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Solid lipid nanoparticles for enhanced oral absorption: A review

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ABSTRACT

Recent trends in nanoparticles-based oral therapy have led to a proliferation of studies to enhance solubility, permeability and chemical stability of many drugs. One of the significant current discussions is achieving high bioavailability of drugs poorly absorbed with an impairing coincidence of oral degradation. Solid lipid nanoparticles (SLNs), absorbed and trafficked *via* transcellular and paracellular pathways, are one of the utmost innovative promising nanocarriers to overwhelm drawbacks of the poorly absorbed drugs. The central topic of this review is focusing on providing brief updates on SLNs for improving drug oral absorption with their evolutions in curing numerous ailments. In order to create a new paradigm of therapeutic formulations, we also highlight the transversal mechanisms of SLNs across the gastrointestinal hurdles and a series of novel researches regarding *in vitro* protocols to uncover the investigations of the transmembrane absorption and transport kinetics of SLNs. The current challenges and future perspectives of SLNs for oral drug delivery are refined and forecasted. Several questions remain unanswered and it is recommended to pay a close attention to the most sophisticated *in vivo*-like culture practices which open new avenues to thoroughly elucidate how SLNs interact with intestinal mucosa at cellular and molecular levels. Additionally, further studies are needed to concentrate on the factors influencing the absorption efficiency, proportion of SLNs in gastrointestinal tract as well as their correlation with their loaded drug bioavailability.

1. Introduction

Oral delivery is evidently proposed as being the most convenient drug administration route, having several advantages over other delivery pathways, including lack of pain sensation, easily self-administration, and excellent patient compliance. All over the world, the vast varieties of marketed drugs are commonly administered *via* the oral route. The efficacy of these drugs depends on the oral absorbability, which, in sequence, mainly relies on drug properties and physiological nature of the gut [1,2]. The adverse characteristics of some drugs, such as poor hydrophobicity, low permeability, chemical instability, and extreme first-pass metabolism, have a negative influence on the passage of drugs through the gastro intestinal (GI) barriers [3]. The GI tract presents physical, chemical, enzymatic and biological membrane barriers for the transport and effectiveness of the poorly absorbed drugs [4,5]. Thus, one of the most potential ways for enhancing the absorption of these drugs is to increase their solubility, stability and transmembrane transport by encapsulating the drug in and absorbing on the surface of the nanocarrier systems [6,7]. These nanosystems represent a smart vehicle for transport of hardly soluble and poorly permeable molecules across the barriers [8]. They could modify the transmembrane transport of the nanoparticle-loaded drugs and favorably improve the diffusion of these drugs across the intestinal mucosal hurdles [9]. The efficacy of the oral absorbability is not only determined by the physicochemical characters of the drug, but also that the nanocarrier delivery system could be implicated in this issue [10]. Solid lipid nanoparticles (SLNs), a novel nanosized drug delivery system, have been gaining more attractive attention as an effective alternative carrier to the traditional colloidal approaches, such as, liposomes and polymeric particles since 1991 [11]. They can overcome some of the major pitfalls of poor stability and low loading capacity that commonly encountered with liposomes [12,13] and the possible biotoxicity and residual organic solvent associated with polymeric nanoparticles [14,15]. Regarding biocompatibility and non-toxicity, SLNs

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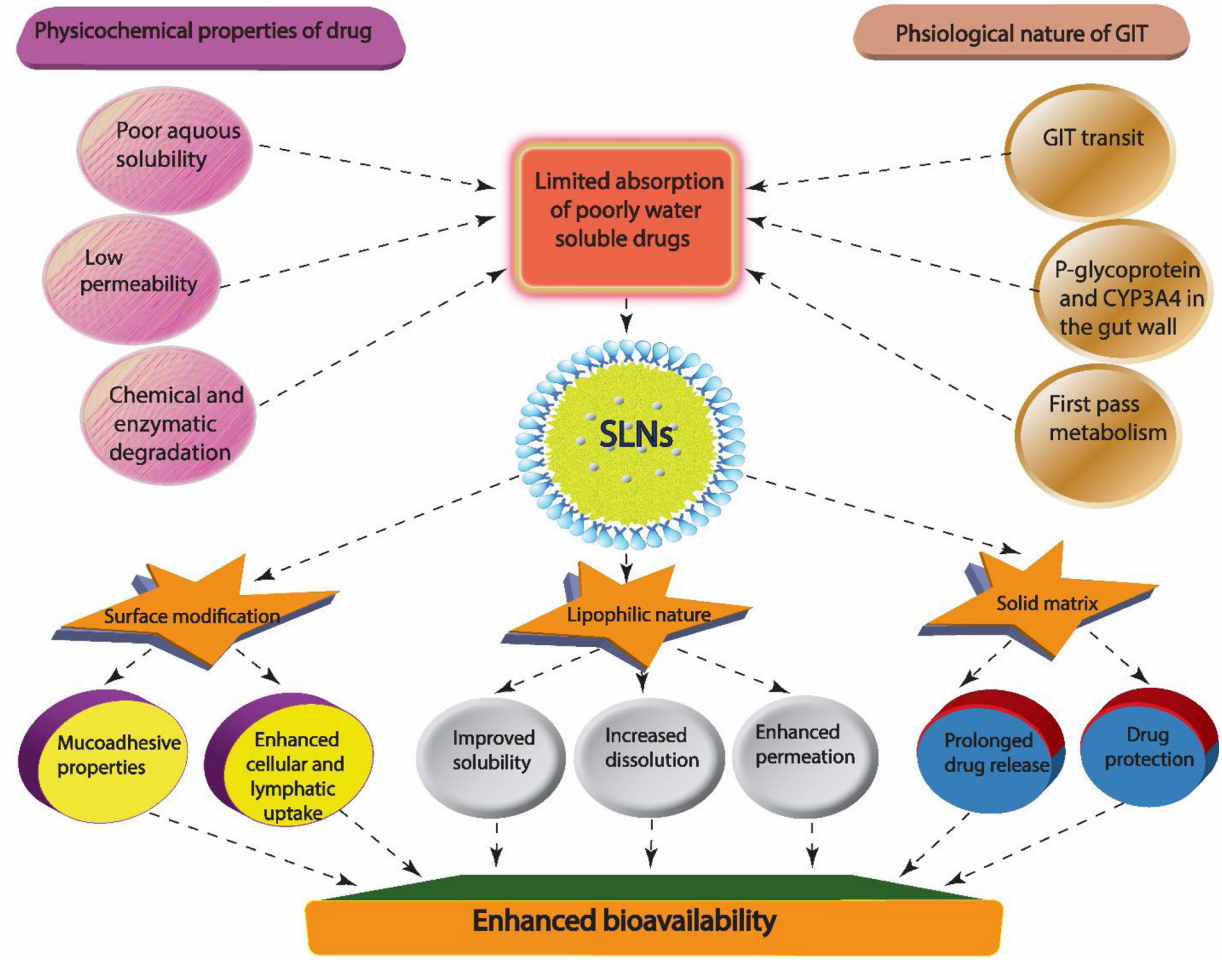

Fig. 1. Schematic representation of the pitfalls of oral drug delivery and SLNs as a promising nanocarrier in the effective delivery of poorly soluble drugs.

are recognized as safe, reliable nanocarrier [16].

SLNs are essentially made of a solid lipid core with a monolayer surfactant shell. Bioactive molecules, especially lipophilic components, can be incorporated into the solid lipid matrix [17] and released in a controlled manner [18,19]. This process of drug entrapment in the core matrix depends on several features, for example, the kinds of solid lipids, drug solubility in the selected lipids, manufacturing techniques, and polymorphic criteria in the lipid matrix [20]. A variety of techniques can be used for fabrication of SLNs. High-pressure homogenization technique (HPH) is strongly chosen to be the convenient popular method because it is easy, time saving and free of organic solvents in the formulation process [20,21]. Recently, a large-scale production of solid lipid-based suspension have been established by a hot melt emulsion combing shear dispersion method, which will promote the industrialization of lipid-based suspension. Lipid nanoparticles with a solid matrix provide ubiquitous advantages such as high drug loading capacity for both hydrophilic and lipophilic drugs [22]. This merit could protect the chemically non stable drugs in external (during storage) and internal (in the gut) environments [22–24]. The lipids used for preparing SLNs should be physiological biocompatible and biodegradable with low or no biotoxicity [25–27]. These lipids have the capacity to promote oral absorption of the entrapped drugs through selective lymphatic uptake [28]. Furthermore, nanoparticles (NPs) formulated by these lipids, result in a higher drug solubility, strong mucosal adhesion with prolonged GI tract residence time [29]. SLNs have the potential to enhance drug oral absorption *via* promoting drug permeation across the GI tract and improving the transcellular uptake of drugs [30–32]. Altogether, lipid nanoparticles based on solid lipid matrix offer a smart potential strategy as effective oral drug delivery.

The objective of this review is to introduce the superiorities and pitfalls of oral drug delivery. Next, recent advances in SLNs for the oral delivery of therapeutic drugs over the last ten years are recapitulated. We provide a detailed overview on the GI uptake and transversal mechanisms of SLNs across the GI barriers *via* different research methods (*in-vitro, in-situ* and *in-vivo*). Finally, the challenges and future perspectives for oral drug delivery by SLNs were also summarized and predicted to explore and design a smart multifunctional nanocarrier. This novel nanocarrier design should confer numerous features to ensure not only superior oral bioavailability by enhanced transcellular absorption, but also ideal sustained release and higher therapeutic efficacy. This review will help the researcher to understand how to discover more efficient and promising SLNs.

2. Superiorities and problems of drug oral administrations

Oral drug delivery system is an ideal and safe drug administration route among other delivery pathways [33,34]. The oral formulations on the market are easier to administer and achieve sufficient therapeutic concentrations *in vivo,* which render the per oral (PO) delivery route the ideal choice [35]. The oral delivery system has shown major advantages over parenteral routes such as eliminating cannula-related infections caused by potential iatrogenic spread of microorganisms through inserted cannula in the patient [36], no risk of thrombophlebitis [37,38] and patient inconvenience is also decreased especially with dangerous infections that could be treated at lower risk and often in a short- term hospitalization or without hospital admission at all [39]. Furthermore,

Table 1
Enhanced absorption of various drugs by SLNs.

