Recent developments in formulation design for improving oral bioavailability of curcumin: a review

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Abstract

Curcumin, a yellow-orange substance that is extracted from the spice turmeric \((\textit{Curcuma longa}, \textit{Zinziberaceae})\), has been attributed with a wide range of pharmacological activities for the prevention and treatment of several disease conditions such as arthritis, hypertension, diabetes, Alzheimer’s, antibacterial and cancer to name a few. However, its potential for use as an orally delivered medicinal product is hindered by its poor solubility and bioavailability. The low oral bioavailability of curcumin is caused by several factors including low aqueous solubility, poor intestinal permeability, unstable at alkaline pH and rapid metabolism. To improve curcumin’s poor oral bioavailability, different formulation strategies such as incorporation into nanoparticles, liposomes, micelles, micro/nano-emulsions and solid dispersions as well as co-administration with piperine have been investigated in both animal models as well as human supplementation studies. In this review, novel formulations of curcumin for oral delivery that were developed in recent years are reviewed and discussed.

Key words

Curcumin; oral bioavailability; delivery system; liposomes; clinical studies; Soluplus®; piperine
1. Introduction

Curcumin is a yellow orange coloured crystalline compound that is extracted from the spice turmeric (*Curcuma longa, Zingiberaceae*). Chemically, curcumin is known as diferuloylmethane (C$_{21}$H$_{20}$O$_6$) with a molecular mass of 368.37 g/mol. It is a polyphenol compound and has a melting point of 183°C. The IUPAC name of curcumin is 1,7-bis (4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione (1E-6E). The two aryl rings in curcumin contain ortho-methoxy phenolic groups are symmetrically linked to a β-diketone moiety (Anand et al., 2007; Araiza-Calahorra et al., 2018; Carolina Alves et al., 2018; Esatbeyoglu et al., 2012). Curcumin exhibits a pH-dependent keto–enol tautomerism, where in an acidic or neutral solution, the keto form of curcumin is predominant while in an alkaline medium the enol form of curcumin becomes predominant (Figure 1) (Anand et al., 2007; Bernabé-Pineda et al., 2004; Jovanovic et al., 1999). The colour of curcumin also changes at different pH levels forming a bright yellow coloured solution at pH range 2.5 to 7.0 with the colour changing to dark red when the pH is increased above 7 (Anand et al., 2007; Esatbeyoglu et al., 2012).

The use of turmeric for medical treatment in Asia can be traced back thousands of years (Araiza-Calahorra et al., 2018). Turmeric has been widely used since ancient times as a herbal medicine for treating many conditions such as cough/inflammation, respiratory diseases, flu, sinusitis, liver disorders, rheumatism and abdominal pain (Ravindranath and
Chandrasekhara, 1980; Shoba et al, 1998; Wahlström and Blennow, 1978). In India, turmeric is traditionally used for treating infections, sprains/swelling and healing burn wounds (Araujo et al., 2001), while in China turmeric is regularly used as herbal medication for treating diseases that are associated with abdominal pain (Aggarwal et al., 2004). With the advancement of science and technology, it had been discovered that curcumin is the key ingredient that contributes to most of the therapeutic effects of turmeric (Mukundan et al., 1993; Pal et al., 2001). Curcumin was found to have a wide spectrum of pharmacological activities. Several studies on curcumin showed that it has anti-inflammatory (Srimal and Dhawan, 1973), antimicrobial (Kim et al., 2003; Kuttan et al., 1985; Prasad et al., 2015; Reddy et al., 2005), antirheumatic (Senft et al., 2010), immunomodulatory (Jantan et al., 2011) and anti-tumour effects (Hatcher et al., 2008). The anti-tumour effect of curcumin is associated with the suppression of early growth of response-1-gene product (EGR-1), protein tyrosine kinase cascade and mitogen-activated protein kinases (MAPK) pathway (Khan et al., 2018). Curcumin also demonstrates antioxidant property based on its ability to scavenge free radicals due to the electron donating property of the phenolic group (Khopde et al, 1999; Masuda et al., 2001; Ruby et al., 1995; Sharma, 1976; Sugiyama et al., 1996). The anti-inflammatory effect of curcumin is associated with its ability to inhibit NFkB (Nuclear factor κB) to bind with DNA. The inhibition of NFkB-DNA binding lead to suppression of pro-inflammatory molecules MMP-3 (matrix metalloprotease
and MMP-9 (matrix metalloprotease 9). It also results in reduction in pro-inflammatory cytokines, such as TNFα (tumor necrosis factor 1α), IL1β (interleukin 1β) and IL8 (interleukin 8) (Esatbeyoglu et al., 2012). In addition, curcumin also exert anti-inflammatory effects by binding to proteins COX-2 (prostaglandin-endoperoxide synthase 2), which leads to reduction in COX-2 expression, prostaglandin and thromboxane synthesis. Subsequently, curcumin inhibits the activity of 5-LOX (Arachidonate 5-lipoxygenase) and leukotriene synthesis. The decreased expression of these compound attributes to the anti-inflammatory effects of curcumin (Hong et al., 2004). The anti-bacterial effect of curcumin is believed to be associated with its ability to inhibit the formation of FtsZ ring (Z ring) at the site of division of bacterial cells, which disrupts the division of the bacterial cells (Rai et al., 2008). Curcumin also showed anti-viral effect on several viruses such as HIV, influenza, HSV-1, coxsackievirus and HBV. The anti-viral activities of curcumin include inhibiting the HIV-1 LTR-directed gene expression, HIV-1/HIV-2 proteases, haemagglutination, reducing HSV-1, coxsackievirus and HBV replication. (Moghadamtousi et al., 2014). The pharmacological effect of curcumin on rheumatic diseases like osteoarthritis is based on its ability to in inhibit the expression of metalloproteinase-3 enzymes (MMP3). MMP3 is highly expressed in synovial cells in patients with osteoarthritis, which results in the degradation of connective tissue components. By inhibiting the expression of MMP3, curcumin inhibits the proliferation of osteoarthritis synovial cells,
increases the cell apoptosis, and eventually ease the inflammation and cartilage degradation of osteoarthritis (Yang et al., 2019). Although the exact mechanisms are still unknown, the immunomodulatory effects of curcumin are most likely due to its ability to inhibit NF-κB target genes that are involved in inducing immune responses (Yadav et al., 2005). Additionally, activity in protecting the heart and kidney against oxidative injury was reported in several studies (Saeidinia et al., 2018; Venkatesan, 1983, Venkatesan, 2000, Venkatesan et al., 2000). Curcumin shows heart protecting effect through several mechanisms that include inhibiting cardiomyocyte fibrosis, increasing ventricular hypertrophy and related-gene expression (Saeidinia et al., 2018). Curcumin protects against renal injury by inhibiting lipid peroxidation in kidneys, which reduces oxidative injury to the kidneys. It also increases levels of natural antioxidants, kidney glutathione content and glutathione peroxidase activity in kidney tissues, which restores kidney functions (Venkatesan, 2000). Curcumin also showed therapeutic activity in diabetes due to its effect in increasing sensitivity to insulin and reducing blood glucose levels in humans (Parsamanesh et al., 2018). Other studies showed that curcumin could be a promising drug candidate for treating or preventing neurodegenerative diseases such as Alzheimer’s disease (AD) (Mutsuga et al., 2012; Ray et al., 2011), Parkinson’s disease (PD) and brain tumours (Hatcher et al., 2008; Mythri et al., 2011). It has been reported that curcumin suppresses the formation of amyloid β protein aggregates in the brain. The suppression of
amyloid β protein aggregates leads to the reduction of reactive oxygen species (ROS) and cytochemokines, which decreases oxidative stress induced damage and neuroinflammation to the brain (Mutsuga et al., 2012; Mythri et al., 2011; Ray et al., 2011).

The safety of curcumin was proven in several animal tests and human studies (Lao et al., 2006a, 2006b; Sharma et al., 2004; Siviero et al., 2015). An oral dose as high as 12g per day was shown to be well tolerated in humans (Lao et al., 2006b). However, despite its wide pharmacological potentials and high dose tolerance, curcumin is still not approved as a therapeutic agent for oral delivery. The main reason is because curcumin has very poor oral bioavailability so it can be barely absorbed in the human body (Anand et al., 2007). Curcumin plasma concentration was under the detection limit at an oral dose of 12 g in healthy male subjects (Klickovic et al., 2014). To overcome curcumin’s problem of bioavailability, numerous research studies have been reported every year. In this review, factors that account for the poor oral bioavailability of curcumin are first explained in detail followed by a review of recent efforts in improving curcumin’s oral bioavailability.

