The Effect of Cis and Trans Butenedioic Acid on the Physicochemical Behavior of Lumefantrine

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Electronic Supplementary Information (ESI)

Table S1. Result of solid-state forms of lumefantrine obtained by solvent evaporation (SE).

Drug	Coformers	Method	Observation	Inference	Melting point
Lumefantrine	Gallic acid	SE	Birefringence	Crystalline	Two separate melting points
	Vanillin	SE	Birefringence	Crystalline	Broad melting point
	Vanillic acid	SE	Birefringence	Crystalline	Melting point depression
	Alanine	SE	Birefringence	Crystalline	Two melting points
	Aspartic acid	SE	Birefringence	Crystalline	Two melting points
	Malic acid	SE	Sticky	Amorphous?	-
	Benzoic acid	SE	Birefringence after 24 h	Crystalline	-
	Citric acid	SE	Sticky	Amorphous?	-
	Para hydroxyl benzoic acid	SE	Birefringence	Crystalline	Broad melting point
	Fumaric acid	SE	Birefringence	Crystalline	Single and sharp melting point
	Maleic acid	SE	No birefringence	Amorphous	-

Table S2. ATR-IR data of lumefantrine (LMF), fumaric acid (FA), maleic (MA), lumefantrine-fumaric acid 2:1 salt (LMF-FA 2:1 salt) and lumefantrine- maleic acid 1:1 coamorphous (LMF-MA 1:1 CAM).

Compound	**Functional group**				
	Amine group (cm^{-1})	C=O stretching (cm^{-1})	Dimeric hydrogen bonding between the O-H and C=O (cm^{-1})	C-H stretching (cm^{-1})	O-H stretching (cm^{-1})
LMF	1634.14	-	-	2925.95	3395.30
FA	-	1660.70	-	-	-
MA	-	1703.92	2600.00	-	-
LMF-FA PM	1636	1670.52		2925.46	3393.6
LMF-MA PM	1633.75	1703.67	2600.00	2925.72	3395.3
LMF-FA 2:1 salt	1693.4	1569.00	-	2964.47	-
LMF-MA 1:1 CAM	1622.3	1706.90	-	2961.43	-

Table S3. ^{13}C chemical shifts (ppm) obtained in ^{13}C ss-NMR of lumefantrine (LMF), fumaric acid (FA), maleic (MA), lumefantrine- fumaric acid 2:1 salt (LMF-FA 2:1 salt) and lumefantrine- maleic acid 1:1 coamorphous (LMF-MA 1:1 CAM).

Position of carbon	**Lumefantrine**	**LMF-FA 2:1 salt**	**LMF-MA 1:1 CAM**
C21	65.4	64.6	61.0
C28, C24	31.42	31.4	-
C22	59.9	60.1	59.7
C23，C27	53.1	53.9	53.3
C25, C29	19.9	20.7	20.5
C7	126.77	126.7	126.9
C in benzene ring	129.79-127.22	127.22	-
Substitutive C in benzene ring	142.3-140.3, 132.3	143.0-140.7, 132.3	-
CH in alkene	-	135.64	-
C in C=O	-	176.27	170.3

Table S4. ^{15}N chemical shifts (ppm) obtained in ^{15}N ssNMR of lumefantrine (LMF), lumefantrine- fumaric acid 2:1 salt (LMF-FA 2:1 salt) and lumefantrine- maleic acid 1:1 coamorphous (LMF-MA 1:1 CAM) using NH_4Cl and glycine as primary and secondary standards respectively.

	Compound	^{15}N Chemical shift (δ ppm)
1	LMF	31.21
2	LMF-MA 1:1 CAM	53.47
3	LMF-FA 2:1 salt	51.75
4	NH_4Cl (Primary reference)	0.0
5	Glycine (secondary reference)	32.94

Table S5. Hydrogen bond geometry in crystal structures of lumefantrine-fumaric acid.