Application	Active agent	Limitation	Formulation/ Modification	Lipid type	Emulsifier	Animal Model	Progress achievedby SLNs	Year	Ref.
Cancer	γ- Tocotrienol	Low Permeability	SLNs	Compritol bATO	Lutrol	Male SD[a] rats	Increased bioavailability by 3-fold	2012	[47]
	Cantharidin	Poor solubility	SLNs	GMS[b]	Poloxamer 188	Male SD rats	Improved solubility and oral bioavailability	2013	[69]
	Doxorubicin	Low permeability and instability	PEG SA[c]-SLNs	GMS	Poloxamer 188	Male SD rats	Enhanced bioavailability and prolonged circulation time	2013	[70]
	Tamoxifen	Low Solubility	SLNs	GMS/Stearic acid	Poloxamer 188/Tween 80	Female SD rats	Improved oral bioavailability by 1.6-fold	2014	[71]
	Docetaxel	Poor solubility, P-gp[d] efflux and first pass effect	Chitosan/ HACC[e]-SLNs	GMS	Tween 80	Male SD rats	Increased AUC[f] and C_{max}[g] by 2.5-fold and 4.5-fold	2017	[72]
	Genistein	Low solubility and bioavailability	SLNs	GPS[h]	Poloxamer 188	Male SD rats	Enhanced dissolution rates, absorption and bioavailability	2017	[73]
	Curcumin	Limited solubility and stability	NCC[i]-SLNs	GMS	Soya lecithin and Poloxamer 188	Male SD rats	Increased AUC and C_{max}	2017	[67]
Cardio-vascular related diseases	Puerarin	Poor solubility	SLNs	GMS	Soya lecithin and Poloxamer 188	SD rats	Increased bioavailability more than 3-fold	2011	[98]
	Candesartan cilexetil	Poor solubility	SLNs	GMS	Soybean lecithin and Tween 80	Male SD rats	Improved oral Bioavailability over 12-folds	2012	[99]
	Rosuvastatin calcium	Extensive first pass effect with bioavailability less than 20%	SLNs	Trilurin	Egg lecithin and Poloxamer 188	Male Wister rats	Improved oral bioavailability 4.6- fold	2017	[74]
	Rosuvastatin calcium		PL and PL-PEG[j] SLNs	Compritol 888	Tween 80	Unisex Wistar rats	Improved C_{max}, AUC and performance	2017	[75]
	Olmesartan Medoxomil	Poor solubility and presystemic metabolism	SLNs	GMS	Soya phosphatidylcholine and Tween 80	Male SD rats	Promoted bioavailability by 2.3-fold	2017	[100]
	Olmesartan Medoxomil		SLNs	GMS	Poloxamer 407 and Tween 80	Male Wistar rats	Increased plasma exposure of the drug by 2.3- fold	2018	[101]
	Carvedilol	Low solubility	SLNs	GPS	Lauroyl macrogolglycerides	Male NewZealand white rabbits	Prolonged MRT[k] to 23 h and improved bioavailability by more than 2- fold	2018	[76]
	Ezetimibe	Rapid first-pass effect, P-gp efflux and low dissolution rate	SLNs	Compritol 888 ATO	Tween 80	Male SD rats	Enhanced oral bioavailability by 16- fold	2019	[77]
Central nervous system related diseases	Apomorphine	First pass effect and very low bioavailability	SLNs	GMS	PMS[l]	Male Wistar albino rats	Improved bioavailability by 12 to 13- fold	2011	[102]
	Quetiapine fumarate	First pass metabolism and poor bioavailability (9%)	SLNs	Dynasan 118	Egg lecithin and poloxamer 188	Male Wistar rats	Enhanced bioavailability by 3.7 times	2013	[103]
	Resveratrol	Variable oral bioavailability and quick metabolism	SLNs	Stearic acid	Poloxamer 188	Male Wistar rats	Increased oral bioavailability by 8-fold	2014	[78]
	Zaleplon	Poor solubility and hepatic first-pass metabolism	SLNs	Compritol 888 ATO	Egg lecithin and Poloxamer 188	Male Wistar rats	Long duration hypnotic effect and improved oral bioavailability by 2.7-fold	2017	[104]
	Domperidone	Poor solubility In alkaline media	SLNs	Dynasan 118	Tween 80 and sodium deoxycholate	Wistar male rats.	Enhanced bioavailability by 2.6-fold	2018	[79]
	Lurasidone hydrochloride	Poor solubility and extensive first-pass metabolism	SLNs	GMS	Poloxamer 188 and sodium deoxycholate	Female SD rats	Promoted bioavailability by 5.2-fold	2019	[80]
	Asenapine maleate	Extreme first pass metabolism	SLNs	GMS	Poloxamer 188 and TPGs[m]	Female SD rats	Improved bioavailability by 50-fold	2019	[81]
Infections Viral	Lopinavir	Poor bioavailability	SLNs	Compritol 888 ATO	Pluronic F 127	Male Wistar rats	Enhanced bioavailability	2011	[82]
	Lopinavir		PEG-SLNs	Glyceryl behenate	Poloxamer407	Albino Wister rats	Increased bioavailability by 3.6-fold	2014	[83]
	Darunavir	Low solubility, first pass metabolism, P-gp efflux and low bioavailability (37 %)	SLNs	Caster oil	Sodium oleate	Rats	Increased C_{max} by 2.7-fold	2018	[84]

(*continued on next page*)

Table 1 (*continued*)

Application	Active agent	Limitation	Formulation/ Modification	Lipid type	Emulsifier	Animal Model	Progress achievedby SLNs	Year	Ref.
Bacterial	Isoniazid	Low permeability	SLNs	Compritol 888 ATO	Soy lecithin and Tween 80	Female Wistar rats	Improved bioavailability in plasma by 6 times and brain by 4 times	2013	[85]
	Enrofloxacin	Variable oral bioavailability and bitter taste	Enteric coated-SLNs	Octadecanoic acid	PVA[n]	Three-way hybrid pigs	Enhanced oral bioavailability by 2.6- fold	2019	[86]
	Enrofloxacin		Docosanoic acid SLNs	Docosanoic	PVA	Pigs	Improved oral bioavailability by 2.4-fold	2019	[87]
Fungal	Miconazole	Poor solubility	SLNs	Precirol ATO5	Cremophor RH40, lecithin and dicetylphosphate	Albino male rabbits	Improved oral bioavailability by 2.5-fold.	2016	[88]
Parasitic	Arteether	Poor solubility, low gastric stability and extreme first pass metabolism	SLNs	GMS	Soy lecithin and pulronic F68	Male SD rats	Increased oral bioavailability by 1.7- fold	2014	[89]
	Lumefantrine	Limited solubility and P-gp mediated efflux	SLNs	Stearic and caprylic acid	Poloxamer 188 and TPGs	Male Swiss albino mice	Enhanced bioavailability about 220 %	2017	[30]
Diabetes	Insulin	Gastric instability	Chitosan- SLNs	Witepsol 85E	Tween 80	Male Wistar rats	Enhanced oral bioavailability by 17 % after chitosan coating	2011	[90]
	Insulin		SLNs	Dynasan 118	Soy lecithin and PVA	Male Wistar rats	Enhanced bioavailability of approximately 5 times, compared with solution	2016	[91]
	Glibenclamide	Poor solubility and variable oral bioavailability	Lecithin- SLNs	GPS	Tween 20 and sodium deoxycholate	Male SD rats	Greater hypoglycaemic effect	2016	[92]
	Linagliptin	Hepatic first pass effect and low bioavailability (30 %)	Eudragit L100- SLNs	Stearic acid	Pluronic F68 and PVA	Albino Wistar rats.	Enhanced bioavailability by more than 1.9-fold	2019	[105]
Osteoporosis	Raloxifene	Low solubility and first pass metabolism	SLNs	Compritol 888 ATO	Lecthin and Tween 80	Male SD rats	Increased C_{max} and AUC	2014	[93]
	Alendronate sodium	Low bioavailability and side effects in esophagus and stomach	Enteric coated- SLNs with Eudragit S100	GMS	Lutrol 68	Albino male rabbits	Enhanced oral bioavailability by more than 7.4-fold	2016	[94]
Multiple applications	Cryptotan-shinone	Poor solubility	SLNs	GMS/Compritol 888 ATO	Soy lecithin and Tween 80	Male SD rats	Improved bioavailability	2010	[6]
	Androgra-pholide	Poor solubility And instability	SLNs	GMS and Compritol 888 ATO	Lecithin and Tween 80	Rats	Promoted bioavailability about 2.4-fold	2013	[95]
	Geniposide	Low permeability	SLNs	GMS	Poloxamer 188	SD rats	Improved AUC by 50 times	2014	[32]
	Magnesium lithospermate B	Low liposolubility and permeability	PEG-SA-SLNs	GMS	PEG-SA	Male SD rats	Improved oral bioavailability by 7.5- fold	2018	[96]

[a] Sprague–Dawley rats.
[b] Glycerol monostearate.
[c] Polyethelene glycol-stearic acid.
[d] P-glycoprotein.
[e] Hydroxypropyl trimethyl ammonium chloride chitosan.
[f] Area under plasma drug concentration-time curve.
[g] Maximum concentration of drug in tested area.
[h] Glyceryl palmitostearate.
[i] N carboxymethyl chitosan.
[j] Phospholipon 90G, PEGlated phospholipid: ligands for specific targeting of low-density. lipoprotein receptors.
[k] Mean residence time.
[l] Polyethelene glycol monostearate.
[m] D-α-tocopheryl polyethelene glycol 1000 succinate.
[n] Polyvinyl alcohol.

the widely used oral drug formulations at the market are less expensive than the parenteral medications. The latter usually needs sterile and isotonic diluents, needles, syringes for administration and nursing time, subsequently, it may cause a financial load for the patient [40,41]. The oral route is the most preferable route for the long-term treatment of chronic cardiovascular and cerebrovascular disorders due to superior patient compliance including painfulness and cost-effectiveness [42]. Although the oral therapy has not been very frequently used in cancer chemotherapy, new cytotoxic drugs of oral formulations undergoing preclinical and clinical trials could be seen during the last decade [43]. However, there are influential hurdles confronting the delivery of drug by oral route (Fig. 1). Oral delivery is significantly affected by the physicochemical properties of the drugs. Some drugs or active ingredients show poor aqueous solubility, *e.g.* candesartan cilexetil [44], genistein [45] and domperidone [46], and low-permeability, *e.g.* γ-tocotrienol [47], isoniazid [48] and geniposide [32] that negatively influence the GI absorption. Drugs are potentially degraded in the GI tract due to the high acid content of the stomach, enzymes present in the lumen of intestine, *e.g.* insulin [49], and arteether [50] or interacted with endogenous components such as bile, which alter their absorption. Extreme hepatic first-pass effect and rapid metabolism of drugs result in poor absorption and low bioavailability, *e.g.* ezetimibe [51], lurasidone hydrochloride [52] and asenapine maleate [53]. The absorption of drugs can also be limited by efflux mechanisms. The drug transmembrane efflux proteins such as P-glycoprotein, enormously presented in the epithelial cell membrane, are responsible for the low and variable bioavailability of various agents, *e.g.* lumefantrine [54] and darunavir [55]. Wholly, these bioactive ingredients are unable to attain satisfactory therapeutic performance.

