European Journal of Pharmaceutics and Biopharmaceutics 88 (2014) 434–442

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Evaluation of critical process parameters for inter-tablet coating uniformity of active-coated GITS using Terahertz Pulsed Imaging

Daniela Brock [a], J. Axel Zeitler [b], Adrian Funke [c], Klaus Knop [a], Peter Kleinebudde [a,*]

[a] Institute of Pharmaceutics and Biopharmaceutics, University of Düsseldorf, Düsseldorf, Germany
[b] Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, United Kingdom
[c] Global Chemical & Pharmaceutical Development, Bayer Pharma AG, Berlin, Germany

ARTICLE INFO

Article history:
Received 5 September 2013
Accepted in revised form 25 June 2014
Available online 15 July 2014

Keywords:
Inter-tablet coating uniformity
Active coating
Gastro-intestinal therapeutic system
Pan coating
Candesartan cilexetil
Terahertz Pulsed Imaging
Coating thickness
Content uniformity
OROS
HPLC

ABSTRACT

The aim of this study was the evaluation of critical process parameters (CPP) for inter-tablet coating uniformity in an active pan coating process using nondestructive Terahertz Pulsed Imaging (TPI). Coating uniformity was assessed by calculating the coefficient of variation (CV) of coating thickness measured by TPI, and the CV of API content measured by high performance liquid chromatography (HPLC). A design of experiments (DoE) was performed at pilot scale with drum load, drum speed, spray rate, run duration and spray pressure as factors. Good agreement in the CV of both analytical techniques was shown. The DoE models both revealed the same CPP: a low drum load, high drum speed, low spray rate and high run duration were beneficial for coating uniformity. The spray pressure was only significant in one of the DoE models. It was further shown that the negative impact of a high drum load on the CV cannot only be compensated by high drum speed, but also be compensated by a low spray rate and long run duration. It was demonstrated that TPI is a feasible tool for the measurement of inter-tablet coating uniformity and for the evaluation of CPP in an active pan coating process.

1. Introduction

In recent years, Terahertz Pulsed Imaging (TPI) has aroused interest in the pharmaceutical sciences as a technique to nondestructively measure coating thickness distributions of both, external and buried layers, over the entire tablet surface. Detailed information on the measurement technique is given in [1,2].

Various applications of TPI have since been reported in the literature. For example, TPI was used as a tool to monitor the increase in film thickness throughout a coating process [3–5] or to evaluate the three-dimensional structure of solid drug dosage forms [6,1] and to identify defects in coating layers [7].

Several studies also deal with the use of TPI to evaluate coating uniformity, utilising the high spatial and axial resolution of the technique. Coating uniformity can be subdivided into intra-tablet uniformity, describing the uniformity of the film coating within a single tablet, and inter-tablet uniformity, which corresponds to the uniformity of the film coating between multiple tablets of a batch. While several studies deal with the investigation of intra-tablet uniformity using TPI [7–10], only [4] made a first approach to use in-line terahertz measurements to evaluate inter-tablet coating uniformity. Up to now, no literature is available that has systematically evaluated the use of TPI in the analysis of inter-tablet coating uniformity.

In the film coating unit operation, a high inter-tablet coating uniformity is desired to maintain a constant product quality of each individual dosage unit in the batch. Inter-tablet coating uniformity is of particular importance in functional film coatings, such as sustained-release coatings or active coatings, where the drug release and API content, respectively, determine the effectivity of the drug product.

Drug dosage forms comprising an active coating need to meet the requirements on uniformity of dosage units described in major pharmacopoeias [11–13]. Herein, the API content of the final product as well as the content uniformity within the batch is assessed. An acceptance value (AV) is calculated to determine whether both API content and content uniformity are within a specified range:

$$AV = |M - \overline{X}| + ks \quad (1)$$

* Corresponding author. Institute of Pharmaceutics and Biopharmaceutics, University of Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany. Tel.: +49 211 8114220; fax: +49 211 8114251.
E-mail addresses: daniela.brock@uni-duesseldorf.de (D. Brock), jaz22@cam.ac.uk (J. Axel Zeitler), adrian.funke@bayer.com (A. Funke), klaus.knop@uni-duesseldorf.de (K. Knop), kleinebudde@uni-duesseldorf.de (P. Kleinebudde).

http://dx.doi.org/10.1016/j.ejpb.2014.06.016
0939-6411/

Here, $\overline{X}$ is the arithmetic mean of the individual contents of the dosage units expressed as a percentage of label claim. M is a reference value that varies depending on the actual $\overline{X}$ of the batch, k is the acceptability constant and s is the sample standard deviation. The acceptability constant k is defined by the number of investigated dosage units (k = 2.4 for 10 dosage units, k = 2.0 for 30 dosage units).

The term $|M-\overline{X}|$ accounts for the average amount of API that is incorporated in the dosage form. If the API content is between 98.5 and 101.5 % of label claim, the term can be neglected and does not contribute to the AV. In that case, only the second term, ks, affects the AV. It accounts for the variability of API content among the dosage units in the batch – the inter-tablet uniformity.

