Novel methods for the inner structure of parts of tablets obtained after subdivision

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Abstract

Subdivision of tablets is a practice which is very popular both among patients and among doctors. Different methods for splitting tablets can be used, including by-hand breaking, cutting with a (kitchen) knife or with scissors, or using a splitter device. In order to assess the safety of this practice as well as its impact on the uniformity of the drug dose in the resulting tablet parts, many research methods are used. To ensure the effectiveness of pharmacotherapy and, above all, the patient's safety, it is important to be sure that the divided parts of the tablets are even and homogeneous. Imaging techniques used in other areas of science and industry may be helpful in this matter. New methods based on advanced spectroscopic techniques are increasingly used to analysis of pharmaceutical preparations. In the present review we aimed to discuss modern methods for analysis of inner structure and uniformity of ingredients in the tablet parts obtained after subdivision. Special emphasis was put on the usage of computer microtomography in the tablet analysis.

Key words:

tablets, subdivision, inner structure, spectroscopy, microtomography, control methods

Introduction

Tablets may be subdivided for various reasons. The need to divide the tablet may result from, among others, problems with taking large tablets by children, geriatric patients or people having difficulties with swallowing due to their health condition.

Sometimes, however, medical doctors prescribe larger doses of active pharmaceutical ingredient (API), but for financial reasons recommend to use only "halves" because most often individual doses cost less than purchasing an additional package [1–4].

Different methods for splitting tablets can be used, including by-hand breaking, cutting with a (kitchen) knife or with scissors, or using a splitter device. The available data show that the most optimal way to divide tablets is to use a pharmaceutical splitter device, because this method is associated with a lower weight loss and, therefore greater uniformity of the tablet pieces [3, 5].

Subdivision of tablets has a number of negative consequences, including:

- part of the tablet crumbling at the point of division,
- spall of the part of API as powder form due to the rupture of the tablet
- change in the release profile of modified release tablets as they formulate a new plane with different dimensions [6, 7].

In the case of tablets containing pellets with active ingredient, their distribution throughout the tablet may not be homogeneous, which in turn may result in different release profile of API from each of these parts. All the above-mentioned phenomena are particularly important and carry the highest risk in the case of narrow therapeutic index drugs (NTID), where even the smallest deviation from the prescribed dose may contribute to treatment failure.

When manufacturing devisable tablets, attention should be paid to three key steps that may lead to mismatches in the formulation of the solid oral form. The first one is the selection of particles of similar size. A different size of the particles in the formulation can lead to an incorrect flow rate as well as to their segregation, which results in a lack of uniformity in the tablet mass. Substances with a similar degree of powder are recommended during tableting process [8]. However, in the case of tableting after granulation, it is recommended to sieve the finished granulate through a set of sieves and separate larger particles. The second step, which ensures that the tablet mass is homogeneous, is the mixing process. In this step attention should be paid to the homogeneity of the powders used. When powder with low homogeneity is used, it will result in a low homogeneity of the substance in the finished tablets. The efficiency of the stirrer used also plays an important role in this process [8].

The homogeneity of the blend used for the production of tablets to be divided is an extremely important factor as the goal is to ensure an equal dose in all parts of the tablet. The third key step is tablet compression. During this stage, particle segregation may also take place as a result of the tablet press operation, inappropriate settings or vibrations it causes. The pressing force should be controlled to ensure the appropriate properties of the tablets, i.e. hardness, thickness and friability [9].

The exact division of the tablet, apart from the properties of this drug form, such as the shape, thickness or depth of the score line, the way of subdivision (with own hands, a knife or a special guillotine), is also influenced by the person/s understood experience of the person in dividing tablets, strength and dexterity of her hands, visual acuity or even her cognitive functions [7].

The aim of the present review was to discuss modern methods of analysis of tablets' inner structure and uniformity of ingredients in the parts of the tablets obtained after subdivision, with special emphasis on computer microtomography.

