Recent advances in solid dispersion technique for enhancing biopharmaceutical properties of lumefantrine: an overview

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Background
Lumefantrine is a widely used antimalarial agent in combination with artemether. It is poorly water soluble and belongs to the biopharmaceutical classification class II. In the last decade, various strategies have been explored for increasing its dissolution rate and oral bioavailability (BA). A literature review revealed that various approaches based on solid dispersion (SD) have been investigated for this purpose and also evaluated for their benefits *in vivo*. Therefore, the major focus of the present article is to review the research carried out on the SD of lumefantrine with different polymers in the last decade. This review also discusses the classifications of SD based on their molecular arrangements and the polymers or carriers used, along with their advantages and disadvantages. This review described different techniques to prepare a SD of lumefantrine and their effects on solubility, dissolution rates, and oral BA. The SD-based approaches showed promising potential for increasing the oral BA of lumefantrine.

Keywords:
antimalarial agent, lumefantrine, molecular arrangement, solid dispersion, solubility enhancement

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Introduction

Malaria is a parasitic disease endemic in 104 countries and territories. The African region accounted for ~94% of all malaria death in the world as reported by WHO in 2018. Moreover, children under five years accounted for 67% of all malaria deaths [1]. Although the African region reported the highest number of malaria deaths in 2018, a decline of 85% in the reported deaths was observed in 2018 compared with 2010. The most effective treatment of malaria includes the combination therapy of lumefantrine (LMF) with artemether (ARTM). LMF also known as benflumetol exhibits effectiveness in the treatment of malaria caused by resistant *Plasmodium falciparum* species, particularly in the African region [2,3]. It is an erythrocytic schizonticide and acts by preventing the polymerization of hemoprotein in the food vacuole [4]. However, it showed low oral bioavailability (BA) (18%) owing to its low aqueous solubility (0.09 μg/ml). The important physiochemical and pharmacokinetic properties of LMF are tabulated in Table 1. Hence, it belongs to BCS II [11–14]. Therefore, it is necessary to increase its aqueous solubility to increase the dissolution rate and, in turn, improve its oral BA [15–17]. In the last decade, different techniques including 'particle size reduction, crystal engineering, solid dispersion (SD), colloidal-based drug delivery system, and inclusion complex' had been investigated to enhance the dissolution rate and oral BA of LMF [18–20]. Among the solubilization techniques, SD is a potentially promising technique for improving the poor release rate, absorption, and therapeutic potency of such drugs in pharmaceutical dosage forms [13]. Other solubility-enhancement techniques like micronization (milling) cannot achieve the required enhancement in the dissolution rate [21–23], which could be attributed to the insufficient degree of particle size attrition achieved by conventional methods of milling, whereas salt formation requires the presence of an ionization function group in the dry molecules. Moreover, it has been shown that it is ineffective to enhance the dissolution rate and absorption of such drugs in the gastrointestinal tract [21,24,25]. Recently, various SD-based formulations have been investigated to improve the BA of LMF and have exhibited promising results in *in vivo* studies. The improvement in the dissolution rate of poorly aqueous soluble drug molecules is a critical factor in achieving enhanced BA via the cyclodextrin inclusion complex, amorphous SD, and cogrinding with hydrophilic polymer [26–29]. Therefore, the major objective of this work is to review the research done to improve the solubility and dissolution rate of LMF, particularly using SD techniques. Furthermore, the fundamentals of SD including its classifications, and

Table 1 The physicochemical and pharmacokinetics properties of lumefantrine

Serial number	Parameters	Data	References
1	State	Crystalline powder	[5]
2	Water solubility	0.09 mg/ml	[6]
3	Log P	8.34	[5,6]
4	Melting point	127°C	[7]
5	Bioavailability	18%	[7]
6	Refractivity	160.81 m^3/mol	[8]
7	Polarizability	60.69 A×3	[9]
8	Number of rings	4	[9]
9	Half-life	4.5 h	[10]
10	Affected organism	Plasmodium	[6]

advantages and disadvantages are also discussed in the present review [30,31]. The basic physicochemical and pharmacokinetic property of LMF is also summarized in the article to help understand the problem of its poor BA.

Solid dispersion

SD is known as 'solid-state dispersions' or a solid 'solution' illustrated by Mayersohn and Gibaldi. Later SD is considered as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid state and prepared by the melting, solvent, or melting-solvent method [29,31]. In 1985, Corrigan defined the term 'SD' as 'a product formed by converting a fluid drug-carrier combination to the solid state.' It consists of either a crystalline or amorphous carrier in which a drug can be dispersed atomically [32,33].

