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Modeling plasticizer uptake in aqueous polymer dispersions

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Abstract

The mass transport of water-insoluble plasticizers, emulsified in an aqueous, colloidal polymer dispersion (Aquacoat®) was investigated. A model was developed, which allows quantitative predictions and gives further insight into the transfer mechanism. Experiments proved the validity of the model under various conditions. There are two important mass transfer processes: (1) dissolution of the plasticizer droplets and (2) diffusion of the plasticizer within the polymer particles. Initially, after adding the plasticizer to the aqueous dispersion, dissolution governs the kinetics (dissolution rate < diffusion rate). But increasing amounts of plasticizer located within the polymer particles lead to decreasing concentration gradients and subsequent declining diffusion rates. A change of the governing mechanism is observed. During the final portion, diffusion controls the transfer kinetics (dissolution rate > diffusion rate). Dissolution and diffusion are taken into account simultaneously in the new model, which was used to determine the diffusion coefficients and dissolution rate constants of various plasticizers. Knowing these parameters, the minimum stirring time, necessary for a complete plasticizer uptake (to avoid inhomogeneous coatings) can be calculated. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Aquacoat®; Colloidal polymer dispersion; Ethyl cellulose; Diffusion; Dissolution; Modeling; Plasticizer; Pseudolatex

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1. Introduction

To avoid the hazards associated with organic solvent-based coatings, aqueous polymer dispersions (latexes and pseudolatexes) are widely used for the coating of solid dosage forms. Several products are commercially available, for example Aquacoat®, which is an aqueous colloidal dispersion of ethyl cellulose. The glass transition temperature (T_g) of ethyl cellulose is approximately 133°C (Sakellariou and Rowe, 1995). Prior to the coating step, a plasticizer has to be added in order to reduce the minimum film formation tempera-

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ture (MFT) below the coating temperature and to allow coalescence of the colloidal polymer particles in a homogeneous film (Lehmann, 1997; Wheatley and Steuernagel, 1997). The added plasticizers are generally classified as being water-soluble (e.g. triethyl citrate) or water-insoluble (e.g. acetyltributyl citrate). A potential disadvantage of water-soluble plasticizers is their leaching from the coating after contact with dissolution or physiological fluids. The release kinetics will vary because of this change in film composition, the systems are therefore difficult to be controlled accurately. Lipophilic plasticizers remain in the coating, assuring more constant conditions during the entire release process.

While water-soluble plasticizers are completely dissolved in the aqueous phase of the colloidal polymer dispersion, water-insoluble plasticizers have to be emulsified in the polymer dispersion. The emulsified plasticizer has then to be taken up by the colloidal polymer particles prior to coating. The mass transfer from the emulsified droplets into the polymer particles is the subject of this study. A new model has been developed for quantitative predictions and elucidation of the transfer mechanism. This is of practical importance because the plasticizer should be taken up completely by the colloidal polymer particles before applying the dispersion. Otherwise a mixture of plasticized polymer and remaining emulsified plasticizer will be sprayed onto the solid dosage forms, leading to inhomogeneous coatings. This could result in uncontrollable drug release or aging effects caused by the redistribution of plasticizer droplets within the polymeric coating.

Plasticizer partitioning in aqueous polymer dispersions has been studied only by a few researchers (Dillon et al., 1953; Lippold et al., 1989; Iyer et al., 1990). Dillon et al. investigated the plasticizing of synthetic latexes (paints) and developed a model in terms of the diffusion properties of a three phase system of plasticizer droplets, water phase and polymer particles. Detailed experimental data on the rate of this process were not obtained because of problems concerning the accurate separation of free plasticizer. In contrast to our model, they reduced the role of the plasticizer droplets to act only as a reservoir, maintaining a saturation concentration of plasticizer in the water phase thus neglecting the dissolution kinetics.

