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Assessment of distribution of pellets in tablets by non-destructive microfocus X-ray imaging and image analysis technique

Zsombor Csobán [a,b], Barnabás Kállai-Szabó [a], Nikolett Kállai-Szabó [a], Tamara Takács [a], Tamás Hurtony [c], Péter Gordon [c], Romána Zelkó [d], István Antal [a,*]

[a] Department of Pharmaceutics, Semmelweis University, Hőgyes E. Str. 7, H-1092 Budapest, Hungary
[b] Formulation R&D, Gedeon Richter Plc., Gyömrői Str. 19-21, H-1103 Budapest, Hungary
[c] Department of Electronics Technology, Budapest University of Technology and Economics, Egry J. Str. 18, H-1111 Budapest, Hungary
[d] University Pharmacy Department of Pharmacy Administration, Semmelweis University, Hőgyes Endre Str. 7-9, H-1092 Budapest, Hungary

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ABSTRACT

In this study, potassium chloride (KCl) containing matrix pellets were compressed into tablets using powder or pellet form of partially spray dried lactose as filler-binder excipient. The spatial distribution of potassium chloride pellets within the tablets was examined by non-destructive microfocus X-ray imaging (MFX) and image analysis technique. The KCl content of the tablets was determined by conductivity measurement and these values were compared to the average gray values of the MFX images calculated by image analysis software. A linear relationship has been shown between the KCl content predicted from average gray values of the MFX images and the actual KCl content measured by conductometry. The non-destructive MFX method was capable to characterize the pellet distribution as well as the pellet content of the multiparticulate dosage form. Based on the observed spatial distribution of KCl pellets within the tablets made using lactose pellets or powder for direct compression as filler excipients the difference in homogeneity was not remarkable besides the applied blending method.

1. Introduction

The use of multiparticulate drug delivery systems can contribute to more efficient and safer therapy due to even distribution of drug containing particles along the gastrointestinal tract [1,2]. Coating of individual particles diminishes the risk of dose dumping effect which can be a major hazard of high dose containing modified release coated tablets [3]. Moreover the independent particles allow tackle with incompatibility issues and help to improve the stability of tablets containing more than one active pharmaceutical ingredients [4].

Divisibility of multiparticulate tablets without compromising the modified release properties provides the possibility of more flexible individual therapy however homogeneous distribution and content uniformity of the drug containing particles within the tablet is a key feature [5]. During the formulation process the different physical characteristics of pellets and tableting excipients must considered then a proper blending and tableting method need to be applied to avoid segregation and ensure decent pellet distribution [6,7].

The distribution of pellets or other types of microparticles within the final dosage form is usually assessed by visual or spectroscopic techniques [8]. The infrared (IR) [9], Raman spectroscopy [10] and mapping methods allow to determine the spatial distribution of the compounds only in thin, sectioned samples (e.g. powders, cast films, coatings) or on the optically flat surface of the dosage forms. Even in diffuse reflectance mode these methods can be used to study the surface of a sample to a relatively shallow depth [11]. Scanning both sides of the tablets by optical microscopy, by image analysis the vertical segregation of the powder blend can be determined during tableting [12,13].

The spatial distribution of pharmaceutical materials can be calculated by magnetic resonance imaging (MRI) [14] or X-ray computed tomography (microCT) [9,15–17]. The MRI and microCT techniques are universal for almost all kinds of excipients and drugs but the process is highly time consuming due to the 2D Fourier imaging of the sections (MRI) or the numerous images captured and 3D reconstruction (microCT).

Microfocus X-ray imaging (MFX) is a promising technique to determine the spatial distribution of an active ingredient within the final dosage form [11]. The main limitation of the method is the necessary presence of heavy atoms in drug molecules that ensures the visibility of the active ingredients in the matrix of the supporting materials. The primary purpose of the present study was to assess the physical parameters and thus the tableting properties of particulate systems of different densities and to non-destructively determine the content and the spatial distribution of microparticles within the dosage form by MFX technology.

* Corresponding author at: Hőgyes E. Street 7-9, H-1092 Budapest, Hungary.
E-mail address: antal.istvan@pharma.semmelweis-univ.hu (I. Antal).

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2. Materials and methods

2.1. Materials

Partially spray-dried lactose for direct compression (Flowlac® 100) was obtained from Meggle Pharma (Wasserburg, Germany), magnesium stearate was purchased from Molar Chemicals (Budapest, Hungary). Model pellets containing potassium chloride were made according to the process published and described earlier [18]. Purified water was gained using a Christ Ministil® P-24 ion exchange column (Ovivo Water, Wolverhampton, United Kingdom).

2.2. Sample preparation

2.2.1. Preparation of filler pellets

The filler pellets were made of Flowlac® 100 via extrusion-spheronization process. 100 g of Flowlac® 100 was wetted by 13 g of purified water then mixed using a mortar and pestle. The wet mass were extruded by a Caleva Multilab extruder (Caleva Process Solutions Ltd., Sturminster Newton, United Kingdom) equipped with a 1.0 mm perforated screen and operating at 175 rpm. The extrudates were spheronized for 10 min in a Locost GSZF-AK 200 spheronizer (Locost Ltd., Tiszaalpár, Hungary) equipped with a 210 mm diameter cross-hatched friction plate operating at 600 rpm. The pellets were dried at 50 °C for 24 h in a Labor Innova drying chamber (Labor-Innova Ltd., Budapest, Hungary), and sieved by a Retsch AS200 vibration sieve (Retsch Gmbh, Haan, Germany). The 500–800 μm size fraction of pellets was used as filler material for tablet compression.