The SD technique possesses numerous advantages over other solubilization techniques. The advantages of SD include a transformation of a liquid form of drug into a solid state and further improved wettability owing to the presence of hydrophilic carriers in SD [15,34].

Moreover, the formation of SD results in reduced particle size, which creates a high surface area and in turn enhances the dissolution rate of poorly soluble drugs. In some methods of preparation of SD, particles with higher porosity are produced, which also contributed to increases in the dissolution rate [28]. The other advantage of SD includes its ease of conversion from crystalline to amorphous form, hence enhancing the dissolution rate and BA [35], and ease of preparation and scale-up using techniques like spray drying and freeze-drying. However, SD also possesses various limitations, as reported in the literature [34–37]. The main limitation of SD is the instability of the amorphous form. This means the appearance of crystalline form during storage and reduction of release rate with aging. Another limitation of SD is phase separation by absorbing moisture or a change from metastable crystalline form to stable form, and hence a decline in drug solubility as well as dissolution rate. Changes in temperature and moisture could have a deteriorating effect on the stability of SD by triggering the transformation of the amorphous form to crystalline form. Handling SD is difficult sometimes owing to its tackiness [38]. Most methods to prepare SD are not suitable for large-scale production; only a few techniques like freeze drying and spray drying are suitable for large scale-up preparation. The preparation of SD is susceptible to 'batch to batch' variations.

Classification of solid dispersion

SD can be classified into different categories based on the molecular arrangements and types of carriers used for their preparations, as shown in Fig. 1 [39,40]. The SD is categorized as generation viz. The first, second, third, and fourth generations of SD based on polymers are depicted in Fig. 2 [41–43]. The advantages and disadvantages of each generation are also discussed in Table 2, along with their possible mechanisms to improve the dissolution rate.

Classification of SD based on 'molecular arrangement.'

Classification of SD on the basis of type of carrier used for their preparation.

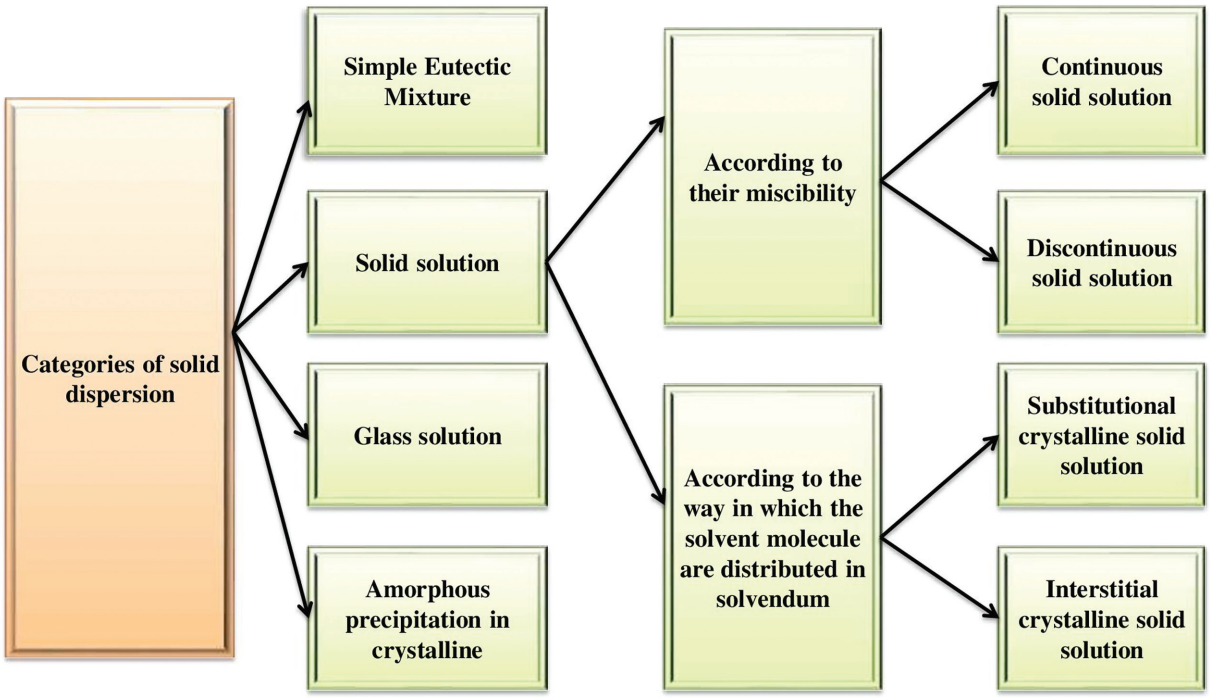
Solid dispersion-based approaches to improve dissolution and bioavailability of lumefantrine

In the last decade, various approaches based on SD have been explored to improve the aqueous solubility, dissolution rate, and oral BA of LMF. Various approaches including wet milling, solvent evaporation, spray drying, liquisolid technology, hot-melt extrusion, and miscellaneous techniques have been used to improve the dissolution rate of LMF (Table 3).

