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Review Article

# NANO-DELIVERY SYSTEMS FOR ENHANCING ORAL BIOAVAILABILITY OF DRUGS

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**ABSTRACT**

The two main issues impacting oral delivery are drug solubility and permeability. The FDA adopted the Biopharmaceutics Classification System (BCS) in 2000. The BCS categorizes drugs into four classes based on their solubility and permeability. For permeability improvement and bioavailability, many experimental systems are utilized. Numerous nanocarrier technologies have recently been utilized to increase drug permeability by employing nanocarrier systems such as lipid vesicles, polymeric and lipid nanoparticles, polymeric micelles, and submicron lipid emulsions. This review proposes innovative nano-delivery systems for permeability augmentation. It focuses on some illustrations of drugs with various nanosystems, how these systems were developed, and how they successfully boost intestinal drug permeability and bioavailability.

**Keywords:** Intestinal permeability, Oral bioavailability, Nanocarriers


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## INTRODUCTION

Since oral administration presents superior patient compliance, safety, simplicity, and lower costs, it is the highly convenient route of drug delivery [1]. Nevertheless, some drugs' adverse characteristics-low hydrophobicity, minimal permeability, chemical instability, and excessive first-pass metabolism—have a detrimental effect on the ability of drugs to cross gastrointestinal (GI) barriers [2]. Most commonly, oral formulations of slowly absorbed, poorly water-soluble drugs have limited bioavailability [3]. As a result, numerous novel drug dosages have been developed, including solid drug dispersions, protein or polymer conjugates, nano-delivery systems, and macroscopic systems like capsules, gels, and films. Among these, nano-delivery systems can potentially solve the issues with oral drug administration [4]. Furthermore, nano-delivery systems have recently gained acceptance due to their remarkable advantages, such as protecting drugs from early degradation and interacting with the physiological environment, promoting intracellular penetration, and enhancing drug absorption [5]. As a result, many nanotechnology-based formulations have been developed and applied to increase oral absorption and bioavailability. The prominent nanosystems for oral drug delivery shown in the following fig. (fig. 1) include polymeric nanoparticles (PNPs), liposomes, micelles, niosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), self-nano emulsifying drug delivery systems (SNEDDS), nanoemulsions, nanocrystals, mesoporous silica nanoparticles (MSNs), and dendrimer.

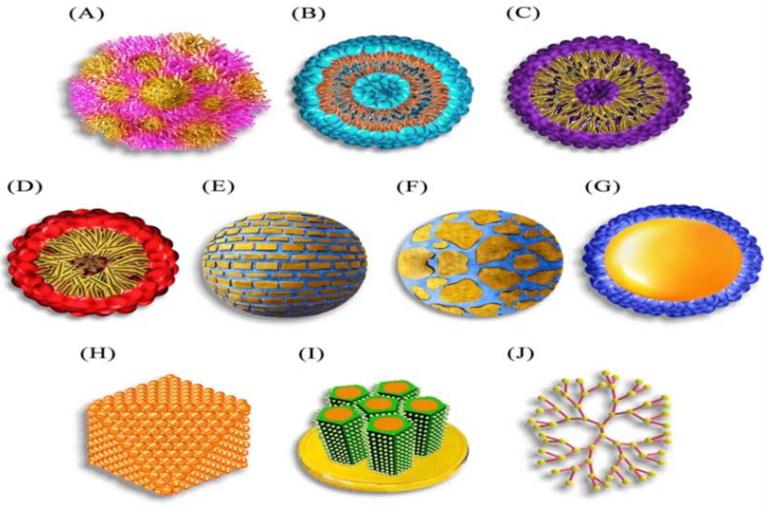


**Fig. 1: Schematic representations of several oral drug delivery nanocarrier forms include (A) polymeric nanoparticles, (B) liposomes, (C) niosomes, (D) micelles, (E) SLN, (F) NLC, (G) nanoemulsions, (H) nanocrystals, (I) MSN, and (J) dendrimers [6]**

## MATERIALS AND METHODS

This article presents an in-depth review of the recently investigated oral nano-delivery systems that improved intestinal permeability and oral bioavailability of different classes of drugs.