Interaction	d(D-H)	d(H···A)	d(D···A)	<(DHA)	Symmetry code
$O_{1A}–H_{1A}···O_{5A}$	0.84	1.71	2.531(5)	165	x,y,1+z
$N_1–H_1···O_{4A}$	1.00	1.75	2.700(6)	158	x,y,1+z
$N_1–H_1···O_{3B}$	1.00	1.62	2.458(14)	139	x,y,1+z
$C_{17}–H_{17}···Cl_1$	0.93	2.85	3.760(6)	163	x, y, z
$C_{19}–H_{19}···O_{5A}$	0.95	2.25	3.187(6)	170	x,1/2-y,1/2+z
$C_{22}–H_{22B}···O_{4A}$	1.03	2.55	3.536(6)	160	1-x,-y,1-z
$C_{23}–H_{23A}···O_{1A}$	0.99	2.37	3.117(4)	131	1-x,-y,2-z
$C_3–H_3···O_{1A}$	0.95	2.53	3.449(3)	163	x,1/2-y,-1/2+z

Table S6. Equilibrium solubility of lumefantrine, salt and coamorphous system

	0.5 % BKC	1 % BKC
LMF	31.16 ± 0.23 µg/mL	63.07 ± 3.68 µg/mL
LMF-FA 2:1 salt	38.23 ± 1.01 µg/mL	61.76 ± 1.67 µg/mL
LMF-MA 1:1 CAM	132.21 ± 17.81 µg/mL	200.26 ± 8.29 µg/mL
LMF: lumefantrine, LMF-FA 2:1 salt: lumefantrine-fumaric acid 2:1 salt and LMF-MA 1:1 CAM: lumefantrine-maleic acid 1:1 coamorphous		

Table S7. Dissolution parameters for lumefantrine, amorphous lumefantrine, physical mixture, salt and coamorphous system.

Dissolution parameter	**LMF**	**A-LMF**	**LMF-FA 2:1 salt**	**LMF-MA 1:1 CAM**	**LMF-FA PM**	**LMF-MA PM**
F2#	-	84.87	20.06	22.73	64.40	86.75
DE_{15}	4.34	4.18	42.77	31.50	4.94	4.23
DE_{120}	17.69	18.13	66.87	84.20	64.73	61.29

with reference to plain lumefantrine
F2: similarity factor, DE: dissolution efficiency
LMF: lumefantrine, A-LMF :amorphous lumefantrine, LMF-FA 2:1 salt :lumefantrine-fumaric acid 2:1 salt, LMF-MA 1:1 CAM : lumefantrine-maleic acid1:1 coamorphous, FA PM : lumefantrine-fumaric acid physical mixture, LMF-MA1:1 CAM : lumefantrine-maleic acid 1:1 coamorphous and LMF-MA PM : lumefantrine-maleic acid physical mixture

Table S8. Dissolution parameters for lumefantrine- fumaric acid 2:1 salt and lumefantrine-maleic acid 1:1 coamorphous after 1-month stability at 40 ^{o}C ± 2 ^{o}C/75% ± 5% RH.

Dissolution parameter	**LMF-FA 2:1 salt**	**LMF-MA 1:1 CAM**
$F2_{\#}$	77.27	64.78

with reference to initial sample
F2: similarity factor,
LMF-FA 2:1 salt: lumefantrine-fumaric acid 2:1 salt, LMF-MA 1:1 CAM: lumefantrine-maleic acid 1:1 coamorphous

