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A Novel Curcumin-Artemisinin Coamorphous Solid: Physical Properties and Pharmacokinetic Profile†

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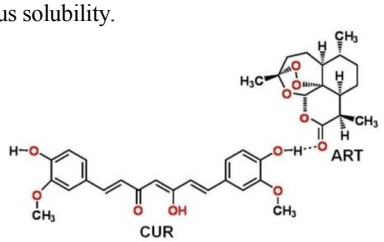
Here we report Curcumin-Artemisinin coamorphous solid (1:1) prepared by rotavaporization and dramatic increase in pharmacokinetic profile of curcumin (AUC_{0-12} 2.6 μg.h/mL, C_{max} 1 μg/mL) administered as CUR-ART to SD rats. PXRD and FESEM analysis explain the molecular basis for the solubility enhancement of coamorphous CUR-ART.

Naturally occurring compounds from traditional herbal medicines represent a rich source of therapeutic molecules to treat human diseases with minimal side effects.[1] The major drawbacks of bioactive herbal drugs are low aqueous solubility, poor bioavailability and stability issues (typically short half life).[1b,c] For these reasons many bioactive molecules fail to reach the market as drugs, a common example being Curcumin.[2] Salt formation[3] is the first-choice method to enhance the solubility and bioavailability of Active Pharmaceutical Ingredients (APIs) and bioactive molecules, but this traditional approach is ruled out for compounds which lack an ionizable functional group, as is the case for curucmin. Other strategies such as polymorphs,[4a] cocrystals,[4b] eutectics,[4c] solid dispersions,[4d] cyclodextrin complexes,[4e] nanoparticles,[4f] etc. are also used depending on the nature of the drug and the specific problem to be addressed. Amorphization of the drug to a high free energy state can result in solubility enhancement due to particle size reduction (nanoparticles).[5] The advantages of amorphous materials in terms of solubility and scalability makes this a preferred method, particularly for those APIs which lack ionizable functional groups. On the down side however, conversion of amorphous to crystalline state is a major concern. The addition of polymers to stabilize amorphous formulations gives plasticizing effect, compressibility and incompatibility problems. Therefore, a strategy that incorporates synergism of the drug and the additive is a desirable goal in molecular pharmaceutics. Development of the optimal solid formulation with high bioavailability and good stability is the end goal.

Drug coamorphous systems is a relatively new approach in which the positive effects of the drug combination (coformer effect)[6] and high thermodynamic functions of the amorphous phase (which confer solubility and dissolution advantage) are synergized to result in an improved pharmaceutical product. A coamorphous system is a multi-component single phase amorphous solid system which lacks periodic arrangement in the lattice and is associated by weak and discrete intermolecular interactions between the components. They can have short range ordering such as hydrogen bonding of carboxylic acids, carboxamides, phenols/alcohols,[7] similar to amorphous solids of single component systems. A coamorphous solid may be contrasted with a cocrystal, salt or eutectic primarily by its amorphous nature in that it exhibits a broad hump ('amorphous halo')[8] when subjected to powder X-ray diffraction. The identity and integrity of the components of coamorphous systems can be established by spectroscopy. Together with the more well known counterparts such as salts, eutectics and cocrystals, coamorphous solids are a new entry to pharmaceutical solid form space.

Curcumin (diferuloylmethane, CUR), a hydrophobic polyphenol derived from the rhizome of the herb *Curcuma longa* of the dietary Indian spice turmeric, has a plethora of pharmacological properties.[9] Artemisinin (ART) is an antimalarial drug, first identified by Chinese researchers in the plant *Artemisia annua*.[10] CUR and ART independently exhibit anticancer activity by suppressing multiple signaling pathways and inhibits cell proliferation, invasion, metastasis and angiogenesis.[11a,b] In addition when ART is combined with CUR it exhibits better antimalarial activity compared to the individual drugs.[11c,d] Despite high safety levels of CUR up to 12 g/day[2b] in humans, the efficacy of CUR as a drug is limited by low aqueous solubility (7.8 μg/mL) and poor bioavailability (0.051 μg/mL),[2] mainly due to its rapid metabolism and short half-life. With the intent of exploring a possible synergism between CUR and ART for both physical form and pharmaceutical property (they have phenol and lactone carbonyl complementary hydrogen bonding groups), we performed cocrystallization to obtain their solid combination product as a cocrystal or eutectic, mediated by O–H···O=C hydrogen bond (Scheme 1).[12] Instead we obtained a 1:1 coamorphous solid form, CUR-ART. This new coamorphous solid was characterized by PXRD, DSC, ss-NMR and IR. The intrinsic dissolution rate of CUR-ART (1:1) in 60% ethanol-water is 2.6 times faster than curcumin. Pharmacokinetic studies on coamorphous CUR-ART in Sprague Dawley rats showed higher curcumin concentration with AUC_{0-12} = 2.59 μg.h/mL after administering 200 mg/kg dose. In contrast, pure CUR dose could not be detected in blood plasma due to its poor aqueous solubility.



