Effects of Storage Conditions on the Free Volume of Polyvinylpyrrolidone: Comparison of Positron Lifetime Data with the Tensile Strength of Tablets

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INTRODUCTION

Materials are usually classified as brittle or ductile depending on the predominant properties of particles. Recently ductile materials as, e.g., amorphous and partially crystalline polymers are getting a remarkable attention in pharmaceutical research because they suffer from problems as strain rate sensitivity and an extreme sensitivity to water content (1–2). Stubberud (3) reported that the absorption moisture had a weakening effect on the tensile strength of compacts of crystalline and partially amorphous lactose. Alderborn and Ahlneck (4) assessed the effect of humidity on the post compaction changes of the tensile strength of tablets formulated with different pharmaceutical excipients. They concluded that the changes of the strengths of tablets were probably due to a rearrangement of the solid material in the tablets caused by the absorbed water.

Water frequently acts as a potent plasticizer for amorphous materials and, since many of these solids absorb water from their surroundings spontaneously, the relationship between the glass transition temperature and the water content of these materials is important (5). This plasticizer effect could generally be described using a simplified form of the Gordon-Taylor/Kelley-Bueche relationships derived from the free volume theory of polymers (6–7). Positron lifetime technique provides a unique possibility to investigate the free volume of polymers through the lifetime of ortho-positronium atoms (8), which might help the interpretation of tensile strength data.

The main goal of this paper was to study the effects of storage conditions (relative humidity and storage time) on the free volume of Kollidon 25 powder samples. Another aim was to find a correlation between the changes of the free volume of the applied binder and the strength of tablets.

MATERIALS AND METHODS

Materials

Polyvinylpyrrolidone (PVP, Kollidon 25, BASF, Ludwigshafen, Germany) was used as the amorphous binder and Anhydrous theophylline (Hungaropharma, Budapest, Batch No. B-16263.95) as the substrate for the preparation of tablets.

Tablet Preparation

9 batches of 300 tablets were produced using a wet granulation procedure beginning with the mixing of 100 g Anhydrous theophylline (Ph.Hg. VII., Hungaropharma, Budapest, Batch No. B-16263.95) and 10 ml of a 15% (w/v) Kollidon 25 aqueous solution. Next the wet granulated mass has been dried in a hot air drier at 60°C for 24 h (Labor-Innova, Hungary). The dried granule mass was fractionated with a vibrating sieve and the fractions of 0.250–0.630 mm particle size range were used for the compression. Tablets of 12 mm in diameter were compressed from the granules using a force of 1000 N with a single-punch tableting machine.

Storage Conditions

The dried tablets were divided into batches and transferred into the 3 desiccators kept at 55%, 65% and 75% R.H. and room temperature for three storage periods of 1 day, 15 days and 30 days. Powder samples of Kollidon 25 were also kept under the same storage conditions.

Water Content Determination

The determination of the water content of the Kollidon 25 samples was performed by Karl-Fischer titration (Methrom, 736 GP Titrino). The applied reagents were Karl-Fischer solution A (Merck 1.092747) and Karl-Fischer solution B (Merck 9246).

Determination of the Tablet Strength

The hardness test was performed on one third of the compact-batches after a storage period of 1 day, while the remaining two parts were stored further and tested for their hardness after 15 days and 30 days (PharmaTest PTB 311, Hainburg, Germany). The tensile strength (σ) of the tablets was determined (9) by the following equation:

$$\sigma = \frac{2P}{\pi D t} \qquad (1)$$

where P is the measured crushing force, D is the diameter and t is the thickness of the tablet.

Positron Lifetime Measurements

In positron lifetime spectroscopy positrons are emitted into materials, usually from radioactive nuclides decaying by positive beta-radiation. As the positron is the antiparticle of the electron, when they meet they annihilate. The lifetime of a positron proportional with the local electron density which depends, in the case of polymers, on the size of the free volume. Sometimes positrons form a bound state with electrons. This

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so called positronium atom is very similar to a hydrogen atom but the proton is replaced by the positron. In studies dealing with polymers this positron state is the most important lifetime parameter.

