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X-ray Microtomography as a Non-Invasive Method for Evaluating the Stability of Commercial Effervescent Tablets †

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Abstract: In the present study, a non-invasive X-ray microtomography technique was applied to assess the internal structure of commercial effervescent tablets with vitamin C. Expired tablets stored under ambient conditions were analyzed and the results obtained were compared with unexpired tablets. Significantly higher density values were found for the unexpired tablets (1.250 g/cm^3) compared to the expired tablets (1.242 g/cm^3). The results indicate a better homogeneity of the unexpired tablets, which may affect their mechanical strength.

Keywords: solid dosage forms; X-ray microtomography; homogeneity

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1. Introduction

X-ray microtomography is one of the non-destructive techniques which are increasingly used in many scientific areas including biomedical and material research, industrial R&D as well as drug quality and control processes [1–3]. Combining this method of analysis with the Bruggeman model, Markl et al. [4] got new data about the shape and orientation of the pores in tablets with calcium carbonate. The authors demonstrated that intermolecular pores were the main reason for anisotropic behavior of the medium [4]. Both the presence and the structure of pores affected the way the liquid penetrates into the tablet, which translates into a distribution of the rate of pharmacological effect [4]. The microtomography method was also used to detect fibres in nanoscale samples of electrospun poly(caprolactone) based materials [5]. In turn, Holm et al. [6] used microtomograhy to examine the effect of microwave radiation on the internal structure as well as the strength parameters and disintegration behavior of multiparticulate drug delivery systems.

The present study aimed to assess the stability of effervescent solid dosage forms using a non-invasive X-ray microtomography technique.

2. Methods

We selected effervescent tablets which contain vitamin C and are popular at the Polish market. One type of the tablets was stored according to the manufacturer's instruc-

tions for several years until the expiration date (expired tablets with expiration date: February 2020) and the other type of tablets was within the expiry date (unexpired tablets with expiration date: April 2023).

Basic parameters of the tablets i.e., weight, diameter, thickness, disintegration time, as well as features of the mechanical strength were assessed according to Pharmacopeia European [7].

The scanning analysis of the selected preparations was made using X-ray microtomography apparatus (GE Sensing & Inspection Technologies GmbH, Wunstorf, Germany). The voltage at which the tablets were scanned was 180 kV. An object analyzed by this method absorbs X-rays proportionally to its density. In the microtomographic image, the density is reflected by the level of gray, i.e., high-density areas are represented by bright pixels whereas low-density areas are dark. To establish dependence between density and the brightness of the pixels we fixed the tablets on a special phantom with areas of known density (Micro-CT HA Phantom D32). In this way, we kept the same analysis conditions for both the phantom and analyzed preparations.

All obtained data were analyzed with the use of the Statistica 13.0 software (STATSOFT; Statistica, Tulsa, OK, USA). A nonparametric test of U Mann-Whitney was used to compare obtained data between expired and unexpired tablets due to the preliminary nature of the research. The results were considered significant at p-value of ≤0.05.

3. Results and Discussion

The stability of the finished medicinal product has a significant impact on the effectiveness of the medicinal product as well as the safety of the patient. With this in mind, stability testing is now a legal requirement for medicinal products throughout the drug development process. Several novel methods were proposed to evaluate the drug forms after storage in both ambient conditions and stressful conditions. X-ray microtomography allows the 3D characterization of the particle structure and, in particular, the solid dosage forms. Furthermore, determining the distribution of active pharmaceutical ingredients (API) in pharmaceutical tablets allows the optimization of formulations of these drug forms. Wagner-Hattler et al. [8] used synchrotron X-ray microtomography to assess the uniformity of distribution of moxidectin in minitablets. Up to 20% drug loading has been shown not to segregate moxidectin [8]. In our previous study, microtomographic analysis was used i.a. to assess the porosity of the effervescent preparation with magnesium and vitamin B6 [9]. In this study, we also used expired tablets, which had a larger pore diameter and a higher percentage of porosity than tablets before the expiration date.

3.1. Basic Parameters of the Analyzed Tablets

The tested tablets were cylindrical with flat top and side surfaces. We observed differences in the weight, thickness, and diameter between unexpired and expired tablets. The disintegration time of expired tablets was significantly shorter than the disintegration time of unexpired tablets (1.37 min. vs. 1.44 min., $p = 0.005$). In addition, expired tablets showed significantly lower mechanical strength compared to unexpired tablets.

The moisture content was 0.4% and 0.2% for expired and unexpired tablets, respectively.

3.2. Microtomography Analysis

For the analysis, we used 20 randomly selected microtomographic slices of each type of the tablet in which a total of 70 regions of interest (ROIs) were evaluated (Figure 1).

