Journal of Drug Delivery Science and Technology 55 (2020) 101458

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Solid lipid nanoparticles and nanostructured lipid carriers in oral cancer drug delivery

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ARTICLE INFO

Keywords:
Solid lipid nanoparticle (SLN)
Nanostructured lipid carrier (NLC)
Oral delivery
Anticancer drugs

ABSTRACT

Most cancer disease can be treated by the parenteral anticancer delivery method. The intravenous route takes the wholly bioavailable, accurate dose of the drug immediately to the body, but high plasma concentration has some side effects. Furthermore, i.v. chemotherapy is painful and may cause bleeding and venous thrombosis and discomfort for the patient. Oral chemotherapy is the most accepted alternative way, but some anticancer drugs have low oral bioavailability. Nowadays, nanoparticles have received much attention, and solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have achieved an important place in oral cancer drug delivery. Many researchers studied these nanoparticles as anticancer drug carriers. In this review, we discussed the effects of SLN and NLC encapsulating on stability, cellular toxicity, tumor inhibitory effects, oral bioavailability, and biodistribution of synthetic and herbal anticancer medicines.

1. Introduction

Cancer is a disease condition that begins by dividing abnormal cells without stopping and spreading to other body tissues. With the spread of cancer, better methods of treatment are needed. Surgical treatment, radiation therapy, and anticancer therapy are used for cancer treatment. Nowadays, most anticancer drugs are administered through i.v. injection. The intravenous route takes the wholly bioavailable, accurate dose of the drug to the body immediately. This is good for killing the cancer cells, but high plasma concentration and high delivery of the drug to the healthy tissues cause many severe side effects [1,2]. The main side effects are neurotoxicity, nephrotoxicity, ototoxicity, myelosuppression, cardiotoxicity, nausea, vomiting, diarrhea, and hair loss [3–6]. Some injectable anticancer drugs are formulated by particular toxic excipients [7,8]. Furthermore, i.v. chemotherapy is painful and may cause bleeding and venous thrombosis [9]. Generally, the patient does not feel comfortable, and his daily life is influenced by the medication program [10]. Compared with the parenteral route, oral chemotherapy is the most accepted way and provides some benefits like patient compliance and ease of administration. This could make a sustained medium concentration of the drug in the plasma and prevents from high excessive concentration above the tolerable amount, which will improve the therapeutic efficiency and reduce the side effects [11]. Nevertheless, most anticancer drugs are not orally bioavailable, and the efficiency of oral drug delivery is limited by the special physiological properties of the GI tract and drug physicochemical properties [12]. In other words, the drug should be stable in a gastric fluid especially acidic condition of the stomach and have an adequate hydrophilic-lipophilic balance to traverse the intestinal epithelium membrane to attain the blood circulation system with no gastrointestinal irritation and toxicity [13–16]. For example, the oral bioavailability of paclitaxel, docetaxel, doxorubicin, tamoxifen, etc. is low and in the range of 5–20% [17–20]. Mostly, this is because of low aqueous solubility of drugs, poor intestinal permeability, high level of P-glycoprotein (P-gp) efflux and intestinal and liver cytochrome P450 metabolization [21]. Therefore, it is necessary to develop new oral drug delivery systems for solving these problems and providing the favorite therapeutic results. Researchers have tried several approaches to overcome these limitations, for instance, salt form and prodrug synthesis and encapsulation of drugs in nanoparticles to improve aqueous solubility and mucoadhesive behavior, controlling their release, and increased gastrointestinal permeability. They also utilize some materials for inhibition of the efflux pumps and the cytochrome [22].

Nowadays, nanoparticles such as polymeric micelles, liposome, lipid nanoparticles, carbon nanotubes, nanocrystals, dendrimers, etc., receive much attention because they could cross through the epithelial barrier that has been found to be a crucial factor [11,14,23,24]. Currently, solid lipid nanoparticles have achieved an important place in

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https://doi.org/10.1016/j.jddst.2019.101458
Received 27 July 2019; Received in revised form 7 December 2019; Accepted 10 December 2019
Available online 12 December 2019
1773-2247/

Table 1
Oral pharmacokinetic and bioavailability of SLNs.

Drug	Formula	Specialty	Size	Effect	References
raloxifene	Compritol 888 ATO, Geleol mono and diglycerides NF, stearic acid and palmitic acid, soybean lecithin, Tween 80		140 nm	Cmax (308%) and AUC (270%) significant enhancement in the rate and extent of bioavailability	[42]
all-trans retinoic acid (ATRA)	Compritol 888 ATO, Pluronic F68, soy lecithin, Tween 80		ranged from 80 to 300 nm	significant increase of the relative bioavailability the amount of surfactant also had a marked effect on the oral absorption of ATRA with SLN formulations.	[46]
tamoxifen	Lutrol F-127 andLutrol F-68, polysorbate 80 (Tween 80)	Alpha-lipoic acid–stearylamine conjugate-based SLN	261.08 2.13 nm	1.59-fold increase in relative bioavailability	[41]
curcumin	Stearylamine, Glyceryl monostearate, Poloxamer 188, soy lecithin	N-carboxymethyl chitosan (NCC) coated SLN	245.1 ± 5.4	6.3-fold and 9.5-fold increase in thelymphatic uptake and oral bioavailability	[61]
N3–*O*-toluylfluorouracil	soya lecithin, Compritol 888 ATO, Hexadecyltrimethylammonium bromide (CTAB)	cationic	178.8 ± 9.99 nm		[101]
docetaxel	soybean lecithin, Glycerol monostearate, Tween 80	chitosan or its derivatives-modified SLN	318.13 ± 4.70 , 311.51 ± 22.76	2.45-fold increase in the AUC	[47]
raloxifene	Glyceryl tribehenate (GB) (C69H134O6, molecular weight 1059.8), Kolliphor P407 (poloxamer 407)		167 ± 3 nm	3.24-fold increase in oral bioavailability	[96]
paclitaxel	Stearic acid, Poloxamer 188, lecithin	surface-modified solid lipid nanoparticles with hydroxypropyl-β-cyclodextrin (smPSH)	251.40 ± 12.0 nm	AUC and Cmax of smPSH were higher than PTX solution.	[50]
docetaxel	Tristearin, Tween 80	surface-modified by Tween 80 or D-alpha-tocopheryl poly(ethylene glycol 1000) succinate (TPGS 1000)	215 ± 27.1 , 189 ± 17.0	relative oral bioavailability was further improved in TPGS 1000-emulsified SLNs,	[58]
vorinostat	Compritol 888 ATO, soybean lecithin, Tween 80		average size of ~100 nm	improved vorinostat plasma circulation time and decreased its elimination rate constant. The AUC of VOR-SLNs was significantly higher.	[78]
phospho-Sulindac (OXT-328)	stearic acid, lecithin, Myrj59		~55 nm	improved pharmacokinetics, an enhanced (~14-fold) accumulation of PS and its metabolites in A549 xenografts	[83]
γ-Tocotrienol	compritol ATO, Lutrol F62 (poloxamer 188)		105 nm	threefold higher relative oral bioavailability	[87]
lupeol	glyceryl monosterate, compritol ATO 888, poloxamer 188, sodium deoxycholate		154–287 nm	increased AUC increased Cmax prolonged t1/2 (dose reduction, prolonged duration, enhanced therapeutic efficacy)	[88]
quercetin	glyceryl monostearate, soya lecithin, Tween-80 and PEG 400		155.3 nm	571.4% increase in the relative bioavailability Tmax and MRT were both delayed.	[92]
raloxifene	Dynasan 114 (Glyceryl trimyristate, TM), Dynasan 116 (Glyceryl tripalmitate, TP) and Dynasan 118 (Glyceryl tristearate, TS), soy phosphatidylcholine (Phospholipon 90G), Polysorbate 80		65–70 nm	a twofold increase in bioavailability	[93]
cantharidin	lecithin, glyceryl monostearate, cholesterol, Poloxamer 188 (F-68), Tween-80		121 nm	the relative bioavailability of CA-SLNs to free CA was 250.8%	[55]
curcumin	Compritol 888 ATOs, soy lecithin, Tween 80		134.6 nm	significant improvement in plasma BA concentration (32–59 times in different doses) by C-SLNs	[45]
curcumin	Glyceryl monostearate, soy lecithin, Poloxamer 188, stearylamine, N-carboxymethyl chitosan	N-carboxymethyl chitosan (NCC) coated SLN	245.1 ± 5.4	6.3-fold and 9.5-fold higher lymphatic uptake and oral bioavailability of NCC-SLN, respectively.	[61]