2. Routes of drug administration reported for curcumin

The delivery routes of curcumin include oral administration, intravenous (IV) injection, nasal administration, topical administration, subcutaneous delivery and intraperitoneal (IP) administration (Prasad et al., 2014).
Among the delivery routes, oral delivery is regarded as the most accepted route for drug administration. It is also the most preferred administration routes over other delivery routes due to its convenience, high patient compliance, cost effectiveness and ease of production (Gupta et al., 2009). Besides, oral administration is the most studied delivery route for curcumin. In most of studies, curcumin was delivered to the subjects (either humans or animals) through oral administration (Prasad et al., 2014). Orally delivered curcumin has exhibited various pharmacological effects such as anti-inflammatory, anti-tumor, antioxidant, antimicrobial, antidiabetic, immunomodulatory, etc.

In IV administration, curcumin is injected directly into blood vessels, which helps curcumin bypass the physiological barriers against drug absorption, leading to highest bioavailability and fastest effect among all delivery routes. However, compared with the oral route, IV injection has some major drawbacks such as poor patience adherence, inconvenience, needle-associated pain, risk of unsafe needle use and the need for trained healthcare personnel (Homayun et al., 2019).

Topical delivery is administration of drugs directly on to the body surfaces such as skin or mucous membranes. Compared with oral administration, curcumin delivered though topical route showed pharmacological effects related mostly to the skin conditions such as skin inflammation, wound healing and skin cancer among others (Dovigo et al., 2013; Lopez-Jornet et al., 2011;
LoTempio et al, 2005; Sun et al., 2013).

Nasal delivery is a drug administration route where the drug is insufflated through the nose and absorbed via the nasal mucosa. Curcumin was used in nasal administration for better brain targeting and it showed pharmacological effects on neurodegenerative diseases such as Alzheimer’s and Parkinson’s diseases (Prasad et al., 2014). Nasal delivery is an easier way for delivering curcumin when compared with IV injection. However, it is still relatively inconvenient when compared to oral delivery route since there is a possibility of nasal irritation for some patients (Türker et al., 2004).

Intraperitoneal injection is an administration route where the drug is injected directly into the peritoneum (body cavity) and in subcutaneous injection the drug is injected into the tissue layer between the skin and the muscle. These two delivery routes were reported more often and used in the administration of curcumin to animals than to humans (Prasad et al., 2014).

The routes of administration played important roles in the therapeutic effects of a drug substance. Among all the delivery routes of curcumin, oral administration is an effective route to deliver curcumin with numerous advantages over other administration routes. Therefore, it is suggested to focus more on the studies of oral administration of curcumin and the development of curcumin formulation for oral delivery.
3. Factors that account for curcumin’s poor oral bioavailability

According to the Biopharmaceutics Classification System (BCS), curcumin could be classified as a class IV substance since it has poor aqueous solubility and limited permeability across the intestinal membranes (Paolino et al., 2016). Apart from the poor solubility and intestinal permeability, curcumin also has low serum concentration, poor pH dependent aqueous-stability and rapid metabolism in animals and humans, which are believed to be the main reasons that account for the poor oral bioavailability of curcumin. (Gantait et al., 2001; Holder et al., 1978; Ireson et al., 2001; Kunnumakkara et al., 2008; Kurien et al., 2007; Modasiya and Patel, 2012; Murugan and Pari, 2006; Perkins et al., 2002; Pfeiffer et al., 2007; Ravindranath and Chandrasekhara, 1981; Sandur et al., 2007; Song et al., 2016; Suresh and Nangia, 2018; Tønnesen and Karlsen, 1985; Wang et al., 1997).

3.1. Poor aqueous and gastro-intestinal fluid solubility

Curcumin is hydrophobic so it has extremely poor water solubility (Lao et al., 2006b). Its aqueous solubility is also pH dependent. At acidic or neutral pH, it is practically insoluble. The maximum solubility of curcumin in aqueous solution at pH 5 was only 11 ng/ml (Gantait et al., 2001; Song et al., 2016). It was reported that the solubility increased to 0.1 μg/ml at pH 6.8. However, it dropped to 0.06 μg/ml when the pH was increased to 7.4 (Modasiya and Patel, 2012). For any orally administrated drug to be absorbed, it needs to
dissolve in the gastrointestinal (GI) fluids. GI solubility of curcumin tested in simulated gastroenteric fluids reported that curcumin showed equilibrium solubility of 2.5μg/ml in the fasted simulated gastric fluid (pH1.6), 3μg/ml in simulated gastric fluid (pH1.2) and 2μg/ml simulated intestinal fluid (pH6.8) (Jaisamut et al., 2013). Compared with the solubilities tested in water or buffer solutions, curcumin solubilities measured in simulated gastroenteric fluids seems to be much higher but still quite low. This reason for the higher solubilities tested in the simulated gastroenteric fluids is unknown but it might be due to the presence of pepsin in the simulated gastroenteric fluids. There were studies which showed that pepsin can improve the solubility of lipophilic drugs although the mechanisms behind have not been founded yet (Nascimento et al., 2012; Pinnamaneni et al., 2015).

Curcumin has a low plasma concentration even after administering a high oral dose. A clinical trial conducted in healthy human males even after an oral dose of curcumin as high as 12 g the plasma curcumin concentration was too low to be detected (Klickovic et al., 2014).

In contrast, when 1 g/kg of curcumin was delivered orally to Sprague–Dawley rats and measuring plasma curcumin concentration showed that the amount of curcumin present in the plasma was less than 1% of the administrated dose (Wahlström and Blennow, 1978). A similar result was also reported by Chang et al (Chang et al., 2013), after an oral dose of 1 g/kg of curcumin in rodents resulted in curcumin plasma concentration of 15 ng/ml
after 50 min (Chang et al., 2013).

When at the same dose, human showed much lower curcumin plasma concentration than rats. The same dose of curcumin (2 g/kg) was delivered orally to rats and humans respectively. The maximum plasma concentration (Cmax) in rats was found to be $1.35 \pm 0.23 \, \mu g/ml$ measured 50 min after taking the dose, whereas the Cmax of curcumin in humans was only $0.006 \pm 0.005 \, \mu g/ml$ measured 1 hour after administration (Shoba et al, 1998).

The results from these studies further suggests that curcumin has a very poor plasma concentration even after a high oral dose in both rodents and humans. When the same oral dose was administered, rats were found to have higher plasma concentration of curcumin than humans.

### 3.2. Low permeability (absorption)

Apart from solubility, permeability is another main factor that affect oral drug administration since the absorption of drugs depends on its permeability across the biological membrane of the GI tract after dissolution (Parikh et al., 2016). Experimental results in *in vivo* animal models and simulated human intestinal epithelium barrier have shown that curcumin is poorly permeable across intestinal membranes even after dissolution (Gao et al., 2013; Righeschi et al., 2016; Volpe et al., 2007; Wahlang et al., 2011). It was found that in the rat small intestine, curcumin was best absorbed at the duodenal segment, followed by the jejunum and colon. The absorption of curcumin in
the ileum was the poorest (Wang et al., 2017a).

Caco-2 cell lines (Figure 2) possess the same cell polarity and compact single-cell layer just like human intestinal epithelial cells and as a result, they are commonly used as the cell model for testing the intestinal permeability/absorption of drugs (Artursson and Karlsson, 1991; Parikh et al., 2018a; Sambuy et al., 2005; van Breemen and Li, 2005; Volpe et al., 2007; Xue et al., 2017). The results from permeability test for curcumin reported by Zeng et al. (Zeng et al., 2017a) in Caco-2 cell lines exhibited that there was a decrease of permeability from the apical side to the basolateral side (A to B direction) with an increase in curcumin concentration. Conversely, permeability from the basolateral side to the apical side (B to A direction) increased along with an increase in the concentration of curcumin added. Furthermore, curcumin at concentration of 5 µg/ml, the value of PappA-B was greater than PappB-A which indicated an increased absorption of curcumin. However, when the curcumin concentration was increased to 10 µg/mL and 20 µg/ml, the value of PappA-B became lower than PappB-A, indicating that the amount of curcumin that is being pumped out from the cells is higher than the amount being absorbed at this concentration range. It also showed that the intestinal permeability of curcumin does not increase in a concentration dependent manner for curcumin (Zeng et al., 2017a).

In transcellular studies, apparent permeability coefficient (Papp) was used to represent the amount of compound transported per unit time (Wang et al.,
It was reported that the value of Papp is correlated to the extent of drug molecules that penetrate across the intestinal tract of the drugs (Artursson and Karlsson, 1991; Ozeki et al., 2015). However, in another curcumin permeability study conducted using Caco-2 cell line it was reported that efflux pathways do not play a role in curcumin intestinal permeability. This observation was based on Papp (A to B) value (2.93 ± 0.94 x 10^{-6} cm/s) was found higher than the value of Papp (B to A) (2.55 ± 0.02 x 10^{-6} cm/s) at curcumin concentration of 62.6 µg/ml (170µM), (Wahlang et al., 2011).

