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Determination of moisture content in relation to thermal behaviour and plasticization of Eudragit RLPO

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ABSTRACT

Coalescence of polymer particles on thermal treatment plays an important role in effective control of drug release from these matrix systems. The water content of the polymer may influence coalescence since it is well established that sorbed water may act as a plasticizer, or cause other changes in mechanical properties. However, these effects depend on the amount and type (plasticizing/nonplasticizing) of water present. The purpose of this study was to determine the accuracy of different methods used to determine moisture content of a polymer (Eudragit RLPO) and to determine the types water present. The polymer powder was stored at various relative humidities (33, 56, 75, 94%). Four water determination methods, [weight loss on drying, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and Karl Fischer titration (KFT)] were utilized to determine moisture content. DSC was used to study the thermal behaviour of moist and dry samples. The Gordon-Taylor equation was used to calculate the amount of plasticizing water. Scanning electron microscopy was employed to examine the morphology of the polymer particles after thermal analyses. It is concluded that KFT accurately determines the total water content but that the thermal methods underestimate total water content. However KFT does not indicate the type of water present. The Gordon-Taylor model suggests that only about 25% of the water in the polymer containing 10% water was acting as a plasticizer. Complementary methods should be used to measure the water content of pharmaceutical polymers.

1. Introduction

Two pre-requisites for studying the effects of water on the behaviour of pharmaceutical formulations are: robust methods to accurately quantify the water; and methods to determine the types (e.g. plasticizing/nonplasticizing) of water present. Thermal methods including oven drying, DSC and TGA have been used in the food and pharmaceutical industries for many years. In the food literature it is recognized that the most suitable method depends on the nature of substances (Adam et al., 2009; Artiaga et al., 2005; Bengoechea et al., 2007; de Angelis Curtis et al., 1999; McMahon et al., 1999; Moro García et al., 1993; Saldo et al., 2002) and that types of water and the property of the dry mass itself affect the performance of water determination methods (Yazgan et al., 2006). However, how to choose for pharmaceutical polymers is not clear.

In polymeric matrix systems control of release can depend on the formation of a stable polymer matrix achieved through coalescence of the polymer particles (Krajacic and Tucker, 2003). Coalescence occurs above the glass transition temperature (T_g) of the polymer and thus thermal treatment of polymer matrices above the T_g of the polymer changes their release behaviour (Abbaspour et al., 2007; Azarmi et al., 2002, 2005; Omelczuk and McGinity, 1993). However, the T_g of a polymer is lowered by any agent which 'dissolves' in it (Ahlneck and Zografi, 1990); so, not only can excipients and drugs have a plasticizing effect on a polymer (Gómez-Carracedo et al., 2004; Nair et al., 2001; Siepmann et al., 2006), but water also has been shown to suppress the T_g of amorphous pharmaceutical solids (Hancock and Zografi, 1994). The water may comprise non-freezable bound water which is strongly interacting with the polar part of a hydrophobic polymer causing T_g suppression conforming to the Gordon-Taylor prediction, and excess water, absorbed in the polymer as clusters, with no effect on T_g (Blasi et al., 2005). Water may have other effects on interactions between particles thereby affecting flow and compaction behaviours or even weakening interparticle bonding (Bravo-Osuna et al., 2007). Accurate assessments of water concentrations are therefore important in polymeric systems.

Acrylic polymers are used for pH-dependent or pH-independent controlled release and site specific formulations (Albers et al., 2009; Glaessl et al., 2010; Sauer et al., 2009; Semdé et al., 2000; Zhu et al., 2006). The acrylic polymer ammonio methacrylate

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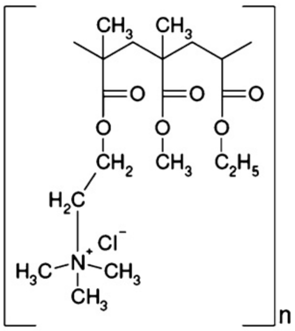

Fig. 1. Chemical structure of Eudragit RLPO [poly (ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2].

copolymer type A, Ph. Eur./NF (Eudragit RLPO) was chosen in this study not only for its pharmaceutical applications but also for its T_g of 55–70 °C (Zhu et al., 2006) it is a useful model to study the effects of water on the coalescence behaviour of polymer particles.