### Search strategy

Data were collected from four international databases, including Scopus, Pubmed, Web of science, and Google scholar, from 2018 to 2022. The search keywords used were enhancement intestinal

permeability, oral bioavailability, and nanoparticles. A study selection flow diagram is shown in fig. 2.

**Chitosan-based nano-delivery systems**

Chitosan (CS) and its derivatives are amino polysaccharides having several biological effects, including improving mucoadhesion and opening tight junctions between intestinal epithelial cells [7]. Recent research suggests that CS may improve intestinal drug absorption through the paracellular and transcellular pathways through electrostatic interactions as the positively charged chitosan interacts strongly with the negatively charged mucin glycoproteins in mucus, prolonging the materials' residence period and increases drug concentration at the absorption site [8, 9]. Several CS-based oral delivery systems with the needed efficacy and oral bioavailability were developed based on this approach.

Du *et al.* developed a unique multifunctional paclitaxel nanoparticle employing co-modified poly(lactide), polylysine (PL), and CS. The thiolated polymers with CS improved PTX absorption by enhancing mucoadhesive properties. Also, PL altered CS as it increased the amino amount and improved electrostatic interaction with negatively charged integrin receptors, thereby prolonging the residence time and enhancing the oral bioavailability of PTX. In comparison to the commercial dosage form (Taxol), the multifunctional nanoparticle demonstrated considerably better oral bioavailability (5.63-fold) and increased PTX accumulation in the tumor site (8.89-fold) [10].

Also, Chen *et al.* developed a copolymer using three polymers to create PTX micelles where CS was utilized to augment the adhesion to mucus, gallic acid (GA) was used to prevent the CYP3A enzyme, and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) was used to inhibit P-gp efflux. The three polymers were combined into a GA-CS-TPGS copolymer and consequently used to fabricate PTX micelles. The PTX-micelles were multifunctional, as the GA-CS-TPGS copolymer improved adhesion to the gastrointestinal (GIT) mucus layer, inhibited P-gp efflux, and decreased CYP3A-mediated metabolism. In comparison to Taxol, PTX-micelles demonstrated a more significant anti-tumor activity. In addition, because of the GA-CS-TPGS copolymer's adhesion and sustained-release profile, PTX-micelles remained in the GIT longer than Taxol, resulting in a lower clearance rate. After loading into the polymeric micelles, PTX's bioavailability was increased by around 3.80-fold [11].

One of the most often used phytochemicals for treating various disorders is thymoquinone (THQ). However, its significant lipophilic properties reduce its bioavailability. Therefore, Rahat *et al.* created SLNs coated with CS. Comparing THQ-CS-SLNs to THQ suspension, the permeability coefficient was around 4 times greater with THQ-CS-SLNs. The THQ-CS-SLNs' reduced particle size, which increased the surface area for absorption, was responsible for this improvement. Additionally, Poloxamer-188 (P-188), which was utilized in the synthesis of SLNs, was responsible for inhibiting the P-glycoprotein (P-gp) efflux pump that was present on the GI mucous [12].

Polymers can be crosslinked to CS to create nanoparticles through electrostatic contact. Fayed *et al.* developed conventional niosomes made of Span 60, cholesterol, and diacetyl phosphate loaded with atorvastatin. The conventional niosomes were coated with CS, then crosslinked with tripolyphosphate to create CS-encapsulated vesicles. The capability of the CS coat to promote local mucoadhesion at the absorption site can be used to explain why CS-encapsulated niosomes were superior in the oral delivery of atorvastatin. Better absorption may result from closer interaction between the biological membrane and the nanostructure as a result [13].

Karami *et al.* used P188 and CS to prepare a surface-modified nanoemulsion (NE) to boost the oral bioavailability of repaglinide, a typical BCS II medication. Repaglinide's oral bioavailability was significantly enhanced after being administered in the surface-modified NE compared to the free drug [14].

