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Glass transitions in binary drug + polymer systems

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ABSTRACT

To evaluate miscibility, glass transition temperatures T_g have been determined for two binary polymer (Plasdone S-630 copovidone or Eudragit® E) + drug systems as a function of composition. Each polymer serves for encapsulation of the anti-HIV drug Efavirenz. In both systems the T_g vs. drug concentration diagrams are s-shaped. T_g s of Efavirenz + Plasdone mixtures with drug mass fraction below $\varphi_{\text{drug}} = 0.6$ are above linear values. This implies enhanced thermal and mechanical stability—an advantage for the drug encapsulation. In the other system, a strong negative deviation of T_g s is observed over the entire compositional range and explained by positive excess mixing volumes. Several equations are used to represent T_g vs. composition diagrams, but only one (Brostow et al. Mater Lett 2008; 62:3152) provides reliable results.

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1. Introduction

The glass transition is the most important feature of all non-crystalline materials, including polymers [1,2] and polymer-based composites [3]. The underlying mechanism demonstrates high sensitivity to even subtle modifications of structure and interactions. Inoue et al. [4], for example, report that in thin films of polystyrene the glass transition takes place at lower temperatures than in the bulk; more complex variations have been reported for other nanoscale confining geometries. Analysis of glass transition characteristics is indispensable, for instance, for copolymers [5], in studies of morphological changes [6], of effects of fillers on polymer dynamics [7], of results of aging [8], temperature dependence of melt viscosity [9], electron beam irradiation [10] or nanoindentation creep [11]. The nature of the glassy state is an object of a variety of studies [12–14], including representation of glass structures by the Voronoi polyhedra [12,14]. We note that the glass transition temperature T_g is a convenient numerical representation of a *glass transition region*; if the required service temperature range is below T_g of a given polymer, severe limitations in usability of that polymer appear.

Increasing demand for polymer-based materials with predefined properties causes more and more polymer *blends* being made, and examined to assert miscibility of their constituents. Typically, fully

miscible binary (A + B) blends show a single T_g value varying with the composition, say mass fraction φ_B , from $T_{g,A}$ to $T_{g,B}$. Compatible (partly miscible) blends exhibit two composition-dependent transitions, while incompatible blends show two glass transitions ($T_{g,A}$ and $T_{g,B}$) unaffected by the composition. Compatibilizing agents are also in use; success of a compatibilization is necessarily evaluated again in terms of T_g results.

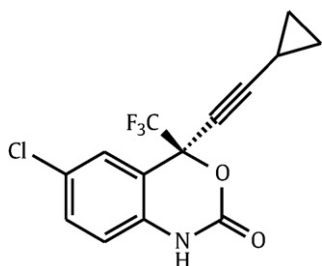
A distinct yet related issue is that of *drug encapsulation* or preparation of *drug + polymer matrices* for controlling the rate at which the drug leaves the material. This objective can be achieved provided there is miscibility of the drug with the polymer matrix [15]. Fusion or solvent evaporation dispersion methods can be used to incorporate drugs into polymers. The use of a hot-melt extruded (HME) system has several advantages over traditional pharmaceutical processing techniques, such as the absence of solvents, few processing steps, continuous operation, and the formation of solid dispersions for improved drug dissolution and bioavailability. As already noted, miscibility can be verified by $T_g(\varphi)$ determination. Along these lines, we report here results on two drug + polymer systems, with the drug Efavirenz the same in both. Both systems have shown miscibility, but unusual s-shaped $T_g(\varphi)$ diagrams. With anomalous $T_g(\varphi)$ plots often reported for binary blends, the best option would be representing experimental data by a *single* analytical equation. Then, among others, development of drug + polymer encapsulating systems would be significantly facilitated since the polymer concentration in the capsule has to be optimized. We describe below the drug + polymer pairs and the method of determination of $T_g(\varphi)$ used. Accordingly, we list important $T_g(\varphi)$ equations and apply them to evaluate their reliability in the representation of $T_g(\varphi)$ diagrams.

