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Technical note

Glass-forming ability of compounds in marketed amorphous drug products

Nicole Wyttenbach [a], Martin Kuentz [b,*]

[a] Roche Pharmaceutical Research & Early Development, Pre-Clinical CMC, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, Basel, Switzerland
[b] Institute of Pharma Technology, University of Applied Sciences and Arts Northwestern Switzerland, 4132 Muttenz, Switzerland

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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%)

* Corresponding author at: University of Applied Sciences and Arts Northwestern Switzerland, Institute of Pharma Technology, Gründenstrasse 40, 4132 Muttenz, Switzerland.
E-mail address: martin.kuentz@fhnw.ch (M. Kuentz).

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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.

with pierced aluminum lids (Mettler-Toledo AG, Greifensee, Switzerland). The melting onset temperatures (T_m) and the enthalpy of fusion (ΔH_f) were determined by heating the samples at 10 °C/min from 25 °C to a maximum temperature of 300 °C. For drug classification and to determine midpoint glass transition temperatures (T_g), the samples were heated from 25 °C to 5 °C above the melting temperature, and held isothermally for 5 min to ensure complete melting. The samples were then cooled to −50 °C and held for 15 min. Finally, samples were heated again to 20 °C above the melting temperature. A constant heating and cooling rate of 10 °C/min was used. All DSC measurements were carried out in triplicate.

Based on the crystallization behavior of the samples during the above-described heat-cool-heat treatment, drug compounds were classified into three categories [2]: class I compounds (nGFs) crystallized during the cooling segment, class II compounds crystallized during the second heating segment, and class III compounds (GF) did not crystallize at all during the heating-cooling-heating process.

2.3. Thermogravimetric analysis (TGA)

Thermogravimetric analyses were performed with a TGA/DSC 1 STARe system from Mettler-Toledo AG (Greifensee, Switzerland). Samples (2–5 mg) were heated at 10 °C/min in 40 µl aluminum pans with pierced aluminum lids (Mettler-Toledo AG, Greifensee, Switzerland) to a maximum temperature of 300 °C. TGA was used to confirm that drugs did not degrade during the DSC heat-cool-heat treatment and to evaluate if the purchased compounds showed any traces of hydrates or solvates. Water content of crystalline samples was confirmed by Karl Fischer analysis (Solvias AG, Kaiseraugst, Switzerland)

2.4. Molecular modeling and statistical analysis

The software package Molecular Modeling Pro®, V.6.2.6 (Norgwyn Montgomery Software Inc., North Wales, USA) was used for calculation of molar volume, the effective number of torsional bonds, τ [6], and the effective hydrogen bond number, HBN_{eff} [7]. Further data evaluation and graphical representation was based on the program Statgraphics Centurion XVI ed. Professional (V. 16.1.15) from Statpoint Technologies Inc. (Warrenton, USA).

3. Results and discussion

3.1. Experimental categorization

Table 1 lists the different amorphous drug products on the market together with their trade names and manufacturing technologies. The majority of these products are solid dispersions for which a carrier polymer was processed either in a melt or with using solvents. The latter process of solvent evaporation is mostly based on spray drying but for example vemurafenib is manufactured alternatively using the microprecipitated bulk powder (MBP) technique. Apart from these solid dispersions, some active pharmaceutical ingredients (APIs) are as amorphous substance formulated in a conventional solid dosage form so they appear to have a special kinetic preference for the amorphous state thereby