Control methods of tablets parts obtained after splitting

Polish Pharmacopeia does not provide the necessary tools to evaluate divided tablets. It should be noted, however, that the European Pharmacopoeia and the Food and Drug Administration (FDA) give some information on the tests which should be considered in the control of tablet parts. They should be

characterized by mass uniformity, which means that no more than one part may exceed the value of 85% -115% of the average weight for a given part and no parts may exceed the range of 75% -125% of the average weight of the part [10]. In addition, the divided parts should meet the requirements of composition uniformity and disintegration time as of undivided tablets. Additionally, the FDA recommends determining the loss of mass resulting from partitioning, which should not exceed 3% [11].

Modern methods of assessing the homogeneity of tablet composition

Due to the technological development, new methods of drug form analysis based on advanced spectroscopic techniques are increasingly used in pharmaceutical preparations analysis. The following techniques may be used to assess the quality of tablets: computer microtomography, Raman spectroscopy, matrix assisted laser desorption ionisation (MALDI), near infrared spectroscopy or Laser Induced Breakdown Spectroscopy (LIBS). These methods allow for testing of the chemical composition of various samples, and the dispersion of the drug substance without the need to crush the tablet, i.e. without disturbing the outer layer [2].

Computer microtomography

The X-ray microtomography (computer microtomography) is a radiographic imaging technique which allows to non-invasively characterize the microstructure of analysed samples. Advances in the development of high-resolution X-ray microtomography have made it possible to accurately determine the three-dimensional structure of opaque objects at a very high resolution. Previously, imaging with the use of microtomography allowed to understand the structure of a wide spectrum of objects, in many areas of science and industry. In biology, a microtomograph has been used to visualize the internal structure of samples in three dimensions of many species of organisms, including humans, mice and insects. Due to its high scanning resolution, microtomography has become a technique widely used to determine the formation of tissues such as teeth and bones. Moreover, the possibility of spatial determination of the structure of soft tissues, e.g. muscles, shed light on the structural basis of their functioning [12].

Microtomography is based on the principle of traditional X-ray tomography. Both methods differed when it came to the scale in which the observed structure is imaged as microtomography focuses on the analysis of small samples and allows to distinguish elements with an accuracy of 1 micrometer. The recent data showed that X-ray microtomography may be considered as a method to give reliable results in the study of cement-based materials with a solid microstructure on the basis of a precise determination of the pore volume of the tested sample. In turn, the number of open pores determine the material's permeability to external factors. In addition, thanks to the described technique, it is possible to evaluate the fractal dimension of the analysed material, as well as the fragmentation of pores, their average size and the presence of microcracks [13].

The microtomograph, similarly to the classic tomograph, uses the ability of X-rays to penetrate the analysed objects. In order to obtain a three-dimensional image of the test sample, several hundred to several thousand two-dimensional images are successively taken. Pictures are taken in precisely defined positions after each rotation of the examined structure. Then, using specially adapted mathematical methods, it is possible to precisely calculate the volumetric model that describes the entire geometry and composition of the sample [14].

In microtomography, X-rays are absorbed while passing through the study sample. The larger the sample / object, the longer the radiation path is and therefore more radiation is absorbed. The material from which the tested object is made is also important for the amount of absorbed radiation - the higher the density of this material, the greater the absorption of X-rays. The X-ray radiation in the microtomograph passes from the lamp through the sample placed on the manipulator. It allows the sample to be rotated 360° during scanning in order to

obtain photos from all sides, which is necessary to obtain a three-dimensional image. Then the tablets are scanned. Figure 1 shows the arrangement of tablets containing trazodone hydrochloride around the barrel of the microtomograph.