One of the most common methods to quantify water present in a solid is the determination of mass loss on drying; however, the sample size needed is relatively large (g), and the results may overestimate water content due to volatile substances (Hinz, 2007). Conversely, moisture content can be underestimated when some tightly bound water is not eliminated during thermal treatment (Towns, 1995). The use of a highly sensitive balance in thermogravimetric analysis (TGA) allows the use of small samples (5–10 mg) and temperature programming means free/bound water, and water of hydration can be identified (Barnes et al., 1993). Through differential scanning calorimetry (DSC), the T_g of the polymer and the mass of bulk water (from the freezing exotherm) can be estimated using a single small sample. In addition area under the water evaporation endotherm can be used to estimate water content on the sample based on the literature value for the molar enthalpy of vaporization (ΔH_v/mol), of water (Khankari et al., 1992). Chemical titration, most importantly the Karl-Fischer method established in 1935, is regarded as the gold standard in water determination. Methanol or other organic solvents which stabilize the reaction, must completely dissolve the components of the matrix to ensure release of all water for analysis (Hinz, 2007).

The aim of this study was to compare methods for the determination of total moisture content of a pharmaceutical polymer and to distinguish the types of water present. We report the difficulties of accurately measuring the water content of Eudragit RLPO and that chemical, gravimetric and thermal methods give different results. Further, we report that only some of the water in the polymer is acting as a plasticizer but surprisingly the nonplasticizing water is not present as bulk water.

2. Materials and methods

2.1. Materials

Eudragit® RLPO (Fig. 1) (ammonio methacrylate copolymer type A, Ph. Eur./NF) was kindly provided by Evonik Industries (Darmstadt, Germany). The one-component Karl Fischer reagent, CombiTitrant® 5, and methanol (analytical grade) were purchased from Merck (NZ) Ltd. (Auckland, New Zealand). Magnesium chloride, sodium bromide, sodium chloride, and potassium nitrate were of analytical grade and were purchased from Biolab (NZ) Ltd., or Ajax Finechem (Auckland, New Zealand). High-purified water was used for Karl Fischer calibration (ion exchanged, distilled, and passed through a Milli-Q water purification system) (Millipore, Bedford, MA).

2.2. Sample preparation

Eudragit® RLPO powder was stored in thin layers in tightly closed chambers over silica gel or saturated salt solutions with relative humidities of 33, 56, 75, 94% (Rockland, 1960). The temperature and relative humidity were monitored with HOBO® data loggers. These samples were measured for moisture content by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and Karl Fischer titration (KFT). In a separate study, samples from the humidity chambers were then stored in an oven at 120 °C for 15 min (simulated TGA heating program). The surface area to mass ratio of samples was the same as those in the TGA pans. The samples were then investigated for moisture content by weight loss, KFT, and DSC. Additionally, thermal behaviours of the moist, and oven dried samples were studied by DSC.

2.3. Moisture content determination

For loss on drying, the samples were accurately weighed before and after oven drying. Moisture content (MC) was calculated as:

$$\text{MC} \quad (\%) = \frac{(W_b - W_a) \times 100}{W_b}$$

where W_b is the weight before drying and W_a is the weight after drying.

For TGA, polymer samples (15–20 mg) were heated at 20 °C/min up to 150 °C in a Q50 TA instrument (USA), with TA instrument universal analysis 2000 software. Moisture content (%) was determined by the stable weight loss (%) at a temperature around 100 °C.