CS interacts strongly with the mucous membrane, reduces electrical resistance at tight junctions between epithelial cells, and encourages passage through mucosal cells, enhancing the penetration of drugs encapsulated in CS-NPs [14]. Therefore, Anwer *et al.* prepared olaparib-loaded poly (d,l-lactide-co-glycolide) (OLP-PLGA) nanoparticles and OLP-CS-PLGA nanoparticles, which were coated with CS. Compared to regular OLP suspension, the bioavailability of OLP-PLGA nanoparticles and OLP-CS-PLGA nanoparticles was found to be 2.0 and 4.75 times higher, respectively, according to the PK data. In addition, the half-life $T_{1/2}$ (h) and mean retention time (MRT) of CS-coated PLGA nanoparticles were significantly ($p$<0.05) higher than the pure OLP suspension; however, these changes were negligible in the case of OLP-loaded PLGA nanoparticles, indicating that CS layers enhanced sustained release of PLGA nanoparticles and facilitated their resident time in plasma [15].

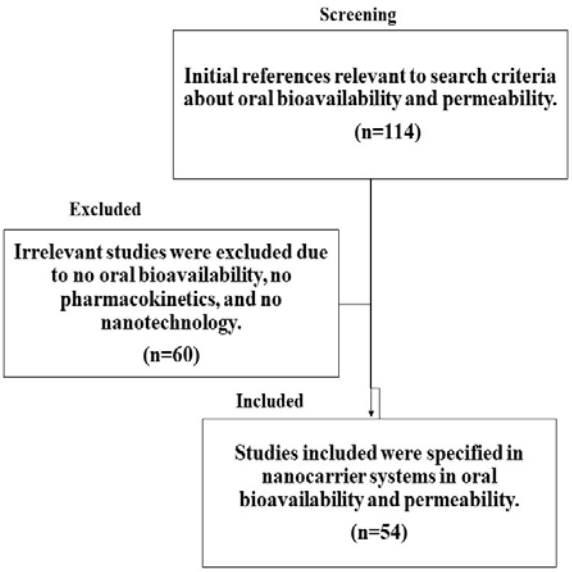


**Fig. 2: Study selection flow diagram**

**Lipid nanoparticles**

In contrast to traditional or typical oral formulations, SLNs and NLCs are regarded as alternate and distinct delivery strategies for increased oral applications. The second generation of SLNs, known as NLCs, includes a core crystalline matrix consisting of solid and liquid lipids [16]. The liquid lipid reduces crystallinity by combining solid and liquid lipids (oil). Therefore, higher deformities in the lipid

matrix occur, preventing drug leakage and increasing drug loading capacity by providing space for the drug molecule to bind [17]. Both SLNs, and NLCs, may offer multiple benefits, such as regulated drug release.

The use of NLCs in the oral delivery of several drugs in recent studies has also been reviewed. Dudhipala and Ayb used hot homogenization combined with the ultrasonication method to formulate ketoconazole (KZ) loaded SLN (KZ-SLNs) and NLCs (KZ-NLCs). The results showed that KZ oral bioavailability was significantly increased by incorporation into NLC and SLN formulations by 2.7-folds and 2.4-folds, respectively [18]. Also, Sun *et al.* examined the incorporation of meclizine (Mz) into NLCs to augment the oral bioavailability of Mz. Superior oral bioavailability from NLC formulations might be caused by liquid lipids, which facilitated the drug loading within the lipid nanoparticle. The PK profile in the rabbit model showed a 2.69-fold increase in the oral bioavailability of the drug from (Mz-NLCs) compared to the Mz powder [19]. Fenofibrate is used to treat hypercholesterolemia and hypertriglyceridemia. It has poor water-soluble. Pyo *et al.* used chitosan as the biodegradable polymer, stearic acid as the solid lipid, oleic acid as the liquid lipid, and Tween 80 as the surfactant to create fenofibrate CS-coated NLCs. Compared to uncoated NLCs, CS-NLCs showed 2-fold greater drug absorption ($p$<0.05) [20].