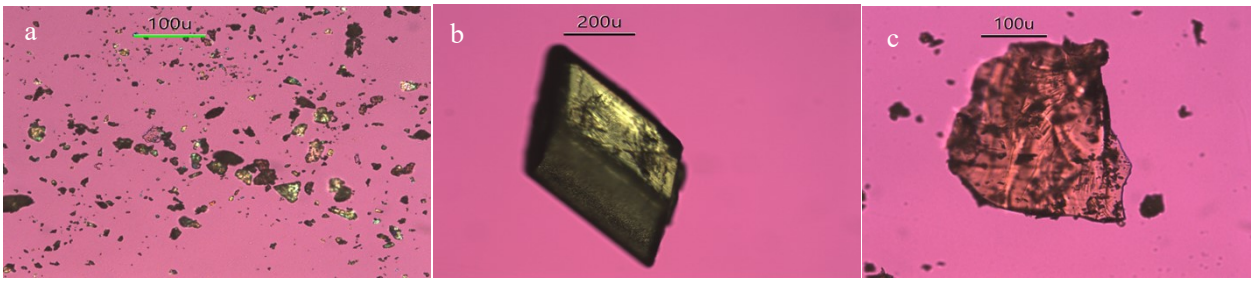

Fig. S1 Polarized light microscopic images of crystalline lumefantrine (a), lumefantrine-fumaric acid 2:1 salt (b) and lumefantrine-maleic acid coamorphous (c).

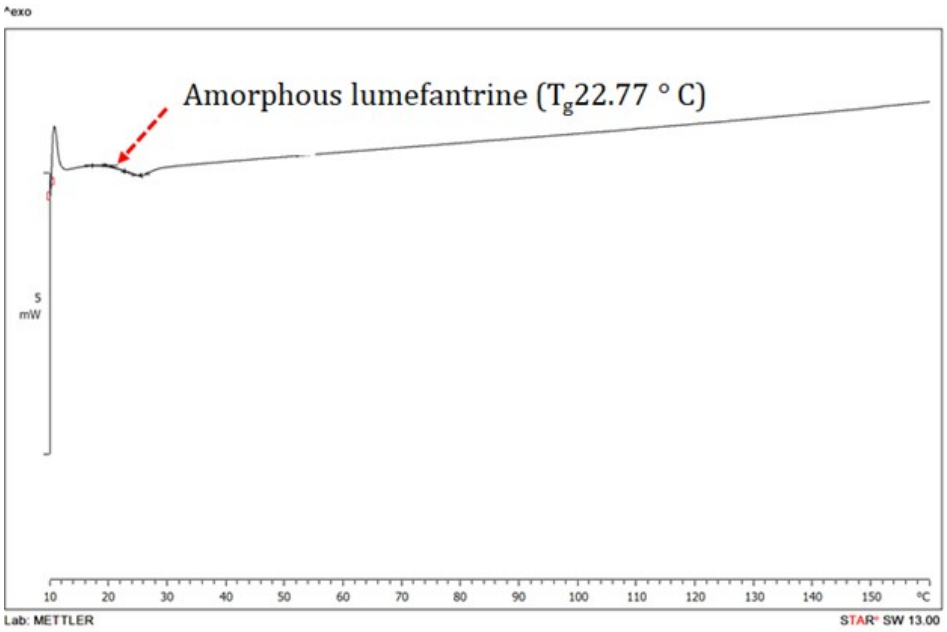

Fig. S2 Amorphous lumefantrine and its glass transition (T_g) event.