2.2.2. Preparation of pellet containing tablets

Different ratios of potassium chloride containing pellets and filler excipients were compressed on a single punch tablet press (Fette Exacta 1, Fette Compacting GmbH, Schwarzenbek, Germany) equipped with flat-faced, beveled-edged punches with a diameter of 14 mm. Pellets with high potassium chloride content acted as X-ray active model material. Flowlac® 100 powder or lactose pellets were used as fillers thus the influence of the particle size difference on blend and tablet homogeneity could be investigated. The 50 g of each blend contained 1% w/w of magnesium stearate as lubricant, and was mixed by a WAB T2F Turbula mixer (Willy A. Bachofen Maschienenfabrik AG, Muttenz, Switzerland) at 49 rpm for 10 min prior to compression. The individual tablet mass was set at around 1000 mg. The KCl pellet-filler material ratios were 1:9, 3:7 and 5:5 respectively as Table 1 summarizes.

Tablets with very low KCl pellet content were made to calibrate the applied X-ray imaging, image analysis and conductivity measurement method. These tablets ($n = 3$) contained 5, 10, 15, 20, and 25 pieces of KCl pellets ($m_{av.} = 2.17 \pm 0.0082$ mg) and 1000 mg of lubricated Flowlac® 100 filler powder. Both the KCl pellets and filler for each individual tablet were weighed on an analytical balance (Sartorius LA 230S, Sartorius AG, Goettingen, Germany) then mixed manually in 5 ml vials for 1 min and filled into the die of tablet press.

2.3. Characterization of samples

2.3.1. Physical characterization of pellets and filler powder

Flowability, bulk density and Hausner ratio of KCl pellets and filler materials (lactose powder and lactose pellets) were measured according to European Pharmacopoeia 8th edition.

Breaking force of KCl and lactose pellets was determined by a texture analyzer (CT-3, Brookfield Engineering Laboratories, Middleborough, USA) operating in compression mode with a 4500 g load cell. 50 individual samples were placed onto the ceramic plate and tested one by one. The stainless steel cylinder probe of 6 mm diameter was moved with a constant speed of 0.05 mm/s and sampling rate of 5 points/s. The target distance was 0.3 mm. For the pellet diameter determination the trigger load was 0.01 N. During the entire measurement a force–distance curve was recorded using TexturePro CT v1.4 software (Brookfield Engineering Laboratories, Middleborough, USA) where the force at the first breaking peak indicated the hardness of pellets.

2.3.2. Determination of shape parameters of pellets by image analysis

Images of 100 randomly selected KCl and filler pellets were captured by a digital microscope (dntDigiMicro 2.0 Scale, Dietzenbach, Germany) and shape parameters were analyzed by image processing software (ImageJ 1.48v, Wayne Rasband, National Institute of Health, USA). Image resolution was 74 pixels/mm. The pellet shape was characterized by circularity, which was calculated using the following formula:

$$C = (4\pi \times A)/P^2 \quad (1)$$

where C is the circularity, A is the projection area of the particle and P is the perimeter of the particle.

2.3.3. Determination of potassium chloride content via conductivity measurement

A conductivity-KCl concentration calibration curve was recorded using an electrical conductivity meter (Radelkis Ltd., Budapest, Hungary). Analytically weighed amounts of KCl (Ph. Eur. 8th) were dissolved in 100 ml of purified water and conductivity of the solutions was determined. Measured linear concentration range was between 0.1–720 mg/100 ml (slope: 0.00227; R^2: 0.9987). The analytically weighed KCl pellets were dissolved in purified water and conductivity was measured then the absolute KCl content of the pellets could be calculated based on the calibration curve. The result was an average of three measurements. Three pieces of pellet containing tablets of each different batch were dissolved in 100–100 ml of purified water then the measured conductivity of the solutions, the calibration curve and the known KCl content of the pellets made possible to determine the exact pellet content of each tablet. The contribution of dissolved lactose filler to the conductivity of the solution was negligible compared to the potassium chloride.

2.3.4. Determination of the potassium chloride pellet content via microfocus X-ray imaging

X-ray images of 5 randomly selected tablets of each batch were captured by a DAGE XD 6600 X-ray inspection system (Nordson DAGE, Aylesbury, United Kingdom). Tube voltage was 1.00 kV, tube power was 1 W and image resolution was 92 pixels/mm. The KCl content (thus the pellet content) was determined using summarized gray values of the images. The gray value (GV) was calculated using the following equation:

$$GV = \sum_{i=1}^{n} A_i \times (255 - AGV_i) \quad (2)$$

where GV is the summarized gray value, n is the number of the particles, A is the projection area of the particle, AGV is the average gray value of the particle (0 is black and 255 is white according to RGB color coding

Table 1
Composition of the KCl pellet containing tablets.

	PE10	PE30	PE50		PO10	PO30	PO50
Filler pellet content (%)	90	70	50	Filler powder content (%)	90	70	50
KCl pellet content (%)	10	30	50	KCl pellet content (%)	10	30	50