Patel and Patel formulated nintedanib esylate-loaded NLCs using high-speed homogenization, followed by the probe sonication method. Compared to suspension, nintedanib esylate-loaded NLCs had a more robust capacity to suppress the proliferation of tumor cells, according to a cytotoxicity study. In addition, compared to nintedanib esylate suspension, the oral bioavailability of nintedanib esylate improved by over 26.31 folds after loading into NLCs [21].

Hu *et al.* studied the incorporation of naringenin (NGN) into NLCs formulation. Using non-ionic surfactants in the NLCs formulae, which inhibit P-gp efflux, increased NGN's oral bioavailability [22].

Murthy *et al.* created raloxifene (RLX) loaded in NLCs to increase RLX's bioavailability. Glyceryl triacetate and oleic acid were utilized to formulate the NLC formulations. In comparison to the RLX-free solution, the RLX-NLC significantly ($p$<0.05) increased oral bioavailability 3.19-fold in female Wistar rats [23].

**Silica nanoparticles**

In general, inorganic drug carriers have developed as desirable substitutes for organic systems. Examples include silicon, quantum dots, iron oxide, carbon, metal-organic, and silica. Silica nanoparticles (SNPs) stand out among them due to their strong surface chemistry, shown biocompatibility, efficient manufacturing, and chemical and enzymatic stability. Also, additional benefits of tuneable porosity, pore diameters, pore morphology, and particle size and shape are mainly present in mesoporous silica nanoparticles (MSNs). More significantly, it has been demonstrated that both porous and non-porous silica nanoparticles disintegrate in aqueous conditions over a short period by hydration and hydrolysis, followed by the generation of silicic acid, which is excreted from the kidney through urine [24].

Choi *et al.* developed a rivaroxaban SNEDDS. To compare the impact of various solidifying agents on drug bioavailability, SNEDDS was suspended with two mesoporous carriers, calcium silicate and colloidal silica. The results demonstrated that SNEDDS with calcium silicate showed a higher released rate than SNEDDS with colloidal silica, with oral bioavailability exhibiting a 3.2-fold increase in the AUC value ($p$<0.05) of rivaroxaban-loaded solid SNEDDS being significantly higher than that of pure drug powder [25].

The biopharmaceutics classification system (BCS) classifies abiraterone acetate (AbA) as a Class IV chemical because of its extremely low water solubility (0.5 g/ml), low permeability, and high lipophilicity. The ability of silica-lipid hybrids (SLH) to improve the oral bioavailability of abiraterone acetate (AbA) in Sprague-Dawley rats was tested by Schultz *et al.*, who incorporated AbA into SLH below the saturation level. The SLH achieved a significantly 1.43-fold greater bioavailability than Zytiga [26]. Also, Meola *et al.* studied the formulation of simvastatin (SIM) as a solid-lipid-based formulation (LBF) using silica-lipid-hybrid (SLH) technology. SLH formulations demonstrated a rapid release of SIM and reached a maximum dissolution concentration up to 3.5-fold greater than pure, unmodified drug. Furthermore, including SIM in the LBF in a non-crystalline state improved SIM dissolution from the SLH formulations [27].

Zhang *et al.* loaded insulin onto synthetic mesoporous silica nanoparticles with modification groups that successfully passed through the intestinal epithelium and the mucus layer by resembling the surfaces of viruses. MSNs were made into drug delivery systems by adding positively charged cell-penetrating pentapeptides (CPP5) and negatively charged carboxyl groups, giving them the same hydrophilic, electrically neutral surface features as viruses. Compared to insulin given directly into the jejunum, the insulin encapsulated in the MSN $NH_2$@COOH/CPP5 nanoparticles had a 2.1-fold higher bioavailability [28].

Ndayishimiye *et al.* described the development of formulations based on SNPs that can increase the epithelial permeability of vancomycin (VAN). They formulated SNPs with 2 nm and 9 nm pore diameters and altered their surface charge and polarity by adding various functional groups (–$NH_2$,–$PO_3$, and–$CH_3$). As a result, VAN's permeability across an epithelial cell monolayer (Caco-2 cell model) was increased up to six times by VAN-loaded SNPs, particularly the 9 nm pore SNPs with a negative charge. This increased permeability of VAN-loaded SNPs over pure VAN results from SNPs' capacity to temporarily open the tight connections of the Caco-2 cell monolayer [29].

