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An update on Nanoparticle Formulation Design of Piperine to Improve its Oral bioavailability: A Review

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Abstract

Piperine, a crystalline alkaloid compound isolated from Piper nigrum, Piper longum, and other types of pipers, has many excellent pharmacological advantages for preventing and treating some specific diseases, such as analgesic, anti-inflammatory, hepatoprotective, antimetastatic, antithyroid, immunomodulatory, antitumor, rheumatoid arthritis, osteoarthritis, Alzheimer's, and anticancer. However, its potential for clinical use through oral administration is hindered by water solubility and poor bioavailability. The low level of oral bioavailability is caused by low solubility in water and is photosensitive, susceptible to isomerization by UV light, which causes piperine concentration to decrease. A lot of nanoparticle formulation approaches have been applied to improve the poor oral bioavailability of piperine. Oral nanoparticle formulation strategies have been successfully implemented in increasing the solubility and bioavailability of piperine within the body, such as the formulation of nanoparticles, nanosuspensions, liposomes, complexation using polymers, and micro/nano-emulsions. This nanoparticle formulation approach has been successful in increasing the solubility, permeability, and bioavailability of piperine effectively. In addition, this nanoparticle formulated piperine can deliver piperine in a targeted manner and increase the efficacy of piperine treatments, such as for Alzheimer's disease, epilepsy, rheumatoid arthritis, diabetes, breast cancer, colon cancer, and human brain cancer.

Keywords: Piperine, Bioavailability, Solubility, Nano-formulation, Nanoparticle, Nanoemulsion

Introduction

Piperine is a crystalline, yellow, odorless, and pungent alkaloid compound isolated from Piper nigrum and Piper longum. Piperine is chemically known as (EE)-1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienly]-piperidine, with the molecular formula of $C_{17}H_{19}NO_3$, a molecular weight of 285.34 g/mol, and melting point at 128-130ºC [(1–3)]. The piperine structure consists of three subunits, namely methylenedioxyphenyl ring, side chain with conjugated double bonds, and basic piperidine moiety attached through carbonyl amide linkage to side chain [(4)]. Piperine is unsTable in acidic, alkaline, oxidizing , and sunlight environments. Piperine can be degraded to trichostatin and cis-piperyline under acidic conditions (HCl 2 M) and to piperanine, piperettine, and piperyline under sunlight [(5)].

Piperine contains four isomeric forms, namely trans-trans isomer (piperine), cis-trans isomer (isopiperine), cis-cis isomer (chavicine), and trans-cis isomer (isochavicine) (Fig. 1).

Piperine contains four isomeric forms, namely trans-trans isomer (piperine), cis-trans isomer (isopiperine), cis-cis isomer (chavicine), and trans-cis isomer (isochavicine) (Fig. 1). The isomerization of piperine compounds increases along with the increasing light intensity and exposure. Transformation of piperine into chavicine isomers can be seen in long-term storage and spontaneously which causes a loss of spicy taste [(6)]. The piperine ring influences the chemical stability and reactivity of piperine. This ring greatly influences steric-electronic properties, especially among the aromatic ring, carbonyl group, and alkene system [(7,8)].

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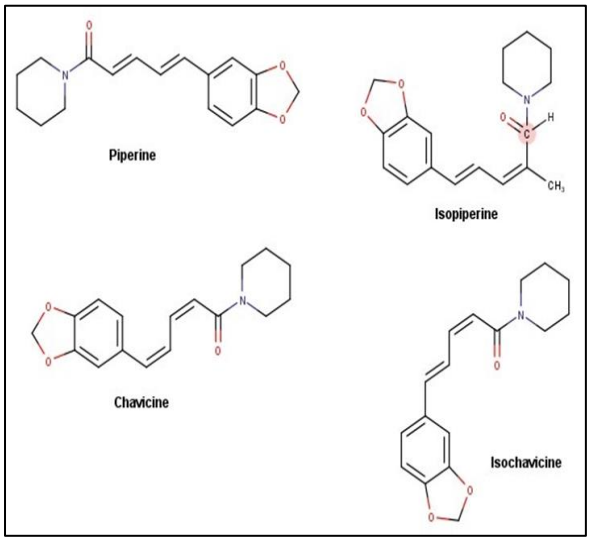

Figure 1. Structure of piperine and its isomers

Piperine can also be isolated from white and black pepper (Piper nigrum) [9,10]; root and fruit of Piper longum [11,12]; Piper chaba [12,13]; Piper guineense fruit [14]; and roots, stems, leaves, and fruit of Piper sarmentosum [15]. The alkaloid compound of piperine extracted from black and long pepper is commonly processed into traditional medicine in some Asian countries. Some medical products such as Ayurveda, Sidda, Unani, and Tibetan have used black pepper for treating cough, fever, sore throats, indigestion, insomnia, and heart disease [16–19].

