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Activation energies of diffusion of organic migrants in cyclo olefin polymer

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ABSTRACT

Cyclo olefin polymer (COP) is an amorphous polymer with good optical transparency and barrier properties, which is increasingly used for pharmaceutical packaging applications like pre-filled syringes, plastic vials, nutrition bags and blisters as well as for micro-well plates. For regulatory purposes, it is important to know the amount and quantity of compounds which migrate from the polymer into the pharmaceutical product. Within the study, diffusion coefficients of organic (model) compounds in COP at various temperatures were determined and the activation energies of diffusion were calculated according to the Arrhenius approach. Correlations were established between the molecular volume V of the migrating compound and the activation energy of diffusion E_A as well as between the pre-exponential factor in the Arrhenius equation D_0 and E_A. From these correlations a prediction model was established for the migration of organic compounds in COP. This might be a useful tool supporting the evaluation process of COP packed pharmaceutical products.

1. Introduction

Cyclo olefin polymer (COP) and the related cyclo olefin copolymer (COC) are amorphous polymers with good optical transparency and barrier properties, which are increasingly used for pharmaceutical packaging applications. Due to this good transparency, its high moisture barrier as well as due to its break resistance COP and COC are substituting glass in many applications. COC is manufactured in a chain copolymerization of cyclic monomers like norbonene with ethylene whereas COP is polymerized with only one monomer in a ring-opening metathesis polymerization of cyclic monomers followed by hydrogenation (Shin et al., 2005). In addition, cyclo olefin polymers show good resistance against e-beam sterilization (Saunier et al., 2006). In contrast to other olefin polymers like high density polyethylene (HDPE), cyclo olefin polymers have relatively high glass transition temperatures (T_g) between 70 °C and 177 °C (Shin et al., 2005). Such high glass transition temperatures give a rough indication for a low diffusion behaviour of migrants in cyclo olefin polymers. Due to its beneficial material properties, cyclo olefin polymers are used for example in pre-filled syringes, plastic vials, transparenteral nutrition bags and blisters. COP and COP are used also for bio-diagnostic applications, e.g. for micro-well plates (Niles and Coassin 2008), microfluidic devices (Nunes et al., 2010) as well as optical-based medical detection devices.

For regulatory purposes, it is important to know the amount and quantity of compounds which migrate from the polymer into the pharmaceutical product. The migration of compounds can be experimentally determined within real time storage tests or under stress test conditions using slightly increased temperatures. Such tests, however, are only possible if the pharmaceutical formulation and the storage conditions are well known. In addition, storage tests with pharmaceutical products even under forced stress conditions, e.g. storage under high temperature, is time consuming and expensive. Manufacturers of syringes, vials, or packaging materials in general, in many cases do not have the complete information about contact media, storage conditions and shelf life of the packed pharmaceutical products. These packaging manufacturers are therefore not in a position to evaluate the amount of compounds migrating from cyclo olefin polymers into the contact medium. Therefore, a more general approach instead of real time storage is necessary in order to optimize and evaluate the plastic syringes and plastic vials.

Mathematical diffusion modelling seems to be such a general approach. An overview of migration modelling is given in a review article (Pocas et al., 2008). In general, Fickian mass transfer of chemical compounds from a polymer plane sheet into a contact medium can be calculated at a certain temperature according to Eq. (1) (Crank 1975). Within this equation, the parameter m/A is the area related mass transfer from the polymer into the contact medium. The concentration of the migrating compound in the polymer at the beginning is $c_{P,0}$. The diffusion coefficient of the compound in the polymer is D_P and t is the storage time. ρ_P is the specific density of the polymer and the wall thickness of the

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packaging material is d_P. The factor α (Eq. (2)) contains the partition coefficient $K_{P,M}$ and the volumes of the packaging P and contact media M (V_P and V_M). The term q_n in Eq. (1) is a correction factor for the positive square roots of the equation $\tan q_n = -\alpha q_n$.

$$\frac{m}{A} = c_{P,0}\rho_P d_P\left(\frac{\alpha}{1+\alpha}\right)\left[1-\sum_{n=1}^{\alpha}\frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n^2}e^{(-D_P t\times(q_n^2/d_P^2))}\right] \quad (1)$$

$$\alpha = \frac{1}{K_{P,M}}\times\frac{V_M}{V_P} \quad (2)$$

For a given polymer, the parameters like specific polymer density, wall thickness, volume of the contact media are easily available. Therefore, most of the parameters in Eq. (1) are well known for a given packaging application. In addition, the concentration of compounds in the packaging material ($c_{P,0}$) are available from extractable studies. Only the diffusion coefficient D_P and the partition coefficient $K_{P,M}$ are typically not directly available. Therefore prediction models for diffusion coefficients (Pocas et al., 2008) and partition coefficients (Ozaki et al., 2010; Seiler et al., 2014) have been developed. On the other hand, for low diffusive polymers the partition coefficient plays a minor role, because the equilibrium will not be reached under normal or increased temperature storage conditions (Franz and Welle, 2008). Therefore, one of the main parameters influencing the migration process in low diffusive polymers like COP is the diffusion coefficient D_P of a compound in the polymer. If the diffusion coefficient is known, the migration can be predicted for any storage conditions from Eq. (1). As a consequence, applying mathematical diffusion modelling for migration evaluation needs detailed information about the diffusion behaviour of polymers and the migrating compounds e.g., diffusion coefficients or activation energies of diffusion. For COP as well as for COC, however, information about diffusion coefficients is not available from the scientific literature.