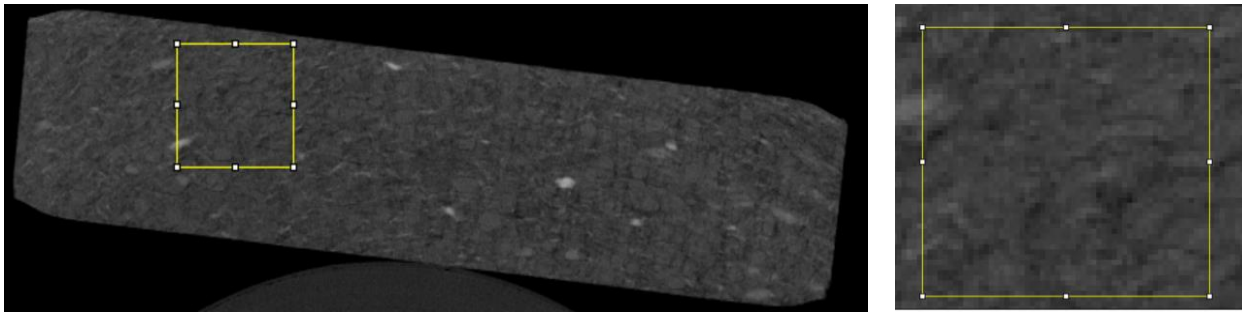

Figure 1. The image shows an example ROI located throughout the tablet (on the left) and the ROI itself with visible pixels (on the right).

The average brightness of the pixels was measured with ImageJ software (ImageJ 1.53a; National Institutes of Health, Madison, WI, USA). A curve of dependence between brightness and density of the known area from the phantom was drawn (Figure 2).

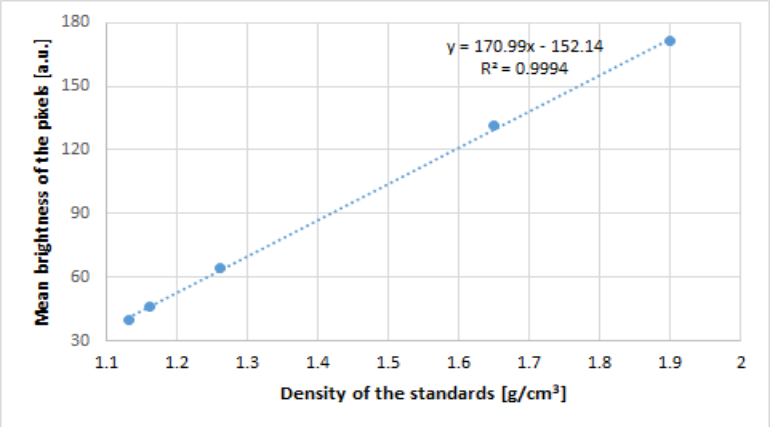

Figure 2. The curve shows the correlation between the brightness of the pixels and the density of the standards in the calibration phantom.

The density of the inner structure differed significantly between the two types of studied effervescent tablets with vitamin C ($p < 0.001$). Tablets within the expiration date had higher mean density than tablets after the expiration date (Figure 3). This may indicate that unexpired effervescent tablets containing vitamin C showed better homogeneity than expired ones.

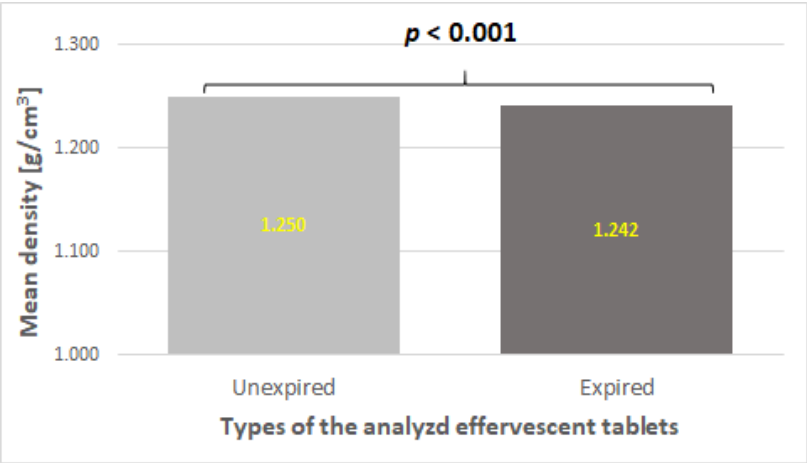

Figure 3. The mean density of unexpired and expired tablets obtained in X-ray microtomography. The *p*-value is in bold for significance.

4. Conclusions

The applied method of three-dimensional microtomography imaging allowed for rapid detection of the differences in the microstructure of expired and unexpired tablets. On the basis of quantitative data, significant differences in the tablet density of the analyzed drug forms were demonstrated which indicated that the homogeneity of the tablets was lower after storage at ambient conditions for a long time.

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