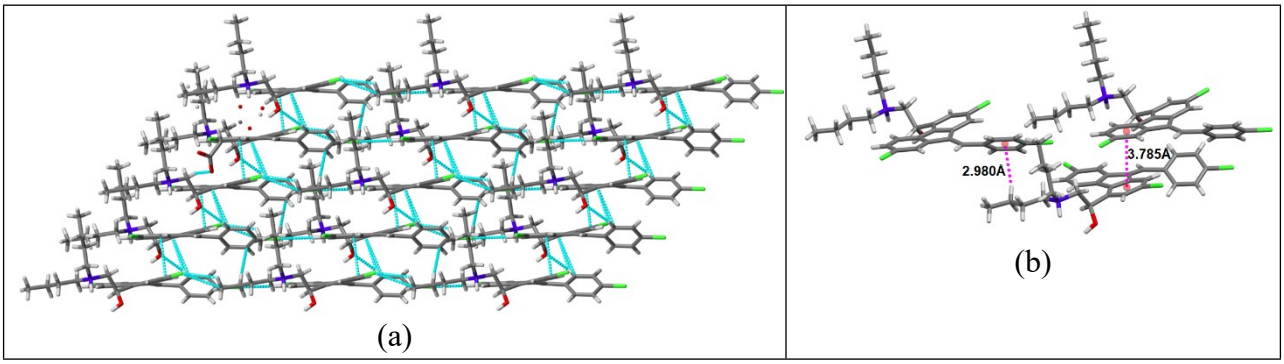

Fig. S3 (a) Packing structure of lumefantrine units connected in 2D array (b) stabilized by weak π···π and C–H···π interactions.

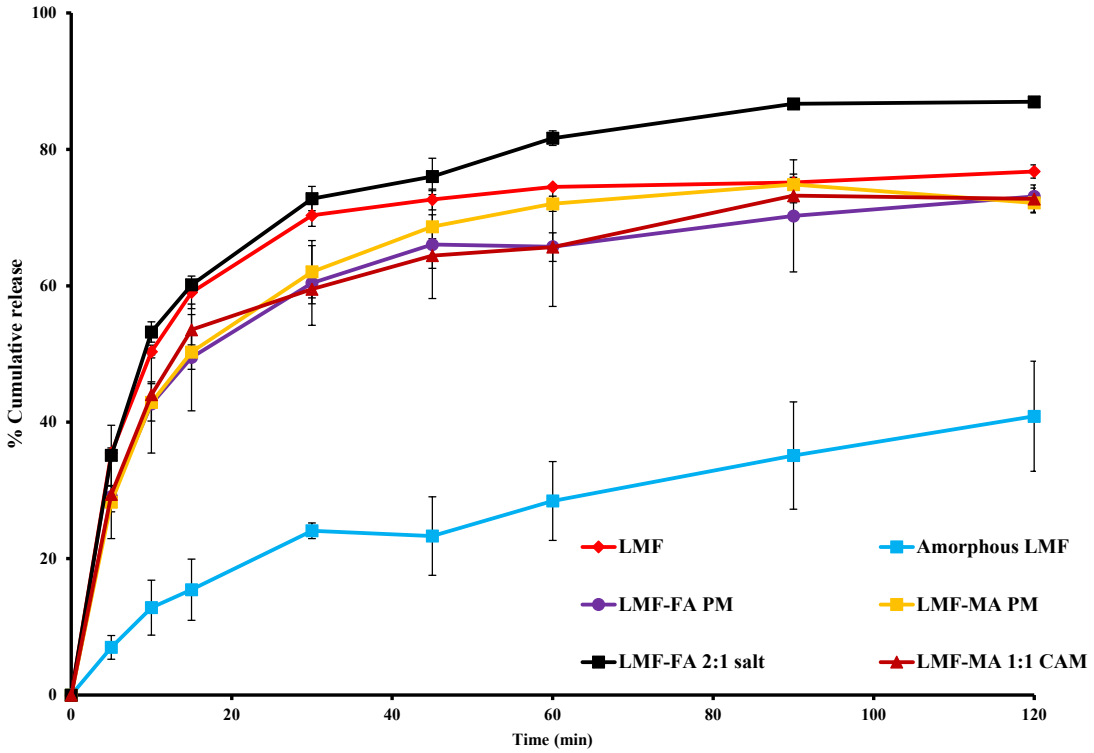

Fig. S4 Dissolution profile lumefantrine (LMF), amorphous lumefantrine (amorphous LMF), lumefantrine- fumaric acid physical mixture (LMF-FA PM), lumefantrine-fumaric acid 2:1 salt (LMF-FA 2:1 salt), lumefantrine-maleic acid physical mixture (LMF-MA PM) and lumefantrine-maleic acid 1:1 coamorphous (LMF-MA 1:1 CAM) in 0.1N HCl containing 1 % w/v BKC.