The objectives of this study are to elucidate the mass transfer mechanism of a lipophilic plasticizer in an aqueous colloidal polymer dispersion and to develop a new model, taking into account all the important transfer steps. The practical benefit of this model is the ability to predict the amount of plasticizer taken up by the polymer phase as a function of contact time and, thus, the minimum stirring time before applying the dispersion necessary to obtain a homogeneous coating.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: Aquacoat® (30% w/w aqueous dispersion of ethyl cellulose) (FMC Corp., Newark, DE), dibutyl sebacate (DBS), diethyl phthalate (DEP), dibutyl phthalate (DBP), acetyltriethyl citrate (ATEC; Citroflex A-2), tributyl citrate (TBC; Citroflex-4), acetyltributyl citrate (ATBC; Citroflex A-4) (Morflex Chemical Co., Greensboro, NC) and methanol (HPLC grade, Mallinckrodt Specialty Chemicals Co., Paris, KY).

2.2. Methods

A previously developed separation method (Bodmeier and Paeratakul, 1994) and a HPLC assay (Bodmeier and Paeratakul, 1991) were used for the analysis of the plasticizers in the ethyl cellulose dispersion. The separation allowed the time-dependent quantification of the plasticizer in the aqueous phase of the polymer dispersion in either emulsified or dissolved form or of the plasticizer taken up by the polymer particles (Bodmeier and Paeratakul, 1997).

3. Theoretical

The investigated system consists of the following three components: (a) water-insoluble plasticizer, (b) water and (c) suspended polymer particles (Fig. 1). The plasticizer transfer is divided into three steps:

1. dissolution: liquid plasticizer droplets dissolve in the water phase,
2. convection and diffusion: dissolved plasticizer molecules are transferred through the well-stirred water phase to the polymer surface,
3. diffusion: plasticizer molecules are taken up by the polymer and diffuse within the particles.

Each of these steps has to be taken into account adequately. As the water phase is well-stirred, the velocity of the convective and diffusional transport through this medium is high compared to the rates of (1) and (3). All processes take place sequentially, therefore this step can be neglected. Three different models are presented for the matter transfer of the plasticizer: (I) dissolution model: the dissolution rate is assumed to be much smaller than the diffusion rate over the entire process, (II) diffusion model: the diffusion within the polymer particles is assumed to be rate-limiting, neglecting the dissolution of the plasticizer, (III) dissolution-diffusion model: both processes are taken into account simultaneously.

3.1. Dissolution model

According to Noyes and Whitney (1897), the dissolution kinetics of the plasticizer droplets are described using the following equation (pseudo-steady-state approach):

$$\frac{dm}{dt} = k'(c_s - c_t) \quad (1)$$

whereby dm/dt is the dissolution rate of the plasticizer droplets in the water phase and k' is a constant. c_s designates the solubility of the plasticizer in the water phase, c_t the plasticizer concentration in the water phase at time t. Noyes-Whitney explained the dissolution process on the assumption that a very thin, unstirred layer is formed at the surface of the droplets, and that the rate of dissolution is governed by the rate of diffusion through this layer into the main body of the solution. Integration of Eq. (1) yields:

$$M_0 - M_{et} = M_0(1 - e^{-k''t}) \quad (2)$$

M_0 represents the total amount of plasticizer in the system, M_{et} the amount of emulsified plasticizer in the water phase at time t and k'' is a constant. Eq. (2) transforms into:

$$\ln\left(\frac{M_{et}}{M_0}\right) = -k''t \quad (3)$$

A straight line is obtained in a $ln(M_{et}/M_0)$-vs.-time diagram. The experimentally determined amounts of emulsified plasticizer are plotted according to Eq. (3).

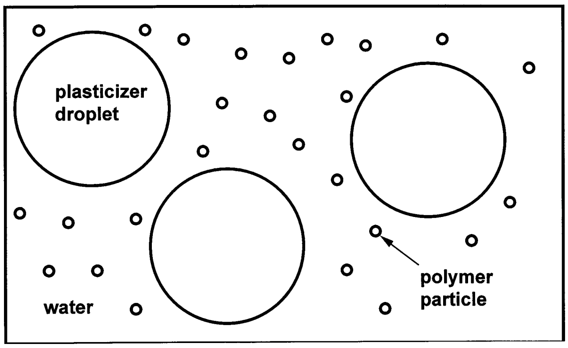

Fig. 1. Scheme of the plasticizer-water-polymer system.