Through the development of science and technology, many pharmacological benefits of piperine compounds have been successfully revealed. Several studies show that piperine has therapeutic effects like antiallergic [20,21], anti-inflammatory [22–25], rheumatoid arthritis [26], osteoarthritis [27], anticonvulsants, anti-epileptic, antidepressants, neurodegenerative disorders, and Alzheimer's disease [24,28–32]. Piperine can also inhibit cell proliferation by reducing cell variability, increasing reactive oxygen species (ROS), inducing cell shrinkage, fragmenting the DNA by blocking cell cycle and Caspase-3 activity [33], and effectively inhibiting cell proliferation and cell migration, inducing apoptotic processes in the HER-2 gene that expresses breast cancer cells, inducing MMP-9, and reducing Epithelial Growth Factor (EGF) [34].

Piperine is safe to take orally at a 20 mg/kg BW [35]. However, piperine is still not used clinically for disease prevention and treatment despite its broad pharmacological potential. Due to its low solubility and bioavailability, piperine is poorly absorbed in the body. However, many scientists have designed the right formulation to solve this issue.

Recent strategies in oral nanoparticle formulated of piperine to increase their solubility and bioavailability are reviewed in detail. This review was conducted using several databases or computer-based electronic searches including Pubmed, Science Direct, and Google Scholar to access all journals related to the nano-formulation of piperine. All major research papers must be published between 2017 – March 2022 with the keywords "piperine", "formulation", "nanoparticle", "polymeric", "nanocarrier", "phospholipid", and "nanoemulsion".

Piperine physicochemistry

Piperine is the main alkaloid found in white pepper, black pepper, and long pepper, having a weak base (pH 8.0 – 8.5) with a pKa of 12.22, and is poorly soluble in water with a solubility of 22.34 mg/L at 25ºC [36]. Piperine has a melting point at 128-130ºC, is soluble in ethanol (1g/15mL), methanol, petroleum ether (1g/1.7mL), and chloroform (1g/1.7mL) [3]. Piperine compounds are lipophilic with a log P value = 2.25 [36], which shows that they can be higher in octanol solvents than in water with a concentration ratio of 177.82:1. Piperine is slightly soluble in water and has a low dissolution level, thus it is less effective for oral use. Based on the results of piperine structure analysis, according to Lipinski's and Veber's rules, piperine compounds have good permeability in the membrane. The results of piperine permeability analysis are presented in the following section [37] (Table 1).

Table 1. Piperine structural permeability analysis [37].

Piperine structure analysis		
Parameter	**Results**	**High permeability requirements**
log P	2.3	5
H-bonding donor	0	5
H-bonding acceptor	3	10
PSA (Polar Surface Area)	38.77 A^o	140 A^o
Number of H-bonding donors & acceptors	3	12
Number of rotating bonds	2	10
Molecular weight	285.34 g/mol	500

Biopharmaceutics properties of piperine

Based on the structural permeability analysis, piperine has good permeability across intestinal membranes. This is supported by some studies Khajuria et al. [38] and Suresh & Srinivasan [39] which showed that piperine can be easily absorbed across the intestinal membrane barrier through passive diffusion and no metabolic changes observed during absorption. Piperine is absorbed into the serosal fluid and intestinal tissue by 47-64%

and found to be transported predominantly to the duodenum [39–41]. Piperine can be rapidly absorbed into the intestine probably because the molecule is non-polar and lipophilic so that it can easily cross and get through the intestinal barriers.

Piperine does not experience biotransformation during intestinal absorption, 7-12% of absorbed piperine is found in the serosal fluid [39,40]. The results of the intestinal examination showed that the highest concentrations in the stomach and small intestine could be reached within 6 hours after application, where less than 0.15% was detected in serum, kidney, and spleen from 30 minutes to 24 hours. The piperine's membrane permeability analysis conducted in a previous study used caco-2-monolayer model, where the results obtained a permeability coefficient of 5.41 x 10^{-5} cm/s and 4.78x10^{-5} cm/s for basolateral-to-apical and apical-to-basolateral [42].

Piperine distribution begins after being absorbed into the intestine and then transported by serum albumin. Piperine is bound to subdomain-1B of human serum albumin which is an important factor in the transport of piperine in the blood [43]. Based on a previous experiment conducted by

Suresh et al. [43] in rats that had been given a dose of 170 mg/kg orally, the maximum concentration of piperine was reached after 6 hours of application with 10.8% found in the tissues, and most of the piperine was found in the duodenum (8.8%). However, the result is in contrast to a study conducted by Liu et al. [44], where the maximum concentration was obtained two hours after oral administration, with the highest concentration was in the liver. This difference may be due to the different forms of applied piperine, and other components may influence the distribution of piperine in the extraction process.