An efflux pump like P-glycoprotein could also affect the permeability of curcumin. P-glycoprotein is an ATP dependent efflux pump that can pump drugs out of the cells thus reducing the bioavailability. In the small intestine, the expression of P-glycoprotein is present at ileum and jejunum (Canaparo, 2007). An in vitro study using Caco-2 cells showed that co-administration of P-glycoprotein inhibitor such as verapamil, along with curcumin could increase the rate absorption of curcumin (Xue et al., 2017). This indicated that curcumin could potentially be a P-glycoprotein substrate and blocking P-glycoprotein can help to improve the permeability as well as the drug absorption in the intestinal tract. Wand et al (Wang et al., 2017a) have investigated a concentration dependent effect of verapamil on the absorption of curcumin in rat intestines. No obvious change to the absorption of curcumin was observed when verapamil concentration was increased from 0.05 mmol/L to 0.1 mmol/L. When verapamil concentration was increased to
0.5 mmol/L, the rate of curcumin absorption was increased by approximately 3%. This showed that P-glycoprotein inhibitor like verapamil is capable to improve both the rate and the amount of curcumin absorbed in small intestines (Wang et al., 2017a).

Overall, from these studies, it can be concluded that curcumin has poor permeability across intestinal barriers even after dissolution, thus confirming that the curcumin can be classified as a class IV drug according to biochemical classification scheme (poorly soluble and poorly permeable).

### 3.3. High metabolism rate of curcumin

Curcumin delivered orally undergoes extensive metabolic reduction and conjugation, which result in poor bioavailability (Garcea et al., 2004). The mechanisms of curcumin metabolism are shown in Figures 3 and 4.

The Phase I metabolism includes the reduction of the four double bonds of the heptadiene-3, 5-dione structure of curcumin. The reduced curcumin metabolites dihydrocurcumin, tetrahydrocurcumin, and hexahydrocurcumin were detected in plasma (rats and humans) following curcumin oral supplementation. The reduction processes were catalysed by NADPH-dependent curcumin reductases that exist in the liver (Hoehle et al., 2007; Ireson et al., 2001). E. coli, the microorganism that commonly exists in small intestine and colon, was found to have the ability to catalyse the metabolic reduction processes of curcumin (Hassaninasab et al., 2011).
During the Phase II metabolism, glucuronidation and sulfation of curcumin and the reduced metabolites take place. The conjugation activities are catalysed by UDP-glucuronosyltransferases and sulfotransferase respectively (Ireson et al., 2002). The conjugated metabolites include curcumin sulfate, curcumin glucuronide sulfate, curcumin glucuronide, dihydro curcumin glucuronide, tetrahydro curcumin glucuronide and hexahydro curcumin glucuronide. *In vivo* studies in rats and humans showed that the curcumin glucuronide and curcumin glucuronide/sulfate conjugates were found in the plasma, jejunum and livers (Asai and Miyazawa, 2000, Hoehle et al., 2007, Ireson et al., 2001, 2002). An *in vivo* study conducted in rats showed that the UDP-glucuronosyltransferases and sulfotransferase enzymes activities were found in livers, kidneys, small intestine mucosa and colon intestinal mucosa. No conjugated enzyme activities were found in the plasma (Asai and Miyazawa, 2000). These observations might indicate that the conjugated curcumin metabolites are probably produced in these tissues before present in the plasma circulation. The glucuronidation activity was found to occur more extensively in human intestines than in rats, while it became less extensive in human liver than in rats. The difference of metabolism extension may be due to the differences in conjugation-hydrolysing enzymes content in intestines & livers of humans and rats (Hoehle et al., 2007, Ireson et al., 2001, 2002).
3.4. Chemical stability of curcumin

Like its aqueous solubility, the chemical stability of curcumin in aqueous solution is affected by change in pH. Curcumin is most stable at pH 1–6, when in the environment of stomach or small intestine. However, the aqueous solubility becomes extremely poor at this pH range while the stability of curcumin decreases significantly when the pH is above 7 (Esatbeyoglu et al., 2012, Wang et al., 1997). In a stability test, using 5 mM curcumin solution (dissolved in methanol and added to 0.1 M phosphate buffer solution at pH 7.2) incubated at 37°C for different lengths of time and analysed by HPLC, the results showed that 90% of the curcumin was degraded within 30 min to various degradation products including vanillin, ferulic acid and feruloyl methane (Figure 5). Vanillin was identified to be the major degradation product in this assay following first-order kinetics (Wang et al., 1997). Overall, the stability problem of curcumin really affects the oral bioavailability since curcumin can be rapidly degraded at alkaline solutions and is poorly soluble in acidic aqueous solutions (even though more stable).

4. Novel formulations developed for improving curcumin’s oral bioavailability

Numerous efforts have been made to find a way to overcome the low oral bioavailability of curcumin and a great number of novel formulations have been developed by researchers to achieve this goal. Details of recent
developments in curcumin formulations are discussed in the following sections.

4.1. Co-administration of adjuvants

Some adjuvants can decrease the metabolism of curcumin which can help to improve the bioavailability of curcumin.

Piperine (Figure 6) is an alkaloid naturally present in black pepper and is the substance that gives black pepper (Piper nigrum) its pungency. Co-administration of piperine with curcumin was found to improve the bioavailability of curcumin (Atal et al., 1985; Shoba et al., 1998). Piperine inhibits the enzyme UDP-glucuronyltransferase in the liver thereby limiting the extent of curcumin glucuronidation. Because of this process, more curcumin is available for absorption (Zeng et al., 2017b). An in vivo study was conducted in both rats and humans at an oral dose of 2 g/kg of curcumin with 20mg/kg piperine, administered simultaneously (Shoba et al, 1998). The relative bioavailability of curcumin in rats was increased by 1.54-fold while in the human volunteers it increased by 20-fold. However, even though extent of increase of bioavailability of curcumin was higher in human than in rats, the amount of curcumin actually being absorbed was in fact higher in rats than in human (Figure 7). In another clinical trial, 2 g of curcumin and 5mg of piperine were co-administered orally to healthy human volunteers (Anand et al., 2007). The test results revealed that there was an increase of absorption of curcumin
by 200%, compared with that of taking curcumin alone (Figure 8). Another study by Zeng et al. (Zeng et al., 2017b) investigated the effect of pre-administration of piperine on the oral bioavailability of curcumin. In this study, rats received 20 mg/kg piperine initially followed by curcumin (200 mg/kg) at various time intervals between 0.5-8 h after piperine administration. The rats that received pre-administration of piperine before the curcumin all showed remarkable enhancement in curcumin oral bioavailability, especially at 6 hours after taking piperine with AUC₀⁻ᵗ increased 97-fold when compared to pure curcumin. In contrast, rats that received the same oral dose of piperine and curcumin at the same time exhibited much lower enhancement in AUC₀⁻ᵗ, by 1.67-fold relative to pure curcumin (Figure 9). It was also found that that piperine causes time-dependent and selective suppression of UDP-glucuronyltransferase and sulfotransferases, which reducing curcumin metabolism (Volak et al., 2008; Zeng et al., 2017b).

Apart from piperine, several other natural compounds such as silibinin, and quercetin have been shown to inhibit the effects of UDP-glucuronyltransferase (Grancharov et al., 2001; Williams et al, 2002). Quercetin is a plant flavonol that is present in many fruits, vegetables and grains (Lund and Pantuso, 2014). Silibinin is a flavonoid that extracted from the medicinal plant Silybum marianum (milk thistle) (Cheung et al., 2010). The effect of co-delivering natural curcumin metabolism enzyme inhibitors on the oral bioavailability of curcumin was studied using a self-emulsion formulation...
of curcumin. The self-emulsion formulation (containing 100 mg/kg curcumin) was delivered orally to mice with or without either piperine (125 mg/kg), quercetin (100 mg/kg), or silibinin (100 mg/kg). The pharmacokinetic results showed that piperine co-administration showed the highest C$_{\text{max}}$ of curcumin. However, curcumin concentration in the plasma was highly variable (0–2.4 μM curcumin plasma levels), which was deemed unacceptable. Co-administration of quercetin or silibinin showed much more stable plasma levels of curcumin and both increased the average C$_{\text{max}}$ of curcumin. Silibinin co-delivery resulted in higher C$_{\text{max}}$ of curcumin than quercetin so the bioavailability study was only conducted for silibinin. The results reported that co-administration of silibinin improved the overall bioavailability of curcumin by approximately 3.5-fold (AUC$_{0-6}$ 0.2613 ± 0.0368 Vs. 0.0808±0.0469 h·μmol/L for SMEDDS without adjuvant co-delivery) (Grill et al.,2014).