For DSC (calibrated for temperature and enthalpy with indium), polymer (about 8 mg) was filled into sample pan and closed with a pin-holed lid. The sample was cooled to −90 °C then heated to 80 °C at 50 °C/min (first heating to eliminate the relaxation endotherm of the T_g). The sample was then cooled to −75 °C, nominally at −20 °C/min, then heated to 170 °C in order to determine the T_g of moist polymer and the moisture content. The sample was then cooled to −75 °C, nominally at −20 °C/min, and reheated at 50 °C/min to 170 °C to determine the T_g of dry polymer. The T_gs are reported at the transition inflection point. The moisture content was estimated from the sample mass, the area under the endotherm due to evaporation of water and assuming a water evaporation enthalpy of 2257 J/g (O'Neil et al., 2001). A Q100 TA instrument (USA), with TA instrument universal analysis 2000 software were used for the DSC studies.

For KFT, the sample (100–200 mg) was titrated using a 736 GP Titrino, Metrohm, (n = 3). The one-component Karl Fischer reagent, CombiTitrant®5 was used as a titrant, and methanol was used as a solvent. The mixture was calibrated against pure water.

2.4. Morphology study

After mounting onto aluminium stubs with double sided carbon tape and coating with a 25 nm gold palladium layer (Emitech 575× High Resolution Sputter Coater, E.M. Technologies Ltd., England), the surface of the sample was investigated by field emission scanning electron microscopy (SEM, JEOL JSM-6700F, JEOL Ltd., Japan). The accelerating voltage was 3 kV and the lower secondary detector (LEI) was used.

3. Results and discussion

3.1. The effect of humidity on moisture content determined using TGA

A typical TGA thermogram from which the moisture content was calculated by determining the weight loss at 100 °C is shown in

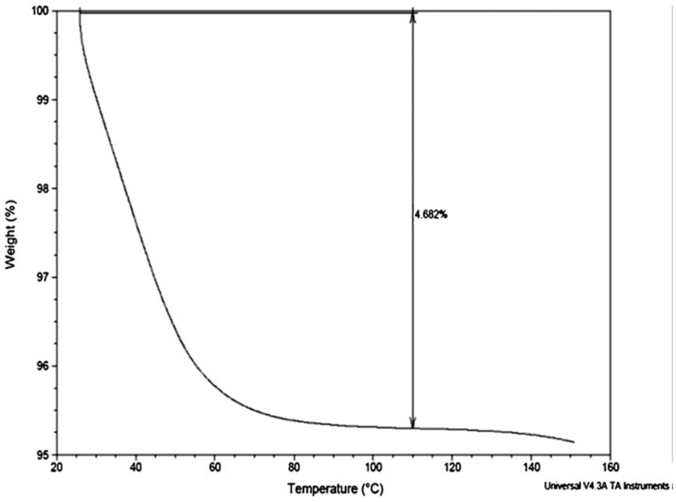

Fig. 2. A typical TGA thermogram in which a single phase water loss was observed.

Fig. 2. The polymer powder absorbed moisture to a level dependent on the RH of storage and reached an equilibrium moisture content within 100 days. The level was the same at one year (Fig. 3). However, the equilibration period would be expected to vary depending on, for example, hydrophilicity of the polymer, thickness of the powder bed, and temperature (Delle Site, 2001; Labuza and Hyman, 1998; Yong and Hahn, 2007).

3.2. The effect of humidity on moisture content and thermal behaviour determined using DSC

Corresponding to the TGA results, the preliminary DSC studies (Fig. 4) showed that the moisture uptake of the polymer increased with the increase in relative humidity under which the samples were stored. Further 3-heating cycle DSC experiments were carried out to examine thermal behaviour and to determine water content from the evaporation endotherm of the second heating profile (Fig. 5).

