REVIEW

Institut für Pharmazeutische Technologie der Heinrich-Heine-Universität Düsseldorf, Germany

Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions

B. C. Lippold and R. Monells Pagés

The formation of film coatings from aqueous polymer dispersions is a complex process, highly dependent on additives and process parameters. Release instability of modified release coatings from aqueous polymer dispersions is a frequently described problem that hinders the general application of such dispersions. However, if some important prerequisites are fulfilled, storage stability should be achievable. Most important are: (a) The appropriate plasticizing time has to be considered, incorporating sparingly soluble plasticizers in the dispersion. (b) Necessary pore formers increase the permeability of the coating to a desired and constant extent only if they are compatible with the polymer. (c) Coating in the fluidized bed at or slightly above the minimum film forming temperature may lead to only incomplete film formation. Curing at higher temperatures improves the polymer particles coalescence to a physically stable state. Other stability aspects such as physical and chemical aging, migration of plasticizers and drugs and incompatibilities are also discussed.

1. Coatings made of organic polymer solutions

Studies on the storage stability of slow release forms of drugs with polymeric coatings made of organic solutions are seldom discussed in the literature.

The film formation of polymers made of organic solutions is based on the rapid evaporation of the solvent, increasing concentration of the polymer within the solvent until a gel is formed [1]. After further loss of solvent, a continuous film in the form of a three-dimensional network is formed [2]. In contrast to coatings made of aqueous dispersions, where the process of film formation is a crucial factor for the release stability, only chemical and structural changes of the polymers, restructuring and migration of additives as well as the effects of residual solvent need be considered as reasons for instability of coatings made of organic solutions.

For example, theophylline diffusion pellets with ethylcellulose coatings and polyethyleneglycol (PEG 1500) as pore formers display a reduction of the release rate after being stored at room temperature for one year. Structural changes in the coating material appear to be responsible for this instability, as it can be attributed neither to a reduction of the extractable PEG fraction, nor to a lowering of the dissolution rate of the drug in the core [3]. Studies on slow release coatings made of Eudragit® RS (quaternary polymethacrylate) and dibutyl phthalate (DBP) as plasticizer show changes in the release rate, depending on the plasticizer content. While there is hardly any change of release rate for film coatings with 20% DBP, films with 5% DBP and 10% DBP show slight increases in release rate as do plasticizer-free films, also. The authors [4] conclude that there has to be a sufficient concentration of plasticizer to achieve an optimal storage stability to prevent the film from getting brittle during storage. Similar results with pellets that were coated with Eudragit® RS after a one-month-storage at room temperature confirm the necessity of a plasticizer to ensure the stability and flexibility of the film [5]. The effect of daylight on samples that were stored for 30 months at 20 °C and 60% relative humidity is also an increase in release rate, that can be attributed to a light-induced change of the plasticizer DBP [4].

Minitablets, coated with ethylcellulose and PEG 1540 or with ethylcellulose and Eudragit® L (acidic polymethacrylate) or with Eudragit® RL (quaternary polymethacrylate) show a decrease in release rate that is proportional to the storage temperature after being stored at 28 °C, 35 °C and 45 °C (all at 55% relative humidity). This aging process takes place especially at the beginning of storage and is independent of the type of polymer. Other relative humidities do not cause a change of the stability behaviour. The authors [6, 7] explain the slowing down of release by the slower diffusion of the active agent through the aged polymer film. This thesis is supported by the work of Okhamafe and York [8–10] on interaction phenomena in coating systems. Changes in crystallinity, glass-transition temperature, polarity, the extent of crosslinking and the binding of the active agent to functional groups of the polymer can all change the permeability of the film.

Instability during storage does not only occur in the case of slow release coatings, but also with enteric coatings. Studies on 181 of such formulations carried out by Thoma et al. [11–14] show that the acid resistance as well as the disintegration behaviour are influenced by storage. Here, the ester hydrolysis of cellulose acetate phtalate (CAP) and of acidic polymethacrylates at high humidity (80% relative humidity) are cited as causes. As a result a decrease in elasticity and an increase in film brittleness are observed. The effect of storage on non-plasticized, isolated CAP-films was studied by Delporte [15] with reference to chemical degradation, dissolution, permeability and mechanical properties. The aging of the CAP-film resulting in a loss of gastric juice resistance, is due to two phenomena: an increase in free phthalic acid and intermolecular rearrangement. Both phenomena are accompanied by a film-constriction, an increase of crystallinity and a decrease in film strength.