An in vitro Caco-2 cell monolayers permeability study examined how oral co-administration of piperine, quercetin or resveratrol can affect the intestinal absorption of curcumin. Resveratrol (trans-3,5,4′-trihydroxystilbene), is a natural plant compound that is present in grapes, berries and other plants. All the three compounds showed an increase in curcumin permeability across the Caco-2 cell monolayers. Quercetin and resveratrol increased the curcumin permeability by 1.46-fold and 1.25-fold, respectively. The highest effect on curcumin permeability was from piperine, which increased the permeability by 2.33-fold. Interestingly, when quercetin and resveratrol were combined
together with curcumin, the permeability increased by 1.85-fold. This indicated that there is an additive effect of resveratrol and quercetin on curcumin absorption (Lund and Pantuso, 2014).

Co-delivery of natural compounds like piperine, quercetin, resveratrol and silibinin decreased the metabolism of curcumin which eventually increased the absorption of curcumin. It is a promising and easy way to improve the oral bioavailability of curcumin and could be investigated further in the development of novel drug delivery systems.

4.2. Nanoparticles

Nanoparticle-based delivery system is another effective strategy to improve the oral bioavailability of poorly water-soluble drugs. The nano-size of the particle (10–1000 nm) leads to a greater surface area for the drug particles thereby increasing the area of physical interaction with the solvent. According to Noyes-Whitney equation, the dissolution rate is directly proportional to the surface area. Therefore, nano-sized drug particles with higher surface area are likely to be dissolved more rapidly. Furthermore, reducing the drug particle size to nanometer size, according to the Ostwald-Freundlich equation, can increase the saturation solubility of the drug. (Jahagirdar et al., 2018; Merisko-Liversidge et al., 2003; Müller et al., 2011).

A list of approved nanodrugs is shown at Table 1. In comparison with the conventional formulations, these nanodrugs benefited from increased
dissolution rate and saturation solubility, which leads to higher bioavailability (Junghanns and Muller, 2008).

Table 1. A List of FDA approved nanodrugs (Junghanns and Muller, 2008).

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Generic name</th>
<th>Route of administration</th>
<th>Indication</th>
</tr>
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<tbody>
<tr>
<td>Emend®</td>
<td>Aprepitant as nanocrystal</td>
<td>Oral</td>
<td>Preventing nausea and vomiting</td>
</tr>
<tr>
<td>Megace ES®</td>
<td>Megestrol acetate as nanocrystal</td>
<td>Oral</td>
<td>Treating loss of appetite and wasting syndrome in people with acquired immunodeficiency syndrome (AIDS).</td>
</tr>
<tr>
<td>Rapamune®</td>
<td>Rapamycin (sirolimus) as nanocrystals formulated in tablets</td>
<td>Oral</td>
<td>Immunosuppressant</td>
</tr>
<tr>
<td>Tricor®</td>
<td>Fenofibrate as nanocrystals</td>
<td>Oral</td>
<td>Treating hypercholesterolemia and hypertriglyceridemia</td>
</tr>
<tr>
<td>Triglide®</td>
<td>Fenofibrate as nanocrystals</td>
<td>Oral</td>
<td>Treating hypercholesterolemia and hypertriglyceridemia</td>
</tr>
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*Compared with the conventional formulations

Nanoparticle technology is widely used for delivering poorly-water soluble drugs or substances (Bisht et al., 2007; Ensign et al., 2012; Singh and Lillard, 2009; Zhang et al., 2008;). A curcumin loaded lipopolysaccharide nanoparticles (C-LPNCs) was developed to improve the oral bioavailability of
curcumin (Chaurasia et al., 2015). Soluthin® MD, a phosphatidylcholine-maltodextrin based hydrophilic lipopolysaccharide, was used as the nanocarrier to load curcumin. Poloxamer 188 was added as a stabiliser to prevent aggregation and size growth of the C-LPNCs. A graphical scheme of this formulation is shown in Figure. 10. Burst dissolution of the curcumin was observed in the first 30 min at pH 7.4 buffer solution, which was due to the amorphous distribution of the curcumin particles in the C-LPNCs. Subsequently the dissolution rate was reported to gradually reduce and became relatively stable after 12 hours. After 24 hours, 80% of the curcumin in the C-LPNCs dissolved in the solution. The C-LPNCs were evaluated in vivo to investigate its effect on the oral bioavailability. A curcumin equivalent dose of 50mg/kg was administrated orally to Albino Wister rats. The C_{max} and AUC_{0–t} of curcumin was found to have increased by 104.8-fold and 55.2-fold respectively when administrated as the C-LPNCs, compared with the unformulated curcumin. Lymphatic transport was found to be involved in the oral absorption of C-LPNCs, which can reduce curcumin hepatic metabolism in liver thus contributing to the increase in curcumin bioavailability. In addition, maltodextrin in the formulation can protect curcumin from degradation in the harsh environment of the gastrointestinal tract, which could be another reason for the improvement of the oral bioavailability. Anticancer activity of C-LPNCs against colon cancer was investigated in vivo in colon-26 tumour bearing rats. A curcumin equivalent dose of 50 mg/kg was delivered orally daily to the rats
for 30 days. At the end of the study, 100% survival rate was observed in the
group being treated with the C-LPNCs while 33.33% survival rate was
observed in the group receiving pure curcumin (Chaurasia et al., 2015).

In another study, a simple method called CO₂-assisted in situ nano-
amorphization was used to prepare curcumin-lipopolysaccharide based oral
nanosuspension to improve the bioavailability and anticancer efficacy of
curcumin (Wang et al., 2017b). In this method, curcumin, citric acid and a
stabilizer, Brij78, were first dissolved in ethanol. The solvent was then
removed via evaporation, resulting in the formation of a solid mixture.
Subsequently carbonated solution was added to the solid mixture to form the
curcumin loaded nanosuspension. In an in vivo test in rats, it was reported
that the oral bioavailability of curcumin had improved by 3.70-fold from the
CUR/Brij78 nanosuspensions compared with that of free curcumin
suspension.

Another novel curcumin-loaded nanoparticle was developed by using an
ionotropic gelation method. Alginate and polysorbate combinations were used
to form the nanoparticles to entrap curcumin (Govindaraju et al., 2019). This
formulation showed low release of curcumin in gastric and intestinal
environments but a sustained release within the colon. This phenomenon was
due to colonic microflora, which helped to digest the alginate thus allowing
curcumin to be released from the nanoparticles. In the human body, at a
curcumin dose of 100 mg, the nanoparticle formulation increased the oral
bioavailability of curcumin by 5-fold than that of free curcumin suspension. Since most of the curcumin was released and absorbed in the colon, this formulation might be a promising approach for oral delivery of curcumin for targeting colonic diseases.

Applying coating to the surface of nanoparticles may help to prevent agglomeration to occur. Commonly used polymers for such coating are polyethylene glycol (PEG), poly(vinylpyrrolidone) (PVP), dextran, chitosan, pullulan etc. Surfactants like sodium oleate and dodecylamine have also been used for nanoparticle coating (De Jong and Borm, 2008). In another study, a curcumin-loaded solid lipid nanoparticles (SLNs) with N-carboxymethyl chitosan (NCC) coating was prepared through a modified hot homogenization and sonication method (Baek and Cho, 2017). The NCC coated SLN samples exhibited 9.5-fold higher oral bioavailability than that of curcumin solution. Inhibition of burst release (over-rapid release) of curcumin was observed in NCC coated SLNs in simulated gastric fluid (pH1.2) thus indicating that NCC coating was able to address the burst release problem that SLNs usually have in an acidic environment.

Among the nanoparticle formulations mentioned above, the nanosuspension prepared by CO₂ assisted in situ nano-amorphization method (Wang et al., 2017b) exhibited the highest curcumin oral bioavailability with the AUC₀⁻₄ value of 365.73 μg·h/ml in rats. A comparison of the curcumin oral absorption data between each nanoparticle formulation is shown in Figure.
4.3. Liposomes

Liposomes are a type of drug delivery system which contain a phospholipid bilayer structure giving them an ability to encapsulate both hydrophilic and hydrophobic substances (Anand et al., 2007). As a drug delivery approach, liposomes have the advantage of being biodegradable, nontoxic, and remarkably biocompatible (Li et al., 2018).