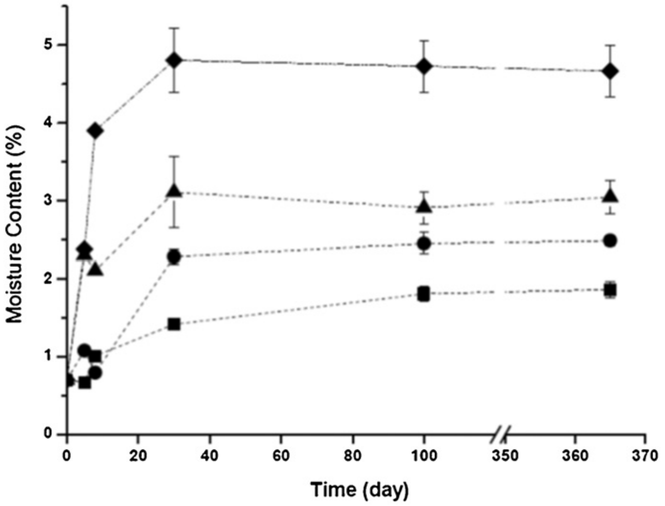

Fig. 3. Change in moisture content over time of Eudragit RLPO stored under various relative humidities. Moisture content was determined by TGA [33%RH (■), 56%RH (●), 75%RH (▲), 94%RH (♦)]. Data are means ± SD ($n = 3$).

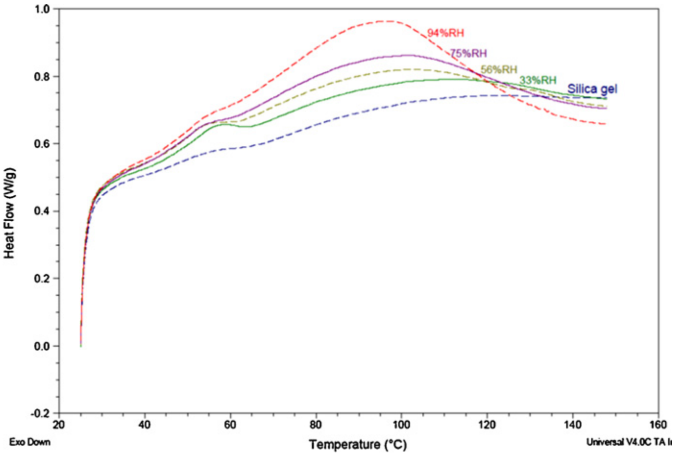

Fig. 4. DSC thermograms of Eudragit RLPO powder stored under different RH conditions (1st heating at the rate of 10 °C/min).

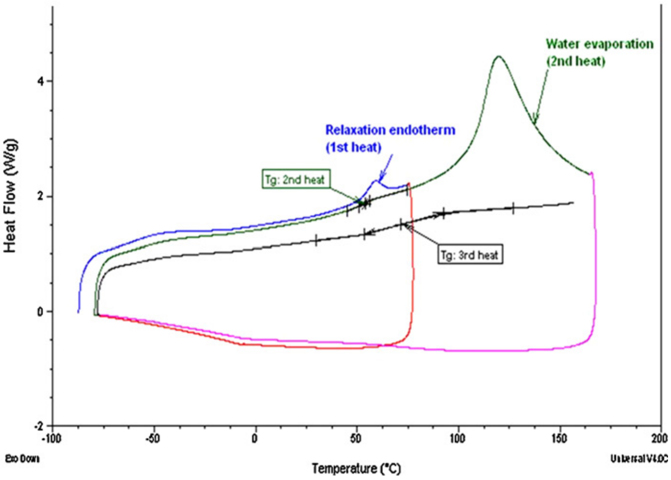

Fig. 5. An example of a DSC thermogram of the polymer powder stored at 94%RH (3 heating cycles at the rate of 50 °C/min), in which the amount of water in the sample was estimated from the evaporation endotherm (2nd heating).

During the first cooling step to −90 °C (data not shown), no freezing exotherm was observed nor was a melting endotherm of water at around 0 °C during heating, suggesting an absence of bulk water (freezable water). The first heating showed evidence of the relaxation endotherm of the polymer separated from the evaporation endotherm. Subsequently the sample was cooled and then reheated and the T_g of the moist polymer determined in this second heating (Table 1; 2nd heat). In this run, moisture content

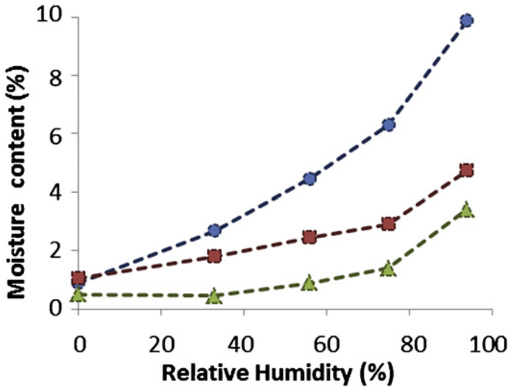

Fig. 6. Moisture content of Eudragit RLPO powder stored under various condition of RH for 100 days, determined by KFT (●), TGA (■), and DSC (▲). Data are means ± SD ($n = 3$), except DSC data ($n = 1$).