Wet milling technique

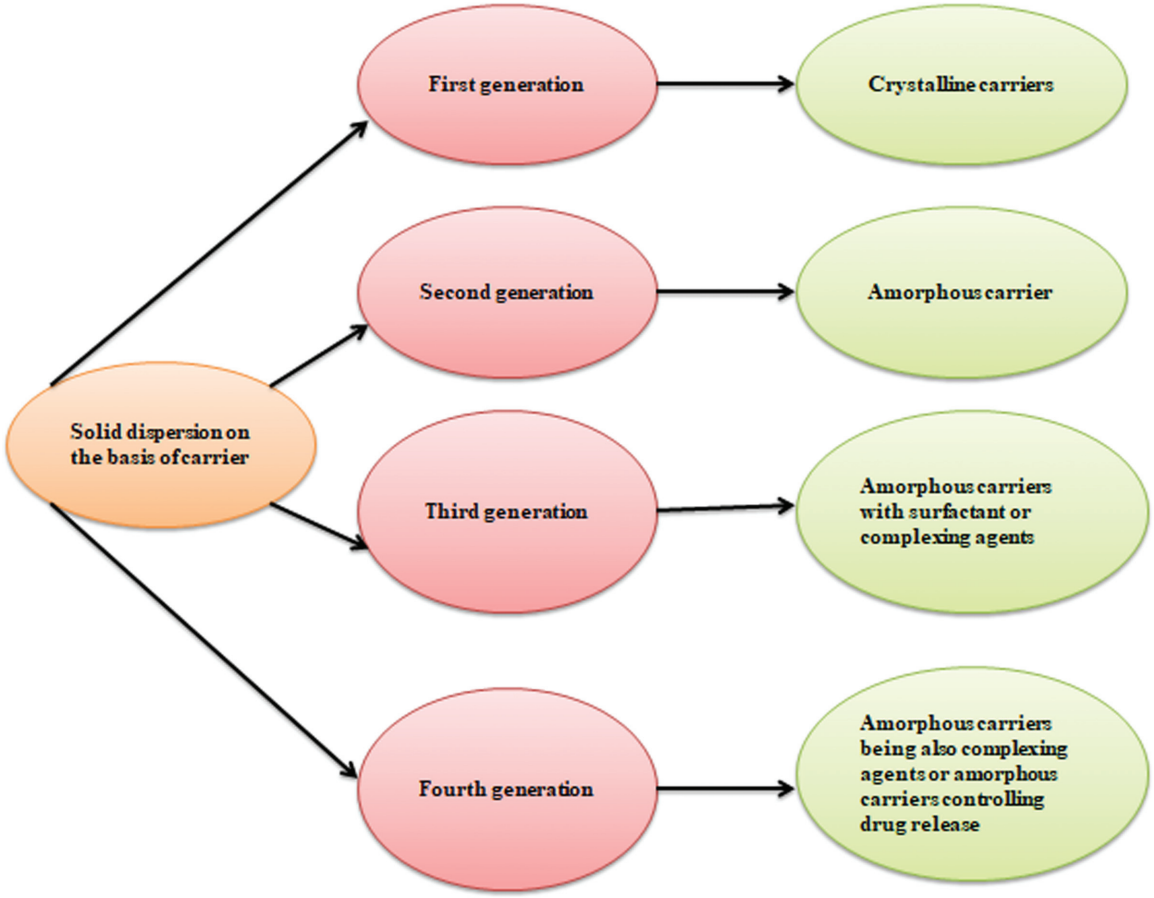
Gahoi and colleagues, milled the LMF with different hydrophilic polymers like HPMC, polyvinyl pyrrolidone (PVP), and surfactants such as Tween 80 and poloxamer, etc., to increase its dissolution rate. The mill was used to prepare the SD of LMF with these polymers and surfactants. The study showed that the highest dissolution was achieved in the SD prepared with HPMC and Tween 80 among the polymers and surfactants used, respectively. The

Figure 1



Classification of solid dispersion based on 'molecular arrangement.'

Figure 2



Classification of solid dispersion on the basis of type of carrier used for their preparation.