A hybrid liposomal formulation that consisted of chitosan and soybean lectithin was developed as a drug vehicle for curcumin (Peng et al., 2017). Bioavailability of curcumin from the liposomal formulation was testing using caco-2 cells. The hybrid liposomes exhibited higher cellular uptake rate than that of phospholipid liposome, 1.66-fold higher at 0.5 hours after incubation and 1.256-fold higher after 4 hours incubation. The researchers reported a sustained release of curcumin, increased positive charge and decreased hydrophobicity from the hybrid liposomal formulation were the main reasons for the increased curcumin bioavailability.

In another study, a liposomal formulation coated with chitosan was tested in simulated gastric fluid (pH between 2 and 3) and in simulated intestinal fluid (pH 7). It was reported that around 80% of the curcumin loaded in the liposome dissolved in the simulated gastric and the simulated intestinal fluids (Cuomo et al., 2018).
In the research area of curcumin liposomal formulation, the current trend is to use hybrid liposomal formulations to help to improve the bioavailability of curcumin. The studies mentioned above showed that the hybrid liposomal formulations have better performance in improving bioavailability of curcumin than the conventional curcumin-loaded liposomes and the unformulated curcumin.

4.4. Micelles and polymer micelles.

Micelles are spherical aggregates of surfactants that form spontaneously when the surfactants reach a critical micelle concentration (CMC) at a certain temperature in aqueous solution (Xu et al., 2013). The size of micelles normally range between 20 to 80 nm. Typical micelles are comprised of an outer shell formed by hydrophilic head groups and a core formed by hydrophobic tail groups. Micelles can be used as vesicles to load and deliver poorly water-soluble drugs. The hydrophobic core can encapsulate the lipophilic drugs and the hydrophilic outer shell to protect the drugs from being inactivated in the gastrointestinal environment. As a result, solubilization and stability of the drugs are improved (Haley and Frenkel, 2008).

A novel curcumin-loaded mixed micelle (CUR-MM) that consist of two surfactants (Pluronic F-127 and Gelucire® 44/14) was developed (Patil et al., 2015). The formulation showed that it can enhance the oral bioavailability of curcumin and its anti-cancer effect. The optimised CUR-MM formulation with
size of 188 ± 3 nm and an entrapment efficiency of 76.45 ± 1.18% w/w exhibited significant enhancement in the oral bioavailability of curcumin (by approximately 55-fold) and cytotoxicity to human lung cancer cell line A549 (by approximately 300%), in comparison with free curcumin. The improved oral bioavailability and anti-cancer effects of curcumin was attributed to the controlled release of curcumin from the CUR-MM, increase of curcumin solubility from micellization and inhibition of P-glycoprotein by the surfactants.

In another study, a sophorolipid nano-micelle formulation was prepared by using a ‘pH-driven method’ (Peng et al., 2018). In vivo test results showed that it increased curcumin’s oral bioavailability by 3.6-fold compared with the unformulated curcumin. This proves that biosurfactants like sophorolipid, obtained from natural sources, could be used for formulating drug delivery systems to enhance the oral bioavailability of curcumin. The preparation method used in this study, the pH-driven method, does not require heat and organic solvents, thus making it a simple and cost-effective way for producing nano-sized curcumin products.

A clinical trial was conducted among 23 healthy human candidates (13 male and 10 female) to assess a micellar curcumin formulation that composed of micronised curcumin powder and Tween-80 (Schiborr et al., 2014). The result of pharmacokinetics studies showed that the ingestion of a single oral dose of 500 mg micelle encapsulated curcumin (equivalent to 410 mg curcumin) resulted in a C_{max} of 3.228 μmol/L compared to 0.007 μmol/L of free
curcumin powder. Both male and female subjects have almost the same $T_{\text{max}}$, but the female subjects exhibited higher $C_{\text{max}}$ of 3.701 μmol/L in comparison with 2.612 μmol/L for male subjects, indicating that women might be absorbing more curcumin than men in this study.

A novel self-assembled, curcumin-loaded polymeric micelle was developed for improving curcumin oral absorption (Wang et al., 2015). It consisted of di-tocopherol polyethylene glycol 2000 succinate (TPGS2 K), octadecanoic acid, 12-hydroxy-, polymer with alpha-hydro-omega-hydroxypoly (oxy-1,2-ethanediyl) and Pluronic F127. Both in vitro and in vivo test results revealed that the micelle system provided a better intestinal absorption of curcumin than free curcumin. Oral administration of the micelle formulation in rats resulted in higher $\text{AUC}_{0-t}$ of curcumin (870.2±466.78 mg·h/L) compared with the standard curcumin ($\text{AUC}_{0-t}$ of 303.58±294.31 mg·h/L). Furthermore, lymphatic transport pathways were found to be involved in the absorption of the micelle system, which helps curcumin to avoid first-pass metabolism.

Overall, a major increase in oral bioavailability of curcumin was demonstrated in the recently developed novel micelles formulations. These results indicate that micelles are a promising way for delivering curcumin orally and worthy of further studies in the future. A comparison plot to describe the results of curcumin oral bioavailability from different micellar formulations is shown in Figure. 12.
4.5. Curcumin-loaded nano and micro-emulsions

Nanoemulsions, also known as submicron emulsions, is another type of nano-sized drug delivery system. They are single phase, isotropic thermodynamically stable systems that consist of emulsified oil, water and amphiphilic molecules (surfactants). The size of the emulsion droplets typically range between approximately 10–1000 nm (Gurpreet and Singh, 2018). A Thiol modified chitosan coated, curcumin-piperine loaded oil-in-water nanoemulsion was developed (Vecchione et al., 2016). The optimised formulation has nano-droplets size of 110nm, weight ratio of curcumin: piperine in 100 to 1 and chitosan thiolation level of 14–15%. At an oral dose equivalent to 8mg/kg of curcumin, the AUCₐ₋ₜ value of curcumin increased by 64-fold (343.3 μg·h/ml) than that of standard curcumin (5.4 μg·h/ml).

Comparing with the two piperine strategies that were reviewed in section 3.1 (Shoba et al, 1998; Zeng et al., 2017b), the optimised curcumin-piperine loaded nanoemulsion formulation is 94-fold and 1505-fold higher in terms of the AUCₐ₋ₜ values. This indicates that the combination of piperine with the nanoemulsion technology is much more effective than only using piperine alone in improving the oral bioavailability of curcumin. In another study, a novel lipid nanoemulsion containing curcumin (CNELNs) was prepared and tested for changes in bioavailability in in vitro and in vivo models (Wan et al., 2016). The mean absorption constants (Kₐ) and effective permeabilities (Pₑffective)
over the whole intestine system were increased by 2.98-fold and 6.65-fold, respectively. The relative bioavailability of CNELNs to standard curcumin was 733.59%, which was possible due to the increase of intestinal absorption. CNELNs also displayed stronger effect in suppressing the growth of human lung cancer cell A549. A curcumin-phospholipid complex was incorporated into a self-nanoemulsion system consisting of castor oil, Tween 80 and PEG 400 (Shukla et al., 2016). The combined formulation showed significant higher serum concentration of curcumin than free curcumin and curcumin-phospholipid complex. Using an oral dose of 100 mg/kg in rats, the \( C_{\text{max}} \) of curcumin from the combined formulation was 487.7 ± 53.4 ng/ml, compared to 21.6 ± 3.6 ng/ml for free curcumin and 54.6 ± 3.7 ng/ml for curcumin-phospholipid complex. The relative bioavailability of curcumin from the combined formulation was 7.67-fold and 52.55-fold higher than that of curcumin-phospholipid complex and unformulated curcumin. Several research studies have been carried out to study the potential for using nanoemulsion strategy to improve the oral bioavailability of curcumin. The results of these studies demonstrated that it is a promising strategy to fulfil the goal of improving curcumin’s oral bioavailability. Among the nanoemulsion formulations reviewed, piperine loaded in an oil-in water nanoemulsion with modified chitosan coating (Vecchione et al., 2016) showed the highest curcumin oral absorption with the AUC\(_{0-t} \) value of 343.8 \( \mu \)g·h/ml. In contrast, the other two nanoemulsion formulations (Shukla et al., 2016; Wan et al.,
2016) have much poorer curcumin bioavailability with AUC$_{0-t}$ value of 0.7μg·h/ml and 2.97μg·h/ml (Figure 13).