Scheme 1 Molecular structure of Curcumin (CUR)-Artemisinin (ART) and intermolecular O–H···O=C hydrogen bonding.

Cocrystallization by grinding (neat, liquid-assisted and mechanical) and slurry crystallization methods were attempted to obtain a novel solid combination of CUR and ART. Due to the bulky shape, lack of robust supramolecular synthon (except a

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† Electronic Supplementary Information (ESI) available, PXRD plots, IR, and NMR spectrum, and Experimental details.

single hydrogen bond), a eutectic was expected as the product.[13] Grinding and crystallization experiments afforded a material that appeared to be crystalline by PXRD (Figure S1a, ESI†). The material was subjected to DSC since it can distinguish between physical mixture vs. eutectic composition. The material displayed thermal behavior typical of an amorphous form (Figure S2, ESI†). This could be due to heat-induced molecular mobility and randomization of the crystalline mixture such that an amorphous/ rubbery phase is formed. The product lacks strong interactions to form a crystalline supramolecular assembly (i.e. eutectic) but sufficient to form a coamorphous system. Such weak and discrete interactions to give a coamorphous phase is possible using conventional techniques in which crystallization is rapid, such as melt-quenching, wet granulation, milling, etc.[7] Melt-quenching cannot be done for CUR-ART combination since it decomposes at high temperature (see Figure S2, ESI†); ball-mill grinding gave a semi-crystalline/ amorphous material (see Figure S1b, ESI†). Rotavaporization is a recent technique to obtain metastable forms,[14] which involves dissolving the components in a solvent and then fast evaporation under vacuum. The use of ethanol resulted in coamorphous CUR-ART of 1:1 stoichiometry. Solution ^{1}H NMR confirmed the chemical purity and equimolar stoichiometry of the product (Figure S3, ESI†). PXRD of the novel solid form CUR-ART showed homogeneity of the novel coamorphous phase (Figure 1) in which the signature diffraction peaks of crystalline CUR and ART are absent. There is possibility of amorphization of the individual compounds upon rotavaporization. An amorphous form of curcumin is known[15a] but there is no reported amorphous phase for ART. Rotavaporization of the individual compounds gave an amorphous form of CUR (Figure S4, ESI†) and a polymorphic mixture for ART[15b] (Figure S5, ESI†). These results suggest that it is CUR which facilitates the amorphization of ART in the coamorphous system CUR-ART, perhaps through the bimolecular O–H···O=C hydrogen bond. Intermolecular O–H···O hydrogen bonding (Scheme 1) was evidenced through changes in OH and C=O stretching frequencies for CUR and ART in FT-IR. When the IR spectrum of CUR and ART are compared to that of the coamorphous system CUR-ART, small 1-2 cm^{-1} shifts were observed in carbonyl region for CUR-ART shifted to 1625.9 cm^{-1} compared to CUR at 1627.5 cm^{-1}; the ester carbonyl of CUR-ART appears at 1735.6 cm^{-1} while the peak in ART is at 1736.5 cm^{-1} (Figure S6, ESI†). The OH stretch region exhibited red shift to 3434.7 cm^{-1} in CUR-ART compared to 3510 cm^{-1} for CUR, a clear indication of strong O–H···O=C hydrogen bonding.

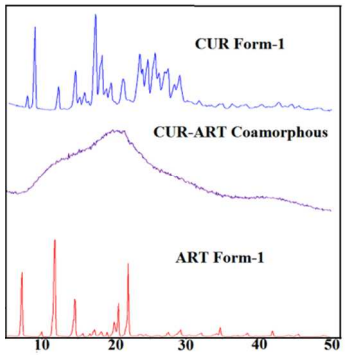

Figure 1 Comparison of coamorphous CUR-ART (1:1) with starting materials CUR and ART Form 1. The coamorphous product is lacking the sharp diffraction lines characteristic of the crystalline starting materials.