(*continued on next page*)

Table 1 (*continued*)

Drug	Formula	Specialty	Size	Effect	References
curcuminoid	Compritol 888 ATO, Precirol ATO 5, LIPOID S 75		200–300 nm	increased oral bioavailability 12 folds when compared with the marketed formulation of Raw Curcumin (Adcumin®)	[95]

oral cancer drug delivery.

1.1. Solid lipid nanoparticles (SLN) and nanostructured lipid carrier (NLC)

Solid lipid nanoparticles are colloidal particles made of biodegradable physiological lipids that remain solid at room and body temperature and are safe for usage. They have 50–1000 nm size depending on the manufacturing method and content materials [25–29]. SLN displays some problems such as the expulsion of the encapsulated drug during storage and relatively low drug loading which caused presentation of NLC that was created of a mixture of solid and liquid lipids to produce nanoparticles that remain solid at room and body temperatures. NLCs show more drug loading and fewer drug lost during storage time [30]. Nevertheless, it has been observed that the controlled release features of NLCs may be compromised due to decrease in the diffusion length of the lipid matrix [31]. However, this drawback can be modified by altering the proportions of solid and liquid lipids [32]. SLNs and NLCs have numerous advantages such as preparation without organic solvents and construction using biocompatible and biodegradable ingredients, encapsulating drugs and decreasing their side effects on the GI tract, saving sensitive drugs from acidic environment, and ability to encapsulate lipophilic drugs more easily [33,34]. Many researchers studied them as anticancer drug carriers. In this review, we discussed the effects of SLN and NLC encapsulating on stability, cellular toxicity, tumor inhibitory effects, oral bioavailability, and biodistribution of synthetic and herbal anticancer medicines (Fig. 1).

1.2. SLN and NLC components

SLNs are composed of solid fat, surfactants, and drug. NLCs are improved SLNs in which the lipid phase is contained of both solid (fat) and liquid (oil) lipids that form a matrix [35]. The choice of a suitable lipid and surfactant combination is one of the effective factors for producing lipid nanoparticles with preferred physical and chemical properties. Commonly used lipids for the production of nanoparticles include mono, di, and triacylglycerol, fatty acids and waxes [36]. Solid fats including glyceryl palmitostearate, glycerol benate, glyceryl monostearate, cetyl palmitate, and stearic acid; and liquid oil such as oleic acid, MCT oil, croton oil and etc are used for SLN and NLC preparation.

Surfactants are another main component of lipid nanoparticles that stabilize the dispersed lipid system in the aqueous phase and prevent the aggregation. These compounds are different types and it consists of ionic and non-ionic emulsifiers with different molecular weights. Various types of polysorbates, poloxamers, lecithin, and bile acids are most frequently used as emulsifiers. Mixtures of emulsifiers are much more useful in lipid nanoparticles preparation and prevent particle aggregation [26]. Other components could also enter the formulation such as lyophilizing agents, buffers and etc [37].

Depending on the type of ingredients and the method of preparation, solid lipid nanoparticles and nanostructured lipid carriers are divided into several types. One type of SLN and NLC are shown in Fig. 2.

1.3. Preparation methods of lipid nanoparticles

Lipid nanoparticles are prepared in various ways, including high shear homogenization and sonication. High-pressure homogenization (HPH) including cold homogenization, and hot homogenization, solvent emulsification/evaporation method, solvent injection method and microemulsion method [36]. Lyophilization and spray drying are methods that are used finally to create pharmaceutical solid products from aqueous dispersion [35]. Hot homogenization and sonication and high-pressure homogenization (HPH) methods are illustrated schematically in Fig. 3 and Fig. 4.

Table 2
Oral pharmacokinetic and bioavailability of NLCs.