3.2. Diffusion model

Fick's second law of diffusion is used to calculate the kinetics of plasticizer diffusion within the polymer particles:

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial r^2} + \frac{2}{r}\cdot\frac{\partial c}{\partial r}\right) \quad (4)$$

D is the diffusion coefficient, c the concentration of the diffusing substance and t and r designate time and radius. Upon putting the function u:

$$u = cr \quad (5)$$

the equation for u becomes:

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial r^2} \quad (6)$$

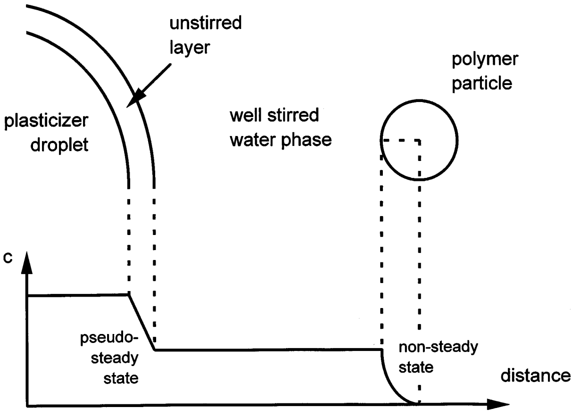

Fig. 2. Scheme of the dissolution-diffusion model.

Using the method of Laplace transform, Eq. (6) has been solved for the following initial and boundary conditions:

$$t = 0, u = 0, 0 < r < R \tag{7}$$

$$t > 0, u = RK_d c_s, r = R \tag{8}$$

$$t > 0, u = 0, r = 0 \tag{9}$$

leading to (Crank, 1975):

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \left(\frac{1}{n^2} \exp\left(\frac{-Dn^2\pi^2 t}{R^2} \right) \right) \tag{10}$$

with K_d being an equilibrium constant. M_t and M_∞ are the amounts of plasticizer within the polymer particles at time t and $t = \infty$, respectively. R represents the radius of the polymer particles. Using a Coulter LS 230 (laser scattering with PIDS technology) $R = 78.5$ nm was found for Aquacoat®. Due to the observed narrow range of diameters, a mono-disperse system was assumed. The experimentally determined quantities of plasticizer taken up by the polymer are fitted to Eq. (10).

3.3. Dissolution-diffusion model

A schematic presentation of the physical processes being taken into account is given in Fig. 2 (for simplicity the distribution coefficients have been set equal to unity in this diagram). The process of dissolution is described by a pseudo-steady state approach, similar to that of Noyes and Whitney, but also taking into account the decreasing dimensions of the plasticizer droplets (time-dependent surface area A). Due to the forced convection caused by the magnetic stirrer (very high transport rate compared to the dissolution and diffusion rates), the plasticizer concentration in the water phase is assumed to be uniform. Non-steady state diffusion within the polymer is calculated using Eq. (4). Because of the complexity of the resulting system of differential equations, no analytical, but a numerical solution has been derived. A finite difference method (Smith, 1985; Vergnaud, 1991, 1993) has been applied. The dissolution of the plasticizer droplets is described by:

$$\Delta M = kA\Delta t(c_s - c_w[j]) \tag{11}$$

During the time interval Δt, the amount of plasticizer ΔM is transferred across the unstirred layer. k is the dissolution rate constant of the plasticizer, $c_w[j]$ the plasticizer concentration in the water phase at time $t = j\Delta t$. For the numerical treatment of diffusion, the spherical polymer particles are divided into $N-1$ (N = integer) hollow spheres (thickness $= \Delta r = R/N$), one outest hollow sphere (thickness $= \Delta r/2$) and a central sphere (radius $= \Delta r/2$). A cross-section is schematically given in Fig. 3A. Fig. 3B shows the respective space-time diagram for numerical analysis and nomenclature of the plasticizer concentrations in various places and times. Calculating the plasticizer concentrations within the polymer particles for a new time step ($[j+1]$), three cases have to be considered, depending on the position r:

1. At the surface of the sphere: assuming an infinite coefficient of matter transfer at the water-polymer interface, the new concentration at $r = R$ is calculated as follows:

$$c[N][j+1] = K_d c_w[j+1], \tag{12}$$

$c_w[j+1]$ designates the new plasticizer concentration at time $t = (j+1)\Delta t$ in the water phase.

