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Technical note

Glass-forming ability of compounds in marketed amorphous drug products

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ABSTRACT

This note is about the glass-forming ability (GFA) of drugs marketed as amorphous solid dispersions or as pure amorphous compounds. A thermoanalytical method was complemented with an in *silico* study, which made use of molecular properties that were identified earlier as being relevant for GFA. Thus, molar volume together with effective numbers of torsional bonds and hydrogen bonding were used to map drugs that are as amorphous products on the market either as solid dispersion of without co-processed carrier as amorphous drug in a solid dosage form. Differential scanning calorimetry experiments showed that most compounds were stable glass formers (GFs) (class III) followed by so-called unstable GFs (class II) and finally, only vemurafenib was found in class I with increased crystallization propensity. The *in silico* results, however showed that all drugs were either clearly in the chemical space expected for GFs or they were borderline to the region that holds for high crystallization tendency. Interestingly, the pure amorphous compounds scattered in a very confined region of the molecular predictors. These findings can guide amorphous product development of future drug candidates. Based on the compound location in the given chemical space, amorphous formulation opportunities can be balanced against the risks of physical instability upon storage.

1. Introduction

The glass-forming ability (GFA) of molecules has fascinated researchers since several decades. For undercooled melts, it was important to understand the concept of critical cooling rates that determine whether or not nucleation and growth can lead to crystallization [1]. A practical approach was to employ differential scanning calorimetry (DSC) for drug categorization from undercooled melts to tell stable glass formers (GFs) apart from non-glass formers (nGFs) [2]. The latter class I compounds crystallize directly in the first cooling cycle, whereas the stable GFs (class III) remain amorphous upon cooling and display a glass transition in a subsequent heating cycle. Some compounds alternatively crystallize in the second heat and were assigned to a category II. This group of unstable GFs is rather heterogeneous when considering rates of nucleation and growth, which has been discussed by Trasi et al. [3]. Another related interest has been to better understand which molecular properties affect GFA. Therefore, it has been tried to predict the categories based on molecular properties that were either selected from an empirical training model [4] or based on theoretical considerations of the Prigogine-Defay ratio [5]. The prediction of GFA has the obvious advantage that *in silico* calculations can replace DSC experiments where not sufficient compound is available at an early development stage. An *in silico* assessment is also helpful in cases where for example thermal instability prevents thermoanalytical categorization. While already several compounds have been assigned to GFA categories, there seems to be no systematic consideration of drugs that were successfully formulated for the pharmaceutical market (Table 1). The present study addresses this research gap and DSC analysis is presented combined with *in silico* categorization of compounds that are amorphous in marketed products.

2. Materials and methods

2.1. Materials

A series of drugs was selected that are as amorphous products on the market (Table 1). Drug compounds of high purity (⩾96%)

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Table 1
Marketed amorphous drug products.

Compound	Trade name	Manufacturer	Carrier	Processing technology	Dosage form
Amorphous solid dispersions (ASDs)					
Etravirine	Intelence®	Janssen	HPMC	Spray drying	Tablet
Everolimus	Certican®/Zortress®	Novartis	HPMC	Spray drying	Tablet
Fenofibrate	Fenoglide®	LifeCycle Pharma	PEG	Spray melt	Tablet
Griseofulvin	Gris-PEG®	Novartis/Pedinol	PEG	Melt extrusion	Tablet
Itraconazole	Sporanox®/	Janssen/	HPMC/	Spray layering (bead coating)/	Tablet/
	Onmel®	GlaxoSmithKline/Stiefel	PVP VA 64	Melt extrusion	Tablet
Ivacaftor	Kalydeco®	Vertex	HPMCAS	Spray drying	Tablet
Lopinavir and Ritonavir	Kaletra®	AbbVie	PVP VA 64	Melt extrusion	Tablet
Nabilone	Cesamet®	Lilly/Valeant	PVP	Melt extrusion	Capsule
Nifedipine	Afeditab® CR	Elan/Watson	Poloxamer or PVP	Melt/absorb on carrier	Tablet
Nilvadipine	Nivadil®	Fujisawa	HPMC	n.a.[a]	Tablet
Nimodipine	Nimotop®	Bayer	PEG	Spray drying/fluid bed	Tablet
Posaconazole	Noxafil®	Merck	HPMCAS	Melt extrusion	Tablet
Ritonavir	Norvir®	AbbVie	PVP VA 64	Melt extrusion	Tablet
Tacrolimus	Prograf®/	Astellas/Fujisawa/	HPMC/	Spray drying/fluid bed/	Capsule/
	LCP-Tacro®	LifeCycle Pharma/Veloxis	HPMC	Melt granulation	Tablet
Telaprevir	Incivek®/Incivo®	Vertex/Janssen	HPMCAS	Spray drying	Tablet
Troglitazone	Rezulin®[b]	Pfizer (Parke-Davis)	PVP	Melt extrusion	Tablet
Vemurafenib	Zelboraf®	Roche	HPMCAS	Coprecipitation	Tablet
Verapamil hydrochloride	Isoptin® SR-E 240	AbbVie	HPC/HPMC	Melt extrusion	Tablet
Pure amorphous drugs					
Cefuroxime axetil	Ceftin®	GlaxoSmithKline	–	–	Tablet
Nelfinavir mesylate	Viracept®	Agouron/Pfizer/Roche/ViiV Healthcare	–	–	Tablet
Quinapril hydrochloride	Accupril®	Pfizer	–	–	Tablet
Rosuvastatin calcium	Crestor®	Shionogi/Astra Zeneca	–	–	Tablet
Zafirlukast	Accolate®	Astra Zeneca	–	–	Tablet