Differential scanning calorimetry (DSC) of an amorphous solid will show a glass transition temperature (T_g), the temperature at which the glassy phase converts to a rubbery phase with properties akin to a liquid phase. DSC of a coamorphous material should show a single glass transition event, indicative that one compound is completely miscible in the second to form a homogenous phase. The melting point of curcumin is 181 °C (Table S1, ESI†) and ART shows two melting endotherms for the two polymorphs.[18b] The amorphous form of CUR reproduced by rotavap technique [18a] exhibits a single exotherm followed by a melting endotherm that matched with that of the crystalline form. In case of ART we did not observe any amorphous form by rotavap technique. The DSC thermogram of coamorphous CUR-ART shows a single glass transition T_g (broad exotherm peak) at 67.58 °C (Figure 2) followed by decomposition at 192.67 °C. The occurrence of a single exotherm peak indicates that the two compounds are freely miscible with each other to form a homogenous phase CUR-ART; there is no dissociation to the crystalline components upon heating (absence of additional peaks).

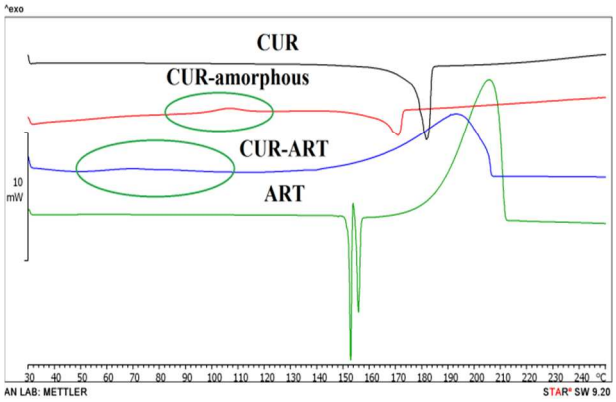

Figure 2 DSC thermogram of CUR-ART coamorphous (prepared by rotovaporization) form compared with the starting materials. The circles indicate glass transition of CUR amorphous (98.9 °C) and CUR-ART coamorphous (67.6 °C).

^{13}C ss-NMR provides detailed information about differences in hydrogen bonding, molecular environment, and short range order in crystalline and amorphous solids. The NMR spectrum of CUR-ART obtained by rotavaporization (Figure S7, ESI†) matches closely with the individual components in terms of chemical shifts but the overall broadening of peaks is indicative of amorphization.

The coamorphous solid was kept in accelerated ICH (International conference on Harmonization)[16] conditions of 40 °C temperature and 75% relative humidity in a stability station. PXRD was recorded on the material at regular intervals up to 45 days to assess sample stability. CUR-ART coamorphous was stable for a brief period of 15 days, and thereafter it showed conversion to a crystalline phase. This transformation could be due to molecular mobility facilitated by moisture and temperature. The PXRD of the semi-crystalline material at 45 days matched with the individual diffraction peaks of CUR and ART (Figure S8, ESI†).

Intrinsic Dissolution Rate (IDR) is a kinetic or time-dependent phenomenon. IDR gives an idea of the time required to reach peak drug concentration (C_{max}), the amount of drug dissolved during time interval (AUC), and the time taken for dissolution before phase transformation of the drug occurs. Faster dissolution rate and high oral drug delivery are the goal in pharmaceutical development. Dissolution was carried in 60% EtOH-H_2O medium for CUR-ART because the components are not soluble in pure water. IDR experiments were performed over 2 h by the rotating disk intrinsic dissolution rate (DIDR) method[17] at 37 °C. The dissolution rate of CUR-ART is 2.6 times faster than curcumin (Figure 3a, Table S2, ESI†), but, surprisingly there is no increase relative to ART (Figure S10, ESI†). PXRD of the residue

remaining at the end of the dissolution experiment matched with that of curcumin Form-1 (Figure S9d-f, ESI†). It was not possible to obtain equilibrium solubility of CUR-ART because the coamorphous form converted to the stable crystalline forms (Figure S9a-c, ESI†).

