International Journal of Pharmaceutics 495 (2015) 312–317

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Physical stability of drugs after storage above and below the glass transition temperature: Relationship to glass-forming ability

Amjad Alhalaweh[a,*], Ahmad Alzghoul[b], Denny Mahlin[a], Christel A.S. Bergström[a]

[a] Department of Pharmacy, Uppsala University, Uppsala Biomedical Centre, P.O. Box 580, SE-751 23 Uppsala, Sweden
[b] Department of Information Technology, Uppsala University, Lägerhyddsv. 2, hus 1, Box 337, SE- 751 05 Uppsala, Sweden

ARTICLE INFO

Article history:
Received 3 July 2015
Received in revised form 28 August 2015
Accepted 29 August 2015
Available online 1 September 2015

Keywords:
Amorphous
Physical stability
Glass-forming ability
SVM
Computational prediction

ABSTRACT

Amorphous materials are inherently unstable and tend to crystallize upon storage. In this study, we investigated the extent to which the physical stability and inherent crystallization tendency of drugs are related to their glass-forming ability (GFA), the glass transition temperature (T_g) and thermodynamic factors. Differential scanning calorimetry was used to produce the amorphous state of 52 drugs [18 compounds crystallized upon heating (Class II) and 34 remained in the amorphous state (Class III)] and to perform in situ storage for the amorphous material for 12 h at temperatures 20 °C above or below the T_g. A computational model based on the support vector machine (SVM) algorithm was developed to predict the structure-property relationships. All drugs maintained their Class when stored at 20 °C below the T_g. Fourteen of the Class II compounds crystallized when stored above the T_g whereas all except one of the Class III compounds remained amorphous. These results were only related to the glass-forming ability and no relationship to e.g. thermodynamic factors was found. The experimental data were used for computational modeling and a classification model was developed that correctly predicted the physical stability above the T_g. The use of a large dataset revealed that molecular features related to aromaticity and π–π interactions reduce the inherent physical stability of amorphous drugs.

1. Introduction

Drugs that are in an amorphous state have significantly different properties from those of their crystalline counterparts. When poorly soluble drugs are in an amorphous state, they have a higher dissolution rate and are more soluble (Hancock et al., 2002; Hancock and Parks, 2000; Marsac et al., 2006a). There has been increasing interest in incorporating poorly soluble drugs in medicinal products in their amorphous form, in order to improve their absorption, and hence their bioavailability. However, amorphous materials are not stable and their tendency to crystallize is a challenge when formulations of the amorphous form of the drug are being developed (Hancock et al., 1995; Yoshioka et al., 1994; Yu, 2001). Research efforts have been directed towards improved understanding of the driving force for crystallization in these materials and the conditions that might prolong their physical stability (Andronis and Zografi, 1998; Hancock et al., 1995, 1998; Kauzmann, 1948; Yoshioka et al., 1994). It has been estimated that the amorphous state can be kinetically stable if it is stored at a temperature well below the glass transition temperature (T_g) (Andronis and Zografi, 1998; Hancock et al., 1995; Kauzmann, 1948). The T_g is an intrinsic property of amorphous materials and is therefore often used to indicate their physical stability (Angell, 1988). The physical properties of the materials above and below the T_g are different and reflect the physical stability of the material (Andronis and Zografi, 1998; Graeser et al., 2009; Hancock et al., 1995; Yoshioka et al., 1994). The material is considered to exist in a glassy (solid) state below the T_g and as a supercooled liquid above the T_g. Currently, the mechanistic understanding of the driving force for crystallization above and below the T_g is sparse and studies of the chemical modifications or formulation strategies that might result in improved performance of amorphous solid dosage forms are warranted.

