeted delivery of anti-cancer drugs: current status and future prospects. Curr Drug Deliv 7:152–161
Varshosaz J, Raghami F, Rostami M, Jahanian A (2019) PEGylated trimethylchitosan emulsomes conjugated to octreotide for targeted delivery of sorafenib to hepatocellular carcinoma cells of HepG2. J Liposome Res 29:383–398
Vimal Kumar Varma M, Amareshwar P (2011) Current pharma research. Curr Pharma Res 1:300–305
Vishwakarma N, Jain A, Sharma R, Mody N, Vyas S, Vyas SP (2019) Lipid-based nanocarriers for lymphatic transportation. AAPS PharmSciTech 20:1–13
Vyas SP, Subhedar R, Jain S (2006) Development and characterization of emulsomes for sustained and targeted delivery of an antiviral agent to liver. J Pharm Pharmacol 58:321–326
Yavarpour-Bali H, Pirzadeh M, Ghasemi-Kasman M (2019) Curcumin-loaded nanoparticles: a novel therapeutic strategy in treatment of central nervous system disorders. Int J Nanomedicine 14:4449–4460
Yilmaz EN, Bay S, Ozturk G, Ucisik MH (2020) Neuroprotective effects of curcumin-loaded emulsomes in a laser axotomy-induced cns injury model. Int J Nanomedicine 15:9211–9229
Zakaria MY, Georghiou PE, Banoub JH (2022a) Inclusion of a phytomedicinal flavonoid in biocompatible surface-modified chylomicron mimic nanovesicles with improved oral bioavailability and virucidal activity : molecular modeling and pharmacodynamic studies. Pharmaceutics 14:905
Zakaria MY, Zaki I, Alhomrani M, Alamri AS, Abdulaziz O, Abourehab MAS (2022b) Boosting the anti MERS-CoV activity and oral bioavailability of resveratrol via PEG-stabilized emulsomal nano-carrier : factorial design, in-vitro and in-vivo assessments. Drug Deliv 29:3155–3167
Zhou X, Chen Z (2015) Preparation and performance evaluation of emulsomes as a drug delivery system for silybin. Arch Pharm Res 38:2193–2200

Publisher's Note