Acidic cellulose ester films (cellulose acetate phthalate (CAP) and hydroxypropyl methylcellulose phthalate (HPMCP)) as well as films consisting of Eudragit® L display a decrease in water vapor permeability during storage at room temperature over silica gel through desorption of solvents that are initially included in the polymer [16]. Changes in mechanical properties in the case of films made of Eudragit® L 100-55, stored at 23 °C and 50%

relative humidity, are also attributed to the evaporation of the residual solvent during storage [17]. How fast the solvent evaporates out of the film depends on the plasticizer concentration. For example, residual solvent in films with 10% plasticizer was found after four days of storage at 40 °C and 60 °C, respectively, but none were found in films with 20% plasticizer [18]. Changes of the release profile for enteric film-coated tablets depending on storage time and storage conditions were also observed [19, 20].
However, stable drug diffusion with polymer coatings made of organic solutions has also been quite often reported in the literature. Coatings made of quaternary polymethacrylates in combination with CAP and waxes [21] display no change in their release characteristics after being stored at 30–40 °C and at a high relative humidity (72 and 90%). The storage of potassium chloride diffusion pellets at 30–50 °C [22] or of sodium salicylate tablets coated with ethylcellulose and various additives [23] over a period of more than 1.5 years at 20 °C has only a small influence on the release of the drug. Films made of polymethacrylate and salicylic acid display a slight decrease in the release of the active agent after storage for five days at room temperature. Further storage up to three months does not cause any change in the release profile [24].

2. Coatings made of aqueous polymer dispersions

In general, problems of release stability occur when the film formation process is not finished during the production of the coating. This is why complete coalescence should be achieved during the coating process (see chapter 2.2.2.) and after a short time of curing (see chapter 2.2.3.) [25].

2.1. Film formation

Film formation from aqueous polymer dispersions is described by many authors [26–32] and can be summarized as follows: After concentration of the latex particles through water evaporation, deformation and almost complete coalescence of the particles takes place at temperatures above the minimum film forming temperature (MFT). Capillary attraction and/or surface tension are responsible for this. The addition of plasticizers is often necessary to make deformation at low temperatures possible. After these processes, further gradual coalescence (FGC) and polymer interdiffusion take place. The particle contours vanish and the macromolecules of adjacent particles partly mix through interparticular diffusion. According to the theory of free volume [33], interdiffusion is only possible, if there is enough intermolecular space between the polymer chains and if the temperature is above the glass transition temperature (Tg). One can study interdiffusion of polymer chains in adjacent particles by SANS-measurements (small angle neutron scattering) [27, 34–36] or by DET (direct non-radioactive energy transfer) [37, 38].
Millili et al. [39] describe the development of interactions between high molecular polymers during the last stage of the film formation process by a diffusion controlled mechanism. This process is also defined as autohesion and depends on the following parameters:
Polymer properties:

- Molecular weight: Autohesion takes place faster with low molecular polymers than with high molecular polymers, as they have more chain endings between the particle surfaces to interact. The activation energy necessary for that process is independent of the molecular weight.
- Structure: Polymers with a high molecular weight and a regular structure have a high value of autohesion.
- Type: Polymers with many polar groups can exercise electrostatic attraction forces which limit their flexibility. The consequences are a lowering of the diffusion rate and the necessity for a higher activation energy. But the addition of polar solvents or plasticizers causes the polar groups to be shielded and the polymer chains to become more flexible.
- Crystallinity: In polymers with a (partly) crystalline structure the polymer chains are in a rigid arrangement which hinders interdiffusion.
- Viscosity: The lower the viscosity of the polymer, the more flexible the polymer chains, which means that diffusion can be achieved more easily. Viscosity that is too low can, however, hinder interdiffusion.

Conditions of production:

- Time: Autohesion increases with longer contact time between the polymer particles.
- Pressure: A certain capillary pressure is necessary to achieve maximum contact between the particle surfaces.
- Temperature: The extent of autohesion increases exponentially with temperature.
- Plasticizers: They reduce the viscosity of the polymer, enhance the flexibility of the polymer chains and increase interdiffusion. Plasticizers can screen off functional groups and make the polymer more “liquid”.
- Antiplasticizers: Substances with a low molecular weight may be trapped between the small polymer particles and can hinder the diffusion of the chains.
- Solvents: These cause effects similar to those of plasticizers.
- Additives: Depending on the substance added, autohesion can be enhanced or physically blocked. An added polymer can interact with the film-forming polymer and can cause hardening of the particle surfaces by adhesion.

