Thermal Expansion of Organic Crystals and Precision of Calculated Crystal Density: A Survey of Cambridge Crystal Database

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ABSTRACT: True density is a physical property of both fundamental and practical importance to the study of pharmaceutical powders. True density may be calculated from crystal structure. However, precision of such calculated density is not well understood. Furthermore, thermal expansion properties of organic crystals have rarely been characterized. A survey of Cambridge Crystal Database is conducted to assess (1) precision of calculated crystal density from crystal structure; (2) thermal expansion properties of organic crystals. It is shown that calculated crystal density exhibits, on average, a relative standard deviation (RSD) of ~0.4%. It is found that crystal density generally increases linearly with decreasing temperature provided no phase change occurs. Slope of the line, termed thermal density gradient, of organic crystals ranges between 0.04 and 1.74 mg cm^{-3} K^{-1} with an average of ~0.2 mg cm^{-3} K^{-1}. It is shown that majority polymorph pairs exhibit significantly different thermal expansion behavior and their density—temperature lines can cross. This likely contributes to the less than perfect prediction of relative stability of polymorphs at ambient temperature using the density rule. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:1043–1052, 2007

Keywords: crystals; true density; thermal expansion; polymorphs; density rule

INTRODUCTION

True density is a physical property of both fundamental and practical importance to the study of pharmaceutical powders. True density has been used to predict relative stability of polymorphs, that is, density rule.[1,2] Conceptually, the density rule can be quite reliably applied at near 0 K where the free energy equals enthalpy. For a given pair of polymorphs, a higher crystal density corresponds to closer packing of molecules. For crystals that are dominated by van der Waals interactions, the closer packing often corresponds to lower lattice energy and thus free energy at 0 K. However, if crystal packing is dominated by energetically more favorable directional or electrostatic interactions, such as hydrogen bonding, crystal with a closer packing may not always exhibit a lower lattice energy and free energy even at 0 K. Moreover, crystal packing efficiency is also dependent on temperature as evident by the thermal expansion properties of crystals. Perhaps for these reasons, density rule is only correct ~90% of the time even after exclusion of polymorph pairs with density difference of less than 1%.[1] True density also plays critical roles in the investigation of powder compaction behavior employing various compaction equations.[3–5] Inaccuracy in true density can profoundly affect the understanding of powder mechanical properties by the means of measuring mechanical properties

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of compressed tablets.[6,7] True density measurements can also be used to assess crystallinity.[8,9] However, these types of study call for the greatest possible precision in density determination since differences in true density may be quite small for solids different only in degree of crystallinity.

The three most commonly used methods for density determination are displacement of a liquid, displacement of a gas, and flotation in a liquid. The liquid displacement method is laborious and not routinely used. Five significant figures may be obtained using the flotation method. Four significant figures may be obtained using the helium pycnometry. However, these methods are not suitable for solids containing volatile components or powder mixtures. Alternatively, true density with four significance figures may be derived by nonlinear regression of pressure—tablet density data.[10] However, typically a few grams of powder is needed and the solid must not undergo phase transition during compaction. True density of highly crystalline particles may also be calculated from corresponding single crystal structures. In early days of X-ray crystallography, density of crystals was determined, typically using the flotation method, prior to X-ray investigation to facilitate correct determination of unit cell dimensions. Advances in X-ray crystallography make rapid determination of crystal structures a routine matter. During the present time, few crystallographers spend effort on relatively laborious experimental determination of crystal density prior to X-ray diffraction study. The determination of experimental densities is becoming a lost art in crystallography.[11] To the opposite, crystal true density is routinely obtained from the unit cell dimensions and contents. Since structures of crystals containing volatile components may be determined at subambient temperature by X-ray diffraction, true density of these crystals otherwise not accessible using other methods may be readily obtained.

Crystal structures are experimentally determined primarily by X-ray, sometimes neutron, diffraction. The experimental nature of calculated true density from crystal structure has not been well recognized in pharmaceutics. It is more often than not that calculated density is perceived as highly accurate and precise. It was recently pointed out that experimental errors in unit cell dimensions of single crystals can be substantially higher than what are suggested by the black-box crystallography data processing software.[12] It follows that calculated crystal density may also exhibit higher degree of imprecision than it is typically viewed. One goal of this study is to better understand precision of calculated crystal density by surveying the crystal structures with multiple occurrences in the Cambridge Structure Database (CSD).[13]

Crystal structures are often solved at a subambient temperature for better data quality because of reduced thermal motions of molecules. For this reason, there has been a trend of increasing percentage of crystal structures solved at subtemperature in recent years.[14] However, the temperature of interest is typically ambient temperature in pharmaceutics. In order to make use of the crystal structures solved at subambient temperature to calculate density at ambient temperature, appropriate corrections must be made to account for thermal expansion of crystals. With an increase of temperature, organic crystal lattices expand anisotropically, that is, expansion along one unit cell axis is often companied by contraction along other axes or the three axes may expand to different degrees.[14] Although thermal expansivities of common gases, liquids, and engineering solids have been very well studied, thermal expansivity of organic crystals has not been systematically studied. Another goal of this study is to better understand the distribution of thermal expansivity of organic crystals by analyzing available crystallographic data as a function of temperature.

The isobaric thermal expansivity, α, may be defined as follows:

$$\alpha = \frac{1}{V}\left(\frac{\mathrm{d}V}{\mathrm{d}T}\right)_P \tag{1}$$

where V is the molar or specific volume. T is the absolute temperature and the subscript P denotes that the pressure is constant. Eq. 1 may be modified based on density, D, as shown in Eq. 2.

$$\alpha = -\frac{1}{D}\left(\frac{\mathrm{d}D}{\mathrm{d}T}\right)_P \tag{2}$$

If α is constant over the entire temperature range, one anticipates the $\mathrm{d}D/\mathrm{d}T$, that is, slope of the line of crystal density versus temperature, to increase with increasing temperature. As we shall see later, the relationship between density and temperature is linear within the accuracy of experiment for almost all organic crystals over a wide range of temperature (ambient to near 0 K). This suggests αD is constant for most organic crystals but α is not. For this reason, we shall focus our