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Stabilization of amorphous paracetamol based systems using traditional and novel strategies

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ABSTRACT

There is a special interest in having pharmaceutical active ingredients in the amorphous state due to their increased solubility and therefore, higher bioavailability. Nevertheless, not all of them present stable amorphous phases. In particular, paracetamol is an active ingredient widely known for its instability when prepared in the amorphous state. In the present work thermally stable amorphous binary paracetamol based systems were obtained showing stability on a wide range of temperatures: below its glass transition temperature (T_g) as amorphous solids in the glassy state and above their glass transition temperature, where these materials exist as stable supercooled liquids. To achieve stabilization of the binary paracetamol based system several strategies were applied and optimized, being the selection of the container material a key and novel approach to control the mechanical stress during cooling, eliminating cracks which act as nucleation centers leading to crystallization.

1. Introduction

A recent and promising approach to solve the problem of a large number of pharmaceutical active ingredients with poor solubility is the conversion of their crystalline form into an amorphous state since it is a documented fact that amorphous solids are in many cases more soluble than their crystalline forms (Gupta et al., 2004; Hancock and Parks, 2000; Kim et al., 2008; Murdande et al., 2010; Zhang et al., 2014). To consider this approach as a viable solution for the formulation of commercial pharmaceutical products, the stability of the amorphous state of these drugs has to be improved since, as expected for a metastable state, they tend to crystallize at a rate which is a function of temperature, relative humidity and storage time (Baird et al., 2010; Karmwar et al., 2011b; Nanubolu and Burley, 2012; Van Eerdenbrugh et al., 2010). Based on the understanding of the role of different experimental parameters such as the thermal history (Greco and Bogner, 2010; Vyazovkin and Dranca, 2007), mechanical stress (Ayenew et al., 2012; Bhugra and Pikal, 2008; Bhugra et al., 2008), sample size (Nielsen et al., 2012) and the addition of a second component to form co-amorphous formulations (Lobmann et al., 2013a,b,b; Masuda et al., 2012), several strategies have been explored in order to avoid crystallization of amorphous active ingredients. Nevertheless, most of these studies search a means to prevent devitrification focusing their attention to a single experimental parameter when in fact there are a number of thermodynamic, kinetic and structural factors that simultaneously affect the recrystallization process; to improve the success of achieving stabilization of amorphous drugs for long periods of storage time it is necessary to study the combined effect of several of these experimental factors. This would allow not only to establish whether an experimental parameter may influence the physical stability of the amorphous material but to explain how or why this parameter has an effect and to what extent. A literature review on the preparation of amorphous drugs focusing on a single parameter is presented.

1.1. Addition of a second component to improve stabilization

It has been acknowledged that promoting inter- or intramolecular interactions by the addition of a second component, either in molar fractions or traces, may inhibit crystallization (Angell and Sare, 1978; Lu and Zografi, 1998). In the selection of a second component to obtain a co-amorphous mixture, either an active ingredient or an excipient can be chosen. Although there are already several studies of co-amorphous drugs (Laitinen et al., 2013) most of them focus on a few specific molar ratios (1:1, 2:1, etc.) of a second component as shown in Table 1. Only a couple of these studies, in which the second component is an active

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Table 1
Glass transition temperatures and thermal stability of co-amorphous drugs prepared by different methods [melt-quenching (MQ), melt-quenching in DSC cells (MQ*), cryo-milling (CM), solvent-evaporation (SE), ball milling (BM)].

Components	Method of preparation	Composition (molar ratio)	T_g (°C)	Stability of the amorphous state		Reference
				Storage conditions at which samples remained amorphous	Time (days)	
Naproxen (NAP)	MQ*	NAP	6.2		Unstable	(Allesø et al., 2009)
	BM	1:2	40.2		Unstable	
Cimetidine (CIM)		1:1	34.5	4, 25 and 40 °C; dry	186	
		2:1	31.5	Just at 4 °C; dry	33	
		CIM	36.1	Not studied		
Naproxen (NAP)	MQ*	NAP	5.04		Unstable	(Löbmann et al., 2011)
Indomethacin (IND)	MQ	2:1	18.9		Unstable	
		1:1	25.3	4 and 25 °C; dry	21	
		1:2	32.0	4 °C; dry	21	
		IND	44.7	Not studied		
Indomethacin (IND)	MQ + CM	IND	45	Not studied		(Chieng et al., 2009)
Raniditine hydrochloride (RCl)	BM	~2:1	34.4	4 °C; dry	30	
		1:1	32.5	4 and 25 °C, dry	30	
		~1:2	29.3		Unstable	
	CM	RHCl	26	Not studied		
Indomethacin (IND)	MQ*	IND	44.8	No studied		(Shimada et al., 2013a)
Lidocaine (LC)		1:1	17.6			
		2:7	−14.7			
		LC				
Indomethacin (IND	MQ*	IND	44.8	No studied		(Shimada et al., 2013b)
Lidocaine hydrochloride (LH)		1:1	37.6			
		1:3	30			
		1:5	~28			
		1:2	~25			
		LH	29.7			
Indomethacin (IND)	MQ	IND	44.7	Not studied		(Löbmann et al., 2011)
Cimetidine (CIM)	SE	1:4	50–65	No studied		(Yamamura et al., 2000)
		1:1				
		4:1				
	BM	CIM	36.1	Not studied		(Allesø et al., 2009)
Simvastatin (SVS)	CM	SVS	31.5	4 °C; dry	67	(Löbmann et al., 2012)
Glipzide (GPZ)				25 °C; dry	11	
		2:1	41.5	4 °C; dry	74	
				25 °C; dry	53	
		1:1	46.7	4 °C; dry	88	
				25 °C; dry	74	
		1:2	53.6	4 °C; dry	95	
				25 °C; dry	74	
		GPZ	69.9	4 °C; dry	74	
				25 °C; dry	60	
Indomethacin (IND)	MQ*	IND	44.7	Not studied		(Dengale et al., 2014)
Ritonavir (RTV)	SE	2:1	47.5	4, 25 and 40 °C; dry	90	
		1:1	46.9	4, 25 and 40 °C; dry	90	
		1:2	51.9	4, 25 and 40 °C; dry	90	
	MQ*	RTV	52.4	Not studied		
Atorvastatin Calcium (ATC)	SE	1:1	78	Not studied		(Shayanfar and Jouyban, 2013)
Carvedilol (CVD)						
Atorvastatin Calcium (ATC)	SE	1:1	85	Not studied		(Shayanfar and Jouyban, 2013)
Glibenclamide (GLN)	MQ	GLN	71.3	Not studied		(Hassan et al., 1991)
Cimetidine (CIM)	BM	CIM	36.1	Not studied		(Allesø et al., 2009)
Diflunisal (DIF)	SE	1:4	~150			(Yamamura et al., 2002)
		2:3	N/A	Not studied		
		3:2				
		4:1				
		DIF				
Paracetamol (PAR)	MQ*	PAR	21.4		Unstable	(Saini and Murthy, 2014)
Aspirin (ASP)		1:1	−7	Not studied		(Johari et al., 2010)
		ASP	−30	Not studied		(Johari et al., 2007)
Paracetamol (PAR)	MQ*	PAR	21.4		Unstable	(Saini and Murthy, 2014)
Quinidine (QND)		1:1	57	Not studied		(Johari et al., 2010)