Coamorphous nanoparticles produced by co-precipitation of two drugs based on liquid-liquid phase separation: Improved solubility and membrane permeability

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PURPOSE

The coamorphous is an amorphous state in stoichiometric binary systems of two compatible compounds between drug and coformer. The formation of coamorphous contributes to enhancing the solubility and oral absorption of the target drugs. Dry milling and spray-drying methods are normally used to prepare coamorphous particles. The particle sizes prepared by those methods are often limited in the order of micrometers. It is reported that nanoparticles can penetrate deeply into the intestinal membrane and enhance the drug permeability. In this study, the coamorphous nanoparticles were investigated by co-precipitation of two drugs based on liquid-liquid phase separation (LLPS). The effect of coamorphous nanoparticles formation on solubility and membrane permeability was investigated.

OBJECTIVE(S)

・A preparation of coamorphous nanoparticles produced by co-precipitation of two drugs.

・A calculation of LLPS concentration of two drugs.

・Elucidation of the mechanisms of nanoparticulation and amorphization.

・Improvement of solubility and permeability of poorly-water soluble drugs.

METHOD(S)

Atorvastatin calcium hydrate (ACT) and nifedipine (NFD) were used as model drugs. They are used as combination therapy for lifestyle disease treatment. ACT and NFD were dissolved in methanol as a molar ratio of 2:1, 1:1, and 1:2. The methanolic drugs solution (50 mg/mL as ACT content) was added into 0.1% or 0.5% PVA aqueous solution using peristaltic pump at a flow rate of 10 mL/min. Then, the formed dispersion was immediately centrifuged for 10 min at 4 ºC and 50,000 rpm using a high speed refrigerated centrifuge. The obtained residue was redispersed in distilled water with sonication. The final dispersion was subjected to freeze drying for 24 h. The crystallinity of freeze-dried powder was evaluated by powder X-ray diffraction measurement. The particle size of the freeze-dried samples was determined after dispersion in distilled water by dynamic light scattering method with Litesizer 500. Phase behavior of supersaturated solutions of drugs were evaluated using μDISS system (Pion Inc.). The solubility and permeability of drugs was evaluated by μFlux system (Pion Inc.). Test concentration of μFlux system was set to 50 μg/mL as NFD concentration.

RESULT(S)

Table 1 Particle sizes of prepared particles before and after freeze drying. Each point represents the mean ± SD (n =3).

	Particle sizes before freeze drying (μm)			Particle sizes after freeze drying (μm)		
	D_{10}	D_{50}	D_{90}	D_{10}	D_{50}	D_{90}
NFD alone PVA0.5%	1533.5 ± 167.7	1998.6 ± 205.4	2618.1 ± 271.4	-	-	-
ATC alone PVA0.5%	993.9 ± 26.0	1313.2 ± 59.1	1900.5 ± 196.2	-	-	-
NFD:ATC (2:1) PVA0.1%	182.1 ± 9.0	310.8 ± 2.5	786.1 ± 319.3	493.0 ± 134.6	942.7 ± 27.2	1572.9 ± 248.4
NFD:ATC (2:1) PVA0.5%	207.2 ± 16.9	392.0 ± 25.2	962.2 ± 282.3	622.8 ± 340.8	951.0 ± 387.6	2201.7 ± 1100.9
NFD:ATC (1:1) PVA0.1%	188.4 ± 14.2	292.2 ± 26.6	461.2 ± 52.7	615.2 ± 13.4	919.3 ± 65.8	1513.6 ± 294.5
NFD:ATC (1:1) PVA0.5%	204.9 ± 3.4	313.7 ± 5.3	519.1 ± 39.2	418.6 ± 33.1	499.0 ± 49.6	600.9 ± 75.4
NFD:ATC (1:2) PVA0.1%	171.5 ± 5.8	263.3 ± 5.3	419.1 ± 33.0	188.2 ± 4.9	284.4 ± 10.2	445.0 ± 40.5
NFD:ATC (1:2) PVA0.5%	185.1 ± 12.7	277.4 ± 28.7	425.8 ± 68.3	192.0 ± 13.9	281.9 ± 6.6	414.1 ± 40.7

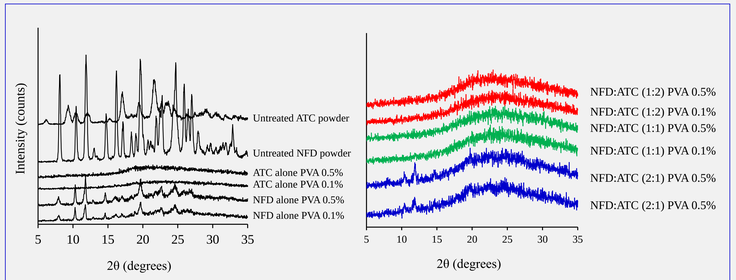


Figure 1 Powder X-ray diffraction patterns of untreated and freeze dried-powders.