2. Within the sphere: the matter balance is written as follows:

$$c[n][j+1] = c[n][j] + \frac{(n+0.5)^2(c[n+1][j]-c[n][j])}{B\left(n^2+\frac{1}{12}\right)} - \frac{(n-0.5)^2(c[n][j]-c[n-1][j])}{B\left(n^2+\frac{1}{12}\right)} \quad (13)$$

with the constant

$$B = \frac{(\Delta r)^2}{D\Delta t} \quad (14)$$

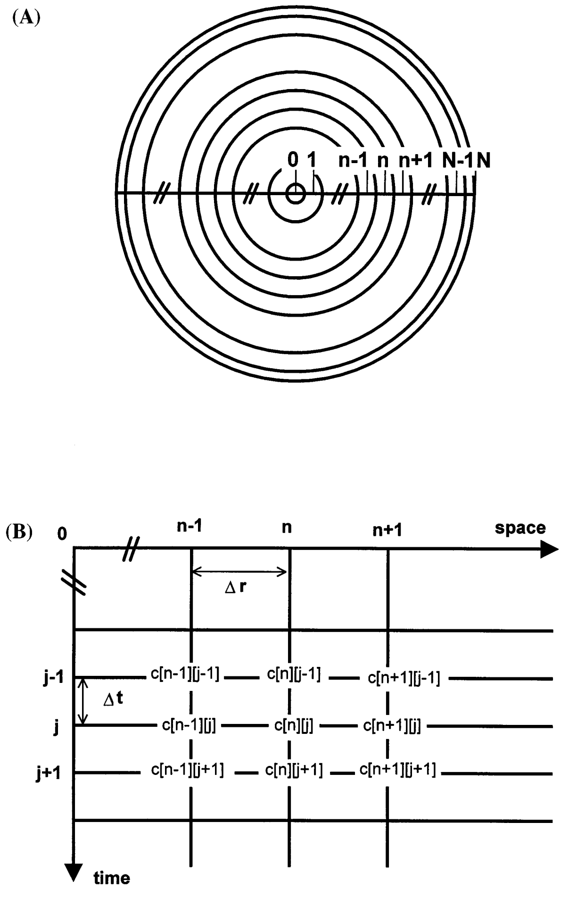

Fig. 3. A. Schematic cross-section of a spherical polymer particle: nomenclature for numerical analysis. B. Space-time diagram for numerical analysis: plasticizer concentration within the polymer particles in various places and times.

3. At the center of the sphere: the new concentration of plasticizer is calculated using:

$$c[0][j+1] = c[0][j] + \frac{6(c[1][j]-c[0][j])}{B} \quad (15)$$

The *total* amount of plasticizer located in the polymer particles at time t (M_t) is obtained by integrating the concentration within the sphere at this time with respect to space:

$$M_t = \int_0^R (4\pi r^2 c_{r,t})dr \quad (16)$$

$c_{r,t}$ represents the plasticizer concentration at position r and time t in the sphere. By using finite differences, this expression becomes:

$$M_t = 4\pi(\Delta r)^3 \times \left[\frac{c[0][j]}{24} + \sum_{n=1}^{N-1}\left(\left(n^2+\frac{1}{12}\right)c[n][j]\right) + \left(N^3-\left(N-\frac{1}{2}\right)^3\right) \times \left(\frac{1}{12}c[N-1][j] + \frac{1}{4}c[N][j]\right)\right] \quad (17)$$

The measured quantities of emulsified plasticizer are fitted to this model.

For the implementation of the mathematical models the programming language C++ was used (Borland C++ V.5.0 Developer).

4. Results and discussion

4.1. Dissolution model

Fig. 4 shows the $ln(M_{et}/M_0)$-vs.-time plot for different ATBC levels (10, 20, 30 and 40% plasticizer, w/w based on polymer) in Aquacoat®. Straight lines starting from the origin of the coordinate system are obtained, suggesting that the dissolution process governs the matter transport. The respective correlation coefficients (linear regression, least squares method) are all >0.99 during the first 2 h. Different slopes for different plasticizer levels are in agreement with the theory: The constant k'' in Eq. (3) depends on the surface area of the plasticizer droplets. Different plasti-