Drug	Formula	Specialty	Size	Effect	References
vincristine	lecithin from eggs, tween-80, sodium dodecyl sulfonate (SDS), capric triglyceride (CT), glycerin monostearate (GMS), and hexadecyl trimethyl ammonium bromide (CTAB)	hyaluronic acid-coated cationic	192 ± 4.41 n	The relative oral bioavailability of HA-NLCs andVCR-NLCs were improved about 1.8-fold and 2-fold compared with VCR solution, respectively.	[74]
sulforaphane	Compritol 888 ATO, Vitamin E, Precirol ATO 5, Labrasol andCapryol 90, Stearic acid and glyceryl monostearate, poloxamer 188, Tween 20, Tween-80 and canola oil		145.38 ± 4.46 nm	5.04-fold increase in relative oral bioavailability	[54]
baicalin	soybean lecithin, glycerol monostearate, medium chain triglyceride, Poloxamer 188		244.7 nm	prolonged MRT and increased AUC	[59]
c-substituted diindolylmethane (DIM) derivatives DIM-10 and DIM-14	Compritol 888, Miglyol 812, Vitamin E TPGS		210–222 nm	Increase in Cmax and AUC values by 4.73 and 11.19-folds,respectively.	[85]
doxorubicin	soybean oil, glyceryl monostearate, soya lecithin, Distearoyl phosphatidylethanolamine (DSPE-PEG, PEG molecular weight: 2000), Polyethylene glycol 40 stearate (PEG-40-St)		170 nm	2–3 times higher relative bioavailability increases (AUC) and (Cmax)	[89]
curcumin	Polyethylene glycol [100]-monostearate, cholesterol oleate, glycerol trioleate, glycerol	N-acetyl-L-cysteine functionalized NLC	89–141 nm	AUC0–t of Cur-NAPG100-NLC was improved by 499.45 and 116.89 folds as compared with that of Cur solution and unmodified Cur-NLC, respectively.	[102]
curcumin	Cholesterol oleate, S100 (ethylene glycol 100), Phosphatidylcholine, glycerol trioleate, glycerol	taurocholic acid-modified NLC	150 nm	Cur-TCA NLCs displayed about a five- to 15-fold higher AUC than unmodified Cur NLCs, depending on the degree of modification	[103]
curcumin	Phosphatidylcholine (Phosal 53MCT), hydrogenated soybean oil	adding Ginsenoside as Pg-p inhibitor	300–500 nm	enhanced bioavailability	[104]
etoposide	glycerylmonostearate, monostearin and soybean oil, soya lecithin, Distearoylphosphatidyl-ethanolamine (DSPEPEG, PEG molecule weight: 2000), Distearoylphosphatidyl-ethanolamine (DSPE-PEG, PEG molecule weight: 2000), PEG 400	PEG40-St-modified NLCs and DSPE-PE- modified NLCs	125.9–91.2 nm	1.8-, 3.0-and 3.5-fold increase in the relative bioavailability of VP16-NLCs, VP16-PEG40-NLCs, and VP16-DSPE-NLCs, respectively,	[76]
docetaxel	glyceryl monostearate, Poloxamer188 (F68)	a novel lipophilic oleate prodrug of DTX in NLC using core-match technology	90–130 nm	the bioavailability ofDTX-OA-NLC showed 4.04-fold and 2.06-fold higher than DTX solution and DTX-NLC, respectively.	[105]

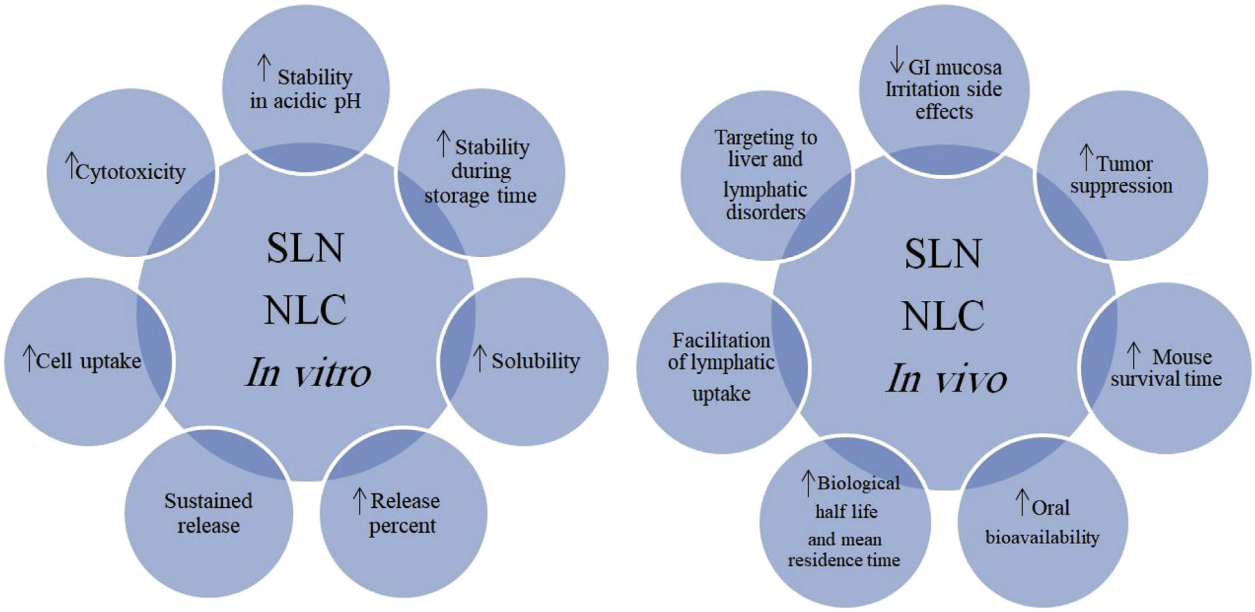

Fig. 1. In vitro and *in vivo* effects of SLN and NLC encapsulation of drugs.

2. SLNs and NLCs evaluations

2.1. Stability

SLNs and NLCs can affect drug-loaded stability, *i.e.*, they preserve sensitive drugs from degradation by the acidic environment and during storage time [38]. Using several excipients in the formulation also could affect stability characters, and as a result, drugs could release at the right place with the highest absorption. Various nanoparticle factors could be representative for stability such as size, zeta potential, PDI, drug encapsulation amount, *etc*.

Pandita et al. studied oral delivery of paclitaxel using SLNs. SLNs were evaluated in the simulated gastric medium for stability. SLNs containing poloxamer 188 showed a protective coating effect, and no aggregation was observed, whereas in the absence of poloxamer 188, SLNs exhibited significant and immediate aggregation after incubation in the gastric medium. The particle size of poloxamer-coated SLNs did not change, and negligible lipid degradation in gastric medium happened. This was due to the sterically stabilizing feature of poloxamer 188, which was not affected by the low pH and created a protective layer around the nanoparticles [39].