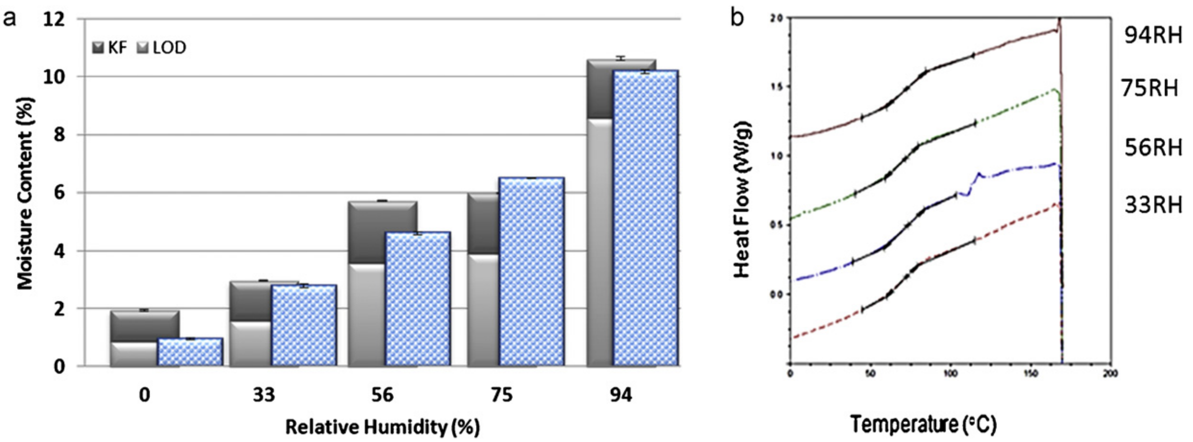

Fig. 7. A simulation of TGA method followed by KFT to reveal residual moisture, together with DSC analysis for comparison. (a) Moisture content determined by loss on drying (LOD), followed by KFT (stacked bar), in comparison with the previous KFT data alone (dotted bar). (b) DSC thermograms of oven dried samples (2nd heating), with an absence of evaporation endotherm for all conditions.

of the polymer was calculated from the area under the evaporation endotherm using a value of 2257 J/g for the water evaporation enthalpy. The third heating revealed the T_g of the supposedly dry sample, when no evaporation incident was observed (Table 1; 3rd heat). These T_gs were considerably higher than those of the moist polymer acquired from the second heating, suggesting that some of the water was having a plasticizing effect. However, the T_gs from the 2nd heat remained stable irrespective of the relative humidity or moisture content. It is hypothesized that different "types" of water exist in the polymer.

3.3. The effect of humidity on moisture content determined using KFT and method comparison

The KFT method gave higher values for MC than those obtained using TGA and DSC (Fig. 6). The chemical method, KFT, entails complete dissolution of the polymer, thereby releasing all water for the reaction suggesting this to be an accurate measure of total water content. However, it does not distinguish the types of water which might be present.

Since the samples used in the TGA and DSC methods were too small to be analysed for residual moisture by the KFT method, larger samples, with the same surface area to mass ratio as the TGA samples, were put in an oven at 120 °C for 15 min, to simulate the TGA conditions.

On removal from the oven these samples were weighed to determine the moisture loss on drying (Fig. 7a – stacked bar) then analysed for residual moisture by KFT (Fig. 7a – stacked bar), and also by DSC to note the absence of a water evaporation event (Fig. 7b). The KFT titration showed that there was some moisture still left in the samples after oven drying (Fig. 7a) but this moisture was not detectable by DSC (Fig. 7b). The result from a combination of two moisture detection methods (oven drying plus KFT, Fig. 7a – stacked column) was in reasonable agreement with the moisture content of the samples determined by only KFT alone (Fig. 7a – dotted column).