CUR-ART coamorphous and pure curcumin were administered orally (200 mg/kg) to Sprague Dawley male rats (200±50 g, n = 6 for each drug). The oral dose solubility profile can be estimated by measuring the AUC (area under the concentration curve) and C_{max} (peak plasma concentration). Administration of pure curcumin did not show any detectable levels in plasma due to its very low water solubility (<8 mg/L) and short elimination half-life (<2 h). This observation is consistent with recent reports wherein pure curcumin could not be detected by HPLC.[18] Oral administration of CUR-ART coamorphous (after correcting for the same molar amount of curcumin administered), gave C_{max} value of 1.003 µg/mL of curcumin at T_{max} = 30 min; thereafter, the concentration dropped with a $T_{1/2}$ of 6.4 h and $AUC_{0-\infty}$ = 24.7 µg.h /mL (Figure 3b and Table 1). It was not possible to detect the concentration of ART (typically at ng/mL conc.) by the same method because the limit of detection by PDA detector (photodiode array) of HPLC is much higher (20 µg/mL) for a molecule devoid of chromophore group. ART is detected using an electrochemical assay.[19] In summary, CUR-ART coamorphous solid exhibits ehnanced solubility and pharmacokinetic profile of the bioactive herbal ingredient curcumin. A high C_{max} value of 1 µg/mL at short T_{max} of 30 min and amount of curcumin concentration delivered in vivo of 25 µg .h/mLis one of the highest for curcumin in a solid form (see reported values in Table 2). The preparation of CUR-ART by simple rotovaporization offers distinct advantages for scale up.

Table 2 C_{max}, T_{max}, AUC for soluble curcumin oral forms.

Curcumin form	C_{max} (ng/mL)	T_{max} (min)	Dose (mg/kg)	$AUC_{0-\infty}$ (µg. h /mL)	Relative performance[b] C_{max}, AUC	Ref.
CUR-ART coamorph.	1003	30	200	24.7	100, 2.5	This work
CUR liposome	43	30	100	0.1	8, 0.02	18a
CUR crystalline	35	80	100	11.0	7, 2.2	20a
CUR cryst. disp.	194	55	20	36.2	194, 36	20a
CUR amorph. disp.	147	60	20	27.1	147, 27	20a
Nano CUR	451	9	20	20.0	451, 20	20a
CUR powder	37	120	300	0.1[a]	2.5, 0.006	20b
Thera CUR	1697	120	300	9.3[a]	113, 0.62	20b

[a] Estimated for 24 h from Fig. 3 of ref. 20b.
[b] Based on a dose of 20 mg/kg and assuming linear profile. This comparison is qualitative because different additives and solubilizers and polymers are added to each formulation.

The underlying basis for the fast dissolution and enhanced pharmacokinetic profile for CUR-ART was understood by FESEM analysis (Figure 4). Not only there is amorphisation of CUR-ART (halo in Figure 1) but even at the microscopic level the coamorphous solid has smaller grains of irregular shaped 2-8 µm and mini rods of <1 µm width (Figure 4c). In contrast, the individual components and the physcial mixture (Figure 4a, b, d) are several microns in size. Overall, there is micronization upon amorphization even as the particles' composition is somewhat heterogeneous in size and shape distribution. Thus, coamorphization offers a simple approach to not only combine multiple drugs but also enhance their pharmaceutics for oral delivery.

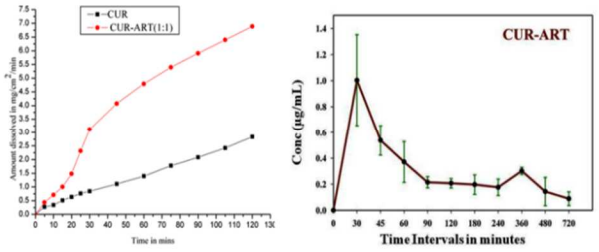

Figure 3 (a) Intrinsic dissolution rate curve of curcumin concentration in 60% EtOH-H_2O for pure CUR and CUR-ART. (b) Mean Plasma concentration of Curcumin vs. Time profile of CUR-ART coamorphous in SD rats. No curcumin concentration could be detected with pure CUR.

Table 1 Pharmacokinetic parameters of CUR-ART coamorphous.