The major obstacle for the oral drug delivery is the fact that the drug should successfully traverse several natural barriers in the GI tract before it can reach lamina propria [56]. The GI tract presents several physical, chemical and enzymatic barriers that hinder drug oral absorption [57]. Poor GI permeability, due to the absorptive epithelial cells, mucus secreting goblet cells and follicle-associated epithelium, including M cells, is another main cause that remarkably affects the oral uptake of many drugs [58]. The highly viscoelastic and adhesive mucus make the oral administered drugs to be rapidly trapped and cleared and, in turn limit their paracellular permeability across the epithelial cell monolayer of the GI tract [59–61]. As well, intercellular tight junctions (TJs) prevent most paracellular trafficking of drugs [62]. Once the drug transverses the layer of epithelial cells, before reaching the blood stream, it encounters another difficulty involving the endothelial cell layer of blood vessels [63]. So, it is fundamental to emerge novel drug delivery systems to conquer these constrains.

3. Progress of SLNs in improving oral absorption of drugs

Parallel to the great development in nanomedicine, SLNs for active ingredient delivery has also emerged rapidly due to their relatively small size (50 − 1000 nm) [11] and thus bypass the physiological barriers more freely. It is noteworthy that the decrease in particle size lead to a significant increase in the surface area of insoluble drug particles, which subsequently results in enhanced absorption *via* monolayer cells of the GI tract [64]. Moreover, the lipid degradation products of SLNs in the intestinal fluid such as glycerides and fatty acids are capable to enhance intestinal transport by production of mixed micelles and subsequently enhance the uptake of drug into the enterocytes [65]. Besides enhanced absorption by the cellular uptake, SLNs can improve the lymphatic delivery through microfold cells (M cells). The improved lymphatic transport decreases the first-pass metabolism, which, in turn, improves drug bioavailability [66]. SLNs have shown a major promising potential to enhance GI absorption and bioavailability of various drugs. These carriers are also valuable for controlled drug release. SLNs are appreciated for a category of versatile drug delivery strategy that have been applied for the treatment of several diseases affecting the heart, blood vessels, brain, central nervous system as well as cancer and infectious diseases. It also recognized as being the most promising approach to the oral delivery of peptide-based drugs, so this important carrier system is urgently needed for a protection against the proteolytic milieu in the stomach. There is a large body of ongoing studies discussing the oral drug absorption improvement by SLNs (Table 1).

3.1. Anticancer drugs

SLNs have been prepared in many studies to orally deliver active agents with great anticancer effect. Baek et al. [67] reported that the surface-modified curcumin-loaded SLNs with N-carboxymethyl chitosan improved the oral bioavailability by 9.5-fold *via* enhancing the cellular uptake and lymphatic uptake (6.3 fold) pathways. In another study, the prepared paclitaxel-loaded trimyristin SLNs with Egg L-α-phosphatidylcholine (PC) and DSPE–methyl polyethylene glycol-2000 (mPEG2,000) as emulsifiers [68] showed enhanced intracellular uptake of paclitaxel in MCF7/ADR by caveola-mediated endocytosis and MCF7 by clathrin-and caveola-independent mechanism. Several other drugs such as γ-tocotrinol [47], cantharidin [69], doxorubicin [70], tamoxifen [71], docetaxel [72], genistein [73] have been successfully shown to have achieved enhanced bioavailability and site targeting, indicating the superiority of SLNs for oral drug delivery.

3.2. Cardiovascular drugs

Many SLNs or modified SLNs payload cardiovascular drugs showed an improved bioavailability, which can further validate their cardioprotective efficacy. For instance, the optimized glyceryl trilaurate SLNs displayed a 4.6-fold increase in oral bioavailability of rosuvastatin calcium as compared with the suspension [74] and thus significantly reduced the lipid profile for 36 h in hyperlipidemic rats. In accordance with this study, a novel surface-engineered SLNs of rosuvastatin was developed for enhancing oral bioavailability [75]. The superficial layer of SLNs was decorated with Phospholipon 90 G (PL) and DSPE-mPEG-2000 (PEGylated phospholipid as ligands for specific targeting to the low-density lipoprotein receptors. The modified SLNs enhanced cellular uptake and permeability across caco-2 cell. The area under plasma drug concentration-time curves (AUC) for the plain SLNs, PL-SLNs and PE-Gylated phospholipid -SLNs was 16.6, 21.2 and 25.1-fold improvement, respectively, over pure drug suspension. The bioavailability of carvedilol was increased more than 2-folds after incorporation into SLNs. Besides improved absorption, the half-life and the mean residence time (MRT) of carvedilol were prolonged from 5.6 to 15.3 h and from 8.7 to 23.19 h by the SLNs [76]. The limited solubilization and bioavailability of ezetimibe can be ameliorated by using SLNs. SLNs made up of Compritol ATO and Tween 80 showed 3 and 16- fold increase in bioavailability as compared to the marketed product and drug suspension, respectively [77].

3.3. Central nervous system drugs

SLNs represent a promising nanocarrier to treat illnesses related to the central nervous system. For instance, resveratrol-loaded stearic acid SLNs stabilized with poloxamer 188 showed a significant 8-fold elevation in the oral bioavailability of resveratrol as compared to pure drug [78]. After inclusion of domperidone into SLNs using Dynasan 118 as the solid lipid and Tween 80 as stabilizers, the oral bioavailability was enhanced more than 2.6-fold compared to domperidone tablet [79]. SLNs could enhance the bioavailability of lurasidone hydrochloride by 5-fold, compared with the suspension. Additionally, they enhanced cellular uptake of lurasidone across the Caco-2 cell line by a clathrin/caveolae mediated endocytosis mechanism [80]. It is more interesting that asenapine-loaded SLNs showed a 50-fold improvement in oral bioavailability compared with the dispersion [81].

3.4. Antimicrobial agents

The SLNs as drug carriers have great potential to achieve the broad intentions for transferring anti-infection agents to treat viral, bacterial, fungal and parasitic infections.

3.4.1. Viral infection

Some studies have shown that the SLNs can enhance the oral absorption of some antiviral drugs and thus improve the therapy effects against different viral infections. Lopinavir is a human immunodeficiency virus (HIV) protease inhibitor used in antiretroviral therapy. SLNs enhanced the cumulative percentage dose of lopinavir secreted into lymph by 4.5-fold higher than pure drug in methylcellulose solution. Higher AUC was obtained for SLNs (2.13-fold) in comparison with lopinavir solution [82]. In another study, lopinavir loaded SLNs showed 4.9 and 3.6-fold increase in C_{max} and bioavailability compared to solution due to higher lymphatic uptake [83]. Darunavir, a second-generation potent protease inhibitor, is used in the treatment of HIV-1 infection. Lymphoid organs are the major reservoirs of HIV. The use of SLNs can enhance the bioavailability of darunavir undergoing hepatic metabolism as well as target the drug to the lymphoid tissues. Darunavir incorporated SLNs showed a 5.7-fold increase in bioavailability as compared to the suspension [84].

3.4.2. Bacterial infection

The enhanced oral absorption for antibacterial agents is widely studied. Isoniazid is the most effective drug recommended by the World Health Organization (WHO) for the management of all forms of tuberculosis. Isoniazid loaded SLNs were developed to achieve improved bioavailability and prolonged circulation retention. Following oral administration, a remarkable enhancement of bioavailability in rat plasma (6 times) and the brain (4 times) was obtained by the SLNs compared to the free drug [85]. Enrofloxacin, known as ethyl ciprofloxacin, is used as a veterinary medicine for the treatment of bacterial infection, such as *Salmonellosis* and *S.aureus* mastitis because of its strong antibacterial activity and effective diffusion across cells. Our group explored SLNs with enteric coating of polyacrylic resin to overcome the limited palatability, variable bioavailability and light instability of enrofloxacin. The bioavailability and MRT of enteric granules containing enrofloxacin SLNs as the core was 2.6 and 2.7-folds greater than that of soluble powder, respectively [86]. In our previous research, the formulated enrofloxacin-loaded docosanoic acid SLNs provided 1.6 and 2.4-fold increase of the oral bioavailability in comparison with the commercial injection and soluble powder, respectively [87].

3.4.3. Fungal infection

The treatment of fungal infections is very difficult and thus it is necessary using SLNs to improve the treatment effects of antifungal drugs. Miconazole is a broad-spectrum antimycotic drug with poor aqueous solubility. Encapsulation of miconazole in SLNs exhibited better *Candida albicans* killing in the diffusion disk test. The maximum inhibition diameter of SLNs was 22 mm longer than that of the marketed capsule (14 mm). Miconazole loaded SLNs was more effective in the treatment of candidiasis with improved oral bioavailability by 2.5-fold [88].