Moreover, Chanburee et al. observed the particle size of polymer-coated NLCs suggesting good physical stability in physiological fluids (simulated gastric fluid (SGF) and simulated intestinal fluid (SIF)) whereas uncoated-NLCs showed aggregation in SGF [40]. Freeze dried tamoxifen citrate in nanostructured lipid carrier system (Tmx-NLC) could withstand various gastrointestinal tract (GI) media (pH 1.2, pH 3.5, pH 4.5, pH 6.8, and pH 7.4) and had no significant variation in characteristics of Tmx-NLCs during three months of accelerated stability studies. Physical stability of TMX-SLNs and lyophilized TMX-SLNs containing 10% w/w trehalose as cryoprotectant was evaluated in 3 months at 4 and 25 °C and showed no considerable change in particle size, zeta potential, PDI, or entrapment efficiency [41]. Also, raloxifene SLN formulations were quite stable at 25 °C for more than two months [42]. Kushwaha et al. studied the stability of SLNs at 30 ± 2 °C/65% ± 5% RH for 90 days. After 90 days, they observe that the SLN formulations had long-term stability because there was no significant change in the nanoparticle size, zeta potential, or % EE. It is mentioned that it was because of the higher solubility of their drug in the lipid matrix and presence of poloxamer 188 and its nonionic nature and forming a coat around nanoparticles surfaces that decreases the electrostatic repulsions between the particles result in stabilizing them

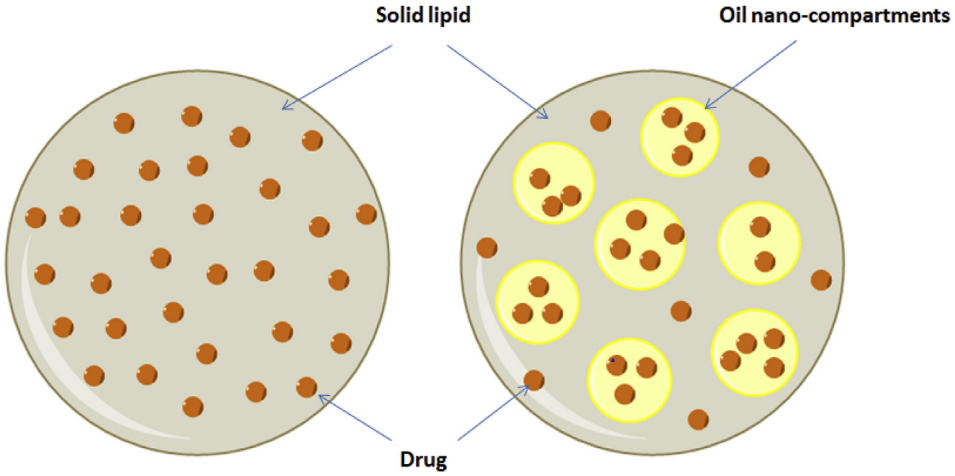

Fig. 2. Solid lipid nanoparticle (left) and nanostructured lipid carrier (right) schematic structure.

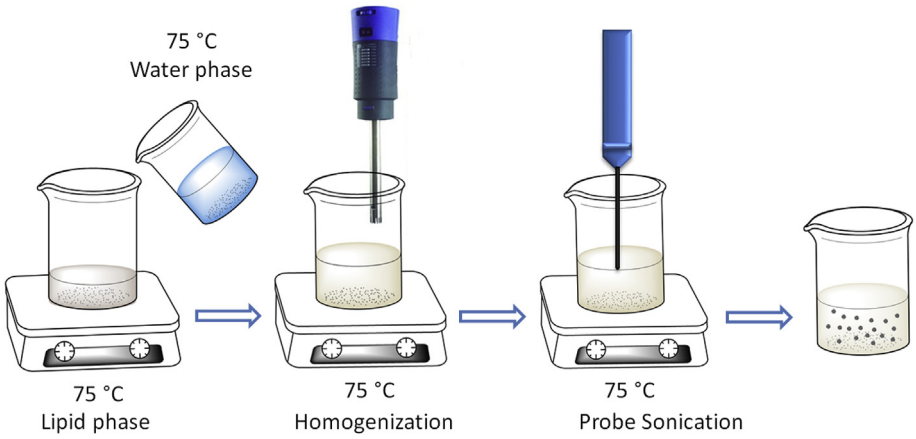

Fig. 3. Schematic of hot homogenization and sonication methods.

[43]. Furthermore, a physical-chemical stability study on PM02734 (a new anticancer drug) containing solid lipid nanoparticles after six months of storage concluded that SLNs at 4 °C had more stability than at 25 °C [44]. In another study by Kakkar et al., curcumin loaded solid lipid nanoparticles (C-SLNs) showed no significant alteration in curcumin content and particle size during 12 months storage at 5 ± 3 °C [45]. All-trans retinoic acid (ATRA) SLNs were compared with an emulsion formulation by Hu et al., which showed both formulations could increase ATRA absorption, but emulsion does not have good stability for clinical usage; in comparison SLNs display high physical stability [46]. Shi et al. worked on positively charged chitosan (CS)- or hydroxypropyl trimethyl ammonium chloride chitosan (HACC)-modified SLNs containing docetaxel and showed that the hydroxypropyl trimethyl ammonium chloride chitosan (HACC)-modified solid lipid nanoparticles loading docetaxel (DTX), *i.e.*, HACC-DTX-SLNs were extremely stable in SIF and SGF while the positively charged chitosan (CS) DTX-SLNs were more stable in SGF than in SIF [47].

Studies on NLCs showed the same results. For example, stability studies on nanostructured lipid carrier for decitabine revealed that nanoparticle parameters did not change significantly in 45 days ($p > 0.05$) [48]. In a study in 2018, NLCs were coated by PEG and polymer. Coating NLCs by PEG could save 90% of curcumin after 6 h incubation in the culture medium. Moreover, the physical and chemical stabilities, *i.e.*, the mean particle size and the amount of curcumin of the lyophilized curcumin-loaded polymer coated NLCs, and uncoated NLCs showed no significant change after six months storage at 4 °C [49].