In compliance with the pharmacopoeial regulation, an AV $\leqslant$15 has to be met. In the case that a mean content of 98.5% $\leqslant \overline{X} \leqslant$ 101.5% is achieved, a relative standard deviation of $\leqslant$6.25% is sufficient to meet the pharmacopoeial requirements on uniformity of dosage units (for n = 10 dosage units, k = 2.4). If $\overline{X}$ exceeds these limits, s needs to be lower to attain an AV $\leqslant$ 15.

It is evident that both, the accurate determination of the coating endpoint and the achievement of a low standard deviation, are of key importance to meet the required AV.

In the present study, the active coating process of a recently developed dosage form – an active-coated push–pull osmotic system – is investigated. Ref. [14] showed that the accurate API content at coating endpoint can be precisely determined and controlled via in-line Raman measurements. To achieve a high inter-tablet coating uniformity as the second premise for an acceptable AV, the critical process parameters (CPP) in the active coating process need to be identified and a parameter space needs to be defined within which the requirements on coating uniformity are met.

In the literature, several articles address the influence of process parameters on inter-tablet coating uniformity and the mixing behaviour of tablets in the coating drum. They determine inter-tablet coating uniformity by (i) the weight variability of the coated and uncoated tablets [15,16] or the individual coating weights [17], (ii) the variability in tablet diameter or in layer thickness determined by NIR [18], and (iii) dyes or marker substances in the coating to quantify the amount of coating that is applied to the individual tablets [19,20]. Other approaches to investigate inter-tablet coating uniformity are based on computer simulations [21–24]. Up to now, no literature is available that has evaluated the use of TPI in the assessment of inter-tablet coating uniformity and the related CPP in pan coating processes.

The aim of this work was the evaluation of critical process parameters for inter-tablet uniformity in an active pan coating process using Terahertz Pulsed Imaging. As a first step, the linear correlation of layer thickness and CAN content at coating endpoint is evaluated. A high correlation over a broad range of layer thickness and API content was already reported by [5]. The coefficient of variation (CV) of content and layer thickness obtained by HPLC – as a well-established analytical tool – and TPI are then compared for a number of batches. Subsequently, a design of experiments is investigated by both, HPLC and TPI to evaluate whether TPI can resolve the same CPP as HPLC does and to identify a parameter range within which acceptably low CV can be achieved.

2. Materials and methods

2.1. Materials

Gastro-intestinal therapeutic systems (GITS, Bayer Pharma AG, Berlin, Germany) were used as starting material in the active coating process. The tablets were made from a two-layer tablet core surrounded by a semipermeable membrane consisting of cellulose acetate and polyethylene glycol 3350. One half of the tablet core contained the active pharmaceutical ingredient nifedipine (NIF). Given its colour, this face of the tablet is referred to as the yellow tablet face in the remainder of this work. An osmotic blend was incorporated in the other half of the tablet core. Owing to its high content in iron oxide, this face is referred to as the red tablet face. A laser-drilled hole was positioned in the semipermeable membrane on the centre of the yellow tablet face, to enable the release of NIF from the dosage form by contact with water. Three different dose strengths of the GITS were used in this study. The GITS with a drug load of 20 mg NIF were 8.4 mm in diameter and 4.3 mm in height with a mass of 217 mg per tablet. GITS with a drug load of 30 mg NIF were 9.1 mm in diameter and 4.8 mm in height with a mass of 280–283 mg per tablet and GITS with a drug load of 60 mg NIF were 10.6 mm in diameter and 6.6 mm in height with a mass of 531 mg per tablet.

2.2. Pan coating

2.2.1. Preparation of the coating suspension

The aqueous coating suspension consisted of 40% (wt/wt) candesartan cilexetil (CAN) as API and 60 % (wt/wt) polyvinyl alcohol based polymer mixture (Opadry®, Colorcon, Dartford, UK) at a total solid content of 29% (wt/wt). The API was dispersed in water using either an Ultra-Turrax homogeniser (batches A and B, TP18/10, Janke und Kunkel, Staufen, Germany) or a dissolver stirrer (other batches). Subsequenty, Opadry® was added and the suspension was stirred for at least 45 min until all polymer particles had dissolved.

2.2.2. Coating trials in lab scale

Pan coating in lab scale (3 and 8 kg) was performed using side-vented pan coaters (BFC5 and BFC5/10, L.B. Bohle, Ennigerloh, Germany). The process conditions and theoretical API content at process endpoint are listed in Table 1. In batches A and B the spray rate was increased from 8 g/min to 12 g/min after 60 min process time.

2.2.3. Design of experiments in pilot scale

Pan coating in pilot scale (38–43 kg) was performed using a side-vented pan coater (BFC50, L.B. Bohle, Ennigerloh, Germany). A 2^{5-1} fractional factorial design of experiments (DoE) was performed using GITS with a drug load of 30 mg NIF. Drum load

Table 1
Process parameters and API contents in the fixed-dose combination for the investigated lab scale batches of active-coated GITS at different scales.

Batch no.	loa (kg)	rpm (rpm)	spr (g/min)	dur (min)	pres (bar)	NIF load (mg/tablet)	CAN load (mg/tablet)
A	3	18	8/12	340	0.8	20	32
B	3	18	8/12	348	0.8	20	32
C	8	15	25	396	1.1	20	32
D	8	15	21	180	1.0	60	32
E	40.1	11	123	80	1.5	30	8
F	40.1	11	126	150	1.5	30	16
G	44	11	78	140	1.5	60	16