It is apparent that some moisture was trapped in the oven heated polymer but no evaporation endotherm was observed in DSC thermograms (Fig. 7b). As shown in Fig. 8, after completing thermal analysis by TGA, the polymer powder transformed into a transparent solid, suggesting a change to its glassy state. The SEM images (Fig. 9) of the polymer before and after TGA, confirm that the coalescence occurred during TGA analysis for both dry and moist samples, but to a greater degree with the moist samples (Fig. 9c and d). It is proposed that this coalescence prevents or slows water evaporation, leading to an underestimation of the amount of water present in the sample. The greater coalescence at higher relative humidity,

Table 1
Glass transition temperature detected by DSC, and moisture content determined by four methods. *This KFT was performed immediately after loss on drying method (LOD). Data are means ± SD ($n = 3$), except DSC and LOD ($n = 1$).

Treatment	T_g (°C) (Inflection point)		Water content (%w/w)				
	2nd Heat[a]	3rd Heat[a]	KFT	TGA	DSC	LOD	KFT[a]
Silica gel	54.3	78.8	0.90 ±0.03	1.06 ±0.04	0.50 N/A	0.86 N/A	1.08 ±0.03
33% RH	54.6	67.5	2.68 ±0.06	1.81 ±0.10	0.45 N/A	1.58 N/A	1.38 ±0.02
56% RH	55.3	68.3	4.46 ±0.05	2.45 ±0.14	0.90 N/A	3.57 N/A	2.15 ±0.01
75% RH	54.6	69.6	6.30 ±0.03	2.91 ±0.21	1.40 N/A	3.90 N/A	2.09 ±0.02
94% RH	53.9	71.6	9.88 ±0.07	4.73 ±0.33	3.41 N/A	8.57 N/A	2.05 ±0.07

[a] DSC samples were exposed to three heating cycles: the first to eliminate the relaxation endotherm, the 2nd to determine the T_g of the 'moist' sample, and the 3rd to determine the T_g of the 'dry' sample.

Fig. 8. Typical appearance of a 94%RH sample in a platinum TGA pan, after completing the TGA analysis at 150 °C.