2.2. Solubility and release

Suitable solubility of the drug at the absorption place is necessary for achieving acceptable oral bioavailability, but some anticancer drugs have hydrophobic structure and low aqueous solubility, and finally, they show low oral absorption. Encapsulating in SLNs and NLCs could solve this problem with some mechanisms. For example, Hu et al. obtained exciting results indicating that ATRA absorption was enhanced significantly by employing SLNs. They explain that the particles size

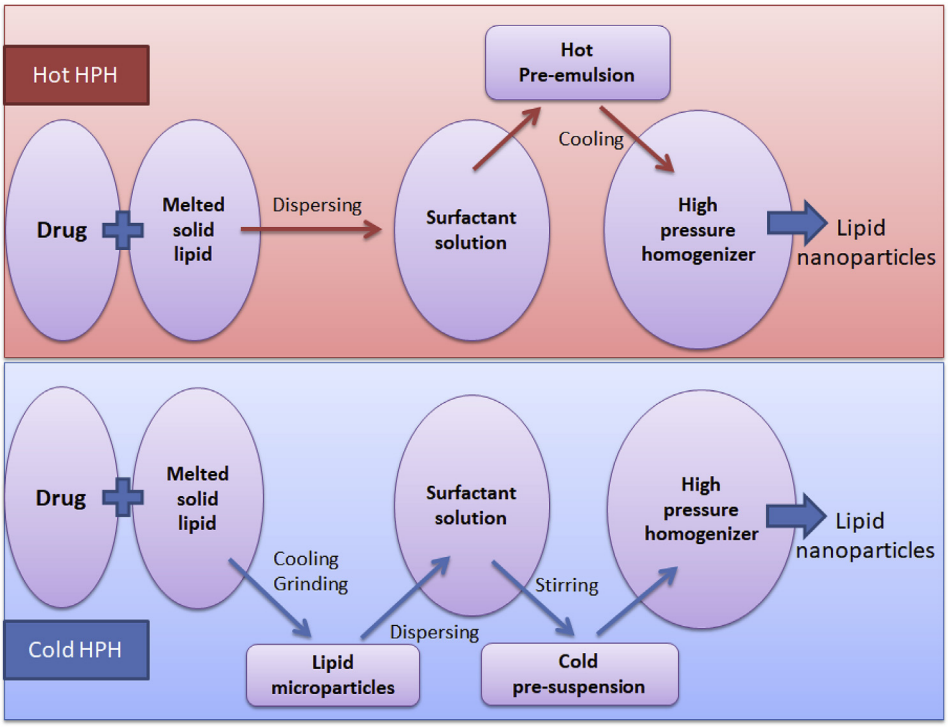

Fig. 4. High-pressure homogenization (HPH) method (Hot and Cold HPH).

reduction is an important reason for the peroral performance improvement of poorly soluble drugs. SLN encapsulation of drug results in increased surface area and saturation solubility [46]. Baek et al. revealed that SLNs of paclitaxel strengthened by hydroxypropyl-β-cyclodextrin (smPSH) increased solubility of PTX about 15- or 17-fold compared with PTX solution [50]. Also, PEG-coated NLCs showed significantly improved curcumin water solubility more than 60-folds compared with curcumin dispersion [49]. Nanoparticle content material and coating them showed an interesting effect on drug solubility and also increased their potential. In another study, Das et al. demonstrated that Precirol®ATO5 and Compritol®888ATO had a reasonable capacity for tretinoin solubilization and efficient encapsulation of poorly aqueous soluble tretinoin into nanoparticles [51]. Also, novel lipid nanocarriers, GeluPearl (GP) loaded with Quercetin display that lipidic nanocarriers (GPSLNs and GPNLCs) can improve QR solubilization [52]. Orally administered SLNs release drugs mainly by degradation and/or diffusion through the solid lipid matrix in the gut through a pattern [53]. The release pattern of nanoparticles is associated with some characteristics such as kind of material content including lipids and surfactants. Also, NLCs and SLNs showed different activities due to different material preparation that made a looser matrix for NLCs due to having some oil. Some studies showed that the encapsulation of drugs in SLNs displayed better dissolution and release pattern. Researchers studied these features in different media. For example, *in vitro* drug release tests revealed that the release of sulforaphane (SFN) from optimized NLC formulations in 24 h was significantly greater (86.52 ± 5.48%) than SFN suspension (38.47 ± 5.52%) [54].

In a study in 2013, cantharidin (CA) SLNs had a sustained release profile without a burst effect and significantly higher CA dissolved from the solid lipid nanoparticles compared with free CA at each time point [55]. Studies contend that the release of drug solution was higher and SLNs and NLCs sustained drug release. For example, novel quercetin-loaded cationic nanostructured lipid carriers (QR-CNLCs) displayed slower *in vitro* release compared with quercetin solution [56]. Also, the dissolution profile of Tmx-NLC in various pHs of medium showed a sustained release pattern [57]. Also, docetaxel SLNs was compared with Taxotere. The results showed the slower release of docetaxel from SLNs, sustained release, and homogeneous and amorphous entrapment of the drug inside the systems [58]. Also, some SLNs and NLC showed a pattern in two phases, including initial burst and prolonged sustained release. For example, studies on poor aqueous soluble raloxifene HCl have shown release from drug solution was higher, nearly 100% in 4 h, whereas SLN formulations sustained the drug release up to 24 h by biphasic release behavior involving 60% of drug released within 2–3 h as initial burst release followed by 95% of drug release at 24 h as sustained release. It was mentioned that presence of the adsorbed drug on the surface of nanoparticles caused the initial burst release of the drug, and prolonged diffusional distance and prohibition effects of surrounding solid lipid shell applied sustained pattern [43]. NLC encapsulation also showed this pattern in baicalin release from baicalin-loaded nanostructured lipid carriers (BA-NLCs(that revealed a biphasic drug release pattern with initial burst release and later sustained release [59]. Raloxifene loaded solid lipid nanoparticles that exhibited *in vitro* prolonged release for 72 h in phosphate buffered saline and was stable in simulated gastrointestinal fluids consisting of pH 1.2 and pH 7.4 [60]. The N-carboxymethyl chitosan (NCC) coating curcumin-loaded SLNs (NCC-SLNs) made suppressed burst release in simulated gastric fluid while in simulated intestinal fluid sustained release was shown [61]. Jain et al. compared two forms of novel lipid nanocarriers loaded with quercetin GPSLNs and GPNLCs; they saw more QR release from GPNLCs compared with GPSLNs. It could be due to the looser nanoparticulate matrix of GPNLCs due to comprising oil and lipid mixture compared with GPSLNs matrix [52]. Preparation methods also affect the release pattern of nanoparticles. A study in 2007 showed that the rate of the hot silymarin solid lipid nanoparticles (hot-SM-SLNs) release prepared by the hot method was faster than that of the cold one. 72% of the total dose for the hot-SM-SLNs and 54% for the SM-SLNs produced by cold homogenization (cold-SM-SLNs) were released within 36 h. The *in vitro* release experiments showed that cold-SM-SLNs achieved a prolonged drug release [62]. Some SLNs and NLCs coated with other materials had impact on the release pattern. For example, coating curcumin SLNs by N-carboxymethyl and N-trimethyl chitosan affected the release feature as it was negligible in SGF and moderate controlled release of drug in SIF [61,63]. Kim et al. studied newly designed microcapsules combining a core of solid lipid nanoparticles and a mesoporous silica shell of curcumin and found that the mesoporous shell caused the protection and controlled the release of the drug and made SLNs as a reservoir of curcumin. It is obviously shown that silica shell affects the release kinetic profile of curcumin related to the release media pH. This study explains retaining curcumin at pH 2.8 without burst release at the initial release time was due to the isoelectric point of silica that is between 2 and 3 (*i.e.*, the average basal pH value of the stomach) [64]. De Mendoza et al. compared SLNs and cyclodextrins formulation of the drug and concluded that SLNs could sustain the release of the drug for a longer period than cyclodextrins [44]. In some studies, drug or lipid complexed with some derivatives as cyclodextrins. In a research by Lin et al., VP–b-CD–TA loaded NLCs exhibited a higher dissolution rate at pH 6.8 and pH 7.4 media compared with vinpocetine suspension and NLCs. TA could increase drug release slowly by providing a slightly acidic environment, and ternary complexes have solubilizing influence [65]. Alpha-lipoic acid–stearyl amine (ALA-SA), conjugate-based SLNs of tamoxifen, showed a higher release at acidic medium pH [41].