Microemulsion is an isotropic colloidal system of micron-sized droplets that consists of water, oil, surfactant and cosurfactants. When in a microemulsion system, drug compounds can be entrapped within the oil droplets, which protect them from both enzymatic and chemical degradations thus increasing the residence time and bioavailability of the drugs (Constantinides, 1995). Interestingly, the droplet size of microemulsion is not in micrometre but between 10 to 100 nm. Microemulsion is fairly similar to nanoemulsion in terms of the structure. What differentiating it from nanoemulsion is that microemulsion is thermodynamically stable whereas nanoemulsion is not. Also, microemulsion normally have a narrow particle size distribution compared to nanoemulsions (McClements, 2012). A self-emulsifying microemulsion drug delivery system (SMEDDS) was developed to improve the oral bioavailability of curcumin (Dhumal et al., 2015). A semi-synthetic bicephalous heterolipid known as E1E was used in this formulation, along with Solutol HS15 (a surfactant) and Transcutol HP (a cosurfactant) to form the microemulsion encapsulating curcumin. An optimised SMEDDS formulation with drug loading efficiency of 70.52 ± 2.46 mg/g was orally administrated to rats at a curcumin dose of 50 mg/kg. Plasma analysis showed that the C$_{max}$ and AUC$_{0-t}$ of curcumin from the SMEDDS were 4.921± 0.42(μg/mL) and 17.30 ± 1.50 (μg.h/ml) respectively, in comparison with free curcumin
suspension with 0.186 ± 0.006 (µg/ml) and 0.234 ± 0.023 (µg.h/ml) respectively. $T_{\text{max}}$ remained unchanged in both SMEDDS and the free curcumin suspension 60 min after oral administration. In another study, a self-microemulsifying curcumin (SME-Cur) entrapped in a hydroxypropylmethyl cellulose (HPMC)-based sponge was developed to study oral absorption of curcumin (Petchsomrit et al., 2015). The in vivo study was performed in rabbits at a curcumin equivalent oral dose of 12.5 mg/kg. The HPMC sponge entrapped SME-Cur showed significantly higher $C_{\text{max}}$ and $\text{AUC}_{0-t}$ ($1.77 \pm 0.13 \text{ mg/ml and } 2615.68 \pm 97.79 \text{ ng/h/ml}$, respectively) than unformulated curcumin at dose of 50 mg/kg (0.30 ± 0.03 mg/ml and 509.49 ± 47.77 ng h/ml, respectively). The in vitro drug release test found that the HPMC-based sponges entrapped SME-Cur provided a sustained release of curcumin and led to a higher percentage release compared with the unwrapped SME-Cur and free curcumin. The improved drug release could be attributed to the drug-polymer interaction leads to the inhibition of precipitation and crystallization of curcumin in solution.

Compared to nanoemulsions, microemulsions have received less attention since there were only a few studies on their use in improving the oral bioavailability of curcumin (Figure 14). However, the studies of microemulsions reviewed in this article both showed considerable improvement in curcumin’s oral bioavailability (Dhumal et al., 2015; Petchsomrit et al., 2015). All of these indicate that microemulsions are still a
potent and promising technology to overcome curcumin’s oral delivery problems and it is worthy of further studies in the future.

4.6. Solid dispersion

By definition, a solid dispersion is a solid product where at least one drug is entrapped in a hydrophilic polymeric carrier and the drug(s) is/are molecularly dispersed in the polymeric carrier (Chiou and Riegelman, 1971). The principle of solid dispersion to improve the drug bioavailability was to first rapidly release the drug particles from the polymeric carrier to create a supersaturated solution after which the concentration is maintained long enough for the drug to be absorbed (Craig, 2002; Kumar and Gupta, 2013; Vasconcelos et al., 2007). Drugs in supersaturation state tend to precipitate rapidly before the absorption to take place which results in reduced bioavailability. Fortunately, the polymer excipients that are commonly used for preparing solid dispersion also have the ability to inhibit drug precipitation and prolong the supersaturation, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropylmethyl cellulose acetate succinate (HPMC-AS) and vinyl polymers such as poly (vinylpyrrolidone) (PVP). The mechanism of how polymers prolong drug supersaturation is still not fully understood. Nevertheless, it is generally believed to be as a result of hydrogen bond formation between the polymers and the drugs, based on the observation that polymers are effective in inhibiting precipitation of drugs rich in hydrogen-bond
acceptors (Bevernage et al., 2011; Gao et al., 2009; Miller et al., 2008). Solid
dispersion continues to be a widely studied strategy to improve oral
bioavailability of poorly water-soluble drug candidates (Chuah et al., 2014;
Onoue et al., 2010; Seo et al., 2012). A list of FDA approved solid dispersion
drugs is shown at Table 2.

Table 2: A list of FDA approved solid dispersion drugs (Baghel et al., 2016)

<table>
<thead>
<tr>
<th>Trading name</th>
<th>Active ingredient</th>
<th>Carrier</th>
<th>Preparation method</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalydeco®</td>
<td>Ivacaftor</td>
<td>HPMCAS</td>
<td>Spray drying</td>
<td>Tablet</td>
</tr>
<tr>
<td>Zelboraf®</td>
<td>Vemurafenib</td>
<td>HPMCAS</td>
<td>Coprecipitation</td>
<td>Tablet</td>
</tr>
<tr>
<td>Incivek®</td>
<td>Telaprevir</td>
<td>HPMCAS</td>
<td>Spray drying</td>
<td>Tablet</td>
</tr>
<tr>
<td>Intelence®</td>
<td>Etravirine</td>
<td>HPMC</td>
<td>Spray drying</td>
<td>Tablet</td>
</tr>
<tr>
<td>Novir®</td>
<td>Ritonavir</td>
<td>PVP/PA</td>
<td>Melt extrusion</td>
<td>Tablet</td>
</tr>
<tr>
<td>Kaletra®</td>
<td>Lopinavir</td>
<td>PVP/PA</td>
<td>Melt extrusion</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

A recent study combined solid dispersion strategy with nanotechnology
and developed a novel self-nanomicellizing solid dispersion (NCF) for
delivering curcumin orally (Parikh et al., 2018a). Soluplus® (polyvinyl
caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) was used
as a carrier for curcumin in the NCF formulation. NCF exhibited significant
increase in aqueous solubility of curcumin (over 20,000-fold higher than the
Curcumin control). Considerable improvement in dissolution rate and small-intestinal permeability of curcumin were also found with the NCF formulation. Furthermore, improved curcumin stability in alkaline environment was found. As a result of the increased dissolution, solubility, permeability and alkaline solution stability, the oral bioavailability of curcumin from the NCF was significantly enhanced by 117-fold compared with pure curcumin.

In another study, an amorphous curcumin solid dispersion was prepared with disodium glycyrrhizin (Na₂GA) via ball milling (Zhang et al., 2018). Na₂GA was able to form micelles when dissolved in water and encapsulate the amorphous curcumin particles. In vivo evaluation showed that the self-micelle forming solid dispersion provided a 19-fold increase in curcumin oral bioavailability over free curcumin. In addition, the solid dispersion formulation improved curcumin permeability across the gastrointestinal membranes.

A curcumin-loaded ternary solid dispersion system was prepared by using mannitol as the hydrophilic carrier and d-α-Tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGs) as the surfactant (Song et al., 2016). TPGs was selected due to its safety and potential to inhibit P-glycoprotein efflux. The aqueous solubility of curcumin from the solid dispersion formulation remained stable across a pH range from 1.2 to 7.4, which diminished the pH-dependent solubility pattern in pure curcumin powder. Pharmacokinetics studies revealed that the Cₘₐₓ and AUC₀₋ₜ of curcumin were increased by 86- and 65-fold respectively, in comparison with pure curcumin powder. The solid
A curcumin-loaded solid dispersion formulation was developed by using Gelucire 50/13 (a non-ionic water-dispersible surfactant) as the carrier material (Teixeira et al., 2015). The solid dispersion formulation was prepared by spray drying. The aqueous solubility of curcumin was significantly increased by the solid dispersion (2700 μg/ml), which was 3600-fold higher than the unformulated curcumin (0.75 μg/ml). The solid dispersion demonstrated rapid release of curcumin at 10 min, with 90% and 73% of curcumin being released at pH 1.2 and 7.4, respectively. The percentage of curcumin released was also considerably higher than pure curcumin. Results from rat plasma sample analysis indicated a 5.5-fold increase of curcumin plasma concentration from the solid dispersion compared with the unformulated curcumin under the same oral dose (500mg/kg). Since spray drying is a technique that is suitable for scaled-up production, solid dispersion formulation developed in this study could be a promising way to improve curcumin bioavailability from an industrial perspective.