Formulation design developed to increase piperine's oral bioavailability

The oral method is ideally applied for drug administration because it makes the patients easily consume the medicine. Oral administration can improve patients' compliance, especially for long-term use compared to other consumption techniques [45]. However, some latest chemical compounds being developed have low water solubility and low bioavailability, but high intra- and inter-subject variability [46], and one of which is piperine. Piperine has poor solubility, dissolution, and oral bioavailability (24% in rats) which are the main problems limiting its absorption [47]. Piperine is classified into the Class II Biopharmaceutics Classification System (BCS) based on its poor solubility in aqueous media and good permeability across the intestinal membrane barrier. Many attempts and nanoparticle formulation designs have been developed to solve its low solubility and bioavailability. Details of recent developments in the oral nano-formulation of piperine are discussed in the following sections:

Liposomes

Liposomes are spherical vesicles with an aqueous core and vesicle sizes from 30 nm to several micrometers, consisting of one or more phospholipid bilayer membranes or lamellae in which the polar head leads to the inner and outer aqueous phase of the vesicle [48]. Liposomes can deliver both hydrophilic and hydrophobic drugs. Liposomes contain a lipid bilayer similar to the cell membrane. Liposomes are made from a mixture of phospholipids, surfactants, and cholesterol. They function to increase the solubility of lipophilic and amphiphilic drugs, increase stability through encapsulation, reduce the toxicity of encapsulated drugs, are biodegradable, biocompatible, non-toxic, and non-immunogenic for systemic and non-systemic administration [49]. Liposomes can increase the bioavailability of lipophilic drugs through oral administration by increasing cellular contacts and diffusion across epithelial and mucosal layers [50].

The encapsulation of piperine into liposomes can increase the piperine's dissolution and bioavailability levels. Dutta & Bhattacharjee [51] formulated piperine nanoliposomes for oral usage taken from soy phosphatidylcholine and Tween 80 in a ratio of 1:1.2 and generated 78.6% entrapment efficiency, 29.75 ± 0.84 nm vesicle size, and resulted in 70% of piperine release for 8 hours in pH 6.4 buffer. Imam et al. [52] formulated chitosan-coated piperine liposomes to improve the mucoadhesive properties of piperine liposomes. The liposomes were prepared through the thin-film dispersion method using a rotary evaporator and chitosan coating by electrostatic deposition. The chitosan functioned to increase the stability of piperine liposomes and protect them from chemical and enzymatic degradation in the digestive tract. The presence of chitosan on the liposomes' surface showed an increase in stability and mucoadhesive properties by 2.8 times compared to those not coated with the chitosan.

Microemulsion, self-emulsifying drug delivery system (SEDDS), and self-nano emulsifying drug delivery system (SNEDDS)

Microemulsions are single-phase isotropic mixtures consisting of thermodynamically sTable and transparent oil, water, surfactant, and cosurfactant with an average droplet diameter of 10 to 140 nm [53,54]. Microemulsions are good candidates for oral drug consumption which is poorly soluble in water. They function to increase drug solubility, absorption rate, and bioavailability and reduce inter- and intra-individual variability in drug pharmacokinetics [55,56]. Microemulsions can improve the bioavailability of lipophilic drugs in several ways, such as protecting drugs from oxidation and enzymatic degradation and increasing

membrane permeability through lymphatic transport [57]. Lymphatic transport is the most contributing element to drug absorption in the intestine because it can protect against first-pass metabolism [58].

The findings of a study by Etman et al.[59] showed that piperine microemulsion for Alzheimer's therapy via oral route has succeeded in supporting and accelerating its delivery to the brain and producing better therapeutic results than pure piperine. Piperine microemulsion has been successfully formulated with Capryol 90 oil, surfactants tween 80 and cremophor RH40, and cosurfactant transcutol, which finally generates a particle size of lower than 150 nm with a negative zeta potential -30.36 mV. The size of the SEDDS particles lower than 500 nm enables an increasing absorption level of piperine through the lymphatic route [60]. Negatively charged nanoparticles can increase lymphatic uptake higher than positively and neutrally charged surfaces [61–63].

A self-emulsifying drug delivery system (SEDDS) is an isotropic mixture of oils, surfactants, and cosurfactants that spontaneously forms an oil-in-water emulsion during contact with gastrointestinal tract (GIT) fluids with mild agitation. The SEDDS system was then modified into self-micro emulsifying drug delivery systems (SMEDDS) and self-nano emulsifying drug delivery systems (SNEDDS) [64]. SEDDS, SMEDDS, and SNEDDS formulations have some specific benefits, such as increasing the drug solubility and bioavailability, increasing drug absorption rate through the lymphatic pathway, decreasing the effects of first-pass metabolism, and increasing physical and chemical stability in long-term storage [65].

The SEDDS, SMEDDS, and SNEDDS formulations can improve the bioavailability of lipophilic drugs through some mechanisms. They include lipid droplets built within self-emulsifying dispersions that can directly facilitate drug absorption and protect drugs from chemical and enzymatic degradation. They are localized in aqueous environments, influence the changes in gastrointestinal membrane permeability, and increase the drug absorption level via lymphatic pathways [66,67]. The lipids in the GIT (gastrointestinal tract) stimulate the excretion process of bile salts and endogenous bile lipids which also supports lipid emulsification to form micelles and improves drug solubility in the GIT [65].Surfactants can cause fluidization of intestinal membranes and opening of tight junctions which result in increased membrane permeability [68,69].