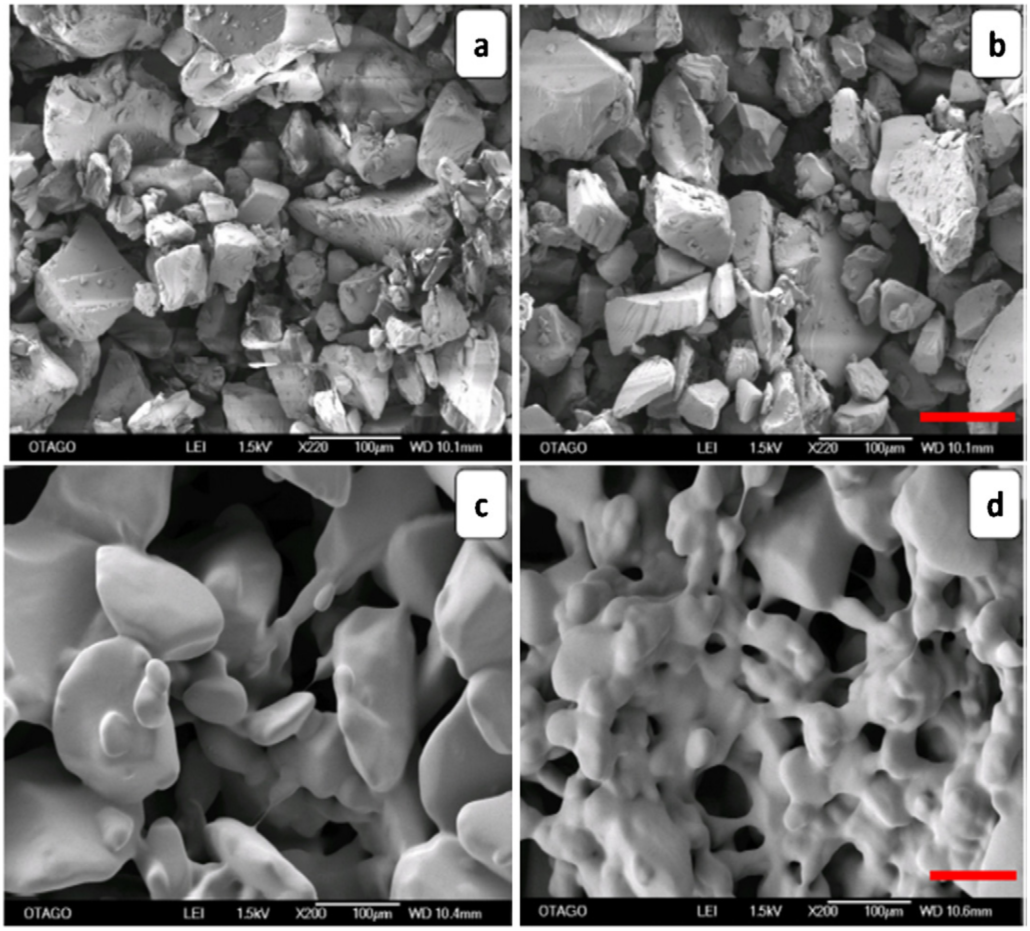

Fig. 9. SEM images of untreated dry polymer (a), untreated 94%RH polymer (b), post-TGA dry polymer (c) and post-TGA 94%RH (d). Bar is 100 μm.

correlates with the degree to which moisture content is underestimated.

Similar results were found in the DSC samples confirming that coalescence occurred during the DSC scan, resulting in a lower value of moisture even though the heating rate was faster than that of the TGA experiment. Indeed, TGA and DSC gave different values for the moisture content which may due to the differences in heating rate, sample size, pan geometries/closures.

It is apparent that the thermal methods underestimate the moisture content of the polymer sample, and that there are various types of water in the polymer, some of which is tightly bound to the polymer requiring a dissolution process to free it for analysis.

3.4. Gordon-Taylor equation and amount of plasticizing water

The simplified Gordon-Taylor/Kelley-Bueche equation (Hancock and Zografi, 1994) was used to predict the T_g of the polymer at a given water content, assuming the T_g of water to be $-138\,^{\circ}\mathrm{C}$ (Chen et al., 2000).

$$T_{g\ \mathrm{mix}} = \frac{w_1 \cdot T_{g1} + K \cdot w_2 \cdot T_{g2}}{w_1 + K \cdot w_2}; \quad K = \frac{\rho_1 \cdot T_{g1}}{\rho_2 \cdot T_{g2}}$$

where T_{g1}, T_{g2}, $T_{g\,\mathrm{mix}}$ correspond to T_g of the dried polymer, water, and mixture, respectively. w_1 and w_2 refer to mass fraction of the polymer and water. ρ_1 and ρ_2 represent densities of the polymer and water.

The T_g of the sample dried over silica gel was $54.3\,^{\circ}\mathrm{C}$ (2nd heating – Table 1). This sample lost 0.5% water in this 2nd run leading to a T_g in the 3rd run of $78.8\,^{\circ}\mathrm{C}$. However, KFT showed that the sample dried over silica gel contained 0.9% water and therefore the water remaining after the 2nd run was 0.4% (0.9–0.5%). Assuming that this remaining water is plasticizing water, the T_g of the completely "dry" polymer, based on the Gordon-Taylor theory, is $81.5\,^{\circ}\mathrm{C}$ obtained by extrapolation from 0.4% to 0% moisture (Fig. 10). The Gordon-Taylor equation predicts that the sample stored at 94% RH with a T_g