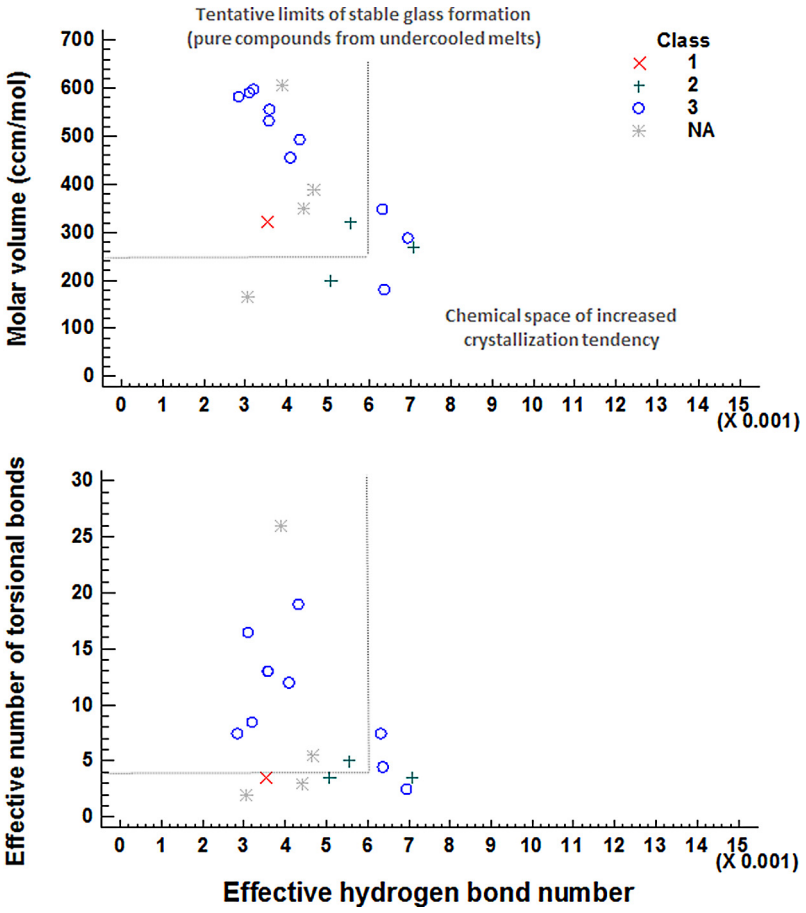

Fig. 1. Mapping of the different marketed drugs in oral solid dispersions according to relevant molecular properties. Arbitrary limits are given (dotted lines) to separate the chemical space of stable glass formation from that of relatively higher drug crystallization propensity [5]. Details are given in the text.

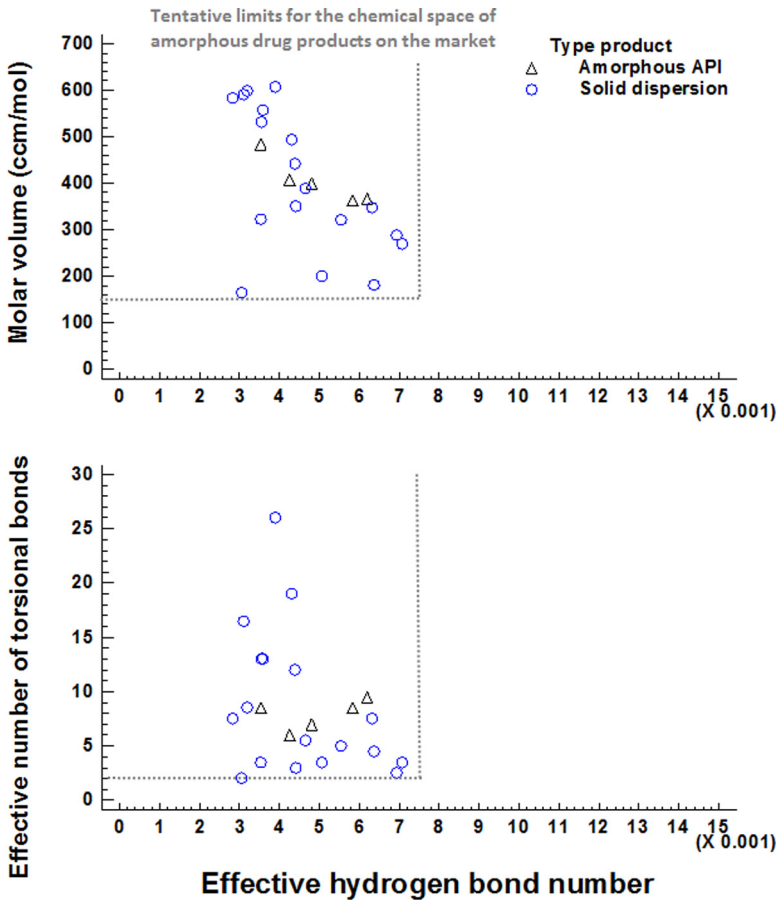

Fig. 2. Mapping of drugs that are on the market either as solid dispersion or as amorphous drug substance formulated in a solid dosage form. New tentative limits are proposed (dotted lines) to confine the chemical space of these marketed active pharmaceutical ingredients. Details are given in the text.

enabling sufficient physical stability without a carrier in solid dispersion. Products of these pure amorphous drugs were often developed in an opportunistic way in the case that already chemists encountered difficulties to produce crystalline material. A nearby hypothesis is that such compounds are likely to fall in category III of GFs but this has so far not been experimentally demonstrated. It is also theoretically unclear if relevant molecular predictors of such drugs differ from those being formulated as solid dispersions.