Table 2 Advantages and disadvantages of different generations of solid dispersion

Generations	Nature	Advantages	Disadvantages	Mechanism
First generation	Use crystalline carriers, for example, urea and sugar [44]	High thermodynamic stability. Formation of an eutectic mixture and improve dissolution [45]	Less enhancement of the dissolution rate as compared to other generations is due to high thermodynamic stability. Formation of crystalline solid dispersion	Small particle size, increased surface area with improved wettability [46]
Second generation	Use amorphous carriers, e.g., polymer like PEG and HPMC [47]	Drugs and carriers are totally miscible and soluble. As a result, they have a homogeneous molecular interaction. High dissolution less possibility of recrystallization and precipitation due to self-emulsifying properties. Exhibits high physical and chemical stability with enhanced BA [48] owing to low thermodynamic stability [48]	Low thermodynamic stability due to crystallization that occurred during storage. Also possess the tendency to nucleate and precipitate from the solution during dissolution due to its super saturated state. Showed high melting point	Small size and exists in a super saturation state in amorphous carrier because of forced solubilization [49]
Third generation	Use amorphous carrier with surfactant (Poloxamer 407, Polysorbate 80, Gelucire 44/14) [50]	Less possibility of recrystallization, and precipitation. Possess self-emulsifying properties. Exhibits high physical, and chemical stability with enhanced BA [46]	Presence of surfactant due to which chronic use lead to adverse effects	Promotion of wetting facilitation of solubilization and absorption [51]
Fourth generation	Use polymers that can control the release, like Eudragit RL, HPC [52]	Improvements in solubility and release rate	Short biological half-life	Carriers form the matrix and control the release of drugs [21]

BA, Bioavailability; HPMC, hydroxypropyl methylcellulose; HPC, Hydroxypropyl cellulose; PEG, Polyethylene glycol

dissolution study indicated 73 and 23% dissolution of LMF after milling with Tween 80 (LMF-SD) and unmilled LMF (UM-LMF), respectively, within 30 min. The IC50 values of UM-LMF and LMF-SD were found to be 0.380 and 0.1 ng/ml, respectively. The result showed higher *in vitro* antimalarial activity of LMF-SD as compared with UM-LMF. Furthermore, the mean survival time of mice infected with malarial parasites was more than 28 days when treated with LMF-SD at a dose of 15 mg/kg compared with 24 days for UM-LMF. Hence, the prepared LMF-SD showed a significant increase in the mean survival time of mice infected with the malaria parasites. The high antimalarial activity could be owing to the fast dissolution rate, which in turn, overcome dissolution-limited oral BA of LMF. The stability study indicated that there was no significant changes in organoleptic characterizations, X-ray diffraction (XRD) spectra, Differential Scanning Calorimetry (DSC) thermograms, and dissolution rate of LMF-SD when it was stored at 40±3°C/75±5% RH for 3 months.

Recently, a nanocrystal of LMF with different polymers and surfactants such as PVP-30, HPMC, and SLS was fabricated by wet milling and also evaluated for acute and sub-acute toxicity [54]. The solubility study showed the highest solubility enhancement of LMF nanocrystals with PVP, and SLS was found to be 684.6 μg/ml±2.0, whereas the solubility stabilizer solution (HPMC, PVP, and SLS) of LMF was found to be 248.2.1±2.7 μg/mL and in water 0.009 μg/ml. The dissolution study indicated 81.5, 3.5, 2.5, and 47% release from nanocrystal, pure drug, micronized drug, and microsuspension at 5 min [55]. Hence, the study indicated the highest dissolution from the prepared nanocrystals. The highest dissolution rate could be attributed to their nanosize and in turn, the enhanced surface area of particles. In addition, the wettability of LMF could also be increased owing to the presence of surfactants and polymers on the surface as indicated by the lower and broadening of melting endothermic peak (123.0°C) as compared with the unprocessed form melting endothermic peak (130.0°C) observed in DSC thermogram of Nanocrystal. The PXRD studies also indicated that the produced LMF nanoparticles were crystalline in nature. The stability study indicated no significant changes in organoleptic characterizations, XRD spectra, DSC thermograms, and dissolution rate after storage of nanocrystals, which were found to be stable and maintained their size and shape at 2–8 and 25°C for 90 days.