All this information from the polymer and coatings industry can be of use for the pharmaceutical application of polymer dispersions. The degree of autohesion can be influenced by the choice of polymer, plasticizer, and additives and by the conditions of production.

2.2. Conditions for reproducibility and comparability of film formation

2.2.1. Incorporation of plasticizers into the dispersion

Plasticizers are substances with a low molecular weight and a low vapor pressure. They are added to improve the physical properties of polymer films, e.g. the flexibility.
Typical plasticizers are polyols and polyethers (e.g. glycerol, PEG) as well as organic esters (e.g. citric or phthalic acid esters). An effective plasticizer should penetrate between the polymeric chains and should reduce their inter- and intramolecular adhesive forces. The polymeric network can therefore be loosened [40].
An opposite effect of antiplasticizing action is described by Guo [41–44]. Here, interactions between plasticizers and polymer molecules only emerge at low plasticizer concentrations. These interactions restrict the flexibility of the polymer chains, causing a decrease in water vapor permeability and coefficient of elasticity. With an increase of temperature above the Tg, the polymer molecules have enough energy to overcome the interaction and the antiplasticizing effect vanishes. Wang et al. [45] consider the antiplasticizing action to be the cause of an increase in tensile strength of Eudragit® RS-films with 5 and 10%

triacetin or diethyl phthalate compared to the non-plasticized film. This effect is also seen with the thermal properties of the films: The Tg of the polymer hardly changes after the incorporation of 5% of plasticizer, but it decreases strongly with a plasticizer concentration of 10% or more.
How plasticizers support the diffusion of polymer molecules through the surface between polymer particles during film formation can be shown by DET-studies [37]. The results show an increase in diffusion coefficient with an increasing concentration of plasticizer. The choice of plasticizer and an adequate concentration as well as its proper incorporation into the aqueous polymer dispersion are of great importance for the resulting coatings and their stability behaviour.

2.2.1.1. Affinity of the plasticizers for the polymer

The affinity or suitability of a plasticizer is characterized by its compatibility, effectiveness and persistency [40, 46–48].
The compatibility can be characterized by the miscibility of the components with each other on one hand, and by the similarity of its solubility parameters, on the other [26, 49, 50]. It can also be characterized by interaction coefficients [26]. The compatibility may also be defined by measurement of the intrinsic viscosity [51, 52], by the degree of transparency of isolated films [47] and by tensile strength measurements [53, 54]. Nakagami [55] evaluated the compatibility of plasticizers and polymers by determination of the cloud point and by the dissolution temperature.
Plasticizers are used to decrease the glass transition temperature (Tg), the plasticizing temperature (Ts) of the polymer and the minimum film formation temperature (MFT) of the corresponding dispersion. This decrease is often used as a measurement of effectiveness and it depends on the type of plasticizer and its concentration. Plasticizers with a low molecular volume are better able to break or loosen the interactions between polymer chains [56]. Measurements of the mechanical properties of the films by tensile strength studies [45, 57–59] or creep measurements [44, 60] give further information on the effectiveness of a plasticizer.
The persistency of a plasticizer in the film is of especially interest when high temperatures are involved, e.g. during curing and storage. The volatility of a plasticizer depends on its effective vapor pressure and its diffusion rate in the polymer film. The effective vapor pressure does not relate to the volatility of the pure plasticizer. It depends on the interactions and compatibility between polymer and plasticizer. Partial loss of the plasticizer occurs by migration into the core, to the film surface and/or into the packaging material. Thus, mechanical stability can be decreased during production or storage and the release rate of the corresponding formulation can be changed [40] (see also chapter 2.2.3.4.).
Heaps [46] describes the loss of plasticizer by evaporation (loss at the surface during contact with air), by migration (during contact with a solid), or by extraction (during contact with a liquid). Films consisting of Eudragit® E (basic polymethacrylate), containing PEG 200, Propyleneglycol, Diethyl phthalate (DEP) or oleinic acid as plasticizers stored at 37 °C and 75% relative humidity display an increase in their rupture strength and a decrease in elasticity. These changes in mechanical properties are attributed particularly to the volatility of the plasticizers caused by storage at high relative humidity [47].