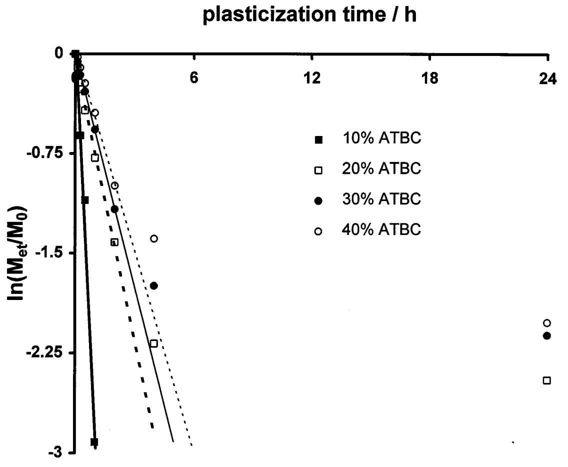

Fig. 4. Dissolution model: experimental and theoretical data; $ln(M_{et}/M_0)$-vs.-time plot for different ATBC levels (10, 20, 30 and 40% plasticizer, w/w based on polymer) in Aquacoat® (solids content of the polymer dispersion = 15% w/w).

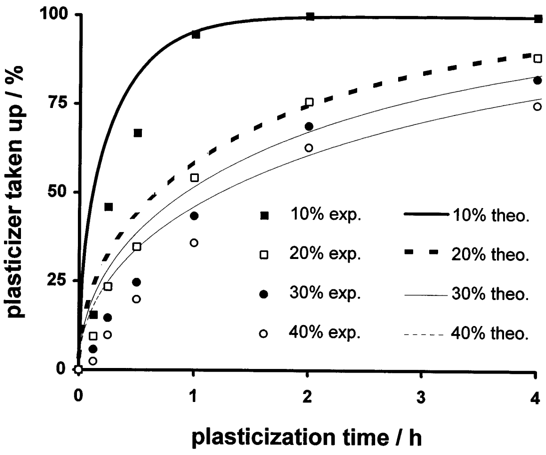

Fig. 5. Diffusion model: experimental and theoretical data for different ATBC levels (10, 20, 30 and 40% plasticizer, w/w based on polymer) in Aquacoat® (solids content of the polymer dispersion = 15% w/w).

cizer levels lead to different surface areas and subsequent different slopes. But the linear relationship between $ln(M_{et}/M_0)$ and t is only achieved during the initial period of the plasticizer transfer. Significant deviation is observed after 2 or 3 h (depending on the relative amount of plasticizer). Thus, the dissolution model holds only over the initial portion of the matter transfer.

4.2. Diffusion model

Fig. 5 shows the experimental and theoretical data of different ATBC levels in Aquacoat®. Good agreement between theory and experiment is only obtained during the final portion of the process. As expected, the time necessary for complete plasticizer uptake is ranked in the order of $10 < 20 < 30 < 40\%$ w/w ATBC, based on polymer. This is due to the different absolute amounts of plasticizer to be transferred. In the case of 40% w/w ATBC, the 4-fold of mass has to be transferred into the same absolute amount of polymer particles (same surface area) compared to 10% w/w ATBC. The good agreement between theory and experiment suggests that diffusion controls the final portion of the process, whereas during the first hour there is significant deviation between the calculated and the measured data (Fig. 5). Therefore, this model holds only over the final portion of the matter transfer.

4.3. Dissolution-diffusion model

Good agreement over the entire process between theory and experiment is found for the

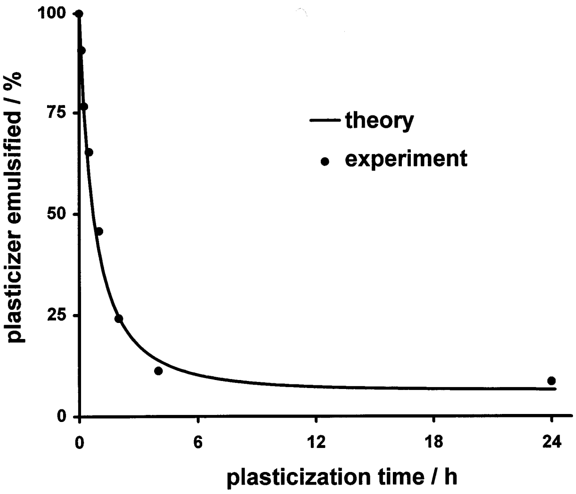

Fig. 6. Dissolution-diffusion model: fit of the experimental data to the theory (ATBC uptake in Aquacoat®, solids content of the polymer dispersion = 15% w/w, plasticizer concentration = 20% w/w based on polymer).