X-rays passing through the tablet are converted into visible radiation by means of a scintillator, which allows the image to be registered with the appropriate resolution. A two-dimensional (2D) image of the interior of the sample is obtained. This image has a certain brightness level which correlates with the density of the analysed object. During the device operation, the test sample is rotated 360° and a series of 2D photos is taken (from several hundred to several thousand), and then all the photos taken are superimposed using a computer software. Thanks to the use of various types of filters, it is possible to obtain a three-dimensional (3D) image of the tested sample, with the possibility of analysing its internal structure in every place on the 3D image. The advantage of this method is undoubtedly the fact that the test sample is not damaged in any way, thus it is known that any possible defects detected happened earlier, for example at the production stage. This technique makes it possible to see all the defects resulting from mechanical damage as well as those arising in the process of manufacturing a given object, such as microcracks, air bubbles, delamination [13, 15].

X-rays passing through the tablet are converted into visible radiation with a scintillator, which allows the image to be registered with the appropriate resolution. In order to obtain the maximum resolution of the image, i.e. the smallest possible voxel, it is necessary to set the appropriate distance between the scanned tablet and the matrix. This distance is limited by the rotation of the tablet, since the entire rotating tablet has to match the detector matrix. Absorption of X-rays by an object is proportional to its density, while in the microtomographic image the gray level is the measure of the object's density. In order to establish the reference density, a calibration phantom containing 5 templates is scanned and reconstructed under the same conditions as the analyzed tablets. Average grayscale values are determined for them; "light" pixels represent high-density areas, and "dark" pixels represent low-density areas. Figure 2 shows templates with known density, on the basis of which the density-to-brightness calibration curve can be determined.

The data regarding the usage of computer microtomography in the evaluation of inner structure of tablet parts obtained after subdivision are scarce. Wilczyński et al. [14] has analyzed the modified release tablets from theophylline, comparing wit using a microtomograph, the sum of the volume and the surface area of pellets filling the tablets. The authors

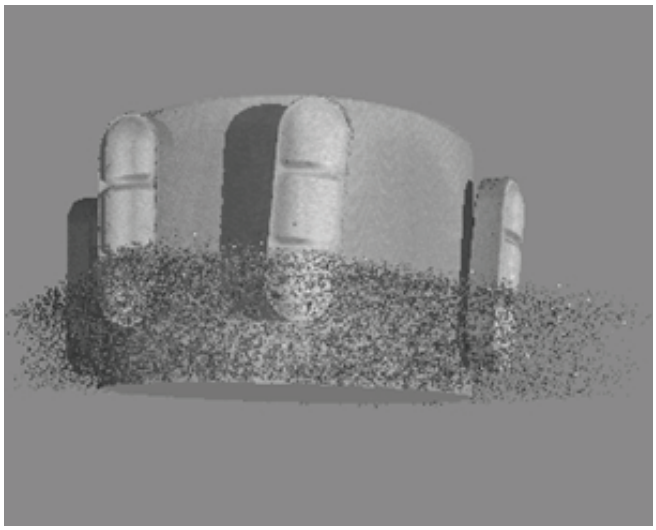

Fig. 1.
The arrangement of tablets containing trazodone hydrochloride around the barrel of the microtomograph (own study).

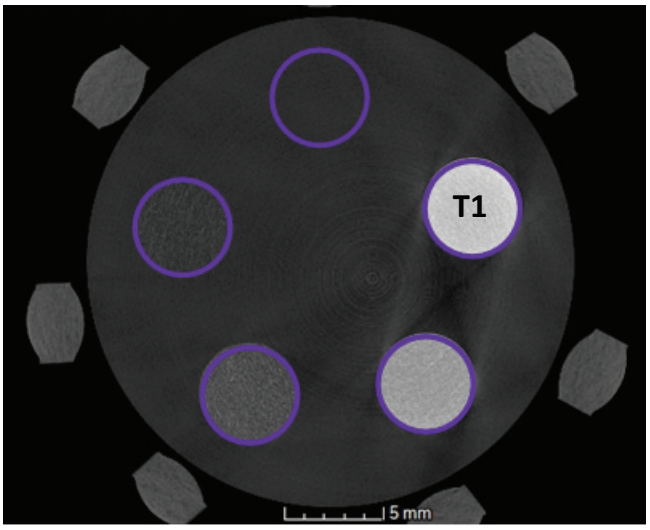

Fig. 2.
Templates (marked in purple, the brightest is T1, numbering clockwise) on the basis of which the density-to-brightness calibration curve was determined. The analyzed tablets are placed around the microtomograph barrel (own study).

