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Tuning physicochemical properties of theophylline by cocrystallization using the supercritical fluid enhanced atomization technique

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ABSTRACT

Formation of different micro- to nanosized cocrystals of theophylline is addressed by using the supercritical enhanced atomization (SEA) process. The experimental results presented here help to highlight how to prepare cocrystals of theophylline (TPL) using a supercritical fluid-based technique to accomplish the required physicochemical properties of that active pharmaceutical ingredient (API). The SEA process shows a strong versatility and feasibility towards the formation of highly pure theophylline cocrystals, using tetrahydrofuran as a solvent. The formation of TPL cocrystals with different types of morphology and dissolution behaviour/properties is induced by using different coformers, such as urea, saccharin, gentisic acid, salicylic acid, glutaric acid, sorbic acid, 1-hydroxy-2-naphthoic acid, oxalic acid, maleic acid and nicotinamide. The solubility of each coformer in the dissolution medium of phosphate-buffered saline (pH 7.4 at 25 °C) could determine the dissolving rate behaviour of the produced cocrystals. Consequently, the low-soluble coformers generate TPL cocrystals with a slow-dissolving rate, while the use of highly soluble coformers produces faster-dissolving TPL cocrystals. Albeit the SEA process operating temperature influences the mean cocrystal particle size, this technique shows a high potential as an effective cocrystal screening tool.

1. Introduction

Pharmaceutical cocrystals, i.e. multicomponent crystalline systems comprising a coformer and an API (active pharmaceutical ingredient) in a single unit cell, have been intensively studied over the past years by both the academic and industrial environments due to their improved physicochemical properties (e.g. solubility, stability, and bioavailability) compared to those of the corresponding pure APIs. Cocrystals can be designed using crystal engineering approaches, providing interesting alternative solutions to other forms of APIs such as polymorphs, salts or solvates/hydrates [1–7].

Classical techniques to produce cocrystals include mechanochemical methods (neat and liquid-assisted grinding), solvent-evaporation and reaction crystallization in suitable solvents. These technologies present issues that should be taken into consideration in cocrystal production and scale-up, like solid phase impurity, presence of amorphous impurities in the cocrystal product or uncontrolled formation of polymorphs or hydrates/solvates of cocrystals. In addition to this, robust and scalable methods need to be developed.

Classical spray-drying methods have been applied for a controlled particle design of APIs [8,9] and also for the generation of cocrystals [10]. Interestingly, the latter authors reported that spray drying of stoichiometric solutions of cocrystals components under incongruent conditions resulted in pure cocrystals due to the fast kinetics of crystallization, while using slow evaporation techniques resulted mostly in a mixture of phases (API + coformer + cocrystal). However, spray-dried materials have a tendency to be amorphous due to its rapid solidification during the process. Depending on the cocrystal system used, the product outcome from a classical spray-drying process can be either a crystalline or an amorphous form.

The use of supercritical fluids (SCF) in the development of spray-assisted based methods has revealed high potential [11–15]. Briefly, the depressurization of a liquid together with a supercritical fluid (at high pressure) enhances the liquid jet breakup into sub-micrometric droplets. The use of the supercritical enhanced atomization properties was first described as the CO_2-assisted nebulization with a bubble dryer (CAN-BD) [16–18]. However, many variants have emerged with different nozzle design [19]. Recently,

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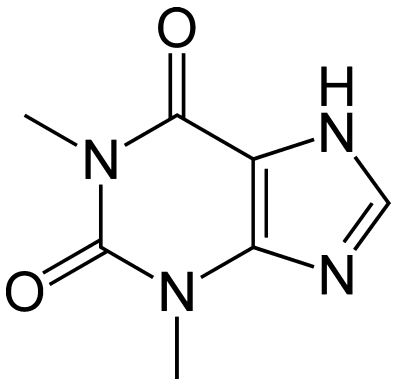

Fig. 1. Molecular structure of theophylline (TPL).

the supercritical enhanced atomization (SEA) technique has been established for the screening of cocrystals [20] for simultaneous cocrystallization and lipid dispersion [21] and for the preparation of a vaccine for equidae [22].