presented, new model for the case of 20% w/w (based on polymer) ATBC in Aquacoat® (Fig. 6). This diagram shows the fit of the experimental data to the numerical model. At the beginning the transfer velocity is rather high, but then declines in a complex manner with time. The diffusion coefficient D as well as the dissolution rate constant k of ATBC have been determined. D and k equal 4.4×10^{-14} cm^2/s and 0.77 cm/h, respectively. The rather low value of D results from the glassy state of the unplasticized ethyl cellulose at room temperature ($T_g \approx 133$°C). The mobility of the polymer chains is significantly lower at temperatures below the T_g, compared to the rubbery state. According to the free volume theory of diffusion, this leads to small voids available for diffusion and thus low diffusivities (Fan and Singh, 1989). The advantage of the dissolution-diffusion model (considering dissolution *and* diffusion simultaneously), when compared to the other models, is the fact that it describes the plasticizer transfer for the entire process and not only for a certain period.

4.4. Validity of the dissolution-diffusion model

Once the necessary parameters had been determined, the model was used to calculate the amount of plasticizer dissolved in the water phase and taken up by the polymer particles vs. time. The latter was also measured experimentally. Comparison between predicted and experimental data is shown in Fig. 7 for the case of 20% w/w ATBC (based on polymer) in Aquacoat®. Good agreement concerning the amounts of plasticizer taken up by the polymer proves the validity of the presented model. The quantities dissolved in the water phase were too low to be detected accurately, but they could be calculated. The new model gives further insight into the transfer kinetics: The amount of dissolved plasticizer in the water phase increases rather fast at the beginning of the process and then remains constant for the rest of the transfer. Due to this constant level of plasticizer in the water phase, the decrease of emulsified ATBC corresponds directly to the increase of ATBC in the polymer phase. This fact is confirmed theoretically as well as experimentally (Fig. 7).

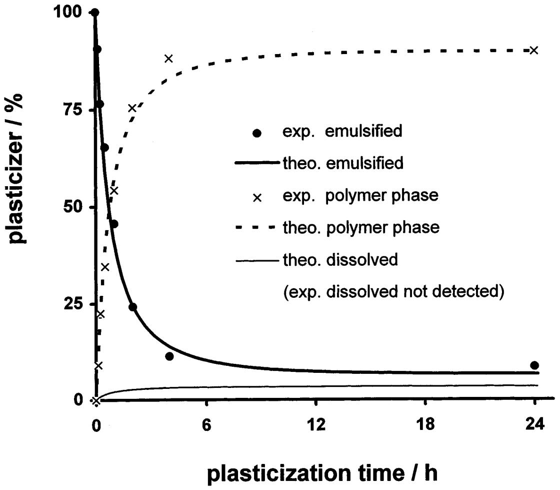

Fig. 7. Validity of the presented dissolution-diffusion model: comparison between theoretical prediction and experiment (ATBC uptake in Aquacoat®, solids content of the polymer dispersion = 15% w/w, plasticizer concentration = 20% w/w based on polymer).

4.5. Mechanism of matter transfer

None of the two models taking into account either dissolution or diffusion is able to describe the experimentally determined matter transfer kinetics during the entire process. Significant deviation between experiment and theory is observed, either for small or for high values of t. The dissolution model holds only over the initial portion of the matter transfer, the diffusion model only over the final portion. Thus, at the beginning dissolution is rate-limiting (dissolution rate < diffusion rate) and at the end diffusion governs the process (dissolution rate > diffusion rate). This phenomenon can be explained as follows: According to Fick's first law, the diffusion rate of a substance is proportional to the concentration gradient. At time $t = 0$, the plasticizer concentration within the polymer particles equals 0. This concentration increases with time and the concentration gradient decreases, resulting in a decreasing diffusion rate. Thus, the proportion between the dissolution rate and the diffusion rate changes during the transfer process; the governing transfer mechanism changes. The beginning of the process is dissolution-controlled, the end diffusion-controlled, whereas in the middle part both mechanisms determine the overall transport kinetics.