3.4.4. Parasitic infection

Many antiparasitic drugs, such as praziquantel, albendazole, and fenbendazole, have very low oral bioavailability due to their low solubility and first-pass effects. How to improve the oral absorption of these antiparasitic drugs has always been a difficult scientific problem for many pharmaceutical researchers to overcome. Arteether is an artemisinin analog used for curing the multidrug-resistant malaria. It has a therapeutic effect on *falciparum* malaria and cerebral malaria. SLNs were used to address the low stability in the gastric fluid as well as the short half-life of arteether. Arteether SLNs could improve oral bioavailability compared to arteether in ground nut oil by 1.7-fold [89]. Lumefantrine possesses antimalarial activity by inhibiting detoxification of haem, this toxic haem and free radicals induce parasite death. SLNs were used to alleviate the poor and variable oral bioavailability of lumefantrine. The relative bioavailability of lumefantrine was 220 % and the C_{max} was increased to 2.7-fold following administration of SLNs in mice [30].

3.5. Antidiabetic drug

SLNs were developed to protect insulin from the harsh GI environment [90,91]. Approximately 90 % of diabetic patients are suffering from non-insulin-dependent type 2. Glibenclamide, a poorly water-soluble drug used in the treatment of type 2 diabetes. SLNs were prepared with lecithin or PEG coating to increase glibenclamide stability in simulative gastric solution. The oral administration of SLNs in diabetic rats produced a rapid onset of glucose lowering and maintained the reduction for 8 h [92].

3.6. Osteoporosis drugs

Oral raloxifene is approved for treatment of postmenopausal osteoporosis. Tran et al. [93] designed SLNs composed of Compritol 888 ATO as solid lipid for raloxifene delivery. The AUC and C_{max} of SLNs were increased by 2.7 and 3.1-fold compared to the free drug. The enteric-coated SLNs for alendronate delivery were developed to conquer the challenge of crossing GI membrane. The oral bioavailability of alendronate in rabbits was improved 7.4-fold by SLNs [94].

Further bioactive agents with multiple pharmacological activities were predicated for oral absorption improvement by SLNs [95,96]. It is noteworthy that SLNs and modified SLNs are promising colloidal formulation for oral delivery of phytocompounds as curcumin, resveratrol and ferulic acid. SLNs could improve the bioavailability of these bioactive components about 5–10 times greater than that of their natural form. Moreover, surface modification of the SLNs with chitosan, trimethyl chitosan and N -trimethyl chitosan provided a sustained release of their payload bioactive compounds, which lay a cornerstone for fabrication of novel phytocompounds encapsulated into SLNs [97].

4. Absorption and transport mechanisms of SLNs across GI tract

Following oral administration, the NPs must go through the oral cavity, the gastric fluid, intestinal content, and then gets contact to the mucus layer coating the GI tract and lastly the epithelial cells villi. The stomach is lined by a mucous membrane known as gastric mucosa that contains glands which secrete gastric fluid. The gastric mucosa is always covered by a hydrogel layer of thick mucus, composed of large glycoproteins, that is secreted by epithelial cells [106,107]. The continuous mucus secretion and its clearance rate can remove any foreign material, limiting the residence time of orally delivered NPs. To address this obstacle, mucus penetrating particles were developed to effectively enhance the oral drug delivery by penetrating the rapidly cleared, loosely adherent mucus film and be retained longer in the tightly adherent layer [108]. PEGylation of NPs has been used as a strategy to achieve such mucus-penetrating surface properties. In a prior study, the SLN formulation with 10 % PEG (pSLN-10 %) provided the highest levels of drug permeation across the cell layers of a coculture of Caco-2 and mucus-secreting HT29 cells. The oral dosing of pSLN-10 % to rats displayed higher bioavailability 2 and 7.5- fold compared to SLN and drug solution, respectively [70]. A variety of mucoadhesive drug delivery approaches have been engineered to maximize the association between mucus and NPs, and thereby improving mucosal delivery of therapeutics [109]. Chitosan-based or chitosan-coated NPs are considered the most common design of mucoadhesive systems [110,111]. Chitosan coating was found to increase intestinal absorption of SLNs payload insulin [90] and curcumin [112]. Intestinal villus, the complex

structure of the GI tract, is covered by different intestinal cells as absorptive enterocytes, mucus secreting goblet cells, and M cells. These cells are linked together *via* TJs that massively increases the surface area available for drug absorption [113]. The biological and peristaltic nature of the GI tract together with its content can lead to low accessibility and absorption of the drug active ingredients due to the chemical and enzymatic degradation, the clearance of the drug and the low epithelium permeability [114,115]. SLNs play important roles in enhancing the oral absorption of water insoluble drugs by solubilization of the digestion products (micelles, mixed micelles, vesicles and free fatty acids) in the lumen of the gut [116]. The NPs and degradation products are taken up by passive diffusion, facilitated diffusion and active transport across the enterocyte membrane. In order to reach blood circulation, the absorption of SLNs can be initiated through different routes such as paracellular, transcellular and lymphatic transports.

4.1. Paracellular uptake

The paracellular gap constitutes not more than 1% of the intestinal mucosal surface. The smaller hydrophilic and charged particles may cross the epithelial cell layer through the paracellular route. Particles could pass through the TJs in the paracellular pathway. The space and environment between cells regulate the drug translocation across the intercellular route [117,118]. In most approaches of nanocarrier, the paracellular transport may be toxic when inevitably other constituents of the feces are diffusing *via* the opened TJs and also simply not feasible for some drug translocation due to size restrictions and lack of sensitivity of transport molecules once opened up [119]. The TJs block the most paracellular transport of drug molecules larger than 1 nm [120] and weighing more than 200 Da. However, hydrophilic drug molecules weighing less than 200 Da can freely move to pass through this route [121].

The TJs comprises of three distinctive parts: tight junctions or zonula occludens, zonula adherens and macula adherens. The division of TJs is known to have a pivotal role in the nonspecific translocation of NPs that do not have receptors or mediators on the epithelial cell surfaces. The paracellular transport of NPs can occur through the closing and opening of TJs between epithelial cells. The negatively charged proteins of TJs are amino acids with ionizable side chains which may alter the paracellular translocation of drug molecules due to charge-charge interactions. Nonetheless, this transversal route can be improved by applying permeation enhancers such as calcium chelators, polyacrylic acids and polymers. The latter has been found to be able to reversibly open TJs *via* induction of a cascade of reactions and interactions between the negatively charged cell membrane and the positive charges on the polymers, which ultimately result in TJs disassembly and in turn improve the particle transport between adjacent cells. From another point of research, calcium chelators based nanocarriers could reversibly disrupt the TJs through activation of protein kinase C, which subsequently increased the paracellular permeation through the intestinal epithelial cells [122–124]. Also, chitosan could increase the paracellular permeation *via* reversible distribution of TJs. This virtue has been emphasized in the Caco-2 cell monolayers model, in which, transepithelial electrical resistance (TEER) diminution and actin filaments redistribution were observed [125]. However, this paracellular permeability enhancing mechanism is likely to be safe since it does not result in increased absorption of the common lipopolysaccharide endotoxin found within the GI tract. This indicates that TJs disruption is not accompanied with increased permeability to endotoxins [126].

4.2. Transcellular uptake

In the GI tract, particles can be absorbed through different sites and mechanisms according to their actual size. For example, active molecules with a diameter of 1 μm could be absorbed *via* intestinal phagocytosis, whereas smaller particles (< 10 μm) may be absorbed through the Peyer's patches associated M cells. NPs (< 200 nm) can be transported by endocytosis process through intestinal enterocytes [127]. Intestinal epithelial cells can uptake NPs *via* various facilitated transcellular mechanisms. Transcellular uptake of NPs is mainly initiated by energy-dependent specific endocytic mechanisms [128] or by non-specific processes, which rely on particle diameter, surface charge and mucobioadhesive properties [129]. Transcellular uptake process encountered a major epithelial barrier to transport NPs from the intestinal lumen to systemic circulation [130]. The transcellular transport is an active energy dependent mechanism that occurs *via* specific receptors and carriers [131].

Generally, the transcellular transport of NPs is operated by one of these active endocytic processes: phagocytosis (zipper and trigger like mechanism) and pinocytosis including (macropinocytosis, clathrin-mediated and claveolin mediated endocytosis as well as clathrin non -mediated and claveolin non-mediated endocytosis (*e.g.*, Arf6, flotillin, Cdc42 and RhoA-dependent endocytosis). Through these mechanisms, NPs are engulfed at the apical membrane, and then released into the basolateral compartment of enterocytes. The process is started by pinching of vesicles from the membrane followed by internalization of the extracellular contents and transferring to subcellular compartments [132] (Fig. 2).

The transcellular transport of SLNs across intestinal epithelial barriers could be characterized *via* several techniques, including flow cytometry (FM), transmission electron microscopy (TEM), confocal laser scanning microscopy (CLSM), total internal reflection fluorescence microscopy (TIRFM) [133] and addition of endocytic inhibitors and transcellular tracers [134]. The CLSM can efficiently evaluate the co-localization of nano delivery systems with specific endocytosis markers. For example, cholera toxin is used as a marker of caveolae raft-mediated endocytosis and transferrin is a marker of clathrin-mediated endocytosis [135]. As well, the localization of NPs within the cell organelles could be identified through the probe labelling. LysoTracker, ERTracker or MitoTracker probes can be used to image the lysosomes, endoplasmic reticulum (ER) and mitochondria, respectively [136]. However, *in vitro* cell monolayers grown on inserts using specific chemical inhibitors are common to investigate cellular mechanistic studies. The transport mechanism across the Caco-2 cell monolayer was assessed in the presence of different inhibitors, such as sodium azide, that has been reported to inhibit endocytosis [137]. Other uptake inhibitors, including chlorpromazine (clathrin inhibitor), MβCD, filipin (claveole inhibitor), cytochalasin D, EIPA (macropinocytosis inhibitor) were used to deeply identify the process of endocytosis. Endocellular transport between organelles was evaluated by addition of different inhibitors, such as brefeldin A inhibits transfer between ER and Golgi apparatus, monensin inhibits conveyance between the Golgi apparatus and cell membranes, nocodazole inhibits of microtubule, bafilomycin A1 inhibits the maturation process of lysosomes [133]. In addition, propranolol was used as a tracer for transcellular pathways [138].