2.2.1.2. Particle size of the dispersion

Small size of the polymer particles in the dispersion (Aquacoat® EC-D30, ethylcellulose: 100–300 nm [106], Eudragit® RS 30 D, quaternary polymethacrylate: 15–100 nm [61]) is an important factor in film formation and permits rapid distribution of the plasticizer into the polymer particle if the plasticizer is not extremely hard to dissolve in water.
A comparison of an aqueous suspension consisting of micronized ethylcellulose and an ethylcellulose latex shows the influence of the particle size on film formation [30]. The suspension displays a higher MFT and needs at least a 15% addition of plasticizer to develop a complete film. It is obviously easier for the plasticizer to diffuse between the polymer chains of the ethylcellulose latex. Furthermore, ethylcellulose latex contains emulgators such as sodium laurylsulfate and cetylalcohol, which supposedly also act as plasticizers. The particle size of the suspension is 30 times the size of the latex. The capillary attraction, necessary for film formation is, however, proportional to the particle diameter and it contributes less to the coalescence of the suspension. Similar studies on ethylcellulose as an aqueous dispersion or suspension [54] show that the ethylcellulose latex without a plasticizer develops a film at 100 °C, while the suspension needs a temperature of 140 °C. This confirms the difference in film formation between the two systems. The fact that film formation is different is confirmed by the influence of curing. After one hour of curing at 80 °C, a decrease in release rate takes place with a granulate coated with ethylcellulose latex, which can be explained by non-complete coalescence after the coating process. However, curing the granulate coated with the suspension, displays no effect on release.
The necessity for different moisture conditions or spraying rates at similar temperature conditions during the production of isolated films consisting of Aqoat® (aqueous dispersion consisting of hydroxypropyl methylcellulose acetatesuccinate) and Eudragit® L 30 D−55 (acidic polymethacrylate) can also be explained by the different size of the polymer particles. The particles in the Aqoat® dispersion have a diameter of about 5 μm, while the latex particles in the case of Eudragit® have an average size of 0.22 μm. A higher relative humidity is necessary during the production process for complete coalescence of the larger particles (Aqoat®) [57].

2.2.1.3. Plasticizing time

The plasticizing time is defined as the time period between the addition of the plasticizer into the polymer dispersion and the coating process [62, 63]. The standing time is the time that follows after the end of the mixing of the dispersion with the plasticizer (e.g. 30 min) up to its application. In this period of time, the plasticizer should be distributed into the polymer particles according to its partition coefficient.
If there is insufficient plasticizing time, plasticizer drops are sprayed on the cores during the coating process. Films produced in this way display an irregular distribution of plasticizer, that can improve during curing and that can change the properties of the coatings. The distribution rate of the plasticizer into the polymer particles is strongly dependent on its water solubility. In principle, one can divide plasticizers into two groups: water soluble or hydrophilic plasticizers and non-soluble or lipophilic plasticizers.

Table: Solubility of the most common plasticizers in water at RT or 20 °C [40, 55, 61, 62, 66]

Plasticizer	Solubility (% m/V)
Triacetin (TA)	6.7–7.8
Triethyl citrate (TEC)	5.5–6.9
Acethyl triethyl citrate (ATEC)	0.72
Diethyl phthalate (DEP)	0.15
Dibutyl phthalate (DBP)	0.04
Dibutyl sebacate (DBS)	0.01
Tributyl citrate (TBC)	<0.002
Acetyl tributyl citrate (ATBC)	<0.002

The Table summarizes the water solubilities of the most common pharmaceutical plasticizers. Plasticizers such as ATEC and DEP are considered either as water soluble [64] or non-water soluble [65], depending on the author.

Plasticizers that are poorly water soluble need longer stirring and standing times to be incorporated by the polymer and to ensure a maximum lowering of the MFT [63, 66, 67]. Studies on the standing time of Aquacoat® dispersions with 20% DBS display a continuous decrease of the MFT, until the final value is reached after 5 h [67]. Frohoff-Hülsmann [66] finds similar results with 10% plasticizer addition, where the standing time for DBS and DBP is 7 and 3 h, respectively. In the case of the hydrophilic plasticizers TEC and DEP, the MFT is lowered after some minutes of standing time and stays constant for 48 h. Lehmann [61] defines the MFT for Eudragit® dispersions after 30 min stirring independently of the plasticizer solubility. The water soluble plasticizers are dissolved in water and the non-water soluble plasticizers are dispersed into a 1% solution of polysorbate (Tween® 80) and are added to the dispersion.