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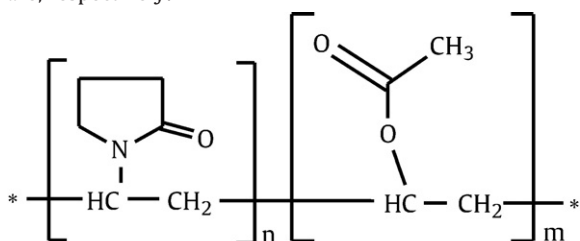
2. Experimental

Efavirenz + PLS S-630 (Plasdone S-630 copovidone) and Efavirenz + Eudragit® E have been studied. The chemical formula of the drug Efavirenz is:

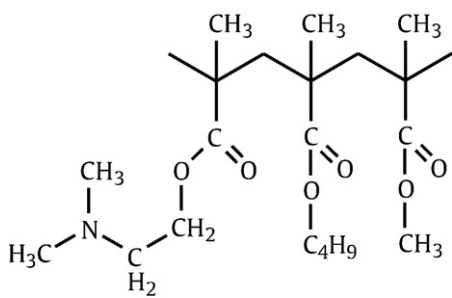


It is used as a part of an antiretroviral therapy for the treatment of human immunodeficiency virus (HIV) type 1. This drug is not absorbed well through the gastrointestinal tract due to its poor water solubility. The dissolution of Efavirenz can be increased by preparation of HME blends of this drug and the polymers under examination.

Chemical formulae of the polymers PLS S-630 and Eudragit® E (EE) are, respectively:



PLS S-630



Eudragit® E

The copolymer PLS S-630 copovidone was developed for use as a binder in the pharmaceutical dry granulation and direct-compression tablet making—with better drug dissolution profiles than the other binders. The applications of the Eudragit® copolymer series range from simple taste masking through gastric resistance to controlled drug release in all sections of the intestine.

In order to determine the $T_g(\varphi)$ diagrams, differential scanning calorimetry (DSC) [2] was applied (model Q200 DSC apparatus, TA Instruments, Newcastle, Delaware) and the Universal Analysis 2000 software was used. The experiments were conducted under nitrogen flow rate of 50 mL/min. Binary drug + polymer mixtures in various ratios (0:1; 1:4; 1:1; 4:1 and 1:0) were prepared. The samples were thoroughly mixed, the mixtures were passed through a 60 mesh screen, and then further vortex mixed for 5 min. Samples were

prepared in hermetically sealed pans and subjected to heat–cool–heat cycles at 10 °C/min. The single T_g values reported here correspond to the midpoint temperature of the heat capacity change during DSC scans.

3. $T_g(\varphi)$ equations

In Table 1 we have tabulated several T_g equations for miscible binary polymer blends, ending the list with our own equation. We have discussed previously origins of the above equations [24]. The Couchman

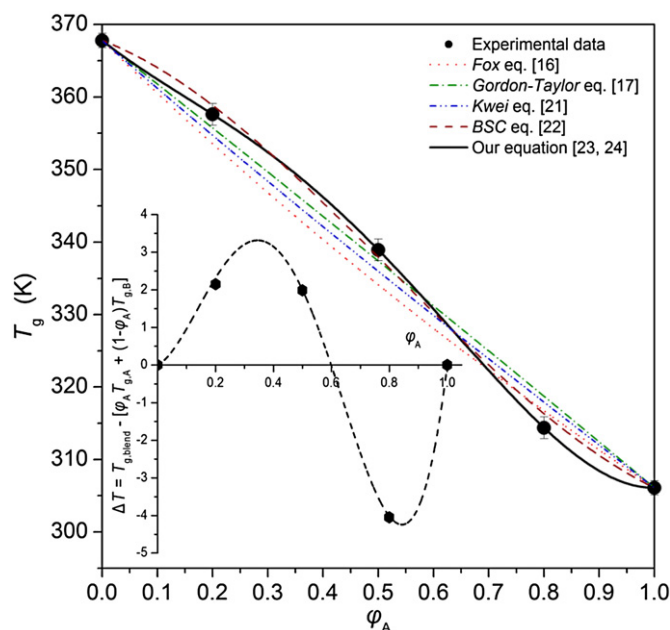


Fig. 1. Glass transition temperatures vs. drug concentration for the miscible Efavirenz + PLS S-630 copovidone blends. The deviation from linearity, $\Delta T = T_{g,blend} - [\varphi_A T_{g,A} + (1 - \varphi_A) T_{g,B}]$ vs. φ_A , is shown in the insert.