Clathrin-mediated endocytosis and caveolin-mediated endocytosis appear to be key mechanisms in most of the examined nanomaterial in different cell lines [8,80,81,139]. It is validated that more than one pathway has been utilized by various NPs for the endocytic uptake. Desai and Thakkar demonstrated that the Caco-2 uptake of SLNs was mediated *via* clathrin- and caveole-mediated pathways and not *via* macropinocytosis and SLNs preferably used caveole dependent endocytic pathways [84]. Transport of NPs *via* the transcellular pathways depends on the physicochemical properties of NPs, for instance, the more NPs diameter decreases, the more NPs transcytosis increases [140,141]. After the occurrence of NPs cellular uptake *via* one of the endocytic mechanisms, further trafficking lines are then determined; the particle may be degraded in lysosomes or passed to a specific cellular organelle or released its content inside the cytosol, the cell might also withdraw it out to the extracellular space [142]. The available data *in vitro* demonstrated that SLNs were destined in the lysosomes and endoplasmic reticulum after uptake [99]. Nonspecific passive diffusion

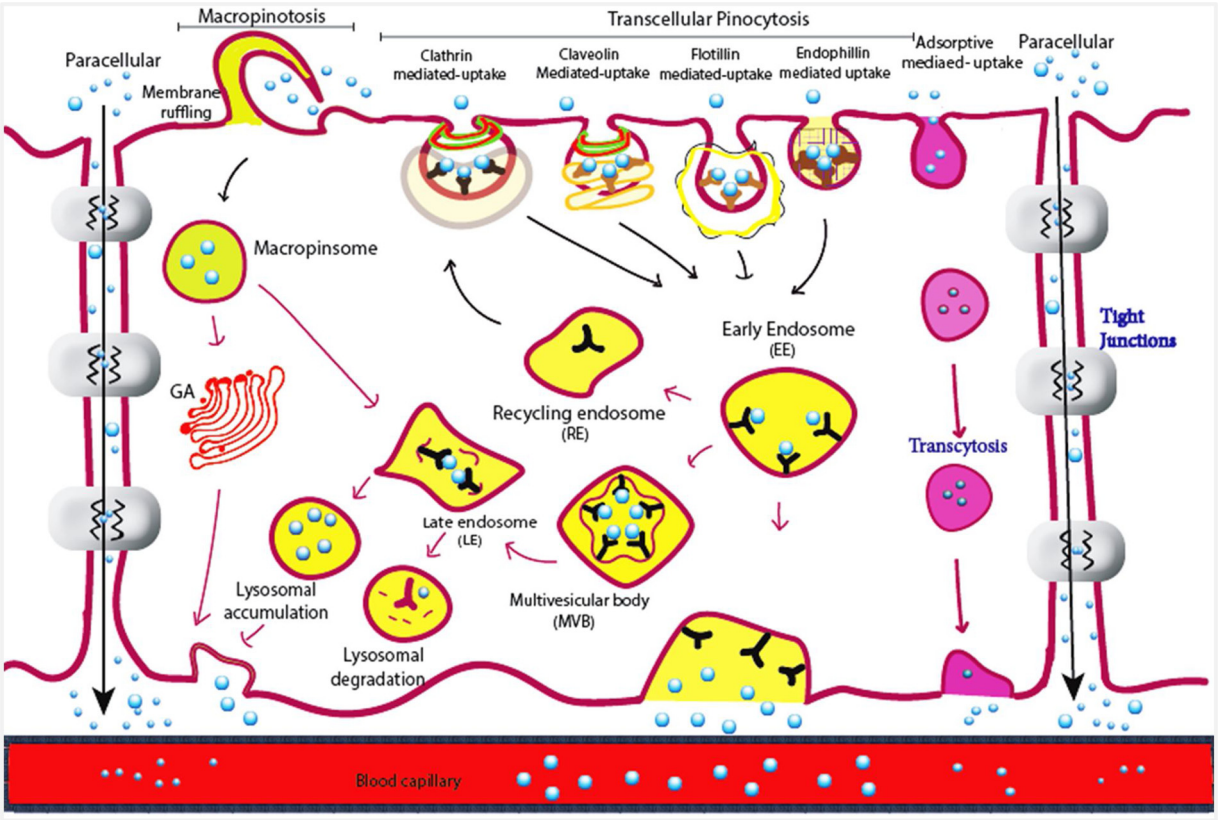

Fig. 2. Schematic of different mechanisms of NPs intracellular pathway. There are multiple routes for the cellular entry of drug nanoparticle. This entry is initiated by receptor and non-receptor mediated endocytosis as clathrin, claveolin, flotillin and endophilin mediated uptake, in addition micropinocytosis and adsorptive mediated transport. After the nanoparticle entry, complex intracellular trafficking is induced to release the nanoparticle outside the cell through the exocytosis mechanism or degrade it within the cell through the endolysosomal trafficking.

mechanism usually transports hydrophobic NPs through the apical cell membrane. However, the majority of hydrophilic particles cannot be absorbed *via* this inactive permeability route [143]. Once NPs reach the apical side of the cells, another possibility of drug uptake is performed through the active transcytosis process, the process starts with endocytic uptake, then intracellular vesicle transport within the cell, finally a vesicle withdrawal from the interior of the cell by exocytosis [144]. After the cellular uptake of nanocarrier, the vast majority gets passed along the endolysosomal trafficking pathway involving a transport from early to late endosomes and their fusion with lysosomes [145–147]. Within the lysosomal stage, NPs either get degraded *via* enzymes or is markedly accumulated depending on the nanoingredients. So, the potential challenges of drug transcellular trafficking are to mitigate or completely avoid endolysosomal pathway or to elicit endosomes or lysosomes to fuse with the cell membrane releasing nanoparticle or nanocarrier get away from the endolysosomal system to exit from the cell [148]. The process, called cellular exocytosis, is proposed to be a vital process with high interest in the most nanocarrier application systems due to the fact that NPs need to be successfully released from the cell [149]. Efficiency of transcytosis of NPs is proportionally related to their cellular exocytosis events. Several exocytosis pathways can be initiated depending on endocytosis mechanism. For instance, lysosomal escape subsequent exocytosis or lysosomal fusion with the plasma membrane and, multivesicular body (MVB) or late endosome fusion with the plasma membrane and fusion of caveolae with the plasma membrane [150,151]. Up to now, the exact mechanisms of transcellular translocations of NPs are still not totally understood. The proceeds of transcellular transport especially endolysosomal trafficking, mark a key challenge, are not sufficient to appreciate the potential application of a majority of nanocarriers [152,153]. It is evident that the transcytosis efficiency differs according to the charge of NPs. The positively charged NPs are able to evade the lysosomes, whereas the negatively charged NPs concentrate inside lysosomes [154].

Most of SLNs transport studies have been presented in terms of permeability and not in terms of transport mechanisms. However, some mechanistic studies of SLNs transport across Caco-2 cell monolayers have been developed. One important example, the endocytosis and transcytosis of the SLNs were mediated by micropinocytosis, clathrin- and caveolae pathways. SLNs were distributed in the transferrin related endosomes, lysosomes and endoplasmic reticulum after internalization. The endoplasmic reticulum, Golgi apparatus, and microtubules were determined to be the main organelles for transport of the SLNs to both the basolateral and apical membrane sides and discharging the SLNs out of the cells. The transport of intact SLNs to the basolateral membrane side were demonstrated. These results indicated that the SLNs can protect the loaded drugs from degradation in the GI tract and enhance the permeability of drugs crossing the intestinal epithelial cell monolayers [133]. Similarly, the uptake of SLNs occurs largely through a clathrin-mediated endocytosis mechanism. Caveolae-mediated endocytosis also displays a prominent role in the uptake of SLNs. Regarding the transcytosis pathway, SLNs were able to traverse the intestinal barrier by a preferential transcellular route [8].

4.3. Lymphatic uptake

The lymphatic system holds a basic role in absorption of triglycerides, long-chain fatty acids, lipid soluble vitamins, and xenobiotics [155]. Drug delivery *via* the lymphatic system provides major benefits, involving circumventing hepatic first-pass metabolism and targeting active drugs to infection that circulate through this system. For NPs cellular uptake, lymphatic capillaries of the lymphoid follicle-