The influence of the standing or stirring time of the dispersion on the permeability properties of the coating is discussed from various points of view. Diffusion pellets using a plasticizer-containing ethylcellulose dispersion with sufficient standing time display a higher permeability than those with insufficient time. The longer the standing time, the more the plasticizer is capable of penetrating the polymer particles, and the faster the release of the active agent. This effect is stronger at higher plasticizer concentrations. A long storage time of the coated pellets cannot even out the differences in penetration and distribution of the plasticizer into the coatings that result from various standing times [68]. An extension of the standing time of plasticized Eudragit® RS dispersions from 12 h to 3 days gives denser films and lower release rates. This effect is explained by complete penetration of the plasticizer into the latex particles and better film formation [69]. Iyer et al. report on the importance of the stirring time when adding the plasticizer DBS to ethylcellulose dispersions [70]. The authors demonstrate that after 30 min, independent of the plasticizer concentration, more than 95% of the DBS is distributed in the polymer.

The distribution of water soluble (TA, TEC) and non-water soluble plasticizers (ATEC, ATBC, TBC, DBS, DEP, DBP) between the water phase and the polymer phase in diluted ethylcellulose dispersions after 24 h of stirring time has also been studied by Bodmeier et al. [65]. Water soluble plasticizers are distributed equally in the water phase and in the polymer phase. Non-water soluble plasticizers mostly distribute in the polymer phase (85–90% of the amount used). The amount of dispersed plasticizer increases when the plasticizer concentration is increased, because the polymer is saturated after a certain level of concentration has been achieved.

In another publication, Bodmeier et al. [62] report on the distribution of plasticizers in relation to the stirring and plasticizing times. The distribution rate of the plasticizer in the polymer defines the amount of plasticizer that is present in the polymer after a certain plasticizing time. The distribution of the water soluble plasticizers TEC and TA is already complete after 5 min. In contrast to this, the distribution rate of non-soluble plasticizers is dependent on many factors:

- plasticizer concentration,
- type of plasticizer,
- type of polymer,
- solids content of the dispersion.

Bodmeier claims that an emulsified plasticizer can only be absorbed by the polymer, if it dissolves in the water phase. First-order distribution rate constants are therefore calculated for the concentration decrease of emulsified plasticizer. The higher the plasticizer concentration, the slower the partition. The rate of plasticizer distribution increases with increasing solids content of the dispersion. The distribution rate constants approximately correspond to the water solubility of the plasticizer:

DEP>ATEC>TBC>DBP>ATBC. Thus, the distribution coefficient of the plasticizer between the polymer and the water phase plays an important role. In the case of Aquacoat®, non-water soluble plasticizers have higher coefficients (between 35–45) than water soluble ones (approx. 3–5). The distribution rate is also dependent on the polymer. Eudragit® RS 30 D displays an increase in viscosity in contact with ATBC due to strong plasticizer-polymer interactions. In the case of Eudragit® L 30 D, 80% of the ATBC remains in an emulsified state. The incompatibility between the two substances has been proved by squeezing out of the plasticizer and also by phase separation, (see chapter 2.3.4.).

Siepmann et al. [71] describe the distribution of non-water soluble plasticizers in the particles of the polymer dispersion by two mechanisms:

- dissolution of the plasticizer droplets in water
- diffusion of the plasticizers in the polymer particles.

Both processes take place simultaneously, although the plasticizer uptake is controlled initially by dissolution and finally by diffusion. After determination of the dissolution rate and the diffusion coefficient, the minimum stirring time until complete absorption of the plasticizer into the polymer particles can be calculated mathematically.

2.2.2. Film formation in the fluidized bed

The polymer particles have to be deformable to a certain degree and the polymer chains have to have a certain mobility, to enable the formation of a complete film. The temperatures necessary are based on the following points:

Only after exceeding the glass transition temperature (Tg) and the softening temperature (Ts) of the water – saturated, additive – containing polymer, are deformation and coalescence of the latex particles and interdiffusion of the polymer chains possible [31, 72]. In fact, film formation in aqueous dispersions takes place below the Tg of the pure polymer at the minimum film formation temperature (MFT), due to capillary attraction and/or surface tension as well as plastification by water. Homogeneous fracture – free films will only be obtained above the MFT. Thus, the bed temperature during the fluidized bed coating process should be approximately 10–20 °C above the MFT of the dispersion [67, 68, 73].

The effect of the bed temperature on film formation has been studied in the case of Aquacoat® and TEC. Incomplete films are developed at high temperatures (50 °C), when rapid evaporation (in an extreme case: dry spraying) takes place and the development of surface tension hardly occurs. At low temperatures (22 °C), the MFT is not exceeded, and the surface tension is not strong enough to cause deformation and fusion of the polymer particles. Furthermore, water soluble drugs such as diphenhydramine HCl migrate into the coating and hinder film formation. Bed temperatures between 30 and 40 °C are high enough to hinder the migration of the active agent and low enough to enable the development of capillary attraction [74].