The stability of amorphous materials upon storage above and below the T_g has been investigated in several studies, but in each of these only a limited number of compounds has been included (Andronis and Zografi, 1998; Graeser et al., 2009; Hancock et al., 1995; Yoshioka et al., 1994). These studies linked the crystallization process to molecular mobility, which increases at higher

* Corresponding author. Fax: +46 18 471 4223.
E-mail address: amjad.alhalaweh@farmaci.uu.se (A. Alhalaweh).

http://dx.doi.org/10.1016/j.ijpharm.2015.08.101
0378-5173/

temperatures and hence is higher above the T_g. Thus, materials have a higher tendency to crystallize above than below the T_g. Other studies have found that molecular mobility is not predictive enough to be used as the only determinant for stability in the amorphous state and that other factors such as the configurational entropy(Zhou et al., 2002) and enthalpy (Marsac et al., 2006b) have significant impact on the stability (Graeser et al., 2009; Hancock et al., 1998).

In the area of material science, the stability of the amorphous state has been defined as the resistance of glasses to devitrification upon reheating (especially near or somewhat above the T_g) (Weinberg, 1994). The relationship between glass stability (GS) and glass-forming ability (GFA) has been explored, but only modest relationships have been reported (Baird et al., 2010; Mahlin and Bergström, 2013; Mahlin et al., 2011; Nascimento et al., 2005). However, a classification system based on the GFA of drug compounds has recently been presented and this system has been related to the GS of the compounds (Baird et al., 2010; Mahlin and Bergström, 2013; Mahlin et al., 2011). In these studies, the crystallization tendency scheme designed by Taylor and coworkers was used (Baird et al., 2010). They divided compounds into three classes, depending on how easily the compounds crystallized during a heat-cool-heat cycle. Class I compounds are defined as those that crystallize upon cooling the melt, whereas Class II and Class III compounds form an amorphous material upon cooling the melt. Class II and III compounds are differentiated in that Class II

Table 1
Compounds used in the study with their molecular weight (MW), melting temperature (T_m), heat of fusion (ΔH), glass transition temperature (T_g), temperature for the stability test above T_g ($T_{above} = T_g + 20$), change in free energy (ΔG) between the supercooled liquid and the crystalline state at T, and result of the stability test (no = crystalline and yes = amorphous). Pi_AQc = sum of absolute values of Hückel pi atomic charges on C atoms; F_AromB = number of aromatic bonds as a fraction of total bonds; TR = training set; TS = test set.