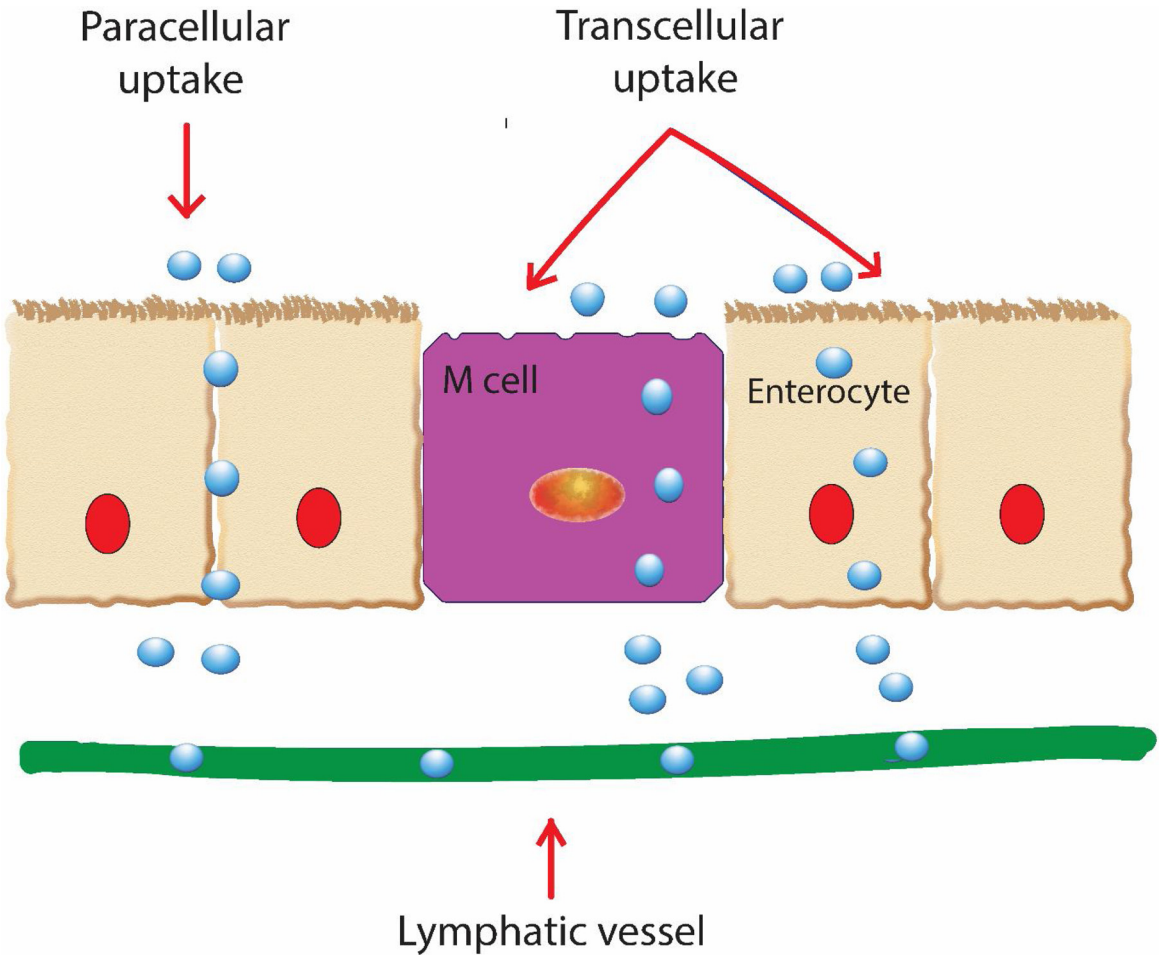

Fig. 3. Schematic of various mechanisms of transporting SLNS through the lymphatic system. The lymphatic transport of SLNS includes M cells of Peyer's patches, transcellular and paracellular pathways.

associated epithelium are significantly more permeable than the adjacent blood capillaries. Various mechanisms of transporting the drug through the lymphatic areas after the oral administration were reported. These encompass M cells of Peyer's patches, transcellular mechanism and paracellular mechanisms. The transcellular pathway is the most fundamental mechanism (summarized in Fig. 3) for the uptake of lipid-based nanocarriers [156]. M cells, located in Peyer's patches in the small intestine, are considered a promising target for the intestinal transcytosis of nanodrugs [157]. M cells embody a potential entry portal for oral drug delivery due to their high transcytotic efficiency [158,159] and low intracellular lysosomal activity [160]. M cells exhibit both specific and nonspecific receptor-mediated mechanisms for NPs uptake, such as actin-dependent endocytosis [161]. The administration of a drug with a long side lipid based nanocarriers, provokes chylomicron formation by enterocytes, which further solubilizes the lipophilic drug into the nonpolar core and thus persuades the uptake of aquaphobic drugs into the intestinal lymphatics [162]. Lymphatic uptake is influenced by the hydrophobicity of NPs, lipid nature, and chain length [163]. The oral route exposes drugs to presystemic hepatic metabolism, which can reduce drug absorption. In order to circumvent this problem, lipid based nanocarriers absorbed *via* the intestinal lymphatic system are basically protected from the hepatic first pass effect. So, the transport *via* the lymphatic system can significantly enhance the oral bioavailability of drugs that extensively metabolized by the liver [164]. Several studies related to the lymphatic uptake of SLNs after oral administration have been carried out [161,162,165]. For example, an attempt to enhance the oral bioavailability and target intestinal lymphatic transport of nimodipine was performed by using SLNs [166]. After a single oral dosing of optimized nimodipine-SLNs with a mean diameter of 116 nm at 8 mg/kg in rats, the bioavailability of nimodipine increased 2-fold compared with the drug alone. Interestingly, the lymphatic uptake of N-carboxymethyl chitosan-SLNs incorporating curcumin were found to be 6.3-fold more than that of drug solution [67]. In another study, the *in vivo* lymphatic transport of hydroxysafflor yellow A (HSYA)-loaded SLNs was determined in animal pretreated by cycloheximide to block the secretion of chylomicrons from the enterocyte afore oral administration. Cycloheximide pretreatment markedly lowered the oral absorption of HSYA delivered by SLNs, which indicated that the oral absorption of HSYA-SLNs largely depended on lymphatic transport in intestine [167].

5. Method developments for oral absorption and transport of SLNs

Some transport studies based on various models (*in vitro*, *in situ* and *in vivo*) have been extensively used to understand the absorption mechanisms of SLNs across the GI tract. The intestinal epithelium is made up of a cell monolayer, which is mainly composed of enterocytes interspersed with mucus-secreting goblet cells and specialized epithelial M cells. Subsequently, a variety of *in vitro* cell models have been developed and further investigations are typically conducted using various cell lines mimicking the *in vivo* intestinal barriers to assess the cellular uptake mechanisms of SLNs.

Table 2
Cellular uptake and transport mechanisms of SLNs across the Caco-2 cell monolayer models.

Formulation	Active ingredient	Lipid type	Surfactant	Study method	Transport mechanism /outcomes	Year	Ref.
Chitosan- coated SLNs	Insulin	Witepsol 85E	Tween 80	- Permeability studies	-Enhanced absorption and permeability	2011	[90]
SLNs	Risperidone	Compritol 888 ATO	Tyloxapol	-Transport studies	-Enhanced transport	2012	[178]
SLNs	Candesartan cilexetil	GMS[a]	Tween 80	-Cellular uptake studies byendocytosis inhibitor	-Clathrin and caveolae mediated endocytosis	2012	[99]
Stearic acid–octaarginine modified SLNs	Insulin	Stearic acid	Poloxamer 188	-Transport experiments	-Increased the internalization of insulin 18.4 times.	2012	[175]
Chitosan -coated SLNs	Iron	Stearic acid	PVA[b]	- Absorption studies	-Improved iron absorption	2013	[173]
SLNs	Androgra-pholide	GMS and Compritol 888 ATO	Tween 80	-Transport studies in presence of P-gp substrates	-The cellular transport associated with active carrier P-gp	2013	[95]
SLNs	Carvedilol	Compritol 888 ATO	Poloxamer 188	Cellular uptake-investigation	-Prolonged drug release	2014	[174]
SLNs	β-carotene	Sodium caseinate/ Whey protein isolate (1% fat)	Sodium caseinate/ Whey protein isolate	-Cellular uptake studies	-Enhanced transport	2014	[179]
SLNs	Zanamivir	GMS	PVA/Poloxamer 188	-Transport studies	-The uptake ability of zanamivir loaded SLNs significantly decreased.	2015	[177]
ODA-FITC[c]-Labeled SLNs	Au Nanoparticle	GMS	Poloxamer 188	-Transport studies *via* endocytosis and endocellular inhibitor	-Clathrin and caveolae mediated endocytosis -Micropinocytosis -Vital organelles in transport include, lysosome, ER[d] and Golgi apparatus	2016	[133]
Phospholipon 90 G And DSPE-mPEG-2000[e]-SLNs	Rosuvastatin calcium	Compritol 888	Tween 80	-Endocytotic uptake study in presence of filippin and Sucrose	-Enhanced cellular uptake	2017	[75]
HA2[f] peptide-SLNs	Insulin	Tripalmitin and stearic acid	Pluronic F68			2018	[176]
				-Permeability studies	-Clathrin-mediated transport.		
				-Cellular uptake study by flow cytometry, endocytic inhibitor and Eliza method	-Improved permeability from 1.5- to 2.4-fold		
				-Intracellular endolysosomal study	-Clathrin-mediated endocytosis		
				-The transepithelial transport study	-Lower colocalization of insulin noticed with late endosomes and lysosomes		
SLNs	Lurasidone hydrochloride	GMS	Poloxamer 188	-Uptake study using confocal microscopy and endocytosis inhibitor	-Both clathrin and lipid raft/caveolae mediated endocytosis	2019	[80]
				-Permeability study	-Improved permeability and transport efficiency across the intestinal barrier		
SLNs	Asenapine maleate	GMS	Poloxamer 188	-Cellular uptake study by confocal microscopy, flow cytometry and endocytosis inhibitor	-Increased permeation by 7.6 times *via* both clathrin and claveolae mediated endocytosis	2019	[81]

[a] Glycerol monostearate.
[b] Polyvinyl alcohol.
[c] Octadecylamine fluorescein isothiocyanate.
[d] Endoplasmic reticulum.
[e] PEGylated phospholipid.
[f] Hemagglutinin-2 peptide endosomal escape agent.

5.1. In vitro cell culture models

5.1.1. Caco-2 cell type

As an alternative to the animal models, Caco-2 cell type is the most extensively used as a model of intestinal cell barrier. In culture, Caco-2 cells, a human epithelial colorectal adenocarcinoma, differentiate spontaneously into a polarized epithelial cell monolayer which has remarkable morphological and biological similarity to that of intestinal epithelium. When they reach a confluent monolayer on cell culture filter, Caco-2 cells well express TJs between adjacent cells, microvillar transporter and efflux proteins [168]. As well, a considerable amount of P-glycoprotein is established, which frequently proposed as an additional factor affecting drug absorption and pharmacokinetics [169]. This makes these cells a powerful excellent tool to predict and understand underlying carrier mediated mechanisms of uptake of NPs, therapeutically relevant proteins, peptides and chemical compounds across human intestinal tissue [170–172].

Caco-2 cell monolayer was selected as a model for absorption and transport studies of drug loaded SLNs [99,173,174]. Table 2 summarizes *in vitro* cellular uptake and internalization studies of various active ingredients loaded SLNs using the Caco-2 cell as type model. Absorption improvement of insulin by SLNs and chitosan-coated SLNs were identified through the Caco-2 cell monolayer [90]. In another study, the SLNs consist of the stearic acid octaarginine increased the Caco-2 cell's internalization of insulin by up to 18.4 times compared to the insulin solution [175]. In a novel study, SLNs with an endosomal escape agent efficiently facilitated the escape of the loaded insulin from the acidic endosomes [176]. The iron absorption of Caco-2 from chitosan coated SLNs was greatly higher than ferrous sulphate and unmodified SLNs [173]. The asenapine -SLNs permeation increased 7.6 times across Caco2 compared to the asenapine dispersion at 4 h [81]. In contrast to the above positive results, SLNs prepared from glyceryl monosterate significantly decreased the potential transport of zanamivir across the Caco-2 cell monolayers at 4 h [177]. Consequently, the more tests and errors lead to faster advances. The actual absorption mechanism of developed SLNs is needed to be tried using different *in vitro* permeability paradigm, which can express the *in vivo* intestinal mucus conditions.