The API under consideration in this work is theophylline (TPL), a dimethylxanthine drug used in therapy for respiratory diseases such as asthma, chronic bronchitis, and other lung diseases. Fig. 1 presents the molecular structure of TPL. Because this drug has a relatively narrow therapeutic index, bioavailability differences may cause substantial therapeutic nonequivalence. TPL is rapidly absorbed but conventional rapid release formulations usually produce excessive fluctuations in serum concentrations. Sustained release formulations show pH-dependent dissolution behaviours, with a much more rapid and complete absorption when taken after food or in the evening [23,24]. Cocrystallization is an emerging technique for controlling the pharmacokinetics of unstable molecules such as TPL. The physicochemical properties of an API depend of its crystalline form and therefore by selecting the appropriate cocrystal former, the consistency of the dissolution or the stability during storage can be substantially enhanced. Several cocrystal forms of TPL with coformers produced by classical methods, reported in the literature [25,26], evidence the stability of some theophylline cocrystals under relative humidity conditions. A particle design study involving cocrystals has only been addressed specifically for indomethacin–saccharin cocrystal using different supercritical fluid techniques [27]. In this work, several coformers were used to cocrystallize with TPL and generate different cocrystals with distinct physicochemical properties using a supercritical enhanced atomization (SEA) process. The physicochemical properties of these different forms of theophylline, such as particle size, morphology and dissolution rate are presented and compared with those of pure unprocessed theophylline.

2. Experimental

2.1. Chemicals

Theophylline and the coformers urea, saccharin, gentisic acid, salicylic acid, glutaric acid, sorbic acid, 1-hydroxy-2-naphthoic acid, oxalic acid, maleic acid and nicotinamide were purchased from Sigma Aldrich (purity of these chemicals was >99.9%). Tetrahydrofuran (99.9%) was supplied by Sigma–Aldrich. Carbon dioxide and nitrogen (99.998%) were supplied by Air Liquide (Portugal).

2.2. Experimental apparatus and procedures

2.2.1. Solution preparation for SEA processing

The cocrystal components (TPL and a coformer) were dissolved in 100 g of tetrahydrofuran (THF). The solutions containing TPL and each coformer were prepared according to Table 1.

2.2.2. Particle production by SEA

Cocrystals were prepared using the SEA setup schematically shown in Fig. 2.

In previous works we have observed that for the supercritical enhanced atomization techniques the critical pressure of the mixture before the nozzle is determining of the precipitation mechanism [28,29]. Above critical pressure particles may precipitate by CO_2 anti-solvent effect, while below the critical pressure of the misture this is unlikely and supersaturation shall be driven by spray-drying. The critical pressure of the mixture THF-CO_2 at 50 °C is approximately 9 MPa [30], therefore we used 8 MPa as the reference atomization pressure.

The solution of THF containing TPL and the selected coformer is pumped (by a TSP metering pump, model 2396-74) through a coaxial nozzle where it mixes with the supercritical fluid (CO_2) before

Table 1
Experimental conditions used in the preparation of solutions and for particle production by SEA processing. *n* is the amount of substance used of each component (TPL or coformer); *P* is the pressure before the nozzle; *t* is the temperature in the mixing chamber; *R* is the mass flow-rate ratio of the aqueous feed to the supercritical fluid; TPL, theophylline; URE, urea; SAC, saccharin; GEA, gentisic acid; SAA, salicylic acid; GLA, glutaric acid; SOA, sorbic acid; HNA, 1-hydroxy-2-naphthoic acid; OXA, oxalic acid; MAA, maleic acid; NCT, nicotinamide.

Reference samples	Molar proportion	TPL, *n* (mmol)	Coformer, *n* (mmol)	*P* (MPa)	*t* (°C)	*R* (g/g)
TPL	–	2.8	–	8.0	50	0.08
TPL–URE	1:1	2.8	2.8	8.2	50	0.09
TPL–GEA	1:1	2.8	2.8	8.2	50	0.28
TPL–SAA	1:1	2.8	2.8	8.0	50	0.12
TPL–GLA	1:1	2.8	2.8	8.1	50	0.16
TPL–SOA	1:1	2.8	2.8	8.4	50	0.26
TPL–HNA	1:1	2.8	2.8	8.1	50	0.09
TPL–OXA	2:1	2.8	1.4	8.1	50	0.13
TPL–MAA	1:1	2.8	2.8	8.0	50	0.13
TPL–NCT	1:1	2.8	2.8	8.0	50	0.12
TPL–SAC 1	1:1	0.3	0.3	8.0	50	0.15
TPL–SAC 2	1:1	1.4	1.4	8.0	50	0.28
TPL–SAC 3	1:1	2.8	2.8	8.0	50	0.19
TPL–SAC 4	1:1	2.8	2.8	8.0	40	0.22
TPL–SAC 5	1:1	2.8	2.8	8.0	60	0.27
TPL–SAC 6	1:1	2.8	2.8	8.0	70	0.22
TPL–SAC 7	1:1	2.8	2.8	4.0	50	0.18
TPL–SAC 8	1:1	2.8	2.8	10.0	50	0.22