Positron lifetime measurements were performed with a conventional fast-fast coincidence system [10]. The system was constructed from standard ORTEC electronic units and the detectors from BaF_2 scintillation crystals and XP2020Q photomultiplier tubes. The time resolution of the system was about 200 picoseconds.

The spectrum evaluation was done by the RESOLUTION computer code [11]. Three lifetime components were found in every case from which the longest one was used to determine the average size of free volumes. This lifetime component is associated with the annihilation of positronium atoms and it is proportional with the free volume size [12]:

$$\tau = \frac{1}{2}\left[1 - \frac{R}{R + \Delta R} + \frac{1}{2\pi}\sin\left(\frac{2\pi R}{R + \Delta R}\right)\right]^{-1}, \qquad (2)$$

where τ is the positronium lifetime, R is the radius of the free volume hole, and ΔR is a constant. Note that the shape of free volumes is supposed to be uniformly spherical in this approximation.

The medium long lifetime component is associated with positrons which are not able to form positronium atoms in the polymer but, instead, annihilate directly with the electrons of polymeric chains. Usually the lifetime of these positrons reacts to the structural changes of polymers very sensitively.

Statistical Experimental Design

A two-factor, three-level symmetric factorial design (13) was applied to construct a polynomial model describing the effects of storage conditions (relative humidity and storage time) on the strength of tablets (y_1) prepared with Kollidon 25 and on the free volume of Kollidon 25 applied as a binder (y_2) in the course of tablet formulation. The two factors, as well as their levels, are shown in Table I. The levels for all the parameters are represented by a (−) sign for the lower level, a (+) sign for the higher level and by (0) for the base (0) level. To avoid the artefact caused by the different magnitude of the factors, coded levels of variables were applied. The TableCurve 3D (Jandel Scientific, SPSS, Erkrath, Germany) software was applied for the multiple regression analysis. The expected form of the polynomial equation is:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1\,x_2 \qquad (3)$$

where y is the response, x_i-s are the factors, and b-s are the coefficients characterizing the main (b_1, b_2), the quadratic (b_{11}, b_{22}), and the interaction (b_{12}) effects.

Table I. Experimental Design with Factors and Their Levels

Levels	χ_1 Relative humidity (%)	χ_2 Storage time (day)
Lower (−)	55	1
Base (0)	65	15
Higher (+)	75	30

Table II. Randomized Matrix of the Two-Factor, Three-Level Factorial Design

Trial	Controlled factors		Response parameters			
			y_1 σ (Mpa)		y_2 V (A^{o3})	
	x_1	x_2	Measured	Predicted	Measured	Predicted
1	−	−	0.95	0.926	23.192	22.946
2	−	0	0.78	0.747	23.500	23.356
3	−	+	0.58	0.638	23.157	23.547
4	0	−	0.32	0.380	22.217	22.585
5	0	0	0.24	0.283	22.817	23.353
6	0	+	*0.36*	*0.257*	*24.806*	*23.902*
7	+	−	0.10	0.064	26.205	24.684
8	+	0	0.06	0.050	26.203	25.811
9	+	+	0.06	0.106	26.203	26.717

RESULTS AND DISCUSSION

The following polynomial equations ($r_1 = 0.9851$, $r_2 = 0.9426$), obtained after significance testing at the confidence level of 95%, represent the effects of independent variables (x_1, x_2) on the tensile strength of tablets (y_1) containing Kollidon 25 and on the free volume of Kollidon 25 (y_2).

$$y_1 = 0.283 - 0.348\,x_1 - 0.061\,x_2 + 0.115\,x_1^2 + 0.035\,x_2^2 + 0.083\,x_1x_2 \qquad (4)$$

$$y_2 = 23.353 + 1.227\,x_1 + 0.659\,x_2 + 1.230\,x_1^2 - 0.109\,x_2^2 + 0.358\,x_1x_2 \qquad (5)$$