The difference between SEDDS, SMEDDS, and SNEDDS systems can be viewed from oil and surfactant concentration. In this case, the SEDDS uses a surfactant with an HLB value lower than 12, while SMEDDS and SNEDDS use a surfactant with an HLB value higher than 12. Kusumorini et al. [70] have formulated SNEDDS piperine for oral administration using Miglyol 812N oil, surfactant Cremophor RH40, and cosurfactant PEG400 with a ratio of 1:5, 6:2.9 w/w and piperine content of 2% w/w, with nanoemulsion size of 33.35 ± 1.97 nm and zeta potential of -22.87 ± 3.31 mV. The size of the particles is less than 200 nm. Therefore, they can be easily absorbed by the intestinal epithelium and can prolong their living period which contributes to increased oral bioavailability. Then, negatively charged drug carriers can also easily penetrate and cross the mucus barrier in the digestive tract, so that the drug can be smoothly consumed and enters the blood circulatory system [71].

Solid self-nano emulsifying drug delivery systems (S-SNEDDS)

The solid self-nano emulsifying drug delivery systems (S-SNEDDS) are the changes of the SNEDDS from liquid to dry powder supported by an inert adsorbent through a solidification process which can then be used to produce solid preparations, such as Tablets, capsules, and pellets [72]. S-SNEDDS has several advantages, like increasing solubility and bioavailability, increasing stability, being easier to use for the scale-up process, to obtaining content uniformity, increasing patients' compliance, and providing more accurate dosage [24,73]. S-SNEDDS, the solid form of liquid SNEDDS, can form nanoemulsions within the droplets sized lower than 300 nm in aqueous media. It has the same solubility and bioavailability enhancement mechanism as the liquid SNEDDS [74].

Piperine has been successfully formulated in the form of S-SNEDDS using 9.39% Glyceryl Monolinoleic oil (GML), 17.38% Poloxamer 188 surfactants, 9.39% Transcutol cosurfactant HP, 56.33% adsorbent Avicel PH-101, and 7.51% piperine using adsorption technique [75]. S-SNEDDS formulation results in a globule size of 73.56 ± 3.54 nm, a zeta potential of -28.12±2.54 mV, and bioavailability of 4.92 times higher than that of pure piperine dispersion. Meanwhile, S-SNEDDS piperine results in increased dissolution, bioavailability, hypertension effect, and better antioxidant and antibacterial activities than pure piperine.

Polymeric nanocarriers

Some polymeric nanocarriers such as dendrimers, polymer nanoparticles, micelles, nano gels, nanocapsules, and vesicles have recently been intensively used for drug delivery for their potential to modify the surface through chemical transformations to enhance drug loading and controlled release of specific ligands to reach specific sites where the drugs are designed [76,77]. Polymeric nanocarriers can increase the solubility of hydrophobic drug compounds, increase drugs bioavailability, pharmacokinetics and

biodistribution, minimize drug toxicity at the targeted sites, increase the stability of various therapeutic agents, and deliver drugs to the central nervous system by penetrating the blood-brain barrier (BBB) [76,78,79]. Ideally, polymeric nanocarriers should be biodegradable and non-toxic to minimize hypersensitivity reactions and provide good tissue compatibility [79]. The polymeric nanocarrier systems are classified into nanocapsules and nanospheres. Nanocapsules are vesicular systems in which drug molecules are surrounded by a membrane (encapsulated and trapped in lipids), while nanospheres are matrix systems in which drug molecules are dispersed across the particle surface [79].

Polymeric nanocarriers can increase the solubility and bioavailability of hydrophobic drugs in several specific ways, such as through diffusion-controlled drug release where the polymer matrix does not have a membrane that acts as a barrier to diffusion. The drug release is controlled by the solvent, in which polymeric materials having a three-dimensional connective tissue structure can control the drug release by biodegradable polymer degradation through enzymatic decomposition. Finally, the targeted drugs will be released at specific sites [80].

Therefore, polymeric nanocarriers play a crucial function in the piperine formulation for oral drug and piperine delivery in treating cancer. Several formulations of piperine polymeric nanocarriers to increase piperine solubility are listed in Table 2. The piperine nanocarrier formulation enhances the anti-cancer effect compared to pure ones, such as MCF-7 breast cancer, triple-negative breast cancer (TNBC) and MDA-MB-468 cells, A549 cell lung cancer, HepG2 cell liver cancer, HeLa cervical cancer, and Hs683cell brain cancer [81–86]. The piperine nanocarrier formulation can increase solubility and bioavailability, extend drug circulation time, decrease toxic effects on normal cells, deliver the drugs to specific sites, penetrate the blood-brain barrier (BBB), and increase the piperine storage time.

Inorganic nanoparticle

Inorganic nanoparticles have more benefits than polymer and lipid ones. They have higher stability levels and are non-toxic and non-immunogenic. There are inorganic carriers that have been used in drug delivery systems for drug therapy such as mesoporous silica, alumina, and zinc. Mesoporous silica enforces higher encapsulation efficiency of the active ingredients, controlled structural properties, and biocompatibility [79]. Another example of an inorganic carrier for nanocarriers is hydroxyapatite. Hydroxyapatite is a component of teeth and bone that exhibits good biocompatibility for delivering of prolonged-release drugs [87]. Piperine has been formulated with nanohydroxyapatite for anticancer therapy in vitro and performs a better anticancer effect on HCT116 monolayer colon cancer cells [88]. Piperine nanohydroxyapatite produces spherical and amorphous nanoparticles with an average pore size of 9.7 ± 0.1 nm, drug loading of 16-22%, entrapment efficiency of 75-85%, and longer release at pH 7.4 [88]. Inorganic nanoparticles have increased the solubility and bioavailability of piperine through particle size reduction. They target the piperine at specific sites and release it controllably [89].

