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Predicting final product properties of melt extruded solid dispersions from process parameters using Raman spectrometry

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ABSTRACT

Raman spectrometry was utilized to estimate degraded drug percentage, residual drug crystallinity and glass-transition temperature in the case of melt-extruded pharmaceutical products. Tight correlation was shown between the results obtained by confocal Raman mapping and transmission Raman spectrometry, a PAT-compatible potential in-line analytical tool. Immediate-release spironolactone–Eudragit E solid dispersions were the model system, owing to the achievable amorphization and the heat-sensitivity of the drug compound. The deep investigation of the relationship between process parameters, residual drug crystallinity and degradation was performed using statistical tools and a factorial experimental design defining 54 different circumstances for the preparation of solid dispersions. From the examined factors, drug content (10, 20 and 30%), temperature (110, 130 and 150 °C) and residence time (2.75, 11.00 and 24.75 min) were found to have significant and considerable effect. By forming physically stable homogeneous dispersions, the originally very slow dissolution of the lipophilic and poorly water-soluble spironolactone was reasonably improved, making 3 minute release possible in acidic medium.

1. Introduction

Non-invasive in-line and on-line analytical techniques have grown to be important in pharmaceutical development and manufacturing, because they are the sinews of Process Analytical Technology (PAT) and Quality by Design (QbD) concepts, with which technological innovation is nowadays more and more frequently associated [1]. It is, therefore, of distinguished importance to find and examine the analytical tools which can provide information on multiple product attributes and properties at a time. Formation of solid dispersions is a typical example for processes during which materials can be subject to desired and undesired physical and chemical changes that are highly necessary to detect. For example in the case of crystalline Class II drugs (classified according to the Biopharmaceutics Classification System [2]) of low water solubility it is the goal itself to destruct the crystal lattice in order to achieve immediate release, and through this an enhanced bioavailability. Thus, a certain molar percentage of the drug becomes molecularly dispersed or amorphous without degradation (x_a), another percentage degrades (x_d) after having lost the stabilizing crystal lattice, while the rest of the drug remains crystalline (x_c). (x_a, x_c and x_d add up to 100%.) The degree of residual drug crystallinity (x_c) influences several product properties, such as dissolution behaviour, glass-transition temperature and stability. These facts indicate that both x_c and x_d must be detected or monitored in the case of solid dispersions.

Vibrational (such as infrared [3] and Raman [4]) spectroscopy is one of the most eligible tools to show chemical changes in materials. Besides references, precise quantum mechanical calculations and chemometric tools can help with the identification of the resulting compounds [5–7]. Raman spectrometry can also provide feedback control for pharmaceutical processes, as first shown recently by Pataki et al. [8]. A potential non-invasive analytical technique for the determination of x_c and x_d is the recently rediscovered *transmission Raman spectrometry* (TRS), which provides a mean vibrational spectrum characterizing a large sample volume [9]. A probe can be easily mounted at the production line using optical fibres [10], facilitating real-time detection and the possibility of process-control based on x_c. Although TRS has not yet been employed for x_c measurement, a reassuring indication for

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its applicability is the eligibility of other Raman-based techniques for the determination of chemical composition [10], the quantification of polymorphs in a mixture [11,12] and the measurement of the degree of crystallinity [13]. Another advantage of TRS is the suppression of surface-generated Raman and fluorescence signals [10]. Despite these reasonable benefits, the exploitation of this technique for the bulk testing of pharmaceutical samples has only recently begun [14]. As opposed to TRS, the nature and abilities of *backscattering Raman spectrometry* have already been thoroughly studied and it was also employed for crystallinity degree determination in a few cases [13]. In order to avoid subsampling, which is a clear disadvantage of this technique [15], multipoint measurements can be carried out [11], a larger area of the sample can be illuminated [16], or the sample holder can be rotated [13]. Moreover, Larkin et al. found that drilled cylindrical-conical holes in the sample can improve precision in the case of backscattering FT-Raman [17]. Multipoint backscattering measurements are usually carried out by *confocal Raman mapping*. As it has already been used to quantify polymorphs [15,18] and investigate the distribution of amorphous and crystalline material [19,20], it seems to be applicable to quantify the crystalline API fraction. However, as subsampling was found to be an issue in comparison with TRS [15], it still remained a question whether x_c values obtained by TRS and Raman mapping are comparable. This question is to be answered using samples prepared by an industrially relevant technology.