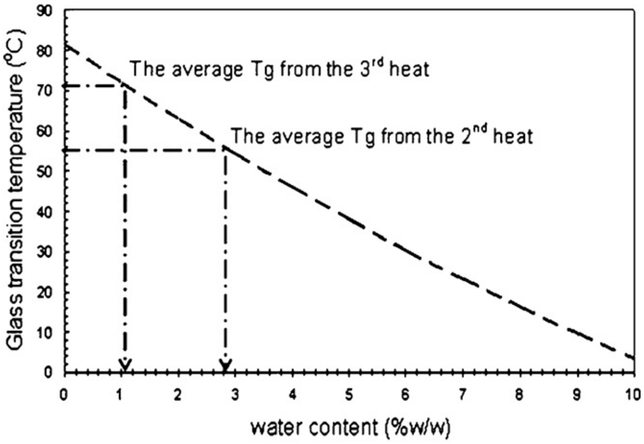

Fig. 10. Glass transition temperature (T_g) predicted by the Gordon-Taylor equation. The difference of water content determined by DSC and KFT was used to calculate the T_g of $81.5\,^{\circ}\mathrm{C}$ of the dry polymer. The arrows show water content (%) corresponding to the average T_gs from DSC 2nd and 3rd heating data.

of 53.9 °C (Table 1) contains 2.8% of plasticizing water (Fig. 10). But the KFT indicates that this sample contains 9.88% water; so only about one quarter of the total water is plasticizing water. Similarly, the 3rd run T_g of 71.6 °C (Table 1) corresponds to a plasticizing water content of 1.1% (Fig. 10), whereas the total water content is 6.47%. In spite of the observation that about 75% of the water is non-plasticizing water, there was no exotherm observed due to the freezing of bulk water when the sample was cooled to −90 °C and no melting endotherm on heating of the cooled sample.

This concept of plasticizing and non-plasticizing water has been discussed by Campillo-Fernández et al. (2008) who suggested that water can induce re-organization of polymer chain conformations leading to hydrophobic aggregation and phase segregation at a nanoscale (Campillo-Fernández et al., 2008). Thus they found that the difference in T_g between dry and very wet polymer samples was only 7 °C and largely independent of water content. No freezing exotherm was observed in thermograms suggesting the water-rich nanodomains do not behave like bulk water (Campillo-Fernández et al., 2008). This finding is in agreement with (Krakovský and Székely, 2011) who investigated water distribution in an epoxy network by DSC and small-angle neutron scattering (SANS). They also witnessed an absence of water crystallization in samples containing up to about 50% water, attributed to the isolated nano-sized domains process (Krakovský and Székely, 2011). Recently, the mean size of water filled domains was reported to be 4 nm (with a distribution of 1–1000 nm) (Hwang et al., 2011).

This has important implications for understanding the role of water in the behaviour of polymeric matrix systems undergoing thermal treatment. During thermal treatment, it is understood that polymer particles undergo coalescence to form a stable matrix and thereby affect the release of drug (Krajacic and Tucker, 2003). This coalescence is thought to occur provided the polymer is in the rubbery state (i.e. temperature > T_g) but the T_g is dependent on the level of plasticizing water present, not the total water present. However, the situation is further complicated by the possible role of nonplasticizing nanodomain water which may affect particle interactions by other mechanisms. Therefore, it is important to use complementary methods to quantify the water content of pharmaceutical polymers and to determine the types of water which may be present.

4. Conclusion

It is concluded that different methods for the determination of water content of Eudragit RLPO produce different results. The reasons for the differences are (1) due to morphological changes in the polymer during thermal treatment thereby restricting the evaporative loss of water, and (2) due to the different types of water (plasticizing/nonplasticizing) in the polymer mass. It is cautioned that similar observations may be made on other pharmaceutical polymers but this will depend on the behaviour of the moist polymer on heating and its ability to interact with water. Only about one quarter (25%) of the water in a sample of Eudragit RLPO which contains 10% water is ‘plasticizing’ water. The remaining water is probably dispersed in nanodomains which do not freeze on cooling to sub-zero temperatures. A knowledge of the amounts of water present and the different types of water present is important in understanding the behaviour of polymeric matrix systems on thermal treatment.

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