Solid lipid nanoparticle (SLN) and Nanostructured lipid carriers (NLCs)

SLNs and NLCs are the two main types of lipid nanoparticles formulated by combining non-toxic lipid nanoparticles and excipients properties. SLNs and NLCs are promising drug carriers for delivering poorly water-soluble drugs [90,91]. Muchow et al. [92] stated, that SLN is the first generation of lipid nanoparticles that structurally resembles an emulsion. SLNs are made of solid lipids at room and body temperatures stabilized by surface surfactants [93,94]. Meanwhile, NLCs are the second generation of lipid nanoparticles where generated lipid particles are a mixture of solid and liquid lipids and will be solid at a temperature of around 40ºC [92]. Generally, the lipid excipients used to formulate SLNs and NLCs are biocompatible, biodegradable, and safe to use. SLNs and NLCs have some clinical advantages like increasing drug solubility and bioavailability, protecting drugs from chemical degradation, smoothly delivering drugs to specific sites, being easier to produce, and being sTable during the storage period [95].

Bhalekar et al. [96] have developed an SLN formulation of piperine for treating rheumatoid arthritis which could be consumed orally. The SLN piperine formulation was prepared using the melt emulsification method with Glyceryl Monostearate and Span 80 as the main ingredients. The SLN piperine dispersion was successfully prepared with a drug and lipid ratio of 1:3 and a span concentration of 1% w/v. The results of the pharmacodynamic test showed that the piperine oral usage could provide a significant response compared to chloroquine suspension.

Chaudhari et al. [97] found a piperine formulation in the form of NLCs. NLCs were chosen because they could load the drugs maximally and had higher stability during the storage period than SLN. Piperine NLCs were made by solvent evaporation through high shear homogenization using solid lipid Compritol 888 ATO (50% w/w), liquid lipid Squalene (25% w/w), piperine (20% w/w), Span 80 (2 .5% w/w), and Tween 80 (2.5% w/w). The piperine NLCs generated spherical particles, which were negatively charged, amorphous, resulting in higher drug release than pure piperine within 12 hours.

Zafar et al. [98] formulated the surface modification of NLCs with chitosan to improve the

therapeutic effect of piperine for diabetes therapy. The characterization of piperine NLCs coated with 0.2% w/v chitosan resulted in piperine encapsulated in lipid and amorphous form, within the size of 149.34 ± 4.54 nm. This could increase the piperine bioavailability ten times higher than pure piperine, and decrease the blood glucose three and half times better than that of pure piperine.

Quantum dots nanoparticle

Quantum dots (QDs) are colloidal semiconductor nanocrystals that consist of atoms of groups II-VI or III-V of the periodic Table and possess unique optical and fluorescent properties. The nanocrystal size of QDs usually ranges from 2 to 10 nm and can be used for marking biological macromolecules, such as nucleosides and proteins [(79)]. Some of the commonly used QDs include cadmium selenide (CdSe), cadmium telluride (CdTe), and indium arsenide (InAs). There have been the latest developments for targeted piperine delivery in the formulation of QDs nanoparticles. Piperine is synthesized with copper oxide (CuO) QDs and coated with hyaluronic acid (HA)/Poly (lactic-co-glycolic acid) (PLGA) [(99)]. Piperine microspheres of CuOQDs aim to deliver the piperine to the brain for treating epilepsy. Piperine loaded in CuQDs HA/PLGA shows enhanced neuroprotection and promoted astrocyte activation in epilepsy-induced mice in vivo. The particle size of CuOQDS HA/PLGA is vital in delivering piperine through the BBB. Smaller particle sizes can easily facilitate the drug delivery process into the systemic circulation.

Drug-phospholipids complexation

Phospholipids are the main components of mammalian cell membranes, are amphiphilic, and perform good solubility in water and oil. Phospholipids are compatible with biological membranes and are hepatoprotective [(100)]. They can increase the drug's bioavailability level with low water solubility and low membrane penetration, enhance drug absorption and release, protect against degradation in the gastrointestinal tract, reduce gastrointestinal side effects, and reduce the bitter taste of orally-consumed drugs [(101)]. One of the benefits of phospholipids in drug delivery is their complexation with piperine compounds. Piperine is complexed with hydrogenated soy phosphatidylcholine (HSPC) with a molar ratio of 1:1.22 and exhibits complexation of the phospholipid group with the –C=O group of piperine through hydrogen bond interactions. The piperine/HSPC complexation generates amorphous particles, increases solubility and sustained release of piperine, and increases piperine bioavailability 10.4 times compared to pure piperine [(102)].