Compound	Class	MW (g/mole)	T_m (K)	ΔH kJ/mole	T_g (K)	T_{above} (K)	T_g/T_{above}	ΔG (kJ/mol)	Stable above T_g[a]	Pi_AQc	F_AromB	TR/TS
Acetaminophen	II	151.2	443	29	299	319	0.94	5.9	No	0.48	0.55	TR
Celecoxib	II	318.4	436	32	331	351	0.94	5.1	No	0.45	0.61	TR
Danazol	II	337.5	500	36	352	372	0.95	6.8	No	0.15	0.17	TR
Estradiol	II	22.4	451	2	358	378	0.95	0.3	No	0.22	0.26	TR
Nifedipine	II	346.3	446	39	320	340	0.94	7.0	No	1.00	0.23	TR
Orlistat	II	495.8	316	56	228	248	0.92	9.4	No	0.72	0	TR
Pimozide	II	461.6	492	50	335	355	0.94	10.1	No	0.53	0.58	TR
Tamoxifen	II	371.5	371	56	263	283	0.93	10.2	Yes	0.24	0.60	TR
Tenofovir	II	28.2	552	3	416	436	0.95	1.2	No	0.29	0.50	TR
Testosterone	II	288.4	426	26	315	335	0.94	4.4	No	0.40	0	TR
Tinidazole	II	247.3	289	36	266	286	0.93	0.4	No	0.20	0.31	TR
Tolazamide	II	311.4	445	41	297	317	0.94	8.3	Yes	0.40	0.27	TR
Aripiprazole	II	448.4	517	48	363	383	0.95	9.2	No	0.94	0.36	TS
Bicalutamide	II	430.4	465	51	323	343	0.94	9.9	No	0.82	0.40	TS
Cinnarizine	II	368.5	394	43	280	300	0.93	7.7	Yes	0.03	0.58	TS
Clemastine	II	343.9	451	48	308	328	0.94	9.6	No	0.09	0.46	TS
Fluorescamine	II	278.3	426	28	299	319	0.94	5.7	Yes	0.83	0.50	TS
Flurbiprofen	II	244.3	388	28	270	290	0.93	5.4	No	0.38	0.63	TS
Acemetacin	III	415.8	421	48	310	330	0.94	8.1	Yes	1.34	0.52	TR
Budesonide	III	430.5	530	39	368	388	0.95	7.6	Yes	0.73	0	TR
Captopril	III	217.3	380	29	277	297	0.93	4.9	Yes	0.46	0	TR
Carvedilol	III	406.5	390	53	315	335	0.94	6.4	Yes	0.83	0.64	TR
Chloramphenicol	III	323.1	425	4	304	324	0.94	0.7	Yes	0.39	0.30	TR
Chlorhexidine	III	505.5	408	43	336	356	0.94	4.7	Yes	0.86	0.34	TR
Clotrimazole	III	344.9	418	35	303	323	0.94	6.1	Yes	0.29	0.82	TR
Emtricitabine	III	247.2	426	27	344	364	0.95	3.4	No	0.41	0.35	TR
Ezetimibe	III	409.4	437	40	338	358	0.94	6.0	Yes	0.74	0.55	TR
Felodipine	III	384.3	420	34	318	338	0.94	5.3	Yes	0.93	0.23	TR
Hydrocortisone	III	362.5	497	45	359	379	0.95	8.1	Yes	0.69	0	TR
Ibuprofen[b]	III	206.3	350	27	228	248	0.92	5.5	Yes	0.30	0.40	TR
Indomethacin	III	356.7	434	42	318	338	0.94	7.2	Yes	1.10	0.59	TR
Itraconazole	III	705.7	441	65	331	351	0.94	10.6	Yes	1.02	0.51	TR
Ketoprofen	III	254.3	368	31	270	290	0.93	5.2	Yes	0.72	0.60	TR
Linaprazan	III	366.5	519	55	373	393	0.95	10.1	Yes	0.73	0.55	TR
Metolazone	III	365.8	539	36	382	402	0.95	6.8	Yes	0.87	0.46	TR
Nizatidine	III	331.5	406	45	286	306	0.93	8.4	Yes	0.50	0.24	TR
Physostigmine	III	275.4	377	32	293	313	0.94	4.5	Yes	0.47	0.27	TR
Simvastatin	III	418.8	412	29	309	329	0.94	4.6	Yes	0.51	0	TR
Spironolactone	III	416.6	486	24	364	384	0.95	4.0	Yes	0.90	0	TR
Sulindac	III	356.4	460	32	348	368	0.95	5.2	Yes	0.74	0.44	TR
Zolmitriptan	III	287.4	410	34	322	342	0.94	4.7	Yes	0.56	0.43	TR
Bucindolol	III	363.5	459	38	356	376	0.95	5.6	Yes	0.79	0.55	TS
Fenofibrate[b]	III	360.8	354	35	256	276	0.93	6.1	Yes	0.91	0.46	TS
Glafenine	III	372.8	437	43	337	357	0.94	6.4	Yes	0.90	0.61	TS
Glibenclamide	III	494	445	51	333	353	0.94	8.3	Yes	0.81	0.34	TS
Hydrochlorothiazide	III	297.7	536	34	391	411	0.95	6.1	Yes	0.61	0.33	TS
Hydroflumethiazide	III	297.9	542	39	373	393	0.95	7.9	Yes	0.48	0.29	TS
Isradipine	III	371.4	432	34	316	336	0.94	5.8	Yes	0.86	0.34	TS
Ketoconazole	III	531.4	423	54	318	338	0.94	8.7	Yes	0.90	0.43	TS
Nandrolone	III	274.4	397	21	310	330	0.94	2.9	Yes	0.41	0	TS
Nimesulide[b]	III	308.3	423	36	296	316	0.94	6.7	Yes	0.43	0.55	TS
Warfarin	III	308.3	435	45	345	365	0.95	6.0	Yes	1.03	0.68	TS

[a] No = not amorphous after the stability study; yes = amorphous after the stability study.
[b] Behaved like a Class II drug after the stability study.