When using Aquacoat® as the coating material for propranolol HCl pellets, migration of the drug into the ethylcellulose film also takes place during the coating process [75]. A heterogeneous membrane with incorporated drug particles is developed, as shown by REM. When coating the pellets with Surelease®, no essential migration of the active agent can be observed. Aquacoat® and Surelease® have pH values of approximately 7 and 12, respectively. Thus, propranolol ($pK_a = 9.45$) exists protonated in the water phase of Aquacoat®. This enables more of the drug to dissolve and migrate into the film.

Lorck et al. [76] report on the influence of the bed temperature on the release of coated pellets dependent on the aqueous dispersion used. The release rate of pellets coated with Eudragit® RS 30 D/RL 30 D, increases with increasing bed temperature (30–50 °C). The highest release, however, can be observed at temperatures between 23–27 °C, which probably lie below the MFT of the dispersion. Pellets coated with Surelease® and coated for 24 h at 60 °C display various release profiles dependent on the product temperature. A product temperature of 50 °C causes a faster release than a product temperature of 40 °C. This can be explained by high spraying loss and/or dissolution of the active agent in the coating. In the case of films made of Eudragit® RS 30 D, the effect of the bed temperature (25–45 °C) on the release rate dependent on the plasticizer used, has been studied [77]. TEC and DBP-containing films display minimal changes of the release profile with increasing bed temperature. Only at a high temperature can a slight slowing down of the release be observed in the case of TEC-containing films. In contrast to this, a marked decrease of release with an increase of the bed temperature can be observed with PEG-containing dispersions. This is not surprising, for PEG 6000 is compatible with Eudragit® RS 30 D only to a limited extent.

Watano et al. [78–81] have intensively studied the influence of the humidity during the coating process on the properties of films made of aqueous dispersions. High humidity during the coating process avoids dry spraying of the dispersion and enhances the coalescence of the polymer particles. At high spraying rates, the active agent is able to dissolve and migrate into the film. This can be avoided by slow spraying at the beginning of the process. Incomplete spreading of the dispersion droplets is the result of too low a spraying rate. Both spraying conditions cause rapid release [82].

Pellets coated with Aquacoat®, TEC and hydroxypropyl methylcellulose (HPMC) show a decrease in release rate after 4 months storage at RT [83]. Far too low a temperature during coating (45–55 °C) and lack of drying after spraying appear to be responsible for this. The drying time and temperature have an influence on the coalescence of the polymer particles [84].

In spite of all efforts to achieve complete coalescence as early as possible during the formation of coatings, coating is in general not yet optimal. This can be achieved by further curing.

2.2.3. Curing of diffusion pellets

The process of so-called further gradual coalescence (FGC) or interdiffusion to achieve stable films takes place at temperatures above the Tg. To enable and accelerate the process the coatings are cured. Curing means that the coating is exposed to temperatures above the Tg for a certain time until complete coalescence is achieved [59, 85].

During the curing the polymer is in a rubber-like state, characterized by high polymer mobility and elasticity [86]. The effect of the additional curing is greater or lesser depending on both the MFT and Tg, and on the coating conditions (temperature, humidity, duration). Curing may be achieved in an oven or a fluidized bed [87].

To study the effect of temperature on Eudragit® RS 30 D films with 20% ATBC and 0.02% polysorbate (Tween 80), Guma et al. [88] developed a dielectrical measuring method. After curing the samples at 60 °C, four states can be observed depending on the time:

undercuring, optimal curing, overcuring and supercuring. In the optimal curing stage, the diffusion pellets show a continuous and smooth surface and the lowest release rate. In the over-cured phase, cracks in the coating develop as the result of loss of plasticizer and water. An increase in release rate and a decrease in film thickness can be observed. Supercuring is accompanied by a decrease in release rate. The cracks formerly developed vanish by restructuring of the polymer molecules, towards a new low energy state.

Numerous studies prove that curing results in slowing down of the release rate, caused by more or less strongly marked changes in the film structure.

For example, films made of silicon latex and 30% PEG 8000 display a decrease in release rate and a more uniform structure than non-cured films after curing at 60 °C for 24 h [89]. Dahl and Sue [90] think that slowing down of release is surprising, as the Tg of this polymer lies far below RT (−123 °C). The curing effects are attributed to coalescence of the latex particles by further water evaporation. Excessive curing (96 h at 80 °C) causes development of cracks in the coating. This is explained by loss of the plasticizer PEG 8000 through oxidative decomposition [90]. Curing at 40–60 °C is necessary to achieve stable release profiles for films made of ethylcellulose and amylose. A decrease in permeability occurs caused by further coalescence of the ethylcellulose latex particles and a change of the physical structure of the coating corresponding to a decrease in the size of the pores formed by amylose [91].