As mentioned above, several models and equations for the prediction of diffusion coefficients of migrants in polymers from their molecular weight M has been developed (Pocas et al., 2008). Typically, the prediction of the diffusion coefficient is achieved in a worst-case scenario, which means that the experimentally determined mass transfer from the polymer into the contact media is in any case lower than the predicted migration. However, the prediction methods for diffusion coefficients summarized by Pocas et al. (2008) also need information about the diffusion behaviour of the polymers, which are not available for COP and COC, respectively. In a previous study from our group, a novel method for the realistic prediction of diffusion coefficients was published (Welle, 2013) for polyethylene terephthalate (PET). According to Eq. (3), the diffusion coefficients can be predicted from the molecular volume V of the migrant. The parameters a to d in Eq. (3) are polymersepcific parameters which can derived from correlations between the molecular volume V versus the activation energies E_A as well as from the correlation between the pre-exponential factor D_0 from the Arrhenius equation versus the activation energies E_A (Welle, 2013).

$$D_P = b\left(\frac{V}{c}\right)^{(a-(1/T))/d} \quad (3)$$

Aim of the study was the determination of the activation energies of diffusion E_A in COP for organic (model) compounds. These activation energies E_A are available from Arrhenius plots of the diffusion coefficients versus the reciprocal temperature. Therefore, diffusion coefficients of model compounds in COP were determined experimentally by diffusion kinetic experiments at various temperatures. From these data, the above mentioned correlations between the molecular volume V and E_A as well as between D_0 and E_A were established in order to derive the parameters a–d for the investigated COP polymer.

2. Materials and methods

2.1. Cyclo olefin polymer material

Cyclo olefin polymer COP (Zeonex 690R) investigated within this study was purchased from Zeon (Zeon Europe GmbH, Düsseldorf, Germany). The investigated polymer (Zeonex 690R) had a glass transition temperature (T_g) of 140 °C, measured by differential scanning calorimetry (DSC). The density of the polymer is 1.01 g cm^3.

2.2. Selection of surrogates

Model compounds were used as surrogates for realistic migrants because COP materials with real migrants in the molecular weight range of interest are rarely available. The following n-alkanes were chosen as model compounds for the migration kinetics assessments: octane (CAS No. 111-65-9), decane (CAS No. 124-18-5), dodecane (CAS No. 112-40-3), tetradecane (CAS No. 629-59-4), hexadecane (CAS No. 544-76-3), octadecane (CAS No. 593-45-3), eicosane (CAS No. 112-95-8), docosane (CAS No. 629-97-0) and tetracosane (CAS No. 646-31-1). In addition, migrants with functional groups or aromatic rings were chosen as model compounds e.g. acetone (CAS No. 67-64-1), ethyl acetate (CAS No. 141-78-6), toluene (CAS No. 108-88-3), chlorobenzene (CAS No. 108-90-7), phenyl cyclohexane (CAS No. 827-52-1), benzophenone (CAS No. 119-61-9) and methyl stearate (CAS No. 112-61-8). These compounds represent the four general categories for organic compounds: volatile and non-polar, volatile and polar, non-volatile and non-polar, and non-volatile and polar.

2.3. Preparation of spiked COP sheets

Two sets of model compounds were spiked to the polymer melt homogeneously during COP sheet production. The surrogates were applied in two sets to two COP sheets. Sheet 1 was doped with n-alkanes (C8, C10, C12, C14, C16, C18, C20, C22 and C24). For this purpose the n-alkanes were mixed in equal concentrations and spiked into the polymer in a concentration of 18 g per 3.6 kg polymer. Sheet 2 was doped with model substances with functional groups (acetone, ethyl acetate, toluene, chlorobenzene,

Table 1
Experimentally determined concentrations $c_{P,0}$ of model compounds in the spiked COP sheets.

Compound	Concentration (mg kg^{-1})
Sheet 1	
n-Octane	499 ± 4
n-Decane	474 ± 5
n-Dodecane	506 ± 6
n-Tetradecane	442 ± 3
n-Hexadecane	412 ± 3
n-Octadecane	392 ± 3
n-Eicosane	407 ± 4
n-Docosane	431 ± 5
n-Tetracosane	430 ± 13
Sheet 2	
Acetone	30 ± 3
Ethyl acetate	120 ± 3
Toluene	245 ± 3
Chlorobenzene	357 ± 5
Phenyl cyclohexane	388 ± 5
Benzophenone	391 ± 6
Methyl stearate	485 ± 8