Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 64 (2006) 38–50
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Quantitative measurements of localized density variations in cylindrical tablets using X-ray microtomography

Virginie Busignies [a], Bernard Leclerc [a], Patrice Porion [b], Pierre Evesque [c], Guy Couarraze [a], Pierre Tchoreloff [a,*]

[a] Centre d'études Pharmaceutiques de l'Université Paris XI, Innovation Thérapeutique: du Fondamental au Médicament, Châtenay-Malabry, France
[b] Centre de Recherche sur la Matière Divisée – UMR 6619, CNRS and Université d'Orléans, Orléans, France
[c] Laboratoire de Mécanique: Sols – Structure – Matériaux – UMR 8579, Ecole centrale de Paris, Châtenay-Malabry, France

Received 5 October 2005; accepted in revised form 17 February 2006
Available online 18 April 2006

Abstract

Direct compaction is a complex process that results in a density distribution inside the tablets which is often heterogeneous. Therefore, the density variations may affect the compact properties. A quantitative analysis of this phenomenon is still lacking. Recently, X-ray microtomography has been successfully used in pharmaceutical development to study qualitatively the impact of tablet shape and break-line in the density of pharmaceutical tablets. In this study, we evaluate the density profile in microcrystalline cellulose (Vivapur 12®) compacts obtained at different mean porosity (ranging from 7.7% to 33.5%) using X-ray tomography technique. First, the validity of the Beer–Lambert law is studied. Then, density calibration is performed and density maps of cylindrical tablets are obtained and visualized using a process with colour-scale calibration plot which is explained. As expected, important heterogeneity in density is observed and quantified. The higher densities in peripheral region were particularly investigated and appraised in regard to the lower densities observed in the middle of the tablet. The results also underlined that in the case of pharmaceutical tablets, it is important to differentiate the mechanical properties representative of the total volume tablet and the mechanical properties that only characterize the tablet surface like the Brinell hardness measurements.

Keywords: X-ray tomography; Compaction; Tablet; Density distribution; Anisotropy; Quantitative analysis; 3D imaging; Mechanical properties

1. Introduction

Direct compaction is commonly used in pharmaceutical industry to produce pharmaceutical tablets. The density distribution inside the tablets is often heterogeneous due to interparticle frictions and die wall frictions [1]. At the beginning of the compaction, interparticle frictions are predominant, but the die wall frictions become more important when the pressures are increased. More, the shape of tablets used in pharmaceutical industry differs from flat-face cylindrical tablet to more complex geometries with various embossing. The consequence is that the density variations in pharmaceutical tablets may be important and affect the compact mechanical properties. Train [1] performed the first study on the density variation in powder compacts. Later, density distribution was investigated using NMR tomography [2] or autoradiography [3]. Sinka et al. [4] also used surface hardness tests on tablets' cross-section. Recently, X-ray microtomography has been successfully used in pharmaceutical development. Farber et al. [5] used this method to study the porosity and the morphology of pharmaceutical granules. Sinka et al. [6] have shown the dependence of tablet shape and break-line on the density variations of pharmaceutical tablets.

The X-ray tomography which allows 3D characterization of micro-structure has some advantages compared to other methods [7]. This is a nondestructive investigation

* Corresponding author. Laboratoire de Physique Pharmaceutique, Centre d'études Pharmaceutiques de l'Université Paris XI, 5 Rue Jean Baptiste Clément, 92296 Châtenay-Malabry Cedex, France. Tel.: +33 1 46 83 56 11; fax: +33 1 46 83 58 82.
E-mail addresses: pierre.tchoreloff@phypha.u-psud.fr, pierre.tchoreloff@cep.u-psud.fr (P. Tchoreloff).

0939-6411/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2006.02.007

from which many 2D sections can be extracted and contrary to 2D observations, there are no artefacts due to sample preparation. More, the micro-structural characterization is possible at high and medium resolution (from 1 to few hundred microns). Nevertheless, as the sample should rotate in the field of view of the detector, a compromise must be found between the maximum sample size and the spatial resolution. One other disadvantage could be the time for a complete scan. It is strongly influenced by the resolution, the size of the sample, the resolution of the CCD camera and the spot size of the X-ray source. For tableting, X-ray tomography is more adapted to the analysis of density variations than the use of surface hardness that is a destructive technique which requires careful specimen preparation. More, the resolution is limited by the spacing between indentations [6].