Even though the Caco-2 cell monolayer model is commonly used and generally accepted as standard for assessment of intestinal transport, this model reveals certain limitations such as lack of mucus that is the main characteristic for the intestinal mucosa. So, a co-culture model, involving human HT29-MTX (goblet-like cells) with Caco-2 cell type has been developed [180] to mimic the mucus barrier covering the intestinal cells. The co-culture model provides a transport environment that is similar to that of the human intestinal epithelium [181]. Consistently, available data demonstrated that SLNs were absorbed in greater extend when HT29 cells were present, emphasizing the role of mucus in the retention of NPs on the intestinal epithelium (summarized in Table 3). For instance, a Caco-2/HT29 co-culture monolayer model was used for understanding the potential role of chitosan on the intestinal absorption of insulin [90]. Compared with the Caco-2 monolayer, chitosan-coated SLNs containing insulin presented greater transport either paracellularly or transcellularly across the co-culture monolayer model. So, chitosan coated SLNs appear to stabilize and protect entrapped insulin from degradation in the GI tract that, in sequence, increase the concentration of NPs at the site of absorption and enhance its permeation. In another study, cationic SLNs loaded with insulin for oral delivery were prepared with average size lower than 300 nm and a zeta potential higher than 33 mV. The cationic SLNs remarkably increased the transport of the encapsulated insulin through the Caco-2/HT29 co-culture monolayer cells from 1.16 to 2.89 % after 4 h [182]. Importantly, polyethylene glycol (PEG) was conjugated onto monostearin to fabricate SLNs with superior mucoadhesive property. The PEGylated SLN exhibited higher permeability of doxorubicin through *in vitro* mucus secreting cells by 5-fold than unmodified SLNs

Table 3
The cellular uptake and transport mechanisms studies of SLNs using Caco-2/HT29 coculture cell monolayers.

Active ingredient	Lipid type	Emulsifier	Modified surface	Study method	Transport Mechanisms	Year	Ref.
Insulin	Witepsol 85E	Tween 80	Chitosan	Permeability studies	-Increased paracellular permeability and mucoadhesion	2011	[90]
Doxorubicin	Monostearin	Poloxamer 188	PEG-stearic acid	Permeability study	-Increased permeability than Caco-2 cell monolayer -Improved permeability of modified SLN by 5- fold, while just 3.9-fold by SLN.	2013	[70]
Curcumin	Trimyristin	Soy lecithin and Poloxamer 407	–	Transport studies	-Simple diffusion transport and enhanced delivery	2013	[183]
Salmon calcitonin	Stearic acid	Poloxamer	CSK[a] or IRQ[b] peptide ligand	Uptake study	-Enhanced uptake by modified SLNs	2014	[184]
	Tripalmitin	188			-Active transport *via* both clathrin- and caveolae-dependent endocytosis		
Insulin	GPS[c]	Lecithin and Poloxamer 124	PEG[d]	Transport study	-Improved passage and transport of cationic-SLNs	2016	[182]

[a] CSKSSDYQC peptide ligand with affinity to goblet cells.
[b] IRQRRRR a cell-penetrating peptide.
[c] Glyceryl palmitostearate.
[d] polyethylene glycol.

[70]. It was proved that SLNs possess potential to deliver curcumin in a coculture cells. The transport pathway of the solid particles was simple diffusion, with permeability rates of about 3×10^{-6} cm s^{-1} [183].

Co-culture of Caco-2 cells with human Raji B lymphocytes has been developed to provoke M cell like phenotype in the Caco-2 cells that mimic the human follicle associated epithelium (FAE) [185,186]. Since the cellular transcytotic capacity is induced by the transformation to the FAE-like phenotype. So, the co-cultures have frequently been used to study transcellular transport of several bioactive molecules and NPs [187]. Remarkably, the caveolin protein expression is increased in the M-cell like cells [188]. Recently, a potential intestinal *in vitro* triple culture model, including enterocytes, mucus secreting HT29-MTX cells and M cells was established [189]. This strategy can offer a further verification to design more efficient orally administered NPs able to overcome transport cellular barriers. However, there is a paucity of studies to date have used triple culture models to evaluate the absorption and transport kinetics of SLNs. Consequently, supplementary researches will need to be performed by an evolutionary procedure to confirm their applicability to the field of nanotechnology.

5.1.2. MDCK cell line

Scientists also investigated the use of Madin-Darby canine kidney (MDCK) as a useful tool to assess the membrane permeation characteristics of early drug ingredient discovery. Under standard culture conditions, MDCK cells express intercellular TJs and form polarized monolayer cells. The main virtue over Caco-2 cells is the shorter culture time till reach confluence. Subsequently, labor and cell contamination are reduced [190,191]. Nevertheless, the canine (non-human) and renal (non-intestinal) origins of the MDCK cells are considered as drawbacks and should also be thought out before using the MDCK cell model as a main screening strategy for drug absorption. Few studies have been reported on the transport mechanism of SLNs in MDCK epithelial cells (summarized in Table 4).

5.1.3. In vitro everted gut sac technique

The everted gut sac model is a convenient and easily handled *in vitro* method to examine the intestinal absorption of drugs [195], in which a segment of the intestine is cut off from animal following laparotomy and then everted and used to evaluate drug absorption under certain conditions. In this model, adjustments and improvements have been performed to increase the viability of tissue, and maintain intact mucosal epithelium that mimics the *in vivo* conditions. The advantages of this model are a relatively large surface area accessible for absorption and the presence of a mucus layer. Nonetheless, the tissue viability is one of the limiting parameters [196,197]. The everted gut sac model is used to assess the intestinal permeability of SLNs and their payload drugs (summarized in Table 5). For example, the *in vitro* permeability of sulpiride after inclusion into SLNs was enhanced to 11.7 mg/cm2 in comparison with the drug (6.6 mg/cm2), which can be explained by the enhancement of the surface area, leading to a higher rate of diffusion [198]. The performance of SLNs for promotion of praziquantel and insulin efficacy were also elucidated [91,199]. In a recent study, greater permeation was noted at each time point of the permeability study of artesunate-encapsulated SLNs [200].

5.1.4. Ussing chamber

Ussing chamber has been used as an intestinal membrane model to evaluate the permeation efficiency of NPs [184]. Recently, isolated intestinal mucosa has been used to be mounted in Ussing chamber as a natural membrane model to assess the absorption efficiency of NPs. This technique is helpful to overcome the pitfalls of monolayer model that lack the three-dimensional (3D) macrostructure necessary for cell differentiation. Although these techniques provide accurate measurement tools of intestinal absorption, they have some limitations. The isolated intestinal segment is rapidly lost, so it is required to repeat experiments to obtain fresh tissue. Subsequently, large numbers of animals are used. However, there is a paucity of information about permeability studies of SLNs by using the Ussing chamber technique. Fan et al. [184] developed salmon calcitonin-loaded SLNs interfused with peptide ligand CSKSSDYQC, which showed an affinity with goblet cells in the epithelium, or IRQRRRR, which is a cell-penetrating peptide. The permeability of salmon calcitonin measured by Ussing chamber technique showed that the apparent permeability coefficients of salmon calcitonin-SLNs, CSK and IRQ-SLNs were 2.1, 5.9 and 4.7-fold greater than that of salmon calcitonin solution.

5.1.5. 3D culture model

At the moment, new cell culture models have been developed to provide a more physiologically microenvironment mimicking the natural extracellular matrix, such as a 3D culture model [62,201]. In 3D culture model, cells are completely embedded in extracellular matrix that maintain cell differentiation, communication between cells and hemostasis [202,203]. As compared to two dimensional (2D) culture model, 3D model induces a more physiologically relevant environment. However, efforts have been made to improve upon 2D Caco-2 cell culture and create a coculture of cells with fibroblast cells to imitate the intact intestine [204]. Up to now, microfluidic organs-on-chip is proposed to be the most advanced *in vivo*-like culture systems. Gut-on-a-chip technology strategy has also been used with Caco-2 cells [205]. Furthermore, cellular mucin expression from Caco-2 cell is increased when 3D collagen villi scaffolds have been used for Caco-2 cell culture type [206]. In recent times, the 3D culture model has been adopted and become valuable techniques to provide a more physiologically consistent micro-environment imitating the natural cellular and extracellular components of intact intestine. This innovative strategy may propose a further evidence to design more efficient orally administered NPs. Nevertheless, this is an under explored area and only a few studies to date have used such 3D culture models to evaluate drug delivery

Table 4
Cellular uptake and transport mechanism studies of SLNs across MDCK cell monolayer model.

Study method	Formulation	Lipid type	Modified surfaces	Transport mechanism	Year	Ref.
Cellular uptake studies	ODA-FITC labeled SLNs	GMS	–	-Micropinocytosis -Caveolae and clathrin-mediated pathways	2014	[192]
Transport studies	SLNs	GMP/[a] GMS/[b] GMB[c]	PEG -SA 2000	-Vesicle-mediated mechanism.	2016	[193]
Permeability studies	Carbamazepine-SLNs	Myristate		-Enhanced permeability of carbamazepine with a confidence of 95 %	2018	[194]
Permeability studies	Magnesium lithospermate B-PEGylated SLNs	GMS	PEG-SA[d], 2000	-Enhanced cellular transport and improved diffusion through the mucus barriers by PEGylation	2018	[96]

[a] Glycerol monopalmitate.
[b] Glycerol monostearate.
[c] Glycerin monobehenate.
[d] polyethylene glycol monostearate.

Table 5
Absorption evaluation of SLNs using *in vitro* everted gut sac technique.

Study method	Active ingredient	Formulation	Average size (nm)	Findings	Year	Ref.
Intestinal permeability study in rats	Doxorubicin	PEGylated SLNs	153 – 160	-Increased permeability -Higher penetration to mucous secretion	2013	[70]
	Sulpiride	SLNs	148 – 299	-Enhanced permeability	2014	[198]
	Praziquantel	SLNs	506	-Increased activity against the parasites located in mesenteric veins of intestine	2014	[199]
	Insulin	SLNs	99	-Improved permeability of insulin by 2-fold	2016	[91]
	Artesunate	SLNs	1109	-Enhanced permeability and therapeutic efficacy	2018	[200]

strategies. In the future, further trials, which take novel models of drug delivery into account, will need to be performed to confirm the applicability of drugs delivered *via* SLNs.