2.3. Cellular studies

SLNs can affect *in vitro* cell toxicity and uptake and drug efficacy. Many researchers studied these cellular effects on numerous cell lines.

2.3.1. Caco-2

Caco-2 cell line is a heterogeneous human epithelial adenocarcinoma cell line that is known to be similar with the gastrointestinal epithelial cells. Caco-2 is frequently used as the *in vitro* model cell for assessing permeability, absorption, and cytotoxicity of oral formulations through the intestine [66]. Although it is derived from colon (large intestine) carcinoma, when cultured under specific conditions, it differentiates spontaneously and becomes polarized, thereby expressing tight junctions at basolateral and apical surfaces, therefore it is used for bidirectional permeability in terms of morphology and performance [67–70]. Caco-2 cells express tight junctions, microvilli, peptidases, esterases, P-gp, uptake transporters for amino acids, bile acids, carboxylic acids, etc. like enterocytes [71].

Baek et al. showed Caco-2 cell uptake of PTX from smPSH with 5.3-fold rise compared with a PTX solution based on a Taxol formulation. Moreover, smPSH showed increased cytotoxicity compared with PTX solution [50]. In another study, Khurana et al. prepared a mangiferin-phospholipid complex that showed 10.1 fold enhancement in the permeation parameters compared with mangiferin solution at the third hour [72]. Shi et al. used Caco-2 cells as test model to discover permeability mechanisms of the HACC-DTX-SLNs. HACC-DTX-SLNs exhibited the highest uptake in Caco-2 cell monolayer, which is mainly related to the caveolae-mediated endocytosis, M cell phagocytosis, and reversible tight junctions. They also observed that SLNs have low toxicity in Caco-2 cells despite positive surface charge [47]. In a study in 2016, newly designed microcapsules combining a core of solid lipid nanoparticles and a mesoporous silica shell of curcumin displayed a good cell tolerance, using neutral red uptake assay together with confocal laser scanning microscopy (CLSM). Also, the Caco-2 cell-uptake test confirmed the possibility of using microcapsules for gut cells targeting [64]. Liu et al. compared cationic and anionic SLNs, liposomes, and an aqueous suspension of N3-o-toluyl-fluorouracil (TFu) in crossing

Caco-2 cells. SLNs enhanced transport of TFu much more than liposomes, especially the cationic SLNs present the most capability [73].

2.3.2. MCF-7

MCF-7 is a breast cancer cell line that has been used for some oral studies. Baek et al. studied NCC coated curcumin-loaded SLNs that revealed increasing cytotoxicity and cellular uptake on MCF-7 cells [61]. Also, hyaluronic acid-coated cationic nanostructured lipid carriers (HA-NLCs) studied by Gao et al. containing vincristine significantly increased the cellular uptake and cytotoxicity in MCF-7 cells compared with other vincristine formulations. HA-NLCs exhibited the strongest effect in promoting MCF-7 cell apoptosis, and the expressions of apoptosis-related protein Caspase-3, Caspase-9, Bax, and Bcl-2 were estimated by Western blot assay [74]. Tea polyphenols (TPPs) solid lipid nanoparticles also exhibited extended free radical scavenging activity in contrast to free TPP. TPP-SLNs showed activation of Caspases-9 and -3 cascades in the MCF-7 cell line *in vitro* [75]. Other researcher worked on different cell lines like B16F10 [63], A549 [76], MDA-MB-231 [77,78], ZR-75-1 [79], HeLa cells [80], HepG2 cell [39,81], and NIH-3T3 [42].

All studies showed improving intracellular concentration and enhancing cytotoxicity effect that might be due to the capacity of the nanoparticles content materials to block the P-gp efflux mechanism crossways the intestinal barrier model, resulting in more permeation [82]. Lipid nanoparticles also showed specific targeting of intracellular components. For example, Zhu et al. studied solid lipid nanoparticle encapsulated phospho-sulindac (SLN-PS) that improved cellular uptake and PS accumulation in mitochondria, leading to oxidative stress and mitochondrial apoptosis [83]. Also, Shete et al. observed that long-chain lipid being used in Tmx-NLCs formulation could increase intracellular uptake and localization in the nuclear and perinuclear region of cells markedly [79].