Solvent evaporation method

Balaji *et al.* [47], developed SD to enhance the dissolution rate and solubility of LMF and ARTM

Table 3 Literature review of explored solid dispersion of lumefantrine

Serial number	Techniques	Polymers	Optimum	Results	References
1	Wet milling technique	HPMC, Tween 80, PVP, Poloxamer	HPMC, Tween 80	The dissolution study indicated 73% and 23% dissolution of LMF after milling with Tween 80 (LMF-SD) and unmilled LMF (UM-LMF) at 30 min, respectively. Hence, the highest dissolution has been achieved with the SD prepared with HPMC and Tween 80	[7]
2	Liquid solid technique	Tween 80, propylene glycol, polyethylene glycol	Tween 80 and PEG 400	The liquisolid formulation with PEG 400 and tween 80 gives higher 97.5% release at 60 min as compared to the pure drug (LMF)	[12]
3	Hot-melt co formulation	Soluplus, Lutrol F127, Lutrol F68, PEG 400	pH 1.2, PEG 400	The highest dissolution rate of ARTM and LMF was found to be from the SD prepared with Soluplus1–PEG 400. The significantly higher oral bioavailability of LMF and ARTM from the selected SD than that of marketed products and pure drugs	[44]
4	Solvent evaporation method	Poloxamer, PEG 6000, PVP k-30	PVP K-30, PEG 6000	The highest dissolution (96%% at 60 min) of LMF from solid dispersion with PVPK30 : PEG 6000 in 3 : 2 ratio as compared to pure drug (LMF).	[47]
5	Nanoparticle formulation and spray drying technique	HPMCAS-126, HPMCE3	Oleic acid	The highest release 96.42% at 60 min from LF-SNEDs with oleic acid as compared to marketed milk formulation	[50]
6	Pheroid technology	Cremophore, α tocopherol, PEG 400	αTocopherol, PEG 400	The higher oral bioavailability of LMF AUC and Cmax (16 035 ng h/ml and 894 ng/ml, 18 038 ng h/ml and 960 ng/ml) from fasted and fed state conditions in rats from Pro-Pheroid formulation than reference LMF product	[53]
7	Spray drying and hot melt	HPMCAS, PAA, Eudragit L100-55, HPMCP, PSSA	HPMCP	The highest release showed ASD with HPMCP as compared to ASD with HPMCAS. The highest protonation showed LMF with HPMCP in the ratio of 3 : 7	[45]
8	Solid lipid nanoparticle	Stearic acid, Caprylic acid, Pluronic, Glyceryl monooleate, TPGS, LC-MS/MS, Tween 80	Stearic acid and myristic acid	The highest release showed 80% at 60 min from LMF-SLN with stearic acid and myristic acid as compare to pure drug (LMF)	[17]
9	Simple solvent evaporation	CAP, MCC and anhydrous lactose	Eudragit L100	The fastest release showed at concentration of 28 μg/ml at 2 h from SD with Eudragit L100 as compared to HPMCAS granules, CAP and MCC	[9]
10	Hot fusion	Stearic acid, glycerol monostearate and cetyl alcohol	Stearic acid	The highest flow property of powder 24.057 from solid lipid dispersion with LMF: stearic acid (0.5 : 1) as compared with glycerol monostearat, cetyl alcohol	[14]
11	Solvent evaporation	PEG 6000, Poloxamer 188,Cremophore, HPMC	PEG 6000 : Poloxamer 188 : HPMC	The highest dissolution at 90% at 60 min from SD with ARTM : PEG 6000: Poloxamer 188 : Olive oil: Transcutol: HPMC (12 : 75 : 5 : 4 : 2 : 2) as compared to pure drug (ARTM) and SD with cremophor	[46]
12.	Hot-melt extrusion	Kollicoat smartseal 30	Kollicoat smartseal 30	The highest release 60% at dispersion concentration exhibits 35.08±0.07% drug content with an estimated 20 parts per million concentration of LMF	[49]
13	Homolipid-based microparticles	Phospholipon1 90 G Phospholipid GmbH Labrasol1, macrogol-8-glyceride Gattefosse, Avicel, microcrystalline cellulose,70 maize starch	Phospholipon1 90 G	SLMs prepared with Irvingia 746 fatty/Phospholipon1 90 G at 2 : 1 ratio, enhanced the diffusion and permeability of ARTM	[51]
14	Antisolvent precipitation and ultrasonication technique	Soy lecithin, PVPK30, HPMC E5, Poloxamer 188 and Polysorbate 80	Soy lecithin	The highest solubility enhancement of LMF from nanosuspension was found to be LLNS, as compared to LMF and LSL-C. The IC50 value of LLNS was found to be 0.375 ng/ml while IC50 value of nano-sized LMF to be 0.1 ng/ml	[54]