To increase the bioavailability of SIM, Meola *et al.* prepared SIM-encapsulated silica-lipid hybrids (SLH) in order to increase absorption and bioavailability during a human *in vivo* PK trial. Twelve healthy male participants were included in a randomized, double-blinded, cross-over trial to compare the safety, tolerability, and pharmacokinetic profile of SIM-encapsulated SLH to that of commercially available SIM. When compared to an equivalent dose of commercial formulation, SLH formulations increased the bioavailability of SIM by up to 1.6-fold and the active simvastatin acid by 3.5-fold. The findings also imply that using SLH technology may significantly decrease the dose necessary to reach therapeutically comparable concentrations [30].

**PLGA nanoparticles**

Biodegradable poly lactic-co-glycolic acid (PLGA) nanoparticles were developed to prepare a formulation with improved bioavailability. PLGA is a biodegradable and safe polymer. To prepare an efficient oral formulation with enhanced bioavailability, PLGA-based nanoparticles are commonly used as PLGA nanoparticles sustain the release, enhance the stability, and improve the oral bioavailability of poorly soluble drugs [31].

Naserifar *et al.* prepared folate-conjugated PLGA nanoparticles loaded with resveratrol (RSV). RSV-PLGA and RSV-FA-PLGA were shown to have encapsulation efficiencies of 59% and 90%, respectively. The difference in encapsulation efficiency may be justified by changes in the physicochemical properties of PLGA following its conjugation with folic acid, which may affect its molecular weight, and hydrophobic-hydrophilic balance [32].

Furthermore, Asal *et al.* used chitosan nanoparticles (CSNps), chitosan gold nanoparticles (CSAuNps), and chitosan gold nanoparticles functionalized with PLGA (CSAuNps/PLGA) to design insulin-loaded nanoparticle systems. The functionalization of CSAuNps with PLGA revealed significant effects in decreasing blood glucose levels within 6 h of oral administration, according to the *in vivo* tests' findings [33].

Also, Prabhuraj *et al.* prepared PLGA nanoparticles that were loaded with curcumin (Cur), coated with polyethylene glycol (PEG), and conjugated with several targeting moieties, such as folic acid (FA), hyaluronic acid (HA), or transferrin (Tf). Cur and its nanoparticle formulations on different cancer cell lines were examined for *in vitro* toxicity at molar concentrations ranging from 10 to 80 M. Because of ligand-receptor interaction on the surface of cancer cells, PLGA-Cur-PEG demonstrated the highest cytotoxicity to cells [34].

**Table 1: Examples of drugs loaded into different nano-delivery systems for improvement of oral bioavailability and permeability**