The randomized matrix of design is shown in Table II. The negative value of b_1 ($b_1 = -0.348$) refers to the effect of relative humidity on the tablet strength which is not dominant because of the positive quadratic effect of the same factor ($b_{11} = 0.115$). With increasing relative humidity and storage time, the absorbed water was also increased. The negative relative humidity and storage time effect ($b_2 = -0.061$) can be explained by the plasticizing effect of the absorbed water. Due to this plasticizing effect, the glass transition temperature of the pure Kollidon 25 samples decreased to room temperature at 75% R.H. (5,14). The negative value of the coefficient for the relative humidity was five times larger than that for the

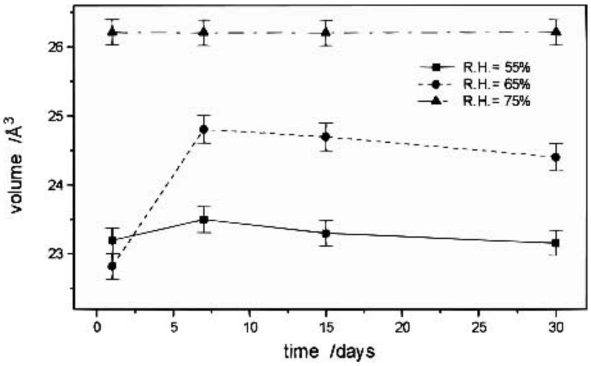

Fig. 1. The average free volume size for Kollidon 25 samples stored under different humidity conditions.

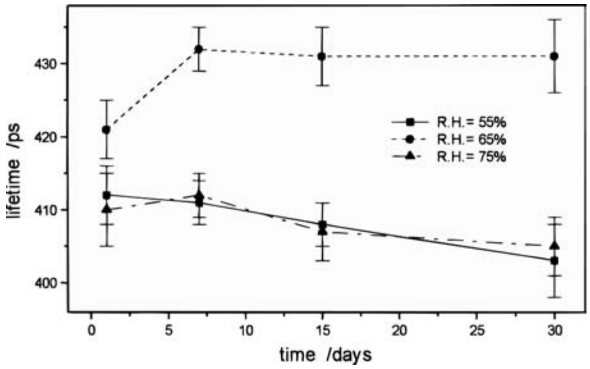

Fig. 2. The lifetime of positrons annihilating without positronium formation.

storage time. The reason for this phenomenon could be the fast water absorption from the storage medium (14).

According to ortho-positronium lifetime data, the average size of free volumes in Kollidon 25 increases considerably with the increasing humidity. The rates of the water absorption and the size increasing processes change with the relative humidity. At R.H. = 65% the maximum size of free volumes was reached in about seven days, while at R.H. = 75% the much higher maximum has already been reached after a day of storage. These facts are expressed in the coefficients of the fitted polynoms ($b_1 = 1.227$; $b_2 = 0.659$). Figure 1 represents the average free volume size for Kollidon 25 samples stored under different humidity conditions. The volumes were determined from ortho-positronium lifetimes using Eq. (2).

If we consider the lifetime of positrons instead of ortho-positronium atoms, we should note the special role of the 65% R.H. Figure 2 illustrates the lifetime of positrons annihilating without positronium formation. The higher values at 65% R.H. indicate a different structure in which positrons see a lower eletron density than in other cases. At this humidity the lifetime of positrons is much longer than in any other case. These larger values indicate that, at 65% R. H., positrons do not have so many electrons to annihilate with. This fact suggests that the transition from the glassy state (at room temperature and 55% R.H.) to the completely plasticized wet rubbery state (at R.T. and 75% R.H.) is not continuous in Kollidon 25. At 55% R.H. and 75% R.H. positrons "feel" almost identical electron densities but during the transition a different structure should be formed. This "transition state" is at present in the samples stored at 65% R.H. which was previously confirmed by DSC (enthalpy relaxation) experiments (14). The sudden increase of tensile strength of tablets stored at 65% R.H. can be explained by the fact that Kollidon 25 is undergoing structural modification under the same conditions.

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