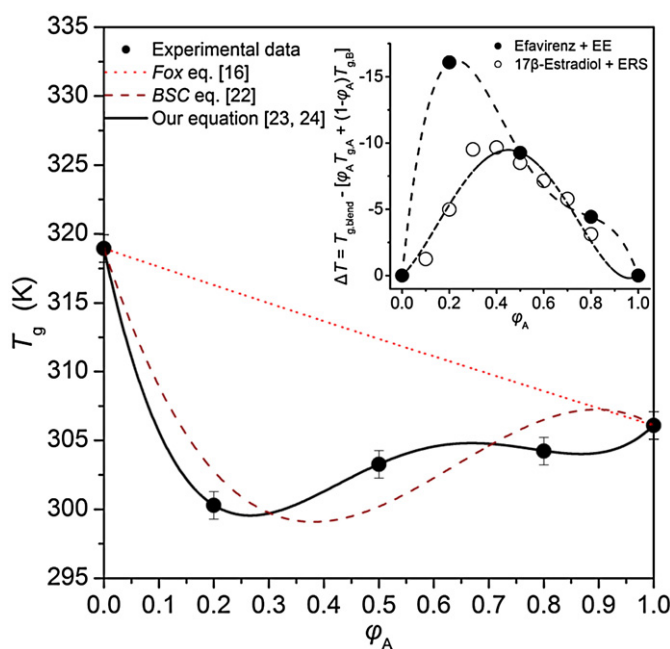


Fig. 2. Compositional variation of the glass transition temperature for the miscible Efavirenz + Eudragit® E blends. Deviations from linearity (ΔT vs. φ_A) for drugs incorporated in different Eudragit matrices are compared in the insert.

Table 1
Equations proposed for glass transition temperatures of binary mixtures.

Function's name	Functional form	Fitting parameters	Eq. number
Fox [16]	$\frac{1}{T_g} = \frac{\varphi_A}{T_{gA}} + \frac{1-\varphi_A}{T_{gB}}$	–	(1)
Gordon–Taylor [17]	$T_g = \frac{\varphi_A T_{gA} + k_{GT}(1-\varphi_A)T_{gB}}{\varphi_A + k_{GT}(1-\varphi_A)}$	k_{GT}	(2)
Jenckel–Heusch [18]	$T_g = \varphi_A T_{gA} + (1-\varphi_A)T_{gB} + b(T_{gB} - T_{gA})\varphi_A(1-\varphi_A)$	b	(3)
Couchman–Karasz [19]	$\ln T_g = \frac{x_A \Delta C_{p,A} \ln T_{gA} + \Delta C_{p,B}(1-x_A)T_{gB}}{x_A \Delta C_{p,A} + (1-x_A)\Delta C_{p,B}}$	–	(4)
Utracki [20]	$T_g = [1 + K^* \varphi_A(1-\varphi_A)](\varphi_A T_{gA}^2/2 + (1-\varphi_A)T_{gB}^2/2)^{2/3}$	K^*	(5)
Kwei [21]	$T_g = \frac{\varphi_A T_{gA} + k_{kw}(1-\varphi_A)T_{gB}}{\varphi_A + k_{kw}(1-\varphi_A)} + q\varphi_A(1-\varphi_A)$	k_{kw}, q	(6)
Brekner–Schneider–Cantow (BSC) [22]	$T_g = T_{gA} + (T_{gB} - T_{gA})[(1+K_1)\varphi_{B,c} - (K_1+K_2)\varphi_{B,c}^2 + K_2\varphi_{B,c}^3];$ $\varphi_{B,c} = \frac{k\varphi_B}{\varphi_A + k\varphi_B}, k \approx \frac{T_{gA}}{T_{gB}}$	K_1, K_2	(7)
Our equation [23,24]	$T_g = \varphi_A T_{gA} + (1-\varphi_A)T_{gB} + \varphi_A(1-\varphi_A)[a_0 + a_1(2\varphi_A - 1) + a_2(2\varphi_A - 1)^2]$	a_0, a_1, a_2	(8)

$\varphi_i, x_i, \Delta C_{p,i}$ and $T_{g,i}$ are, respectively, the weight fraction, the molar fraction, the difference between the heat capacity of the liquid and the heat capacity of the glass forms, and the glass transition temperature of the i -th component.

and Karasz equation requires the knowledge of changes in heat capacities, often not available (T_g values from dielectric or dynamic mechanical relaxation). Gordon–Taylor, Jenckel–Heusch, and Utracki equations can only represent either positive or negative deviations from linearity, and – as happens also with the Fox equation – are inapplicable to our s-shaped diagrams. In the following section we confront the remaining equations with experiment.