4.6. Effect of different plasticizer levels

Using the determined values for D and k, the relative amounts of ATBC emulsified in Aquacoat® (solids content of the polymer dispersion = 15% w/w) have been predicted for the case of 10% w/w plasticizer. Good agreement between prediction and experiment is found (Fig. 8). The presented model can be used to calculate systems of different composition, which is of great practical importance. As discussed earlier, the time necessary for a complete plasticizer uptake decreases with decreasing plasticizer level (Fig. 8). The effect of different plasticizer levels on the absolute amounts of ATBC being transferred is shown in Fig. 9. Higher plasticizer levels lead to higher absolute amounts of ATBC taken up by the polymer. This can easily be explained using the new model: High amounts of plasticizer lead to high surface areas of the droplets (this time-depending parameter is considered in Eq. (11)), resulting in high absolute amounts of plasticizer (ΔM) transferred in a certain time interval (Δt). In conclusion, there is a significant influence of the plasticizer level on the transfer kinetics, which can be predicted with the dissolution-diffusion model.

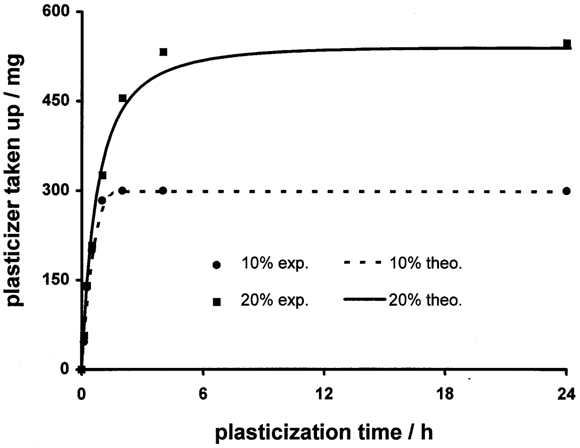

Fig. 9. Effect of different plasticizer levels: absolute amounts of ATBC located in the polymer particles versus time for 10 and 20% w/w plasticizer (based on polymer) in Aquacoat® (solids content of the polymer dispersion = 15% w/w).

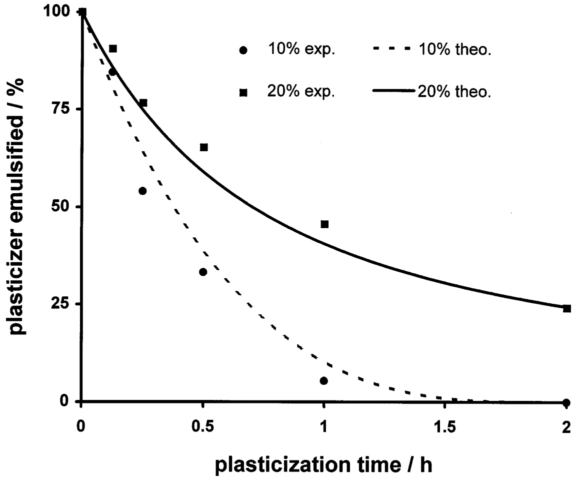

Fig. 8. Effect of different plasticizer levels: relative amounts of ATBC emulsified in the water phase vs. time for 10 and 20% w/w plasticizer (based on polymer) in Aquacoat® (solids content of the polymer dispersion = 15% w/w).

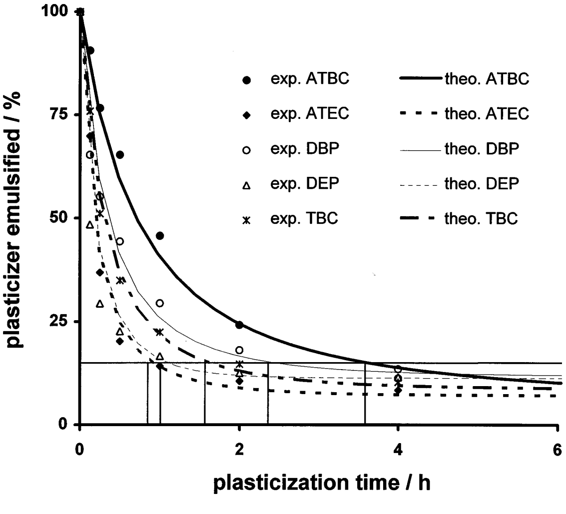

Fig. 10. Effect of different types of plasticizer: curve fits of the experimental data to the dissolution-diffusion model (different lipophilic plasticizers in Aquacoat®, solids content of the polymer dispersion = 15% w/w, plasticizer concentration = 20% w/w based on polymer).