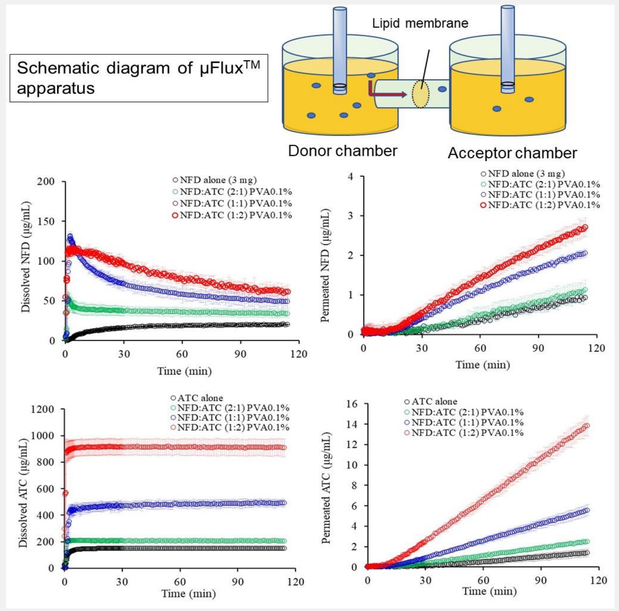


Figure 2 Schematic presentation of one donor- acceptor pair of the μFlux™ apparatus separated by a membrane with UV-vis probes and dissolution and permeation profile of NFD and ATC.

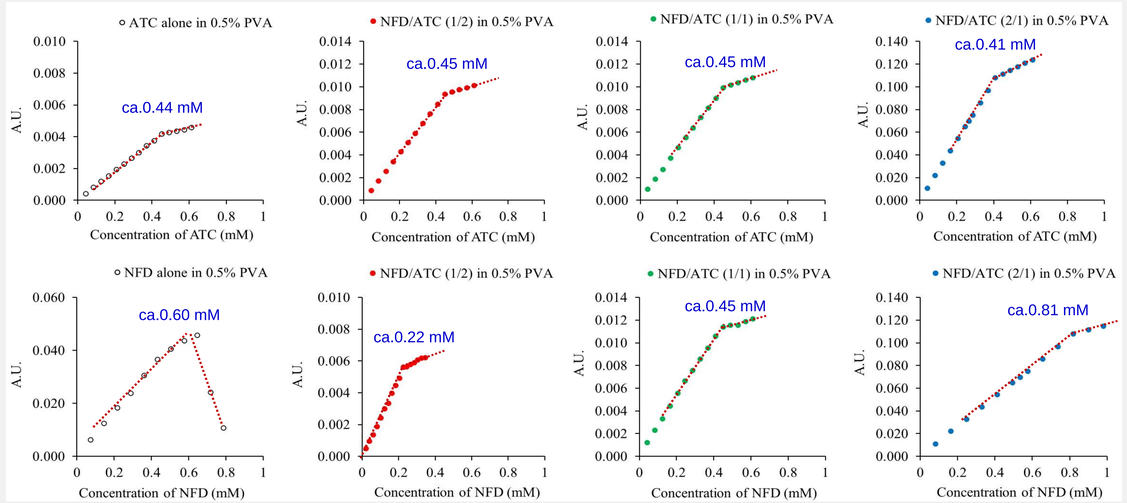
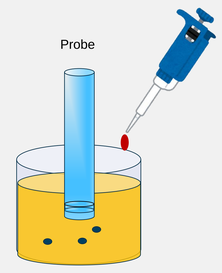


Figure 3 . Phase behavior of supersaturated solutions of NFD and ATC in PVA 0.5% solution at 37 ºC using a μDISS system.



μDISS system

CONCLUSION(S)

Table 1 and Figure 4 (Particle sizes)

Particle size decreased with increasing ratio of ATC and its particle size was maintained after freeze drying. Aggregation of spherical fine particles (several hundreds nm) was observed in SEM images.

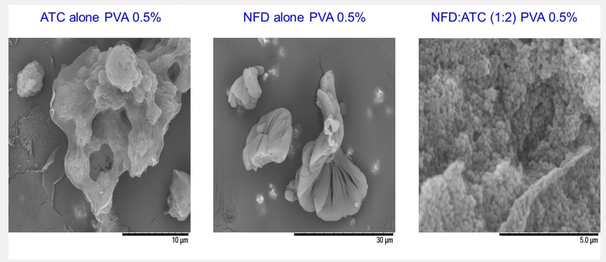


Figure 4 SEM images of freeze-dried powders of ATC alone, NFD alone and NFD:ATC (1:2).

Figure 1 (Powder X-ray diffraction patterns)

The freeze-dried powders of NFD:ATC (1:1), NFD:ATC (1:2) and ATC alone showed the amorphous state. In the FDPs of NFD alone and NFD:ATC (2:1), the crystal peaks originating from NFD were observed.

Figure 2 (Dissolution and permeation)

Almost all of the added ATC dissolved in the donor chamber. The freeze-dried powders of NFD :ATC (1:1) and NFD :ATC (1:2) showed the improved dissolution and permeability of NFD. The formation of supersaturation and nanoparticle was considered to be responsible for the improved membrane permeability.

Figure 3 (Phase behavior of supersaturated solutions)

Phase behavior of ATC did not change significantly in any of the formulations. NFD precipitated at lower concentrations with increasing ATC ratio. It was also observed that NFD precipitation occurred almost simultaneously with ATC precipitation.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

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