4. Calculations and results

Fig. 1 presents the results for the miscible Efavirenz + Plasdone S-630 copovidone blend. The success of each representation of experimental data is judged by the coefficient of determination R^2 (=1 for the perfect fit). We see clear divergence from the Fox, Gordon–Taylor and Kwei equations. The Brekner–Schneider–Cantow equation with $K_1 = -0.4 \pm 0.2$ and $K_2 = -0.9 \pm 0.1$ ($R^2 = 0.997$), provides decent description of the data—slightly inferior to that attained by our equation with $a_0 = 8 \pm 1, a_1 = -32 \pm 3$ and $a_2 = -39 \pm 7$ ($R^2 = 1$). The deviation of the blend T_g from linearity (insert in Fig. 1) demonstrates a sign inversion, with positive deviations below $\varphi_{drug} = 0.6$. In combination with the $a_1 < 0$ estimate [24], the above behavior implies an enhancement of the thermal and mechanical stability at low drug loadings—an advantage for the intended drug encapsulation application.

Fig. 2 presents results for the miscible Efavirenz + Eudragit® E system. The strong sigmoid– negative deviation from the linear mixing rule cannot be accounted for by any of the Gordon–Taylor, Kwei or BSC equations. For the latter equation, the fitting parameters are $K_1 = 0.8 \pm 1.4$ and $K_2 = 9.3 \pm 2.7$ ($R^2 = 0.911$). Application of our equation provided perfect description ($R^2 = 1$) and an interesting set of parameter values ($a_0 = -37.0 \pm 0.1, a_1 = 60.7 \pm 0.1$ and $a_2 = -75.1 \pm 0.1$).

The behavior seen in Fig. 2 can be explained in terms of excess volume V^E :

$$V^E = V - \varphi_A V_A - \varphi_B V_B \tag{9}$$

where V pertains to the blend and all volumes are specific per 1 g. $V^E > 0$ means more space for chain relaxations with a concomitant lowering of T_g . The presence of longer lateral groups in Eudragit® E, compared to those found in Plasdone, gives a reason for the dissimilar $T_g(\varphi)$ dependences, by preventing packed chain conformations. We recall that in the glassy state we have nearly tetrahedral Delaunay simplices (duals of Voronoi polyhedra [14]) while in the liquid state there are less regular simplices forming percolation systems [12]. The latter require more space; hence $V^E > 0$ favors their formation.

Strong negative deviation from linearity has also been reported for homogeneous solid dispersions of steroid hormone 17 β -Estradiol in

Eudragit® RS (ERS) copolymer [15]. This dependence is also more effectively described using Eq. (8) in Table 1 (see insert in Fig. 2), with $a_0 = -37.2 \pm 2.1, a_1 = 14.3 \pm 4.6$ and $a_2 = 34.4 \pm 11.4$ ($R^2 = 0.986$). The significance of the $V^E > 0$ effect is further demonstrated in this last system—given the occurrence of hydrogen-bonding intercomponent interactions [15]. Thus, while our experiments have been on two systems, here we have a third drug + polymer system for which our Eq. (8) in Table 1 provides nearly perfect results.

In conclusion, miscibility has been reported for drug + polymer mixtures and their irregular $T_g(\varphi)$ diagrams were analyzed. Eq. (8) in Table 1 has been shown to be applicable also to highly asymmetric s-shaped $T_g(\varphi)$ dependences – where other equations fail – and to work when one of the components is not a polymer but a low molecular mass organic compound, namely a drug. The number of parameters needed using Eq. (8) in Table 1 is indeed a measure of the system complexity [24–26].

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