Inclusion complexes

Inclusion complexes mean the formation of some complexes between the ligand as a complexing agent with a lipophilic cavity and a hydrophilic outer surface, which can interact with hydrophobic drug molecules [(103)]. Steric and thermodynamic factors function to form inclusion complexes of ligands and drug molecules. Inclusion complexes of ligands and drug molecules may occur through non-covalent interactions such as hydrogen bonds, van der Waals interactions, ion pairs, solvophobic effects, and/or hydrophobic interactions [(104)]. The more hydrophobic the drug molecule, the more sTable the inclusion complexes will be. Applications of inclusion complexes in oral drug delivery include increasing oral solubility and bioavailability, increasing dissolution rate and rate, increasing drug stability at absorption sites, reducing drug-induced irritation, and masking unpleasant tastes [(105)].

There are two types of formulations for forming inclusion complexes of ligands and drug compounds, namely binary and ternary inclusion complexes. Binary inclusion complexes consist of complexing agents and drug compounds, while the ternary ones include complexing agents, drug compounds, and hydrophilic polymers increase drugs solubility [(106,107)]. The binary inclusion complexes of piperine compound with β-cyclodextrin with a molar ratio of 1:1 successfully increase solubility level, dissolution rate, and absorption rate of piperine in the intestine. The aromatic ring of piperine compounds interacts with the β -cyclodextrin cavity to form amorphous solids and work to increase the solubility level, dissolution rate, and bioavailability of piperine compounds [(108,109)]. Other forms of cyclodextrin, i.e α -cyclodextrin and γ-cyclodextrin have also been successful in increasing the solubility and dissolution of piperine through hydrophobic interactions [(110,111)]. The piperine inclusion complexes with ethylenediamine-β-cyclodextrin through hydrogen bonding at a molar ratio of 1:1 can completely increase the solubility and dissolution rate of the piperine. Piperine compounds are present in the ethylenediamine-β-cyclodextrin cavity and build a relatively sTable composite structure [(112)].

The formation of ternary inclusion complexes assisted with hydrophobic polymers can increase the mixture of ligands and drug compounds. This can reduce ligands and the dose of the drug compounds [(106,107)]. One of the polymers used for such complexes is hydroxypropyl methylcellulose (HPMC). The piperine ternary inclusion complexes with β-cyclodextrin and HPMC synergistically increase solubility and dissolution of piperine compared to the piperine binary inclusion complexes with β-cyclodextrin [(106)].

Other ligands that have been commonly used for inclusion complexes with piperine are cucurbiturils [(113)]. They are macrocyclic oligomers that have the potential to increase drug solubility and bioavailability and are non-cytotoxic [(114)]. The interaction between piperine and cucurbiturils occurs due to the interaction of dipole charges and

hydrogen interactions between the hydrogen atoms of methylene cucurbiturils and the aromatic part of the piperine molecules [113]. The formation of these inclusion complexes can prevent the piperine's isomerization reactions.

Table 2. Summaries some types of nanoparticle formulation design of piperine.

Type	Form	Size (nm)	Composition	Method	Results	Reference
Liposom	Globular	243.4 ± 7.5	Cholesterol, Phospholipon® 90H, Sodium cholate, Chitosan	Thin film evaporation method	Increased solubility and permeability. Showed anti-breast cancer effect.	(52)
	Globular	29.75 ± 0.84	Soya phosphatidylcholine, Tween 80	Thin film evaporation method	Increased solubility, stability, and sustained release.	(51)
Microemulsion	Spherical	161.50 ± 4.06	Caproyl 90®, Tween 80, Cremophor RH 40, Transcutol HP	-	Increased solubility and bioavailability. Increased cognitive function in Alzheimer's disease.	(59)
SEDDS (self-emulsifying drug delivery system) **SNEDDS** (self-nanoemulsifying drug delivery system)	Spherical	89.82 ± 2.16	Ethyl oleate, tween 80, transcutol P	-	Increased solubility (5.90-fold), bioavailability (5.2-fold), and permeability.	(41)
	Spherical	33.35 ± 1.97	Miglyol 812N, Cremophor RH40, PEG400	-	Increased solubility.	(70)
S-SNEDDS	Spherical	73.56 ± 3.54	Glyceryl monolinoleate (GML), poloxamer 188, transcutol HP, avicel PH-101	-	Increased solubility (3.51-fold), bioavailability (4.92-fold), and sustained release.	(75)
Polymeric nanocarriers:						
- Albumin nanoparticle	Globular polymer	187.3 5.7	Human serum albumin (HSA), ethanol, aqueous glutaraldehyde 8% (v/v)	Desolvation method, self-assembly method	Increased solubility and anticancer on MCF-7 cells.	(81)
- Micelle	Spherical	61.9	Soluplus®, D-α-tocopherol polyethylene glycol succinate (TPGS)	Thin-film hydration	Increased sustained release, solubility piperine, bioavailability (2.56-fold), physicochemical stability, cellular uptake, anticancer efficacy in A549 and HegG2 cells.	(82)

Continued table 2 .