2.4. GI mucosa irritation test

Incorporation of cytotoxic compounds in SLNs and NLCs may minimize their exposure to the gastrointestinal tract and decrease the irritation and side effects. Shi et al. studied the pathology of GI mucosa of rats to evaluate the irritation of HACC-Docetaxel-SLNs. In the control group, the epithelial mucosa was intact and contiguous without inflammation, and the glands were regularly arranged with clear structure; the epithelial mucosa and fibers were normal, and cell infiltration and ulceration and muscular abnormality were not observed. Interestingly after oral administration of HACC-SLNs, the same results with the control group were observed, *i.e.*, the arrangement of the stomach, duodenum, jejunum, and ileum was still intact and continuous. These results endorse no toxicity of HACC-DTX-SLNs on GI mucosa [47]. Another study on free cantharidin indicates gastrointestinal mucous membrane irritation, but encapsulation in SLNs resolved this problem by entering the drug into the cavity and decreasing direct contact with the gastrointestinal mucous membrane [55]. Similarly, triptolide (TP) often causes orally adverse reactions on the gastrointestinal tract, but triptolide-loaded solid lipid nanoparticles (TP-SLNs) showed reduced gastric irritation in rats [84].

2.5. Tumor inhibitory

Tumor inhibitory effect of anticancer loaded SLNs and NLCs is checked by animal administration of oral formulations and study of anti-tumor outcome with analysis of mice tumor volume and mouse survival during the test. For example, Godugu et al. studied the anticancer effect of C-substituted diindolylmethane (DIM) derivatives nanostructured lipid carriers (NLCs) in MDA-MB-231 orthotopic triple-negative breast cancer (TNBC) models, which proved significant tumor volume decrease [85]. The efficacy study of tamoxifen-NLCs by Shete et al. showed more tumor suppression and revealed 100% survival with 1.5 and 3 mg/kg tamoxifen-NLCs compared with 3 mg/kg tamoxifen suspension and Mamofen (tamoxifen tablet) [57]. In a study in 2015, it was observed that conjugated estrogenic derivative (ESC8) SLNs inhibited breast tumor growth by 74% ($P < 0.0001$, *vs.* control) in mice bearing MDA-MB-231 cells as xenografts [77]. Oral administration study of prodrug form of gemcitabine *i.e.* 4-(N)-stearoyl gemcitabine in solid lipid nanoparticles (GemC18-SLNs) in mice with pre-established tumors (*i.e.* mouse TC-1 or LLC lung cancer cells) showed significant inhibition of tumor growth and enhancement of mouse survival time compared with equivalent dose of gemcitabine hydrochloride or GemC18 prepared in vegetable oil or in Tween 20 [86]. Novel lipid nanocarriers, GPSLNs loaded with Quercetin, also significantly increased the anti-tumor activity of drug against B16F10 melanoma cells in C57BL/6 mice as compared with QR suspension [52]. These results confirm the improvement of anticancer drugs' oral absorbance by encapsulating in lipid nanoparticles and eventually increasing available concentration and effect of drugs on tumor suppression.

2.6. Pharmacokinetic and bioavailability

SLN and NLC encapsulation improve oral bioavailability and pharmacokinetics of drugs, which means effective oral absorbance and changing the rate of absorbance and excretion of the drugs. Many studies on SLNs and NLCs containing drugs such as c-Tocotrienol, all-trans retinoic acid (ATRA), raloxifene, phospho-sulindac, vinpocetine, baicalin, DIM, etoposide (VP16), sulforaphane, curcumin, lupeol, and doxorubicin showed increasing bioavailability from 2 to 14 fold for many drugs [42,46,54,59–61,76,78,83,85,87–90]. Researchers explained the absorbance effect of SLNs and NLCs by pharmacokinetic factors. Paliwal et al. showed that the time for attaining peak plasma drug concentration in the case of methotrexate solution (1 h) was less as compared with methotrexate-SLNs (4 h). That is due to sustained release of drug from SLNs [91]. Li et al. showed that improving the bioavailability of quercetin-loaded SLNs about 571.4% compared with quercetin suspension and SLNs could delay the T max and MRT for quercetin in plasma [92]. Also, Burra et al. showed overall a two folds increase in bioavailability of raloxifene with SLN formulations and enhanced biological half-life and mean residence time for SLN formulations due to slower elimination rate of RXH froms [93]. This event is created by some mechanisms such as increasing solubility of drugs. Cantharidin (CA) is limited by its insolubility, toxicity, and short half-life in circulation, was encapsulated in SLNs and compared by free CA. The relative bioavailability of CA-SLNs to free CA was 250.8%, which shows higher bioavailability than free CA after oral administration [55]. Also, curcumin SLNs improved the bioavailability of curcumin significantly (up to 39 times) [45,61,94,95]. Lipids in lipid nanoparticles could induce bile secretion in the small intestine and interact with bile salts and create mixed micelles. Micelles facilitate entering the intact nanoparticle into the lymphatic vessels and avoid liver first-pass metabolism [65]. This mechanism studied by Ravi et al. demonstrates 3.24 folds increase in the oral bioavailability of raloxifene from SLNs compared with free raloxifene in rats. SLNs uptake is by both clathrin and caveolae-mediated endocytosis pathways. Higher plasma concentration of raloxifene after oral SLNs was attributed to portal absorption and also intestinal lymphatic transport. In this study, cycloheximide, a lymphatic transport inhibitor, could significantly reduce the oral bioavailability of SLNs [96]. Unfortunately, the P-gp transporter in the GI tract recognizes drugs– such as a variety of large, neutral or cationic anticancer drugs, including vinca alkaloids, anthracyclines, epipodophyllotoxins, and taxanes– and passages them back to the GI [97]. A common strategy to circumvent P-gp based MDR is to co-administer a P-gp inhibitor along with anticancer drugs. Baek et al. showed that hydroxypropyl-β-cyclodextrin might contribute as a p-gp inhibitor [50]. Cho et al. showed that tristearin SLNs could bypass P-gp mediated efflux via these mechanisms and enhance the intestinal absorption of docetaxel [58]. D-α-Tocopherol polyethylene glycol 1000

succinate (TPGS 1000) and other nonionic surfactants including Tween 80 have been reported to inhibit P-gp mediated efflux activity [98–100].