Against the conventionally applied batch processes, which are time-varying, seriously interconnected with uncertainties and hence usually not fully understood [21], PAT guidelines clearly prefer the application of continuous processes as they are easier to monitor and automate, and deliver constant product quality [22]. In addition to these, following of QbD guidelines helps getting product quality (i.e. efficacy, safety and effectiveness) 'right the first time'. Adaptation of QbD methodology requires a deep and quantitative understanding of process behaviour–how critical process parameters (CPPs) affect critical quality attributes (CQAs), and how these attributes can be monitored in-line or on-line. When formation of solid dispersions and amorphization are the goals, such an in-line monitorable [23,24] continuous technology can be melt extrusion, which has already been utilized to prepare various dosage forms, e.g. mini matrices [25], granules [26], pellets [27], foams [28], films [29]. It is a high-throughput and solvent-free process which has been spreading over the recent years, not just in pharmaceutical research but also in manufacture (e.g. of Kaletra and Isoptin SR-E) [30–32]. In the course of processing, the crystalline drug is dispersed in a polymer melt while it is being conveyed through heated zones of a barrel by means of a continuously turning screw or by means of twin screws. When extrusion is performed below the melting point of the drug, a certain amount of the active pharmaceutical ingredient (API) gets molecularly dispersed in the polymer melt by dissolution mechanism. After the extrudate has cooled and reached a glassy state, the product can be classified either as a glassy solution (if no fraction of the API forms separate phase) or as a glassy suspension (if some crystalline API has remained undissolved in the matrix or if the API dissolved in the melt has undergone phase separation while cooling) [33].

x_c of the extruded samples can determine multiple product properties, but at the same time it is hugely dependent on process variables (e.g. zone temperatures of the barrel, screw speed and residence time), as shown by Keen et al. [34]. Therefore, it is advantageous to use x_c, when monitored on-line or in-line, as controlled parameter for process control. If the relationship between product properties and x_c is elucidated, this process control can also ensure the desired functional behaviour. Regarding API degradation in the course of melt extrusion, the scientific literature is limited to a few chemical compounds, such as hydrocortisone [35], carbamazepine, dipyridamole and indomethacin [36], meloxicam [37] and vitamin D [38]. API decomposition does not necessarily mean thermal degradation; it can also be initiated by free radicals as described by DiNunzio et al. [35]. Whatever the mechanism of decomposition, as expected, temperature and residence time have reasonable influence on the rate of degradation [35,37]. An in-line applicable spectroscopic technique (e.g. TRS) can help us to gain proper knowledge regarding the relationship of extrusion conditions and achievable purity, and to establish effective quality control.

This study investigates the eligibility of Raman spectrometry (TRS and Raman mapping) to measure drug degradation (x_d) and residual drug crystallinity (x_c) in melt extruded immediate-release solid dispersions, and to predict these along with other product properties deriving from x_c. A new, simple method was used to determine x_c, by which the PAT-compatible transmission Raman spectrometry and the typically offline Raman mapping were compared. A further aim was to understand and describe the dependence of x_c and x_d on melt extrusion parameters. Drug loading, processing temperature, screw speed and residence time were taken as factors in the experimental design. Keeping these purposes in view, spironolactone was selected as model drug. On one hand, it is an orally administered BCS II compound with lipophilic character (its octanol log*P* is 2.6; [39]) and dissolution properties that must be enhanced. On the other hand, it can degrade easily at high temperature when being molecularly dispersed, providing an adequately diverse population for the analytical tests aimed at measuring degradation.

2. Materials and methods

2.1. Materials

Microcrystalline spironolactone with a molar weight of 417 g/mol, a melting range of 207–216 °C, an average particle size of approx. 30 μm and a water solubility of 28 mg/l at 25 °C [40], crystalline canrenone (m.w. 340 g/mol) and Δ^{20}-spironolactone (m.w. 415 g/mol) were kindly provided by Gedeon Richter Plc. (Budapest, Hungary). Eudragit® E PO, a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate, with an average molecular weight of 47,000 Da and a glass transition temperature of 62 °C was kindly donated by Evonik Industries AG (Essen, Germany).

2.2. Experimental design

Extruded samples to be analyzed were produced by melt extrusion under different conditions in order to ensure that they had various degrees of residual drug crystallinity (x_c) and degradation (x_d). For an exact quantification of effects and interactions, process parameters were changed according to a factorial experimental design.

Solid dispersions with different drug loadings (10, 20 and 30%) were prepared using different combinations of the three process parameters, i.e. the zone temperature of the extruder (110, 130 and 150 °C), the rotational speed of the twin screws (20 and 40 rpm) and the residence time of the melt in the machine. In the course of extrusion, dissolution rate of API crystals in the melt is continuously slowing while the system is coming closer to saturation. Hence it was supposed that the time dependence of this process resembles a square root function. For this reason, the square root of the approximated residence time ($\sqrt{2.75}$, $\sqrt{11.00}$ and $\sqrt{24.75}$ $\text{min}^{1/2}$) was used as factor instead of setting equidistant values for residence time itself. The design for sample preparation, consisting of 54 (2×3^3) experimental points, is shown in Table 1.