ARTM, artemether; AUC, area under the curve; HPMC, hydroxypropyl methylcellulose; HPMCP, hydroxypropyl methylcellulose phthalate; HPMCAS, hydroxypropyl methylcellulose acetate succinate; LLNS, lumefantrine lyophilized nanosuspensions; LMF, lumefantrine; MCC, Microcrystalline cellulose; PAA, Poly acrylic acid; PEG, Polyethylene glycol; PSSA, Polystyrene sulfonic acid; PVP, polyvinyl pyrrolidone; SD, Solid dispersion; SLN, Solid lipid nanoparticles; TPGS, tocopherol polyethylene glycol succinate.

using hydrophilic polymers like Poloxamer, polyethylene glycol (PEG) 6000, and PVP K-30 by the solvent evaporation method. The solubilities of pure ARTM and prepared SD with PVPK30, PEG 6000, and Poloxamer were found to be 1.18, 39.21, 29.05, and 30.65 µg/ml, respectively, in the water [56]. Furthermore, the solubility of pure LMF and prepared SDS with PVPK30, PEG 6000, and poloxamer was found to 39.2, 28.10, and 31.52 µg/ml, respectively, in the water, whereas the study showed the highest dissolution (97.8% at 60 min) of ARTM from the SD prepared with PVPK30 : PEG 6000 in a 3 : 2 ratio among the polymers used. Furthermore, the study showed the highest dissolution (96% at 60 min) of LMF from SD with PVP K-30 : PEG 6000 in a 3 : 2 ratio among the polymers used. Therefore, the SD formulation with PVPK30 : PEG 6000 (3 : 2) ratio gives a higher release rate as compared with the pure drug (LMF) [57]. The FTIR studies indicated no interaction between the drug and excipients using formulation SD developed by 3 : 2 ratio of PVPK30 : PEG 6000. The PXRD studies indicated the transformation of crystalline LMF into a microcrystalline state (partially crystalline nature).

In the study by Charde and colleagues, a SD of LMF and ARTM was prepared using PVP K-30 as an amorphous polymer with Soluplus and Lutrol F68 as a surfactant in different ratios to improve their solubility and dissolution rate. The SD prepared with PVP K-30 in a ratio of 1 : 0.2 showed significant improvement in the dissolution rate of both drugs. The study also showed 1.85 and 2.82 times higher area under the curve (AUC) (0–72 h) tablets prepared with SD as compared with plain and marketed tablets of ARTM and LMF. Hence, they concluded that the enhancement of solubility leads to higher oral BA [58,59].

Spray drying technique

Bhujbal and colleagues, prepared the Amorphous solid dispersion (ASD) of LMF employing spray drying with four different acidic polymers viz. as hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), EL100, and Cellulose acetate phthalate (CAP). The study showed the highest dissolution (66% at 2 h) of LMF from ASD with HPMCP (3 : 7 ratio) using a spray drying method, whereas lower dissolution (42% at 2 h) of LMF from ASD with HPMCAS (4 : 7 ratio) [60]. Hence, ASD with HPMCP indicated a higher release rate as compared with ASD with HPMCAS. The FTIR study indicated the change in peak ratio in LMF-ASD. Furthermore, there is a change in carbonyl group interaction between drug and polymer. The functional group is acidic in nature, LMF basic in nature, and there are also changes in IR spectrum. The study showed the highest protonation of LMF in LMF-HPMCP (3 : 7 ratio) SD (40%). The study also indicated excellent flow and compressibility properties of LMF-HPMCP (3 : 7 ratio) SD. Furthermore, the stability studies showed no significant changes in organoleptic properties, PXRD, DSC, flow properties, and dissolution rate after storage at 40°C/75% Relative humidity (RH) for 3 months.

Liquid solid evaporation method

Khan and Agrawal and colleagues, formulated the LMF capsule by using a novel liquisolid approach with different polymers such as Tween 80, propylene glycol, and PEG to increase its dissolution rate. The solubilities of LMF and prepared liquisolid with propylene glycol, PEG 400, tween 80 in water were found to be 0.092, 0.347, 0.389, and 0.548 µg/ml, respectively. The dissolution study indicated a 45.75, 93.75, and 97.5% release of LMF pure drug (LMF), liquisolid of LMF with PEG 400, and Tween 80, respectively, within 60 min. Therefore, the liquisolid formulation with PEG 400 and tween 80 gives a higher release rate as compared with the pure drug (LMF) [61]. FTIR studies indicated no interaction between drug and excipients. Moreover, DSC and SEM studies indicated the conversion of crystalline LMF into an amorphous state in prepared liquisolid. The stability study indicated there was no significant change in organoleptic characterizations, drug contents, and dissolution studies of the liquisolid formulation.