Table 1
Dissolution rate constants and diffusion coefficients of various plasticizers in Aquacoat®

Type of plasticizer	Dissolution rate constant (k/cm/h)	Diffusion coefficient $D/10^{-14}$ cm^2/s
ATBC	0.77	4.4
ATEC	3.27	5.1
DBP	1.62	3.8
DEP	4.90	1.1
TBC	2.13	1.7

4.7. Effect of different types of plasticizer

Applying the presented dissolution-diffusion model to various water-insoluble plasticizers resulted in the transfer kinetics shown in Fig. 10. Good agreement between theory and experiment proves the validity of the model even for different chemical compositions of the aqueous polymer dispersions. This is very important for the practical benefit of the model. In addition, the respective diffusion coefficients and dissolution rate constants of ATEC, DBP, DEP and TBC in Aquacoat® have been determined (Table 1). There are significant differences between the plasticizers. Different chemical structures of the plasticizers lead to different physico-chemical properties, such as different solubilities, molecular dimensions and interactions with the environment. Different D- and k-values result in different transfer kinetics, as can be shown theoretically as well as experimentally (Fig. 10). The most important consequence for the practical use of commercially available aqueous polymer dispersions is the resulting difference of the required minimum stirring times before applying the polymer dispersion.

4.8. Minimum stirring time

A homogeneous coating can only be achieved with a homogeneous distribution of the plasticizer within the polymer. Thus 100% plasticizer uptake should be demanded before using the aqueous polymer dispersion. On the other hand, it is common practice to cure the solid dosage forms subsequent to coating, in order to assure a complete film formation and to avoid aging effects (Gilligan and Li Wan Po, 1991). If there are any plasticizer concentration gradients within the coating, diffusion will occur during the curing period. Elevated temperatures will usually lead to increased diffusion coefficients and, thus, to high transfer velocities. Low concentration gradients could possibly be balanced due to curing. Consequently, there is probably no need to demand a complete plasticizer uptake of 100% prior to coating. To investigate this phenomenon in detail, additional experiments are necessary concerning the release behavior of the coated dosage forms in dependence of the curing conditions and the percentage of plasticizer taken up before coating. In this study, a minimum uptake of 85% was assumed to be reasonable with respect to common curing conditions (60°C, 1 h) (Gilligan and Li Wan Po, 1991). Fig. 10 shows the significant differences of the investigated plasticizers concerning the time to achieve 85% plasticizer uptake. Simulation of the transfer process using the dissolution-diffusion model leads to the following minimum stirring times (20% w/w plasticizer, based on polymer): ATBC: 3 h 40 min, ATEC: 50 min, DBP: 2 h 25 min, DEP: 1 h 10 min and TBC: 1 h 40 min.

Appendix A. List of symbols

A, surface area of the plasticizer droplets; B, constant for numerical analysis; c, concentration; $c[n][j]$, plasticizer concentration within the polymer particle at position $r = n\Delta r$ and time $t = j\Delta t$ (numerical nomenclature); $c_{r,t}$, plasticizer concentration within the polymer particle at position r and time t (analytical nomenclature); c_s, solubility of the plasticizer in the water phase; c_t, plasticizer concentration in the water phase at time t (analytical nomenclature); $c_w[j]$, plasticizer concentration in the water phase at time $t = j\Delta t$ (numerical nomenclature); D, diffusion coefficient of the plasticizer in the polymer; k, dissolution rate constant of the plasticizer in the water phase; k', k'', constants; K_d, equilibrium constant; M_{et}, amount of plasticizer emulsified in the water phase at time t; M_t, amount of plasticizer taken up by the polymer at time t; M_∞, amount of plasticizer taken up by the polymer at time $t = \infty$; M_0, total amount of plasticizer in the system; ΔM, amount of plasticizer transferred across the unstirred layer during the time interval Δt; dm/dt, dissolution rate of the plasticizer droplets; n, N, integers for numerical analysis; r, radius; Δr, space interval for numerical analysis; R, radius of the polymer particle; t, time; Δt, time interval for numerical analysis

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