In another study, an excipient-free co-amorphous curcumin-piperine solid dispersion (co-amorphous CUR-PIP) was prepared by a melting and quench cooling method (Wang et al., 2019). This formulation has a combined solid dispersion effect of increasing drug dissolution along with piperine’s effect of
inhibiting the glucuronidation of curcumin in vivo. In this study, higher
dissolution rate and longer-lasting supersaturated curcumin concentration
were observed from the co-amorphous CUR-PIP. This could be due to
piperine’s effects to suppress UDP-glucuronyltransferase and
sulfotransferases in the intestines and liver (Zeng et al., 2017b). In addition,
the permeability of curcumin across the gastrointestinal membrane was
elevated by 2.67-fold compared with pure curcumin, which was linked to
piperine’s ability to inhibit curcumin glucuronosyltransferases. As a result of
faster, longer-lasting supersaturation dissolution and higher GI permeability,
the oral bioavailability of curcumin was enhanced by 2.16- and 1.92-fold with
the co-amorphous CUR-PIP relative to the crystalline and amorphous
curcumin. Comparing with the previously mentioned strategies that used
piperine for curcumin, the co-amorphous CUR-PIP showed around 8-fold and
134-fold higher AUC_{0-t} values than the curcumin-piperine co-administration
strategy (Shoba et al, 1998) and the pre-treatment of piperine strategy (Zeng
et al., 2017b). However, it is around 11-fold lower compared to the curcumin-
piperine loaded nanoemulsion (Vecchione et al., 2016). A comparative graph
between the solid dispersion formulation and the nanoemulsion formulation is
shown in Figure. 15.

The results from the studies mentioned above suggest that solubility and
dissolution of curcumin can be greatly improved by solid dispersion strategies,
thus leading to improvement in curcumin’s oral bioavailability. The selection of
carriers and surfactants also play a vital role in the performance of solid dispersion formulations in improving oral bioavailability of curcumin.

Among all the solid dispersion formulations reviewed in this article, the self-nanomicellising solid dispersion prepared using Soluplus (Parikh et al., 2018a) exhibited significantly higher curcumin oral absorption compared with the other solid dispersion formulations. A comparative graph is shown in Figure. 16.

5. Conclusions

Decades of studies have proved that curcumin can be well-tolerated in human bodies, with numerous therapeutic potentials. However, despite curcumin’s pharmacological efficacy and safety, it is still not licenced as a valid therapeutic agent mainly due to the very poor oral bioavailability of curcumin. As discussed earlier in this article, the main factors that contribute to the poor oral bioavailability of curcumin are low aqueous solubility, poor intestinal permeability, chemical stability, rapid metabolism and elimination.

A range of novel formulations have been developed in recent years and many of them have demonstrated considerable improvement in the oral bioavailability of curcumin. A summary of these novel developments is given in Table 3. The curcumin oral absorption results of the formulation with obvious increase in curcumin bioavailability are summarised and compared in Figure 17. From this data it can be summarised that the self-nanomicellizing solid
dispersion (NCF) prepared by Soluplus showed the highest curcumin oral bioavailability with the AUC₀₋₄ value of 1998.6 ± 361.5μg·h/ml at a curcumin equivalent dose of 47mg/kg in rats (Parikh et al., 2018a). This shows the great potential of solid dispersion strategy for the application in improving curcumin absorption via oral administration. Whether improvement of oral bioavailability of curcumin can improve the therapeutic efficacy of the compound needs to be evaluated. A follow-up study was carried out to evaluate the efficacy of NCF against Alzheimer’s disease in in vitro (SHSY5Y695 APP human neuroblastoma cell line with induced toxicity) and in vivo (transgenic mice with Alzheimer’s diseases) models. In the in vitro model, NCF (equivalent to 10 μg/mL of curcumin) displayed better efficacy than CUR control (10 μg/mL) against cytotoxicity which induced by CuSO₄, H₂O₂ and Aβ42. This indicated that NCF has better neuroprotective effect than the unformulated curcumin. As for the in vivo study, NCF, curcumin control and donepezil (a medication used for treating Alzheimer’s diseases) were orally administrated to mice in order to investigate their long-term (3 months) efficacy against Alzheimer’s diseases. The efficacy was evaluated by behavioural tests of the mice and the results showed that the NCF has significantly better efficacy to repair the cognitive functions and behaviour of mice than the curcumin control and even donepezil. Also, it has been reported that it prevents any further deterioration in the behaviour of mice. During the in vivo study, the formulation was well-tolerated with no obvious toxicity. This makes NCF a safe and effective option.
for the treatment of Alzheimer’s diseases. It also proved that the improvement of the oral bioavailability of curcumin could lead to good therapeutic effect (Parikh et al. 2018b).

However, it is difficult to directly compare each formulation because of the differences in administered dose, experimental designs, and methods of analysis. No cross-over studies have been conducted for the novel curcumin formulations mentioned in this article. It is suggested that in order to design standardised controlled trials for different curcumin formulations in the future, it is imperative to understand and verify which formulation is the best in terms of oral bioavailability and therapeutic effect.

In summary, curcumin has been demonstrated to have a wide range of therapeutic effects. However, due to its physical properties it is seriously lacking in aqueous solubility, which has been related to its poor bioavailability. Advances in the development of novel formulations should assist in improving bioavailability, which can then be related to categorically demonstrate curcumin’s therapeutic effect in a given condition.
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Amount of curcumin administrated</th>
<th>Formulation</th>
<th>Improved the oral bioavailability of curcumin by</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans</td>
<td>2g</td>
<td>2 g of curcumin + 5mg of piperine was delivered orally simultaneously</td>
<td>2-fold</td>
<td>Anand et al., 2007</td>
</tr>
<tr>
<td>Rats</td>
<td>200mg/kg</td>
<td>Pre-administration of 20mg/kg piperine, then 200mg/kg curcumin after 6 hours</td>
<td>97-fold</td>
<td>Zeng et al., 2017b</td>
</tr>
<tr>
<td>Albino Wister rats</td>
<td>50mg/kg</td>
<td>Curcumin loaded phosphatidylcholine-maltodextrin based nanoparticles(C-LPNCs)</td>
<td>55.2-fold</td>
<td>Chaurasia et al., 2015</td>
</tr>
<tr>
<td>Male SD (Sprague Dawley) rats</td>
<td>50mg/kg</td>
<td>Curcumin loaded nanosuspension, prepared by citric acid and Brij78</td>
<td>3.7-fold</td>
<td>Wang et al., 2017</td>
</tr>
<tr>
<td>Humans</td>
<td>100mg</td>
<td>Curcumin loaded, Alginete and polysorbate nanoparticles</td>
<td>5-fold</td>
<td>Govindaraju et al., 2019</td>
</tr>
<tr>
<td>Male SD rats</td>
<td>50mg/kg</td>
<td>Curcumin-loaded solid lipid nanoparticles(SLN) with N-carboxymethyl chitosan (NCC) coating</td>
<td>9.5-fold</td>
<td>Baek and Cho, 2017</td>
</tr>
<tr>
<td>Caco-2 cells</td>
<td>4μg/mL</td>
<td>Curcumin-loaded hybrid liposomal formulation that consist of chitosan and phospholipid</td>
<td>1.256-fold higher 4h after incubation.</td>
<td>Peng et al., 2017</td>
</tr>
<tr>
<td>Male wistar rats</td>
<td>10mg/kg</td>
<td>Curcumin-loaded mixed micelle (consist of Pluronic F-127 and Gelucire® 44/14)</td>
<td>55-fold</td>
<td>Patil et al., 2015</td>
</tr>
<tr>
<td>Male SD rats</td>
<td>100 mg/ kg</td>
<td>Curcumin-loaded sophorolipid based nanomicelle</td>
<td>3.6-fold</td>
<td>Peng et al., 2018</td>
</tr>
<tr>
<td>Rats</td>
<td>50mg/kg</td>
<td>Self-assembled, polymeric curcumin-loaded micelles, consist of TPGS2 K, HS15 and Pluronic F127</td>
<td>2.87-fold</td>
<td>Wang et al., 2015</td>
</tr>
<tr>
<td>------</td>
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<td>-----------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Male Wistar albino rats</td>
<td>8mg/kg</td>
<td>Thiol modified chitosan coated, curcumin-piperine loaded, oil-in water nanoemulsion</td>
<td>64-fold</td>
<td>Vecchione et al., 2016</td>
</tr>
<tr>
<td>Male SD rats</td>
<td>100mg/kg</td>
<td>Curcumin-loaded self-nanoemulsifying drug delivery system (SNEDDS), consist of ethyl oleate, tween 80 and PEG 600</td>
<td>1.94-fold</td>
<td>Wan et al., 2016</td>
</tr>
<tr>
<td>Rats</td>
<td>100mg/kg</td>
<td>Curcumin-phospholipid complex, entrapped in a self-nanoemulsion that consist of caster oil, Tween 80 and PEG 400</td>
<td>52.55-fold</td>
<td>Shukla et al., 2016</td>
</tr>
<tr>
<td>Rats</td>
<td>50mg/kg</td>
<td>Self-emulsifying curcumin loaded microemulsion that consist of E1E, Solutol HS and Transcutol HP</td>
<td>73-fold</td>
<td>Dhumal et al., 2015</td>
</tr>
<tr>
<td>Adult male Wistar rats</td>
<td>12.5mg/kg</td>
<td>Self-microemulsifying curcumin (SME-Cur) wrapped in a hydroxypropylmethyl cellulose (HPMC)-based sponge</td>
<td>5-fold</td>
<td>Petchsomrit et al., 2015</td>
</tr>
<tr>
<td>Male SD rats</td>
<td>47 mg/kg</td>
<td>Self-nanomicellizing curcumin-loaded Soluplus solid dispersion</td>
<td>117-fold higher than that of 150mg/kg curcumin suspension</td>
<td>Parikh et al., 2018a</td>
</tr>
<tr>
<td>Male SD rats</td>
<td>150mg/kg</td>
<td>Ball milled curcumin loaded, disodium glycyrrhizin (Na2GA) solid dispersion</td>
<td>19-fold</td>
<td>Zhang et al., 2018</td>
</tr>
<tr>
<td>Male SD rats</td>
<td>30 mg/kg</td>
<td>Curcumin-loaded ternary solid dispersion system, prepared with Mannitol and TPGs</td>
<td>65-fold higher than 200mg/kg oral dose of pure curcumin</td>
<td>Song et al., 2016</td>
</tr>
<tr>
<td>Rats</td>
<td>500mg/kg</td>
<td>Curcumin-Gelucre 50/13 solid dispersion</td>
<td>5.5-fold</td>
<td>Teixeira et al., 2015</td>
</tr>
<tr>
<td>Rats</td>
<td>100mg/kg</td>
<td>curcumin-piperine solid dispersion</td>
<td>1.92-fold</td>
<td>Wang et al., 2019</td>
</tr>
</tbody>
</table>
CRediT Author Statement:

Zhenqi Liu: Investigation, Writing-Original draft preparation, visualisation, methodology, resources; John Smart: Supervision, Reviewing; Ananth Pannala: Conceptualisation, Supervision, Writing-Reviewing and Editing

FUNDING:

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

CONFLICT OF INTERESTS:

The authors declare that there are no conflict of interests
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**Figure legends**

**Figure 1:** Keto-Enol tautomerism of curcumin

**Figure 2:** The structure of Caco-2 cell monolayer grown at a permeable filter support

**Figure 3:** Sulphation and glucuronidation of curcumin (adapted from Esatbeyoglu et al., 2012)

**Figure 4:** Reduction and glucuronidation of curcumin (adapted from Esatbeyoglu et al., 2012)

**Figure 5:** Degradation products of curcumin (adapted from Wang et al., 1997)

**Figure 6:** Chemical structure of Piperine

**Figure 7:** Comparison of curcumin oral absorption results of the curcumin + piperine co-administration strategy in rats and humans. (A) 2 g/kg curcumin with 20 mg/kg piperine and (B) 2 g/kg curcumin control administered in rats; (C) 2 g/kg curcumin with 20 mg/kg piperine administered to human volunteers; *: Pure curcumin absorption in humans was reported to be below the detection limit (Shoba et al., 1998).

**Figure 8:** Comparison of curcumin oral absorption results of different piperine strategies tested in healthy human volunteers. (A) 2 g/kg curcumin with 20 mg/kg piperine and (B) 2 g/kg curcumin control administered in rats (Shoba et al., 1998); (C) 5 mg piperine along with 2 g of curcumin and (D) 2 g curcumin control (Anand et al., 2007).

**Figure 9:** Comparison of curcumin oral absorption results of two different piperine strategies tested in rats. (A) 2 g/kg curcumin with 20 mg/kg piperine and (B) 2 g/kg curcumin control administered in rats (Shoba et al., 1998); (C) initial dose of 20 mg/kg piperine followed by 200 mg/kg of curcumin after six hours and (D) 200 mg/kg curcumin control (Zeng et al., 2017b).

**Figure 10:** Graphic scheme of the Curcumin loaded phosphatidylcholine-maltodextrin based lipopolysaccharide nanoparticles (C-LPNCs) formulation (adapted from Chaurasia et al., 2015)

**Figure 11:** Comparison of curcumin oral absorption results of the novel
curcumin-loaded nanoparticle formulations at the curcumin equivalent oral doses of (A) 50mg/kg for the curcumin loaded lipopolysaccharide nanoparticles, curcumin control concentrations below limit of detection in this study (Chaurasia et al., 2015); (B) 50mg/kg for the nanosuspension prepared by CO2-assisted in situ nano-amorphization method and (C) curcumin control (Wang et al., 2017b); (D) 100mg for the Alginate-polysorbate 80 nanoparticles and (E) (Govindaraju et al. 2019); and (F) 50mg/kg for the solid lipid nanoparticles (SLNs) with N-carboxymethyl chitosan (NCC) coating, tested in rats, curcumin control concentrations was reported to be below the limit of detection (Baek and Cho, 2017).

Figure 12: Comparison of curcumin oral absorption of curcumin loaded micelles formulation (A) curcumin oral doses of 10 mg/kg for curcumin-loaded mixed micelle and (B) curcumin control (Patil et al., 2015); (C) 100mg/kg for the curcumin loaded sophorolipid-coated nanomicelles and (D) curcumin control (Schiborr et al., 2014); (E) 50mg/kg for the self-assembled curcumin-loaded polymeric micelle, concentration of curcumin from the control sample was reported to be below the limit of detection (Wang et al., 2015).

Figure 13: Comparison of curcumin oral absorption results of the novel nanoemulsion formulations (A) at an oral dose of 8mg/kg for Chitosan coated, piperine loaded oil in water nanoemulsion (B) curcumin control (Vecchione et al., 2016) and (C) oral dose of 100mg/kg of curcumin-phospholipid complex incorporated self-nanoemulsion, curcumin control values was reported to be below the limit of detection (Shukla et al., 2016).

Figure 14: Comparison of curcumin oral absorption results of the novel microemulsion formulations at the curcumin equivalent doses of (A) 50mg/kg for the self-emulsifying microemulsion and (B) curcumin control (Dhumal et al., 2015) and (C) 12.5 mg/kg for the HPMC sponge entrapped self-microemulsifying curcumin and (D) curcumin control (Petchsomrit et al., 2015).

Figure 15: Comparison of the curcumin oral absorption results at the curcumin equivalent oral doses of (A) 8mg/kg for the curcumin-piperine loaded nanoemulsion formulation (Vecchione et al., 2016) and (B) 100mg/kg for the curcumin-piperine loaded solid dispersion formulation (Wang et al., 2019).

Figure 16: Comparative graph of curcumin oral absorption results of the novel
solid dispersion formulations at the curcumin equivalent oral doses of: (A) 47mg/kg for Soluplus containing self-nanomicellizing solid dispersion and (B) curcumin control (Parikh et al., 2018a); (C) 150mg/kg for ball milled curcumin mixed with Na₂GA in a solid dispersion and (D) curcumin control (Zhang et al., 2018) and (E) 100mg/kg for co-amorphous curcumin-piperine solid dispersion, curcumin levels from the control sample were below the limit of detection; The AUC₀⁻₄ values of the pure curcumin(control) of this study was reported to be below the limit of detection (Wang et al., 2019).

**Figure 17:** Comparison of curcumin oral absorption results of the different curcumin oral bioavailability enhancement strategies, at the curcumin oral doses of: (A) 47mg/kg for the Soluplus containing self-nanomicellising solid dispersion (Parikh et al., 2018a), (B) 50mg/kg for the Nanosuspension prepared by CO₂-assisted in situ nano-amorphization method (Wang et al., 2017b), (C) 8mg/kg for curcumin+piperine loaded nanoemulsion with thiol modified chitosan coating (Vecchione et al., 2018), (D) 100mg/kg for the co-amorphous curcumin-piperine solid dispersion (Wang et al., 2019) and (E) 50mg/kg for the self-emulsifying microemulsion (Dhumal et al., 2015).
Figure 1

Keto form of Curcumin

Enol form of Curcumin
Figure 2
Figure 3

Curcumin

Sulfotransferase

Curcumin sulfate

UDP-glucuronosyltransferase

Curcumin glucuronide sulfate
Figure 4
Figure 5

Curcumin

Feruloylmethane

Vanillin

Ferulic acid

Trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal
Piperine

Figure 6
Figure 7

(A)

(B)

(C)

Rats

Human*

AUC0-t (μg· h/mL)
Figure 8
* Standard deviation not shown in the publication
Figure 9
Figure 10
Figure 11
Figure 12
Figure 13
Figure 14
Figure 15
Figure 16
Figure 17