5.2. In situ perfusion method

In situ perfusion of intestinal segments is generally used to examine the prediction of intestinal permeability and transport pharmacokinetics of drug molecules. The major virtue of the *in situ* system compared to the *in vitro* approach is the presence of normal neurovascular structure suppling intestinal segments [207]. Nevertheless, the use of single pass intestinal perfusion method is strictly limited because this method primarily depends on the luminal disappearance of ingredient as an indicator of absorption, but the rate of decrease of concentration in the perfusate does not always reflect the rate of uptake of the drug into the blood, especially for ingredients undergoing pre-absorption or luminal metabolism. However, a considerable number of studies have used *in situ* intestinal absorption method for assessment of SLNs permeability. One notable example, Li et al. used SLNs as a vehicle for oral delivery of quercetin [208]. It was validated that quercetin loaded SLNs with a mean diameter of 155.3 nm and encapsulation of 91 % could be absorbed from duodenum, jejunum, ileum and colon segment of intestine. The absorption of SLNs mainly occurred through ileum and colon segments, and thus SLNs can be absorbed as nanoparticle phase through Peyer's patches and M cells in the ileum and colon. Similarly, the absorption of simvastatin incorporated SLNs was increased and varied with the site of the intestinal segments [209]. It is more interesting that SLNs improved permeability of γ-tocotrienol by 10-fold, compared to mixed micelles [47]. The *in situ* rat intestine perfusion study demonstrated a 3-fold increase of SLNs encapsulating lumefantrine permeation compared to lumefantrine solution [30]. Recently, SLNs were developed for improving intestinal permeability of bortezomib by using hot oil-in-water emulsification method [210]. The regional intestinal effective permeability (P_{eff}) value of glycerol monostearate SLNs with average particle size of 95 nm was enhanced by 3-fold increase than free control. Consistently, the permeability coefficient values were tripled when nebivolol was encapsulated in SLNs and doubled when the pure drug was used separately with a blank SLNs [211].

5.3. In vivo methods

Despite the fact that *in vivo* methods are highly resource-intensive, these experimental approaches are fundamental in drug industry to evaluate the drug's pharmacokinetics and pharmacodynamics characteristics. The principal advantages of the *in vivo* experimental models are the complete incorporation of the dynamic components of the mesenteric blood circulation, the mucus layer and all the other factors that can affect drug dissolution and absorption. However, when choosing an animal model, the physiological and biochemical similarities between the animal model and humans should be considered. The most common animals used in drug testing are mice, rats, dogs, and non-human primates [212]. In the rat model, the similarity of drug transporters as related to humans provides good prediction values for oral drug absorption [213]. Encapsulation of various drugs into lipid based nanocarrier has attracted much more interest to modify drug release, absorption and permeability for the benefit of improving drug efficacy and safety and thus better outcomes. Various research studies have been focused on the *in vivo* oral drug delivery field [214,215]. For instance, the oral delivery of geniposide-SLNs in rats showed a significant increase of C_{max} and enhancement of relative bioavailability more than 50 times, compared to drug solution. Additionally, higher tissue concentration in liver, heart and brain indicated the pharmacological role of geniposide-SLNs for treatment of hepatic and cardiovascular disease [32]. Puerarin, an effective drug in treatment of cardiovascular disorder, loaded into SLNs and administered orally in rats was reported to show a 3-fold increase in oral bioavailability compared to puerarin solution. Higher tissue concentration was recorded especially in the predilection organs such as the heart and brain [98]. Inclusion of olmesartan medoxomil in SLNs revealed 2.3-fold enhancement in relative bioavailability compared to plain drug, after oral administration in rats [100,101]. A significant amelioration of oral bioavailability of apomorphine 13-fold was found after SLNs incorporation. Further, In the rat model of Parkinson's disease induced by 6-hydroxydopamine, the contralateral rotation number greatly increased from 20 to 115 following oral SLNs applications [102]. Narala and Veerabrahma evaluated the oral bioavailability of SLNs containing quetiapine with average particle size and encapsulation capacity of 175 nm and 92 %, respectively. The *in vivo* study in rats exhibited a 3.7 times increase in oral bioavailability by SLNs [103]. Incorporation of zaleplon in SLNs showed a 2.6-fold improvement in bioavailability following oral administration in rats [104]. Linagliptin is a DPP-4 inhibitor used to treat type II diabetes. An enteric coating of linagliptin with pH sensitive polymer showed higher bioavailability more than 1.9-fold compared to free drug in rats. The C_{max} and T_{max} values of SLNs were 5.5 mcg/mL and 16 h higher than those of the free drug [105].

6. Challenge and future prospective of SLNs for oral delivery

Even though the various potential benefits of oral SLNs as an attractive route for oral drug delivery, several challenges need to be resolved for better application in the future. The current defects of some fabricated SLNs itself, including the relatively low encapsulation efficiency and loading capacity as well as a high initial burst release, should be overcome. Strategies have been exploited to tackle these problems associated with SLNs *via* modifying the preparation technology and the formulation excipients. Entrapment efficiency and controlled release of formulations can be achieved through selecting suitable lipid matrices as triglycerides along with the proper concentration of emulsifiers. Recent developments in SLNs have led to the surface modified SLNs that may overcome the limitation for oral delivery of hydrophilic and phytoactive compounds. The major challenges are that various natural barriers of the GI tract hinder the cellular uptake or traversal of nanocarriers. The low gastric pH may destabilize and aggregate the SLNs. However, *in vitro* optimizing the SLNs mixture and surfactant for each lipid is needed to tackle this problem. The biological nature of the GI tract together with its content provide several natural barriers for cellular transversal of nanocarriers leading to

low accessibility and absorption of the drug molecules. The nanocarriers supposed to pass through paracellular or transcellular pathways to reach the blood stream. The paracellular route is initiated through TJs while transcellular is conducted *via* various receptor and non-receptor mediated endocytosis. After cellular uptake, the vast majority gets passed along the endolysosomal trafficking pathway leading to degrade most of encapsulated drugs. So, the potential challenges of drug transcellular trafficking are to mitigate or completely avoid the endolysosomal pathway or to elicit endosomes or lysosomes to fuse with the cell membrane releasing nanoparticle or nanocarriers escape from the endolysosomal system to get released from the cell again. Moreover, electrostatic repulsion that occurred between the negatively charged surface of SLNs and negatively charged intestinal mucus membranes impedes the availability of SLNs to these membranes and some SLNs can also become trapped by mucus due to their hydrophobic feature. mucus permeation strategy *via* unique surface modifications has been commonly employed and engineered to enhance the nanocarrier penetration of mucus barrier, cellular uptake and bioavailability. Pragmatic SLNs with peptide ligands can provide a key solution to enhance the transport of protein drugs across intestinal barriers. It is still unclear that how much proportion of oral nanoparticle could be absorbed into the body in the intact formulation. What properties of SLNs to be easily absorbed and the relation of their loaded drug oral bioavailability with SLNs absorption have not been reported. All above challenges hindered the progress of SLNs as an effective oral drug delivery system.

A few years ago, great *in vivo* advances in SLNs were revealed to improve oral absorption of poorly absorbed drugs. A relative attractive research gained high levels of interest, but there is a paucity of statistics about how oral absorbability is enhanced *via* SLNs. Subsequently, a variety of *in vitro* cell models have been developed to assess the cellular SLNs uptake mechanisms using various (2D) culture models. At the moment, the greater number of *in vitro* investigations are undertaken these types of cells which cultured on 2D condition. Such *in vitro* models do not exactly imitate the 3D *in vivo* environment due to lack of interactions and communications between cells which are crucial for underlying intracellular trafficking signals. Nonetheless, the transport mechanism of SLNs has not yet been studied across 3D culture models which proposed to be the most advanced *in vivo*-like culture systems. In the future, more trends should be attracted to these models which open the doors to fully authenticate the transport and release kinetics of SLNs through the intestinal epithelium. At some point, it is necessary to adopt contemporary technological methods to shed a new light on the interaction of SLNs with biological tissues and proteins present in GI tract fluids and its implications for transcellular transcytosis. This biological fluid nanoparticle interaction is suggested to be new and most attractive challenges for the development of nanocarriers for oral drug delivery. In addition, we propose that further research should be targeted to enhance nanodrug penetration of intestinal mucus, to achieve an innovative uptake *via* enterocytes and M cells. The signals produced by lymphocytes, responsible for M cell formation, are required to describe the mechanisms mediating transcytosis and to analyze the cellular machinery mediating bioactive molecule translocation through M cells. Furthermore, it is a vital issue for future research to further investigate the cellular uptake processes using gut endothelial cell lines and linking it with transcytosis efficiency. More broadly, the development of reliable NPs proteins bioconjugations strategies and triggering endolysosomal escape is essential to promote transcytosis efficiency and subsequent higher exocytosis rate in both intestinal epithelial and blood endothelial cells. Taken together, this will enhance therapeutic indices and feasibility of medical applications.

7. Summary

Long ago, many advances in SLNs formulations had been shown to enhance oral absorption due to its unique advantages, including increased solubility, improved stability, enhanced permeability and absorption, controlled drug release, site-specific targeting, and minimal side effects. We summarize all transport model developments for absorption of SLNs across GI tract. Up to date, few intensive studies have been performed to investigate the transport mechanisms of various SLNs across the GI epithelial cell monolayer. The endocytosis or transcytosis of SLNs is very intricate involving several complex trafficking pathways through biological tissue. Therefore, the ultimate but challenging goal referring to study and explore the molecular mechanisms of various SLNs which will assist us in designing of ingenious nanocarrier with superior outcomes. Recently and within the next few years, *in vitro* cell models are likely to become an important component and a valuable evidence for cellular permeation prediction of NPs. In future, it is vital to adopt modern technological methods to verify the transport mechanism of SLNs across the intestinal epithelium. This will lay a foundation to create a new paradigm of therapeutic formulations and interventions.

Declaration of Competing Interest

The authors report no conflicts of interest in this work.

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