showed that the potential dose of the drug substance in the half of the tablet may differ from the other half by more than 20% of the dose. The same research team used microtomography to identify counterfeit drugs [16]. The following parameters were evaluated in the processing of microtomographic scans: mean brightness, homogeneity, contrast, quadratic tree decomposition. Differences between genuine medicines vs counterfeit products were found in terms of the parameters analyzed which suggested computer microtomography as a method for identification solid dosage forms with high sensitivity and specificity. In turn, in the study by Novikova et al. [17] the inner structure of multiple unit pellet system (MUPS) tablets was studied using terahertz pulsed imaging (TPI) and X-ray microtomography. The authors detected most of the pellets in the tablets using the TPI images and confirmed these results with the microtomography images. The TPI technique was however demonstrated as a faster method than microtomography, with a pixel size in depth of 4.9μm and the possibility to precisely resolve structures thicker [17]. In another study, synchrotron phase contrast X-ray mocrotomography was used to evaluate drug particle distribution in mini-tablets with moxidectin, a drug for parasitic infections as a model drug [18]. The distribution of the drug was found to be not uniform within the tablet. Results revealed an increasing drug load towards the tablet's outer boundaries.

Raman spectroscopy

Microtomography is not the only imaging technique used in the analysis of solid dosage forms. Methods that enable both 2D and 3D assessment of the tablets, including Raman spectroscopy are also used. In many studies, Raman spectroscopy was proved to be a valuable method for pharmaceutical analysis on dosage forms such as tablets, powders and liquids [19]. This method is a vibrational spectroscopic technique and is based on energy transfer between the illuminated sample and irradiated light [20]. The basis of Raman spectroscopy is the measurement of Raman scattering, or inelastic scattering of photons. The method, using an appropriate algorithm, allows for the quantitative analysis of samples [21]. The technology of Raman spectroscopy may be used for content uniformity testing in tablet parts obtained after division. Undeniable advantage of this technique is its non-destructive nature. Raman spectrometers measure the light scattered from a sample to determine its chemical composition at the atomic scale. The usage of transmission Raman, the measurement transverses the sample volume in contrast to measuring just the surface. API content uniformity in solid dosage forms can be tested with transmission Raman spectroscopy and the method can even quantify sample composition and API concentration through tablet coatings.

The study by Gomez et al. [21] verified whether Raman spectroscopy can be used to determine the content of a drug substance. For this purpose, Sintrom 1 and Sintrom 4 preparations which contain acenocoumarol in the amount of 1 mg and 4 mg respectively were tested. The parts of the tablets formed after manual division were analyzed. For some of the tablets, mass analysis was also carried out in accordance with pharmacopoeia standards. Based on the results obtained from Raman spectroscopy, which were compared with the results of the chromatographic analysis, it was shown that the method is useful for controlling the uniformity of dispersion of the tablet components without the need to interfere with their structure. At the same time, studies have shown that the differentiation in weight in the case of quarter tablets can reach as much as 60%. For this reason, despite meeting the standards for the content of the drug substance in the tablet and despite the very satisfactory distribution of the drug substance, the division of tablets poses a real risk of significant fluctuations in the dose of the drug taken [21].

In the study by Arruabarrena et al. [22], Raman spectroscopy was used to verify the uniformity of warfarin distribution in tablets with score line. The authors demonstrated that the relative standard deviation in warfarin content among the tablet parts was found to be less than 5%.