It is important to note that GFA categories, even though obtained from undercooled melts [2], appear to hold more broadly for different process techniques. Thus, GFA categories from undercooled melts were compared earlier to those of a solvent-shift method and a good correlation was evidenced [8]. This finding is important for the current work and Table 2 displays the obtained categories that were assigned to the different compounds based on DSC results. Experimental classes were not available for etravirine and ivacaftor because of thermal decomposition and we did not measure nabilone due to its restriction as cannabinoid.

For many compounds it is possible to determine a ratio of T_g and T_m which has often been used as GFA indicator in material sciences and was more recently applied for pharmaceuticals by for example Friesen et al. [9]. The latter work used T_m/T_g to plot against log$P$ values of drugs that were formulated as HPMCAS solid dispersions. A recommendation was that high drug loading should be avoided with log$P > 6$ because of dissolutions risks, while high values of $T_m/T_g > 1.4$ were pointing to optional instability, which is likely using a viable drug load. A disadvantage of using T_g as predictor for GFA (or any stability considerations) is that not all compounds exhibit a measurable glass transition. Primarily the fast crystallizing compounds (class I) are critical in that respect so that *in silico* predictors of GFA provide an attractive alternative approach.

3.2. In silico consideration of drug categories

A previous study of undercooled melts identified V_m, τ, and HBN_{eff} as critical properties for GFA of pure drugs [5]. These parameters resulted in a statistical differentiation of stable GFs from other crystallizing nGFs and empirical rules of thumb were proposed for a chemical space of likely glass formation. The tentative limits $V_m > 250$ cm^3/mol, $\tau > 4$, and $HBN_{eff} < 6 * 10^{-3}$ were arbitrarily set using the original dataset to provide "rules of thumb" for pure compounds. This was interesting to compare with the present compounds from amorphous drug products and Fig. 1 displays results in case of the solid dispersions. These drugs were all formulated with co-processed excipients and it was of interest to see whether such obviously stable products would display all categories of drugs. As a result, most compounds were indeed found in the chemical space that was expected for stable glass formation. Some drugs were also identified in a borderline range close to the tentative limits of V_m, τ, and HBN_{eff}. Interestingly, no compounds were rather small and rigid, while displaying high values of HBN_{eff}. The latter chemical space was identified as typical for class I drugs being highly susceptible to crystallization [5]. The only experimentally confirmed class I drug was vemurafenib but it was borderline within the targeted chemical space of GFs using the *in silico* assessment. There were for example no drugs at all with $HBN_{eff} > 7.5 * 10^{-3}$, whereas previously several class I compounds

were found in this chemical space [5]. The fact that no marketed amorphous drug was within this chemical space of fast crystallizers is of high practical importance. New drug candidates of that type would come with a substantial risk of physical instability when amorphous formulation techniques are selected. A formulation rescue option might be here to target a very strong molecular association with excipients or a co-amorphous drug so that the original characteristics of pure compound are substantially altered in a molecular complex. Safer from a development perspective is, however, to try other formulation options than solid dispersions for such class I drugs.

Fig. 2 compares the different types of amorphous products on the market in terms of V_m, τ, and HBN_{eff}. The groups could not be statistically differentiated by means of a discrimination analysis but the pure amorphous drugs appeared to occupy a quite confined chemical space. Thinking of the GFs limits (from undercooled melts) of $V_m > 250\ cm^3/mol$, $\tau > 4$, and $HBN_{eff} < 6 * 10^{-3}$ [5], it seems that slightly modified rules of thumb are needed considering the chemical space of amorphous drug products on the market. These drugs are not exclusively characterized by their GFA but also by their proven interaction with excipients that help to stabilize the amorphous state. With the aim to exclude potential critical drug candidates, we propose the following tentative limits for amorphous formulations: $V_m > 150\ cm^3/mol$, $\tau \geqslant 2$, and $HBN_{eff} < 7.5 * 10^{-3}$. Such arbitrary limits should be revisited once more amorphous drugs are on the market. The value of such proposals is of practical nature to initiate a structured development of an amorphous drug product [10]. Given the current findings, the approach of pure amorphous drugs might not have been sufficiently exploited in the past. If new drug candidates fall into the chemical space of pure amorphous drug, it is hence worth to study physical stability of pure amorphous compound as reference for other solid dispersions formulations. Future work may clarify additional factors such as for example water-uptake and lowering of the glass transition temperature. Drug development projects of amorphous products can profit from the obtained molecular insights and avoidance of class I drug properties might lead to a more focused and thus more cost effective formulation development.

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