Hot-melt based method

Fule and colleagues, prepared ARTM and LMF of SD using the hot-melt extrusion method with different polymers such as soluplus, lutrol F127, lutrol F68, and PEG 400 to increase solubility and oral BA [62,63]. The solubility study showed that the highest solubility enhancement of LMF and ARTM was found with Soluplus and lutrol F127 in the 6 : 36 ratio. The solubility of LMF from this SD was found to be 180, 130, and 120 mg/ml in water, pH 6.8 phosphate buffer, and 0.1 N HCL (pH 1.2), respectively. The solubility of ARTM was found to be 230, 100, and 50 mg/ml in water, pH 6.8 phosphate buffer HCL, and 0.1 N HCL, respectively [64,65]. The dissolution study also indicated a similar enhancement in the dissolution rates of LMF and ARTM. The highest dissolution of ARTM and

LMF was found to be from SD prepared with Soluplus : PEG 400. Furthermore, the *in vivo* BA studies were also performed for the selected SD (i.e. drug : Soluplus : PEG 400) in rats [66]. The results indicated significantly higher oral BA of LMF and ARTM from the selected SD than that of marketed products and pure drugs. The AUC and Cmax for ART were found to be 182.51±110.35 µg h/ml and 12.26±2.75 ng/ml, 401.25±126.21 µg h/ml and 118.25 ±47.24 ng/ml, and 8059.64±154.32 µg h/ml and 389.14±11.22 ng/ml after oral administration of pure ARTM, marketed product, and selected SD, respectively, whereas the AUC and Cmax for LMF were found to be 62.29±11.57 µg h/ml and 2.47 ±1.26 ng/ml, 232.57±28.76 µg h/ml and 7.85 ±2.47 ng/ml, and 62.29±11.57 µg h/ml and 87.97 ±14.58 ng/ml after oral administration of pure ARTM, marketed product, and selected SD. SEM images of ARTM and LMF revealed the large crystalline nature of agglomerates with definite morphology, whereas SD reflected the surface interaction of drug and polymer chains. SD showed rough surfaces with disordered structures. The DSC thermograms of LMF and ARTM indicated a single and sharp melting endotherm at 90.72 and 131.4°C, respectively, whereas no specific melting endothermic peak was observed in the DSC thermogram of SD containing the drugs. Thus, the disappearance of the endothermic peak in the SD indicated that the LMF and ARTM existed in an amorphous state in the dispersion. The XRD studies also confirmed the amorphous nature of the ARTM and LMF in SD. No significant change in organoleptic characterizations, XRD spectra, DSC thermograms, and dissolution rate was observed after storage of selected SD at 40°C/75% RH and room temperature for 6 months, which indicated the stability of prepared SD.

Pheroid technology

Du Plessis and colleagues, formulated a Pro-Pheroid of LMF and compared its oral BA with LMF in DMSO : water (1 : 9 v/v) solution (reference solution). Pheroids are three-dimensional cell aggregates that can mimic tissues and microtumors. Pro-Pheroid was developed by mixing vitamin F ethyl ester, kolliphor EL, and PEG 400 in a ratio of 60 : 30 : 5 at 70°C [67]. The AUC and Cmax of LMF were found to be 16035 µg h/ml and 894 ng/ml and 18038 µg h/ml and 960 ng/ml from the Pro-Pheroid formulation in fasted and fed state conditions, respectively, in rats. The AUC and Cmax of LMF were found to be 13 315 µg h/ml and 950 ng/ml and 18280 µg h/ml and 1273 ng/ml from canola oil in fasted and fed state conditions, respectively, in rats. The AUC and Cmax of LMF were found to be 4680 µg h/ml and 369 ng/ml and 12 709 µg h/ml and 980 ng/ml in fasted and fed conditions, respectively, in rats. Therefore, the results indicated significantly higher oral BA of LMF from the Pro-Pheroid formulation than the reference LMF product. The stability study indicated no significant change in their particles, and furthermore, no phase separation and precipitation in the formulation after 24 h storage at ambient conditions.

Miscellaneous

Patel *et al.* [50], formulated and evaluated a self-nano emulsifying delivery system (SNEDD) of LMF to improve its dissolution and BA. They have screened the best oil, cosurfactants, and surfactants to formulate SNEDD. Oleic acid was selected as the oil phase as it possesses the highest solubility of LMF (157.20 ±1.38 mg/g) among all the oils used in the study. Capmul PG8 was selected as the cosurfactant as it possesses the highest solubility of LMF (18.13 ±0.49 mg/g) among all cosurfactant used in the study [68,69]. Tween 80 was selected as the surfactant as it possesses the highest solubility of LMF (101.63 ±0.37 µg/ml). The dissolution study indicated 96.42 and 76.8% release of pH 1.2 and pH 6.8 (LF-SNEDs) with oleic acid within 60 min, whereas marketed formulation milk indicated 11.72% and 3.94% release of pH 1.2 and pH 6.8 (marketed milk) within 60 min Therefore, the spontaneous formation of the nanoemulsion showed higher dissolution of a hydrophobic drug.