The permeability can also increase with increasing curing temperature, as with theophylline pellets coated with dibutyl sebacate-containing ethylcellulose dispersions. Lippold et al. [68] explain the effect by the fact that the plasticizer is able to penetrate faster and more completely into the ethylcellulose particles at a high temperature. The flexibility of the film is increased by this process. After cooling, the ethylcellulose molecules remain in a loosened metastable state.

Differences with regard to permeability can also be explained by the development of tensions within the polymer film during drying or curing. The dry film has to

cover the same area as the film which still contains water. That is why the film can only shrink in thickness. The tensions that result from this unequally distributed shrinkage, cause partial orientation of the polymer chains and hence a low permeability in these areas. The permeability is higher for films which display little or no tension [92].

In the case of Surelease®, curing should not influence or only insignificantly influence release [93]. Nicotinic acid pellets coated with Surelease® show no change of the release profile after 2 months storage at RT or at 40 °C. On the other hand, a slight decrease in release can be observed at 40 °C and 80% relative humidity. These results show that film development is already complete after coating and that further curing at high temperature is not necessary [94].

Dyer et al. [95] also claim, that, when using Eudragit® RL/RS-dispersions, Surelease® or Silicon latex, complete film formation occurs after coating. Curing, though only at 40 °C for 24 h, does not cause a change in release.

Plasticizers and pore formers can influence the effects of curing. Diffusion pellets coated with Aquacoat® and TEC show a decrease in release with increasing curing. In the case of films containing DBP, an increase in temperature does not cause a change of release. A reason for this is the poor effectiveness of DBP as a plasticizer [96]. Bodmeier [97] reports on the effect of curing on diffusion pellets coated with Aquacoat®, in relation to the TEC-concentration. The curing of coatings with 10% TEC does not cause slowing down of release. The addition of 10% TEC is not sufficient for film formation during the coating process, as the temperature used is above the MFT. The release rate decreases with increasing temperature when 15 to 25% TEC are added. If the concentrations are above 25% to 35% TEC, curing has less or little influence on release. This results in complete coalescence during the coating when there is a high plasticizer content in the polymer. Therefore, a curing process is not necessary.

However, too much plasticizer can cause sticking problems during curing and storage and can influence the stability and release profiles of the drug [77, 86]. To avoid this, an additional water soluble coating, usually hydroxypropyl methylcellulose (HPMC), is often applied [98, 99]. Chang et al. [100] report on an increase in release rate after coating with HPMC. The effect of curing is also influenced by the additional film. Thus, 16 h curing at 50 °C slows down release for diffusion pellets with an additional coating and increases it for those without an HPMC-coating.

For osmotic controlled phenylpropanolamine HCl-pellets, coated with Aquacoat®, Dressman et al. [101] have shown that curing above the Tg of the plasticizer containing film causes stabilization of the release behaviour during storage as well as making release independent of the pH value. Surprisingly, coatings containing 25% DBS show an increase in release rate after 2 h curing at 60 °C. Storage at various temperatures (RT and 37 °C) and moistures (ambient humidity and 75% relative humidity, respectively) hardly changes release from the cured pellets. Pellets coated with Aquacoat® and 24% TEC show no change in release after curing. This different behaviour can be explained by the Tg-values: The Tg is 35.5 °C for TEC-containing films. Both during coating (product temperature 43–45 °C) and during curing (60 °C), loosening of the polymer chains and complete coalescence of the plasticized film can take place. The Tg of films with 24% DBS is 44 °C and complete film formation can only take place during curing. Additional measurements of the wetting angle indicate changes in the film surface during curing. The independence of release from the pH value of the medium can be explained by relaxation processes above the Tg. The loosening of the polymer structure allows uniform distribution of the emulgators and therefore a decrease in surface effects, which are supposed to be responsible for the pH dependence.

Studies on aqueous ethylcellulose dispersions show a dependence of release on curing and on the release medium. The release from the diffusion pellets is independent of the conditions of curing in 0.1 N-HCl. But the release rate decreases with increasing temperature and time in phosphate buffer. The pH dependence and the influence of the curing appear to be caused by the emulsifies sodium laurylsulfate [102]. Lippold et al. discussed carboxyl groups in ethylcelluloses as the reason for pH dependence [68, 103]. The effect of curing is also dependent on the pore former concentration in the film. After curing at 60 °C Aquacoat® coatings with 24% TEC show a smaller decrease in release rate, the higher the HPMC concentration [83].