Type	Form	Size (nm)	Composition	Method	Results	Reference
- Polymer nanoparticle	Globular polymer	95 ± 10	Poly (D, L, -lactide-co-glycolic acid) (PLGA)	Ultrasonic atomization	Increased solubility, efficacy, and in vitro release	(83)
- Polymeric nanoparticle	Globular polymer	53 ± 1	Methoxy poly (ethylene glycol)-poly(lactic-co-glycolic) (mPEGPLGA), dichloromethane, Lutrol® F68, sucrose	Single emulsion solvent extraction and thin-film hydration	Increased solubility and efficacy piperine inhibit breast cancer (TNBC) cells and MDA-MB-468 in breast cancer.	(85)
- Core-shell nanocarrier	Spherical	-	Dimethyl sulfate (DMS), chitosan (C), Pluronic F-127, sodium dodecyl sulfate (SDS), polyvinyl alcohol (PVA), dichloromethane (DCM), aceton, brain cancer cell line Hs683	Nanoprecipitation technique, ionic gelation	Increased sustained release and solubility. Induction of apoptosis and cell cycle arrect in brain cancer cells.	(86)
- Nanoparticle	Globular polymer	130,20 ± 1,57	Piperine, Eudragit S100 (polymer), poloxamer 188 (surfactant) at 1:1:5 (w/w/w) Solvent : Ethanol	Nanoprecipitation	Increased solubility, in vitro release, and bioavailability (2.7-fold).	(115)
- Starch nanoparticle	Globular polymer	88 ± 20	Sago starch powder (natural biopolymer)	In situ nanoprecipitation	Increased solubility and stability.	(116)
- Nanosuspension	Spherical	172.5	HPMC (stabilizer), ethanol (solvent) (0.25% HPMC, 0.13% extract, rasio antisolvent-to-solvent 1:10)	Bottom-up approach	Increased solubility (5.13-fold) and bioavailability (3.65-fold).	(117)
- Nanosponge nanoencapsulation system	Spherical	-	β-cyclodextrin, diphenyl carbonate, ethanol, acetone, dicloromethane	Microwave-assisted synthesis, solvent evaporation	The ratio of -CD: DPC (1:10) resulted in the highest loading efficiency of piperine.	(118)
- Nanosponge nanoencapsulation system	Spherical	-	β-cyclodextrin, diphenyl carbonate, ethanol	Solvent method	Increased loading efficiency and solubility.	(119)
- Core-shell nanoparticle	Spherical	-	κ-Carrageenan, Zein, potassium chloride, Coenzyme Q10	Antisolvent precipitation method, electrostatic deposition, ionic gelation	Increased photodegradation half-life (3.0-fold), control release, chemical and physichochemical stability.	(120)

Continued table 2 .

Type	Form	Size (nm)	Composition	Method	Results	Reference
- Co-encapculation microparticle	Spherical	922	Zein, chitosan, pectin, Coenzyme Q10	Ultrasound-assisted method, electrostatic deposition, solvent evaporation	Decreased chemical degradation. Increased shelflive and physicochemical stability.	(121)
- Starch nanoparticle	Globular polymer	110	Sago starch powder, anhydrous sodium sulfate (Na_2SO_4), propylene oxide, ethanol	In situ nanoprecipitation	Increased solubility and sustained release.	(122)
- Gelatin nanofiber	Globular polymer	-	Gelatin, glutaraldehyde, acetic acid	Electrospinning method	Improved controlled release profile. Increased diffusion barrier and solubility.	
- Nanoencapsulation	Spherical	68.2	Gum rosin (polymer), acetone, oleic acid, pluronic-f	Emulsion-diffusion method	Increased sustained release and solubility.	(123)
Inorganic nanoparticle	Spherical	-	Hydroxyapatite nanoparticle, gum arabic, folic acid	Hydrothermal method, precipitation method	Increased solubility and inhibited monolayer HCT116 colon cancer cell.	(88)
SLN, NLC	Spherical	115,7 ± 6.26	Compritol® 888 ATO, squalene (liquid lipid), Span 80, Tween 80	Solvent evaporation through high shear homogenization method	Increased solubility (2.0-fold).	(97)
	Spherical	128,80	Glyceryl monostearate, Compritol 888 ATO, Precirol ATO 5, Tween 80, Span 80	Melt emulsification	Increased solubility.	(96)
	Spherical	149.34 ± 4.54	Chitosan 0.2% w/v	-	Increased piperine release (4.67-fold), bioadhesive, permeability (10.15-fold), bioavailability (3.76-fold), and antidiabetic.	(98)
QDs	Spherical	-	Copper acetate dihydrate, 0.1 M NaOH, ethanol, PLGA, ethyl acetate, poly (vinyl alcohol) (PVA), hyaluronic acid	Precipitation method, emulsification solvent evaporation method	Increased solubility and anticonvulsive efficiency.	(99)

Continued table 2 .