Researchers also studied the influence of lipid nanoparticle size and zeta potential and content material on the oral bioavailability of drugs. The relative oral bioavailability of vincristine containing HA-NLCs and cationic NLCs was improved about 1.8 and 2 folds compared with vincristine solution, respectively [74]. Liu et al. showed TFu loaded cationic SLNs would facilitate the bioavailability of poorly absorbed oral drugs by enhancing the bioadhesion of the drug carriers with the absorption mucosal surface [101]. Also, Shi et al. showed positively charged chitosan or HACC-SLNs loaded DTX can significantly increase oral absorption by electrostatic attraction with cells [47]. Tian et al. studied an N-acetyl-L-cysteine functionalized nanostructured lipid carrier containing curcumin and N-acetyl-L-cysteine-polyethylene glycol [100]-monostearate (NAPG), concluding that the bioavailability of Cur was related to the degree of functionalization of NLCs with NAPG. AUC 0-t of Cur-NAPG100-NLCs was improved by 499.45 and 116.89 folds compared with Cur solution and unmodified Cur-NLCs, respectively. They suggested that it was due to NAPG mucoadhesion and the mucus penetration effect [102]. Also, Tian et al. used taurocholic acid (TCA) as a ligand for the uptake of nanostructured lipid carriers (NLCs) to improve oral bioavailability of curcumin (Cur). Results showed that Cur-TCA NLCs displayed five-to 15-folds higher AUC than unmodified Cur NLCs after oral administration. It depended on the degree of modification by S100-TCA, which are mediated by a bile-acid transporter [103]. Vijayakumar et al. used ginsenoside to improve the bioavailability of curcumin-loaded nanostructured lipid carriers. Results ascertain that ginsenoside could enhance the NLCs bioavailability [104]. Some researchers conjugated drugs or lipids and coated nanoparticles for improving oral bioavailability. For example, Dhaundiyal et al. showed a-lipoic acid–stearylamine conjugate-based SLNs have a great potential in enhancing the oral bioavailability of poorly soluble drug tamoxifen (TMX). Pharmacokinetic study revealed a 1.59-fold increase in relative bioavailability as compared with TMX suspension [41]. Also, the relative bioavailability of VP–b-CD–TA loaded NLCs was 592% higher compared with VP suspension and also 92% higher than VP–NLCs. It was shown that the VP solubilizing effect and released rate from VP–b-CD–TA loaded NLCs were noticeably increased. Therefore, VP reached the peaked concentration at 1 h in the case of VP–b-CD–TA loaded NLCs, which was quicker than VP–NLCs and was due to a solubilizing effect and the fast release rate as a result of drug complexation [65]. Encapsulating novel lipophilic oleate prodrug of DTX (DTXOA) in NLCs showed 4.04-fold and 2.06-fold higher bioavailability of DTX-OA-NLCs than DTX solution and DTX-NLCs, respectively [105]. Water-soluble drugs encapsulated in lipid nanoparticles also displayed better oral bioavailability. The blood profiles observed after oral use of commercial microemulsion Sandimmun® showed fast absorption of drug and a plasma peak above 1000 ng/ml in 2 h whereas administration of cyclosporine-loaded SLNs led to a mean plasma profile with low variations and no initial blood peak above 1000 ng/ml within the first 2 h without side effects [106]. In addition bleomycin sulphate loaded nanostructured lipid particles (BLM-NLPs) showed significantly ($P < 0.0001$) ~ 3.4 fold (66.20 ± 2.57%) higher bioavailability than BLM solution (19.56 ± 0.79%) [80]. (see Tables 1 and 2)

2.7. In-situ perfusion

In situ intestinal perfusion in rats also known as single-pass intestinal perfusion is a technique that is frequently used for evaluation of drug permeability through the intestines, and it is a vigorous method for simulating real *in vivo* conditions following oral drug administration in order to keep intact blood supply to the intestinal tract during the test [107]. Burra et al. studied in situ perfusion of raloxifene hydrochloride (RXH) SLNs in rat intestines and observed a higher absorption rate constant and effective permeability coefficient for SLNs compared to controls, which showed permeation enhancing potential of raloxifene SLNs across the gastrointestinal barrier [93]. Tian et al. revealed in situ intestinal perfusion of TCA nanostructured lipid carriers containing curcumin improved absorption rate and permeability coefficient. TCA had an important role as a ligand for NLCs uptake by a bile-acid transporter(103).

Also, in situ perfusion method can compare GI segments like stomach, ileum, duodenum, and colon. The absorption of quercetin-loaded SLNs in the gastrointestinal (GI) tract shows that the main absorptive segments were ileum and colon, and the absorption percent in the stomach was only 6.20% for 2 h. Also, the intestinal absorption process was first-process with passive diffusion mechanism [92]. Liu et al. compared anionic SLNs, cationic SLNs, and liposome absorbance efficiency. SLNs exhibited much more capability to enhance transport of TFu than liposomes [73]. Another study on cationic solid lipid nanoparticles showed that the main segments of drug absorbance in the intestines were duodenum and jejunum due to the adhesion mediated by electrostatic interaction between the positively charged colloidal particles and the negatively charged mucosal surface [101].

2.8. Biodistribution

SLNs and NLCs could alter the pattern of anticancer drugs' biodistribution in the body. Biodistribution study shows tumor and organ achievement of drugs and also anticipate probable drugs side effects on other parts of the body. Liu et al. studied QR-CNLCs and observed higher AUC and C_{max} values in the lungs, liver, and kidneys compared with the control group. These findings revealed that QR-CNLCs could significantly accumulate in these organs after oral administration compared with quercetin suspension [56]. Baek et al. studied oral smPSH, and they achieved higher lymph node drug concentration in smPSH treatment than paclitaxel solution, proposing that more paclitaxel was transported to the lymphatic vessels by smPSH [50]. Moreover, long chain lipid-based Tmx-NLCs were targeted to the intestinal lymphatic systems [79].

In vivo studies on nanostructured lipid carriers (NLCs) of silymarin revealed that 19.268 μg of the drug reaches the liver in 2 h whereas drug concentration in other organs was negligible. It was concluded that NLCs were beneficial carriers for targeting the liver and lymphatic disorders [108].

3. Conclusion

SLN and NLC formulations are studied for some anticancer drugs. They can improve the effectiveness of oral drug administration *in vitro* and *in vivo*. They improve solubility and release characters, increase cellular uptake and efficacy, oral bioavailability, and tumor inhibitory effect of drugs. Also, SLNs and NLCs can change drug biodistribution profile, and they are even used as targeting delivery systems to some organs.

Declaration of competing interest

The authors have declared no conflict of interest.

Acknowledgements

This study was partially supported from Mashhad University of Medical Sciences, Iran (Grant number 931408).

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