[a] Not available.
[b] Recalled in 2000 due to toxicity issues.

were purchased from different commercial sources and were used as received without further purification. The identity and crystallinity of the drugs were verified by DSC and thermogravimetric analysis (TGA). Drug characteristics, suppliers, and purities are listed in Table 2.

2.2. Differential scanning calorimetry

DSC thermograms were recorded with a DSC 1 instrument from Mettler-Toledo AG (Greifensee, Switzerland) as described in [5]. Briefly, samples (2–3 mg) were placed in 40 µl aluminum pans

Table 2
Physico-chemical properties of compounds evaluated.

Compound	Class	MW (g mol^{-1})	T_m (°C)[a]		ΔH_f (kJ mol^{-1})		T_g (°C)[a]		Supplier	Purity
Amorphous solid dispersions (ASDs)										
Etravirine	Decomp.	435.3	254.2	±0.4	n.a.	n.a.	n.a.	n.a.	Synthonix	96%
Everolimus	Amorphous	958.2	n.a.	n.a.	n.a.	n.a.	50.3	±0.1	AK Scientific	98%
Fenofibrate[b]	II	360.8	81.2	±0.0	33.7	±0.2	−18.7	±0.6	Sigma-Aldrich	⩾99%
Griseofulvin	III	352.8	218.5	±0.1	40.5	±0.2	90.0	±0.2	Sigma-Aldrich	⩾97%
Itraconazole[b]	III	705.6	168.3	±0.3	61.1	±0.5	59.2	±0.1	Melrob-Eurolabs	⩾98.5%
Ivacaftor	Decomp.	392.5	309.0	±0.7	n.a.	n.a.	n.a.	n.a.	AK Scientific	99%
Lopinavir[c]	III	628.8	∼96	n.a.	n.a.	n.a.	77.6	±0.1	Acros	98%
Nifedipine[b]	II	346.3	172.8	±0.1	37.8	±0.1	46.8	±0.2	Sigma-Aldrich	⩾98%
Nilvadipine	III	385.4	149.0	±0.1	32.6	±0.3	45.5	±0.1	Toronto Research Chemicals	98%
Nimodipine	III	418.4	124.6	±0.1	37.9	±0.2	14.1	±0.2	Sigma-Aldrich	⩾98%
Posaconazole	III	700.8	167.0	±0.1	44.5	±0.7	60.4	±0.1	AK Scientific	98%
Ritonavir	III	721.0	122.2	±0.1	63.8	±0.4	48.7	±0.1	Sigma-Aldrich	⩾98%
Tacrolimus	III	804.0	123.3	±0.2	30.1	±0.5	76.1	±0.5	AK Scientific	98%
Telaprevir	III	679.9	241.8	±0.4	60.9	±1.0	101.0	±0.3	AK Scientific	98%
Troglitazone[d]	II	441.5	111.3/154.4	±1.9/±1.9	17.5/25.5	±1.2/±2.8	63.1	±0.1	Focus Biomolecules	>98%
Vemurafenib	I	489.9	272.4	±0.1	65.1	±0.1	n.a.	n.a.	Roche	99.8%
Verapamil hydrochloride	III	491.1	143.1	±0.2	54.5	±0.1	55.7	±0.4	Sigma-Aldrich	⩾99%
Pure amorphous drugs										
Cefuroxime axetil[d]	Amorphous	510.5	n.a.	n.a.	n.a.	n.a.	77.4	±0.5	Sigma-Aldrich	⩾98%
Nelfinavir mesylate	Amorphous	663.9	n.a.	n.a.	n.a.	n.a.	114.9	±0.3	Sigma-Aldrich	⩾98%
Quinapril hydrochloride[e]	III	475.0	∼97	n.a.	n.a.	n.a.	90.8	±0.1	Alfa Aesar	98%
Rosuvastatin calcium[f]	Amorphous	500.6	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	Acros	98%
Zafirlukast	III	575.7	194.8	±0.1	19.6	±1.7	103.3	±0.3	Focus Biomolecules	>98%

[a] Melting points were determined as onset values and glass transition temperatures as midpoint values. Results expressed as mean (n = 3 for each compound).
[b] Data taken from [5].
[c] Hydrated crystal form (H_2O:drug molar ratio ∼1.4).
[d] Mixture of isomers.
[e] Hydrated crystal form (H_2O:drug molar ratio ∼0.8).
[f] Hemicalcium salt.