| Drug | Nano-delivery systems | Major outcome | References |
|---|---|---|---|
| Quercetin (QT) | Zein nanoparticles (ZNP) with an outer shell of caseinate | *In vivo* bioavailability study in rats: the AUC of SC-ZNP was increased by 2.34 folds compared to QT suspensions | [37] |
| | Supersaturable self-emulsifying drug delivery system (s-SEDDS) | Caco-2 cells: QT-sSEDDS showed significantly ($p$<0.05) higher uptake than free QT. *In vivo* pharmacokinetics (PK) studies in rats: QT-sSEDDS revealed 2.2 and 2-fold increases in Cmax and AUC, respectively, in comparison to conventional QT-SEDDS | [38] |
| | Polymeric micelles | Caco-2 cell: quercetin did not show any significant change in the permeability in free and encapsulated forms. *In vivo* PK in rats: The Cmax values of QT are much higher than that obtained for free QT, and the AUC0–24h value for micellar QT was increased 1.19 times than the free drug. | [39] |
| Methotrexate (MTX) | Complexation of MTX with β-cyclodextrin (β-CD). | *In vivo* PK studies in rats: 2.20-and 3.29-fold increments in AUC and Cmax, respectively, in comparison to free MTX | [40] |
| | Nanostructured polyelectrolytes complexes | Caco 2 monoculture model cells: the complex showed 3 times higher permeability than the free drug and NpHP-MTX. Triple co-culture: the complex increased the permeated drug compared to the free drug. | [41] |
| Thymoquinone (THQ) | Chitosan-modified SLNs (THQ-CS-SLNs) | The everted gut sac of a goat: increase in permeability coefficient (Papp) of THQ-CS-SLNs 4 times compared to THQ suspension. | [12] |
| | chitosan (CS) modified polycaprolactone (PL) nanoparticles | The everted gut sac of the rat: increase in Papp 4.21-fold compared to THQ suspension. | [42] |
| | chitosan nanovesicles (CS-nanovesicles) | *In vivo* PK studies in rats: CS nanovesicles revealed a significantly higher flux (1.9 times) than the THQ solution. | [43] |
| Repaglinide (REP) | chitosan-coated nanoemulsion | *In vivo* PK studies in rats: increase in the AUC0-12h 3.51-fold and Cmax 1.78-fold and compared with the free drug. | [14] |
| | NLCs | In situ single-pass intestinal perfusion study: showed improvement in membrane permeability for NLCs compared with REP-Sol, especially NLCs-Small size preparation. *In vivo* PK studies in rats: the AUC(0→t) of REP-NLC-increased compared with marked REP dosage form, and the Cmax of REP-NLC was significantly increased than marketed REP tablets. | [44] |
| Fenofibrate | Chitosan-coated NLCs (CF-NLCs) | *In vivo* PK study on rats: increased The AUC0 →12h and Cmax values of CF-NLCs were 1.16-fold and 1.25-fold higher than those of the commercial product, respectively. *In vivo* pharmacodynamic study on rats: decrease in total cholesterol and triglyceride levels of the CF-NLCs group a 5-fold and 2.3-fold Compared with the raw fenofibrate group, respectively. | [20] |
| | SNEDDS | Non-everted gut sac apparent permeability study: increased Papp by 2-fold in RBO-EL SNEDDS formulation compared with other SNEDDS formulations. *In vivo* PK study in rats: increased the AUC0 → 24 and Cmax values 1.26 to 1.72-fold, respectively. | [45] |
| Perphenazine (PPZ) | NLCs | *In vivo* PK study on rats: NLCs increased in the AUC0–∞of PPZ formulated as NLCs compared to the suspension of pure | [46] |
| Ergosterol | NLCs | *In vivo* PK study on rats: NLCs increased the AUC0–∞ of 2.78-folds compared to ergosterol suspensions. | [14] |
| Raloxifene (RLX) | NLCs | *In vivo* PK study on rats: The RLX-NLC significantly enhanced oral bioavailability 3.19-fold compared to RLX-free suspension. | [47] |
| | cyclodextrin/chitosan nanoparticles | In situ single-pass intestinal perfusion study: the Papp increased for the encapsulated RXF and showed significant improvement in permeability. *In vivo* PK study in rats: The oral bioavailability of RXF was enhanced by 2.6 folds through NPS compared to RXF suspensions in rats | [48 ] |
| Ropinirole (RP) | NLCs and SLNs | *In vivo* PK study in rats: increase in the AUC 2.1 and 2.7-folds from RP-SLN and RP-NLC formulations, respectively, than RP control formulation. | [49] |
| Candesartan Cilexetil (CC) | NLCs | Caco-2 cell: NLCs increased the accumulation of fluorescent nanoparticles close to the nuclei inside the cytoplasm of Caco-2 cancer cells. *In vivo* PK study in rats: NLCs increased Cmax and AUC0–t 4.5-fold and 2-fold, respectively, than free-CC suspension. | [50] |
| | SNEDDS | Everted and non-everted gut sacs: SNEDDS significantly enhanced CC Papp compared with free CC solution. *In vivo* PK studies in rabbits: SNEDDS formulation increased the Cmax and the AUC0-∞ by 2.4-fold and 1.69-fold, respectively, compared to the brand product. | [51] |
| Insulin | CS-PLGA | *In vivo* PK studies in rats: showed significant and relatively longer hypoglycemic activity after oral administration of insulin/CS-PLGA NPs produced. | [35] |
| | Chitosan coating zein-carboxymethylated short-chain amylose (IN-Z-CSA) nanocomposites | Caco-2 cells: The transepithelial permeability of the nanocomposites was 12-fold higher than that of insulin. *In vivo* pharmacological and PK studies: orally administered nanocomposites had a significantly higher hypoglycemic effect with a relative bioavailability of 15.19%. | [52] |
| | Trimethyl chitosan (TMC)and fucoidan self-assembled nanoparticles | Caco-2 cells: insulin loaded-CS/FD NPs Increased the Papp value compared with the native insulin. | [53] |
| | Folate-chitosan nanoparticles (FA-CS-NPs) | *In vivo* PK in rats: the rats that received insulin-loaded FA-CS NPs had increased AUC0-∞ compared with the injected insulin. | [54] |