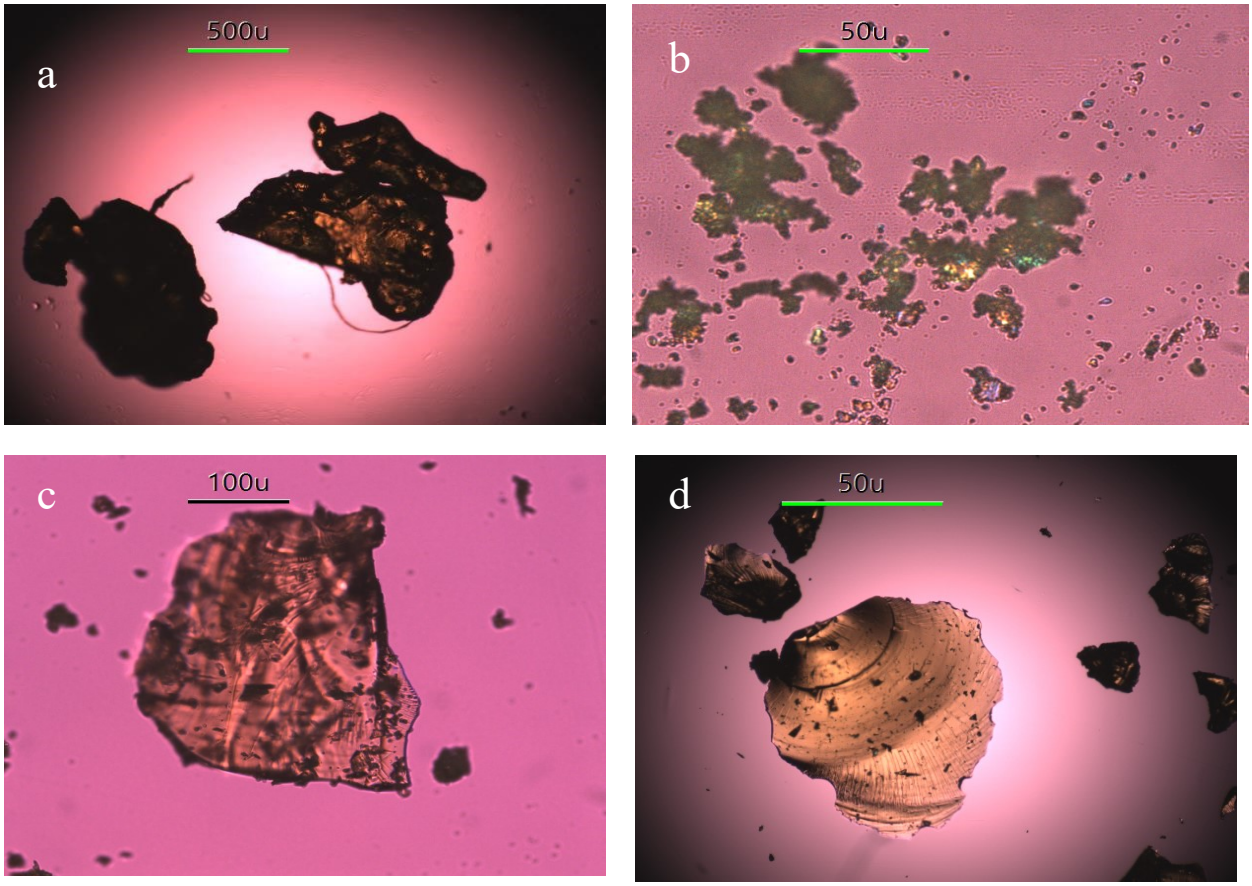

Fig. S5 Polarized light microscopic images of amorphous lumefantrine (a) amorphous lumefantrine after stability, (b) lumefantrine-maleic acid 1:1 coamorphous before stability (c) and lumefantrine-maleic acid 1:1 coamorphous after stability (d).