Type	Form	Size (nm)	Composition	Method	Results	Reference
Drug-phospholipids complexation	Globular	-	Hydrogenated soy phosphatidyl choline (HSPC), dichloromethane, n-hexane	Precipitation method	Increased bioavailability (10.40-fold) and half-life (20.55-fold).	(102)
Inclusion complexes	Cyclic	-	Hydroxypropyl beta cyclodextrin (HP β CD), D-α-tocopherol polyethylene glycol 1000 succinate (TPGS)	Solvent evaporation method	Increased solubility (52.67-fold) and dissolution (5.45-fold).	(124)
	Cyclic	-	Hydroxy propyl methyl cellulose (HPMC), β-cyclodextrin	Solvent evaporation and microwave irradiation methods	Increased stability, solubility and dissolution (4.43-fold),	(106)
	Cyclic	-	β-cyclodextrin	Freeze drying technique	Increased stability, bioaccessability, and antioxidant activity.	(109)
	Cyclic	-	α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin	Physical mixture (PM) & ground mixture (GM)	Increased solubility.	(110)
	Cyclic	-	Mono(6-ethylenediamine)-β-cyclodextrin	Solvent evaporation method	Increased solubility (2-fold).	(112)
	Cyclic	-	Cucurbit[*n*]uril	-	Increased solubility and stability.	(113)

The nanoparticle systems, especially in lipid carriers and biodegradable polymers, have been succesful in increasing the solubility, permeability, and bioavailability of piperine. The polymer nanoparticle formulation is very sTable and can easily modify the surface; thus, drug release at specific sites can be managed well. Biodegradable polymer nanoparticles can act as a drug depot that provides a sustainable supply of therapeutic compounds at the targeted sites [125]. The biodegradable polymers (PLGA and PLA) for nanoparticle production have been widely used for sustainable drug administration because they effectively deliver the drug to intracellular targeted sites [126]. Polymeric nanoparticle piperine using PLGA can also smoothly deliver the piperine to the targeted sites and increase its efficacy on HEK-293 (human embryonic kidney cells) and MCF-7 (Michigan Cancer Foundation-T and breast cancer cells) [83,84].

Lipid formulations can be easily absorbed by the body tissue after experiencing dissociation and release of the lipid system [127]. The lipids in the gastrointestinal tract can also slow gastric emptying. Therefore, drug lipids are stored longer in the small intestine, allowing better drug dissolution at the absorption sites to enhance absorption level. A high lipophilic drug with high solubility in triglycerides can be transported by the lymphatic system. In this way, the metabolism process in the liver can be bypassed, which can increase the drug bioavailability [127,128]. Lipid formulations can also increase drug bioavailability by inhibiting P-glycoprotein efflux at the luminal membrane of epithelial cells in the colon, jejunum, and liver [129].

Although drug delivery on the nanoscale is very promising, nano-based formulations are still difficult to develop. For the pharmaceutical industry, drug formulation in nano form triggers complicated challenges because nanoformulations are easy to self-aggregate on long-term storage, affecting drug stability, variability, and efficacy [130–132]. Other factors are related to the mechanism of solubility increase by nonionic surfactants, co-solvents of propylene glycol and polyethylene glycol, and the use of cyclodextrins. Even though

nonionic surfactants, propylene glycol, polyethylene glycol, and cyclodextrin have shown to increase solubility, they can decrease permeability and lead to lower bioavailability levels despite high solubility [133–137].

Ingels et al. [138] found that the increase in solubility was disproportionate to drug absorption, and drug preparations cannot go through the epithelial barrier. Although the solubility of the hydrobic drug was increased, it did not mean that there was an increase in its bioavailability. Besides, increased solubility due to micellization did not necessarily increase the amount of drug available for passive diffusion across membranes and epithelial barriers in the gastrointestinal tract (GIT) [139].

Another challenge is related to scale-up and manufacturing processes. The nanoparticles are complex three-dimensional multicomponent products with a specific arrangement of components at the nanometer scale. Therefore, they present typical challenges during the scale-up and manufacturing processes. Nanoparticle formulation processes involving high-speed homogenization, sonication, organic solvents, cross-linking, milling, organic solvent evaporation, centrifugation, filtration, and lyophilization pose complex challenges during scale-up and manufacturing processes. Different processing conditions during initial development on a small scale can affect chemical structure and conformation changes, denaturation, cross-linking, coagulation, and degradation of the active substances and excipients [140]. For the scale-up process from small to industrial level, it is necessary to understand the characterization, testing, and release of nanoparticle products to identify critical parameters and analytical criteria; thus, the scale-up and manufacturing processes can result in high reproducibility and consistent products. Identification of processing conditions involving polymer ratio, drug, target site, type of organic solvent, oil and water phase ratio, mixing temperature, pressure, pH of media, emulsifier, stabilizer, and cross-linker is also necessary before coming to the scale-up and manufacturing processes [141].

Conclusions

The brief review shows that various formulation approaches have successfully increased the solubility and absolute bioavailability of piperine within the body. Some approaches include solid dispersion, liposome, microemulsion, SEDDS, SNEDDS, S-SNEDDS, polymeric nanocarriers, inorganic nanoparticles, SLN, NLC, QDs, complexation with phospholipids, and inclusion complexes. However, most of the formulations do not consider the stability of piperine in dosage forms, especially for those in liquid preparations, because piperine compounds are very sensitive to light and can be easily degraded in liquid form. Therefore, it is essential to further study the stability of piperine in the dosage form. Some toxicity testing and demonstration of safety and efficacy should also be carried out to support the success of the piperine nano compounds formulation which later aims to increase its solubility and bioavailability.

Conflict of Interest

The authors have no conflict of interest.

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