Other methods

Another method used to study API homogeneity is matrix assisted laser desorption ionisation (MALDI). This technique consists in covering the sample with a special matrix, and then the coated surface is irradiated with a pulsed laser, as a result of which phase ions are formed. In the next step, the sample is placed on a moving plate, which is moved at an appropriate speed under the pulsed laser beam. The time each particle reaches the detector is measured. This time depends on the mass and charge. Once all particles are detected, the recorded data can be presented as a data bar containing mass spectra with intensity values for each variable. The identification of the test substance is determined by a program that automatically compares the obtained spectrum with the database. Thanks to the use of special algorithms, it is possible not only to identify the compounds in the tablet, but also to distribute them. Moreover, this technique may prove very useful in the analysis of products suspected of being counterfeit [23, 24].

Another method, which is still being developed, is terahertz imaging. Similarly to the above-mentioned methods, it is also a sample-saving technology. Terahertz, called T rays (wave frequency in the range 0.1 THz - 0.3 THz), are able to penetrate deep into objects that are opaque to visible and infrared radiation (such as e.g. plastics, clothing, bones) while they are strongly attenuated in materials conductive, e.g. metals, water, electrolytes. What is important is that these waves are safe for living organisms, which makes them an interesting alternative to X radiation. Terahertz radiation is generated by a polarized photoconductive antenna with ultra-short laser pulses. The emitted pulses with the help of appropriate lenses are collected, arranged using a collimator and then focused on the test sample. Penetrating the sample, these rays are partially reflected at the phase boundary between different substances. In the case of tablets, this can be the boundary between the active ingredient and the fillers as well as the boundary between the coating and the inside of the tablets. The reflected terahertz pulses at the interface are collected and focused on a laser-gated photoconductive antenna for terahertz detection. Before performing a scan with terahertz waves, it is necessary to make a 3D image of the test sample with a laser, which are then superimposed on each other, which helps in accurately reproducing the structure of the tested solid form of the drug [25, 26]. Unfortunately, this method has some disadvantages. Devices emitting such radiation require a lot of space due to their size, however, they are constantly being improved. This method is also used in other fields, there are many publications on the use of terahertz to diagnose various types of tumors in the human body [27, 28]. The use of terahertz imaging can also be used at airports during luggage control. There are studies confirming the usefulness of this technology in the study of the coating of solid drug forms, many of them also indicate the usefulness of this method for examining the inside of tablets, therefore it should be considered in terms of tablet dividing analysis. [25, 26]

Noteworthy is also near infrared spectrometry, a method used in medicine and food industry. It is based on waves in the range 650 nm – 1100 nm. It uses the phenomenon of, in this case, infrared radiation absorption by the tested object, which causes vibrations of chemical bonds of high polarity, such as -CH, -OH, -NH, -SH. The vibrations generated have a characteristic frequency, which allows for the identification of the components contained in the tested material. The main elements of the spectrophotometers are a monochromator, a measuring cell and a detector connected to a computer with software capable of processing the received signal. The obtained spectra are unfortunately burdened with a large so-called photometric noise, therefore special calibrations are given to eliminate them. This allows you to obtain interpretable results [29].

An unquestionable advantage of this method is the possibility of conducting the analysis in real time and, as in the case of the other mentioned methods, saving the sample. [30] Similar to other modern methods, it is quite expensive and requires specialized equipment and trained personnel. The preparation of samples for testing is simple and not time-consuming. There are reports in the literature of the use of this method in the analysis of the tabletting process. [31] We can also find some that refer to the use of the above-described method to assess the homogeneous distribution of an active substance in a solid drug form. [32].

Conclusion

Along with the many advantages of dividing tablets, there are also many disadvantages. The safety of this practice is ambiguous and in general, based on many scientific sources, it is not recommended to neither doctors nor patients. Undoubtedly, in order to thoroughly analyse the problem, additional studies are needed, characterized by high sensitivity and a low margin of error. X-ray microtomography assisted by image analysis and processing techniques can be used to assess the homogeneity of active pharmaceutical ingredient distribution in the tablets.

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