In this work, we try to evaluate quantitatively the density variation in cylindrical compacts of microcrystalline cellulose using the X-ray microtomography. Beforehand, perfecting of the technique is achieved with the demonstration of the validity of the Beer–Lambert law and the construction of a colour-scale calibration plot of density. Then, the density maps are obtained for different tablets and they are discussed.

2. X-ray microtomography principle and its limits

The X-ray microfocus computed tomography (X-ray μCT) method is a nondestructive inspection technique which provides cross-sectional images in different planes from the sample [8]. The principle of the third generation CT imaging is illustrated in Fig. 1. The sample is placed on a precision turntable in a divergent beam of X-rays. A detector (which is in fact a one-dimension or two-dimension array of detectors) is used to measure the local intensity distribution of a diverging X-ray beam transmitted through the sample, as the sample is rotated step-by-step angle in the beam, around its axis. The sample position from the X-ray source determines the geometrical magnification (i.e. the resolution which is also limited by the detector size) according to the principle of the cone-beam geometry. This leads to a series of radiographs also called projection images at different viewing angles. From this set, one can reconstruct a three-dimensional representation of the structure and/or a composition distribution within a sample, using a mathematical algorithm based on the Beer–Lambert law of absorption (see Eq. (1)). This reconstruction is called a tomogram; it has a spatial volume resolution, which is called a voxel. To facilitate the analysis, the tomogram can be decomposed in a series of cross-sectional images in a chosen plane, and these cuts can be interpreted in terms of density or composition distribution after the calibration process. According to the Beer–Lambert law, the dependence of the intensity $I(x)$ of the X-ray beam after its crossing through a layer of homogeneous material of thickness x is related to the initial intensity I_0 and the linear attenuation coefficient μ through

$$I(x) = I = I_0 \, e^{-\mu x} \quad \text{or} \quad -\ln(I/I_0) = \mu x, \tag{1}$$

where μ is a local coefficient which characterizes the material; it is expected to depend on the chemical nature of the compounds and to vary linearly with each local amount of compound [9,10] according to Eqs. (2) and (3)

$$\mu = \rho_i(\mu_{i0}/\rho_{i0}), \tag{2}$$

where ρ_i is the real local density of chemical i, and μ_{i0}/ρ_{i0} is the ratio of its normal absorption coefficient to its normal density ρ_{i0} (in g cm^{-3}). When few chemical compounds are mixed one uses the additivity property of local absorption coefficient and writes

$$\mu = \sum_i \rho_i(\mu_{i0}/\rho_{i0}) \tag{3}$$

leading to the generalised Beer–Lambert law for monochromatic X-ray beam

$$\ln(I/I_0) = -\int \mu(l)\,\mathrm{d}l, \tag{4}$$

where $\mathrm{d}l$ is the infinitesimal length along the trajectory of X-ray beam in the material, and the summation runs over the whole path. Neglecting refraction effect from local heterogeneities, one can use the linearity of Eq. (4) to reconstruct the density distribution by inversion of the set of Eq. (4) obtained at different angles.

Things become more intricate when X-ray beam is non-monochromatic, since it is known that the μ_{i0} coefficients depend on X-ray wavelength λ and because a sum of exponentials is not an exponential. Indeed, imagine that a lower energy X-ray beam is more strongly absorbed than a higher energy one, and that the initial beam is composed of these two wavelengths, then the energy distribution spectrum of the beam changes as it passes through the sample and the beam becomes harder, this effect is called "beam hardening". Consequently for polychromatic X-ray source, the attenuation of a homogeneous sample is not always strictly proportional to its thickness. In other words, the Beer–Lambert law is not valid any more. As, the projection data are not linear with the sample thickness, the reconstruction

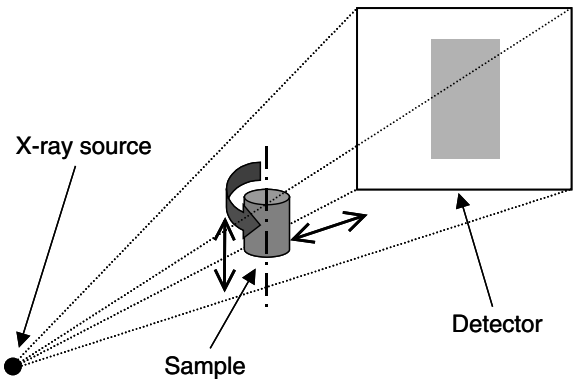

Fig. 1. X-ray microtomography principle.