Wu *et al.* used a double-emulsion-solvent evaporation approach to prepare core-shell insulin/CS-PLGA nanoparticles. The synthesis parameters were tuned using an orthogonal experimental design to prevent damage to insulin in the stomach and regulate insulin release. As a result, most PLGA nanoparticles entered Caco-2 cells, showing that CS-PLGA nanoparticles can pass through intestinal epithelial cells and exert hypoglycemic action. Also, the core-shell insulin/CS-PLGA nanoparticles were proved to be an effective carrier for oral insulin delivery to treat diabetes in the *in vivo* investigations on rats. These results showed that oral administration of insulin/CS-PLGA nanoparticles caused considerable and relative long-term hypoglycemic action [35].

Haggag *et al.* studied the bioavailability and pharmacological activity of Zaleplon-loaded PLGA nanoparticles (ZPPLGA) following oral or parenteral administration for ZP PLGA, and ZP commercial tablets, the bioavailability of ZP was increased by more than three times. The superior sedative and hypnotic effect of ZP-PLGA nanoparticles compared to the traditional dosage form further supported the enhanced biological activity of these compounds [36].

From the previous data, we can conclude that several research works were conducted to enhance the oral bioavailability of different types of drugs. Table 1 summarizes some of the recent studies.

As mentioned before, the oral route is the most convenient route for drug administration; however, the oral delivery of some drugs is still challenging due to low drug solubility, low bioavailability, low permeability, first-pass metabolism, and P-glycoprotein efflux pumps. Unfortunately, some of these drugs are highly valuable therapeutic moieties such as peptides, RNA-based drugs, and chemotherapeutic drugs; therefore, there is a demand to improve oral delivery systems for these drugs to provide more convenient and painless administration. Recent advances in pharmaceutical research have focused on designing new and efficient nano-drug delivery systems for site-specific targeting, thus leading to improved bioavailability and pharmacokinetics. The results achieved so far using different nano-drug delivery systems seem to be very encouraging and promising to increase the oral bioavailability of numerous drugs. However, more stringent research attempts are needed to translate laboratory success into product development. This could be achieved by improving drug loading and release kinetics and using cost-effective materials and methods. Also, a detailed toxicological evaluation of the nanocarriers is needed to support the efficacy and safety of the formulation to be developed as a safe dosage for commercialization.

## CONCLUSION

The oral route is the most convenient route for drug administration, however, due to the poor oral bioavailability of numerous drugs. Several approaches have been developed to enhance drugs' oral bioavailability. Nano-delivery systems have succeeded in enhancing the oral bioavailability of various classes of drugs by enhancing the drug solubility, protecting the drug from degradation in the gastrointestinal environment, and enhancing the drug permeability and bioavailability. This enhancement in the oral bioavailability of poorly bioavailable drugs should encourage researchers to explore novel types and modified nano-delivery systems to formulate these drugs as oral dosage forms.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

Declared none

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