Parameter	CUR-ART	
	Mean	SD
C_{max} (µg/mL)	1.003	0.350
T_{max} (min)	30	-
Half life (h)	6.4	2.2
AUC_{0-12} (µg. h /mL)	2.59	0.60
$AUC_{0-\infty}$ (µg. h /mL)	24.7	7.4

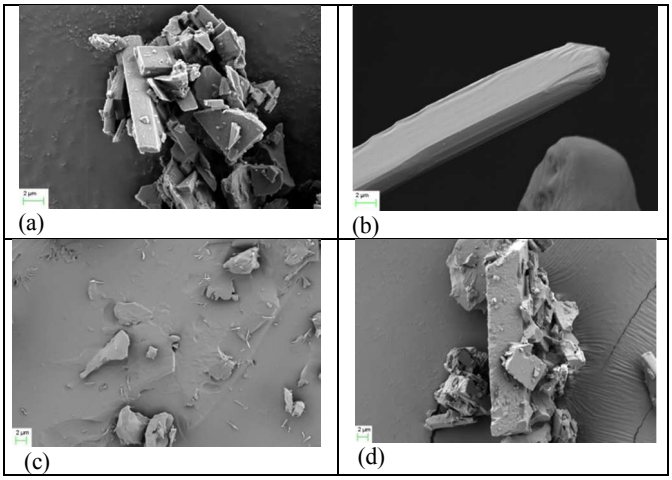

Figure 4 FESEM images at 2 µm resolution. (a) Curcumin shows 2 x 10 µm particle size, (b) ART is rod-like morphology of 2 x 25 µm, (c) CUR-ART coamorphous has much smaller grains of about 2-8 µm irregular shape and tiny rods of <1 µm width, and (d) particles of CUR + ART physical mixture resemble those of pure curcumin and artemisinin (large irregular morphology and long rods). The scale bar on the left hand corner is 2 µm.

Our result is significant in light of the fact that curcumin has low bioavailability due to short half life of 30-120 min in vivo system. The application of coamorphous systems is a promising strategy to enhance the physicochemical properties of drugs. Further, they add to the category of supramolecular solid state assemblies, apart from

eutectics, that can be formed when the attributes of geometric compatibility and/or strong heteromolecular interactions are not favorable for a given combination of materials. The methodology appears to be general enough to exploit the wonder molecule curcumin for solubility and pharmacokinetic profile enhancement with other herbal and synthetic bioactive molecules.

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Notes and References

‡ Curcumin and Artemisinin were taken in an equimolar stoichiometric ratio (368.38 mg CUR and ART 282.33 mg) and dissolved in 100 mL ethanol and rotavaporized at 50-55 °C in a Büchi rotavap. The coamorphous CUR-ART product was characterized by ^{1}H NMR to confirm the stoichiometry (Figure S3, ESI†). Proton NMR spectra were recorded on Bruker Avance 400 MHz spectrometer (Bruker-Biospin, Karlsruhe, Germany). Chemical shifts are quoted in δ scale and J coupling in Hz.

CUR. ^{1}H NMR (DMSO-d_6): 3.82 (6H, s), 6.04 (1H, s), 6.76 (2H, d, J 16), 6.82 (2H, d, J 8), 7.15 (2H, d, J 8), 7.31 (2H, s), 7.51 (2H, d, J 16), 9.66 (2H, s). OHs (CUR) exchange in solvent.

CUR-ART (1:1). ^{1}H NMR (DMSO-d_6): 0.91 (3H, d, J 6), 1.15 (5H, m), 1.34 (5H, m), 1.52 (1H, d, J 4.4), 1.63 (1H, d, J 12), 1.78 (2H, dd, J 5, 4), 1.90 (1H, d, J 3), 2.04 (1H, d, J 13), 2.28 (1H, t, J 12), 3.15(1H, t, J 12), 3.87 (6H, s), 6.04 (1H, s),6.10 (1H, s), 6.76 (2H, d, J 16), 6.82 (2H, d, J 8), 7.15 (2H, d, J 8), 7.31 (2H, s), 7.55 (2H, d, J 15), 9.64 (2H, s). OHs (CUR) exchange in solvent.

ART. ^{1}H NMR (DMSO-d_6): 0.91 (3H, d, J 6), 1.15 (5H, m), 1.34 (5H, m), 1.52 (1H, d, J 4.4), 1.63 (1H, d, J 12), 1.79 (2H, dd, J 4, 4) 1.91(1H, d, J 3), 2.05 (1H, d, J 13), 2.48 (1H, t, J 1.6), 3.14 (1H, t, J 13), 6.11(1H, s).

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TOC

Curcumin and Artemisinin natural compounds of anticancer and antimalarial activity are combined as coamorphous solid with faster dissolution rate and enhanced pharmacokinetics.