Antisolvent precipitation and ultrasonication technique

Shah and colleagues, fabricated lumefantrine lyophilized nanosuspensions (LLNS) using antisolvent precipitation and ultrasonication techniques with different polymers such as soy lecithin, PVPK30, HPMC E5, Poloxamer 188, and Polysorbate 80. The solubility study showed the highest solubility enhancement of LMF with soy lecithin and PVP K-30 in a ratio of 1 : 4 : 1. The solubility of LMF was found to be increased in nanosuspension prepared with a high ratio of soya lecithin. The solubility of LMF was found to be 615 µg/ml increased from 921 µg/ml upon increasing the ratio of Soy lecithin from 1 : 1 : 1 to 1 : 4 : 1. The saturation solubility of LMF, LSP-C (LMF soya lecithin PVP K-30 complex), and LLNS was found to be 212.33, 782.66, and 1670 µg/ml in water, respectively. Thus, the study indicated that the

highest solubility enhancement of LMF was achieved with LLNS as compared with LMF and LSL-C. The FTIR study showed no change in major peaks when compared with LSL-C and LMF, which indicated no interaction between the LMF and excipients used to prepare LLNS formulation. The DSC studies LLNS indicated single and sharp melting peaks slightly lower endotherm at 39.01–44.52°C as compared with LSL-C melting endothermic peaks were observed at 87.38–143.69°C [70]. The PXRD studies indicated the transformation of crystalline LMF into an amorphous state. The dissolution study indicated a 10, 90, and 60% release of pure drug (LMF), LLNS, and marketed formulation (dry syrup), respectively, within 15 min [71,72]. Therefore, the LLNS formulation has a higher release as compared with the pure drug (LMF) and marketed formulation (dry syrup). The *in vitro* antimalarial assay results indicated that the stabilizer solution showed no action against the test strains. The IC50 values were found to be 0.375, 16, and 4.5 ng/ml for Nano-sized LMF from LLNS, free and pure LMF, and marketed formulations containing LMF, respectively. The nanosize LMF also shows a significant reduction in the IC50 compared with the standard antimalarial agent chloroquine. The study showed good stability for prepared LLNS stored, indicating that fabricated LLNS showed good stability at 25±2°C/60±5% RH and 40±2°C/75±5% RH for 3 months [73].

Self-nano emulsifying technique

Gaikwad and colleagues, formulated and evaluated a self-nano emulsifying drug delivery (SNEDD) containing ARTM and LMF. The study showed a dissolution rate of 96.34±0.65 and 92.78±0.09% at 60 min for ARTM and LMF, respectively, from SNEDD. However, the dissolution rates of pure drugs (ARTM and LMF) were found to be 24.34 ±0.9 and 7.94±0.12% at 60 min The study showed improved dissolution rates of ARTM and LMF from the prepared SNEDD compared with the pure and reference marketed tablets [57,74]. Moreover, the AUC for lumefanrine after was found to be twofold higher from the SD (190.82 μg/ml) as compared with that of pure LMF (93.51 μg/ml) upon oral administration in rats.

Conclusion

The present review concluded that SD-based approaches could have the potential to improve the oral BA of LMF. This paper looks at the different ways to make SDs with LMF that are easier to dissolve and more effective when taken by mouth. However, the SD prepared by the hot-melt extrusion technique could be the most promising due to its commercialization to improve the oral BA of LMF. The hot-melt extrusion is a continuous process to fabricate SD, and the prepared SD easily transformed to desired shape of pellets. Thus, the SD prepared by this method could be the most promising for further commercialization. In future studies, this technique can be explored using other carriers with LMF as well as other water insoluble drugs. The review also showed how important it is to choose the right carrier and processing method, which can improve the BA of LMF. According to the findings, particle size reduction and the transformation of the polymorphic form of LMF into an amorphous form resulted in an increase in the dissolution rate of SD. Several of the studies in this paper compared the prepared SD with the commercial product and the pure drug. Most of the studies showed that the rate of dissolution was much faster than that of pure and commercially available tablets. A few of the studies also showed that the oral BA of prepared SDs was much better. However, the review of the literature showed that there have not been any clinical tests of the developed SD yet. Hence, clinical studies should be required in the future to establish the benefit of using SD for enhancing the oral BA of LMF in humans.

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Conflicts of interest

There are no conflicts of interest.

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