Not only the temperature of curing, but also its duration changes release. After curing at 60 °C, studies on pellets coated with Surelease® show a continuous decrease of release with increasing curing time. Times longer than 24 h on the other hand do not result in any changes [85]. Amighi et al. [104, 105] show in excellent studies that the curing time necessary at 40 °C and 50% r.h. decreases with increasing plasticizer concentration.

Films made of Eudragit® RS 30 D, 5% HPMC (Pharmacoat 606) and 10% TEC require longer times (3 months) than films with 20% TEC (7 days) to obtain optimally cured coatings. After the addition of 30% TEC the release behaviour of the diffusion pellet is already independent of curing after the coating process. An increase in chain mobility and the free volume of the polymer, decreasing the MFT and Tg, are responsible for this phenomenon. Similar results are obtained with other plasticizers and pore formers [87].

Similar effects have been achieved with increasing relative humidities after one week of curing at 40 °C. The release rate is lower for diffusion pellets cured at 50, 70 or 90% r.h., than for those cured at 0 and 30% r.h.. This implies that there must be a connection between coalescence and the relative humidity for curing. Studies on theophylline pellets coated with Surelease® show that curing over a period of 24 h at 60 °C under different humidity conditions leads to very similar release profiles. The relative humidity (30 to 75% r.h.) does not seem to have an influence on the final release rate for this curing duration. Under both humidity conditions, film formation during curing can be regarded as optimal [76].

An important step which is hardly ever mentioned in the literature, is the cooling process after curing, that is the transformation of the polymer from the rubbery to the glassy state. There is no regular order in the glassy state, since it corresponds to a supercooled melt. The properties of these glasses are influenced by the temperature which was used for their production. Different cooling rates can also produce different glasses. Each glass has a specific Gibbs energy and therefore a different transformation temperature. Hence, there is a large number of glasses with the same chemical composition, which due to their origin, differ in preparation temperature, cooling rate and curing conditions [106].

As glasses are thermodynamically metastable, they are transformed to an energetically more favourable state in

the course of time. These structure changes at temperatures below the Tg are described as relaxation phenomena (see chapter 2.3.2.).

2.3. Reasons for instability

Apart from the film forming polymer, plasticizers, pore formers and emulgators are often also necessary to produce coatings from aqueous dispersions. These components can influence not only the properties but also the release stability of the coatings.
Fundamental conditions for stable coating are optimal incorporation of plasticizers into the dispersion (see chapter 2.2.1.) and adequate curing (see chapter 2.2.3.). As far as the release properties of a coating are concerned, 3 situations can occur during storage [25]:

- the release rate does not change, that is the formulation remains stable, opposing mechanisms can possibly nullify changes,
- the release rate increases in the course of time,
- the release rate decreases in the course of time.

Reasons for changes in release rate are:

- further gradual coalescence (FGC),
- physical aging,
- formation of cracks,
- migration or evaporation of the plasticizer,
- incompatibility or interaction between pore former and polymer coating,
- separation of emulgators,
- chemical aging processes,
- migration of the drug.

The stability of the applied latex/pseudolatex dispersion must be considered apart from stability problems of the final coating. The storage stability of aqueous polymer dispersions is limited since slow agglomeration of the latex particles takes place at room temperature. As long as no sediment develops and the spraying and film formation are not affected, there are no consequences. Serious problems such as the coagulation of the dispersion can arise in the case of temperature increasing, freezing, high shear stress, pH changes or addition of electrolytes and pigments. The storage stability of aqueous dispersions can also be influenced by microbial contamination [73].

2.3.1. Further gradual coalescence (FGC)

Stable coated slow release preparations are achieved through curing at high temperature and relative humidity for a certain period of time. The release then reaches a certain profile or level, which is not changed by further storage at high temperature and/or relative humidity [25, 59, 85], see also 2.2.3.

2.3.1.1. Storage temperature

The literature frequently discusses changes in the release properties of coatings produced from polymer dispersions, at increased storage temperature. Reasons are lack of, or inadequate, curing. Hence, pellets coated with Eudragit® RL/RS 30 D and cured for 1 h at 55 °C, demonstrate a decrease in release rate dependent on storage time and temperature [107]. A slow down of release after storage at ambient conditions can also be observed with non-cured propranol HCl pellets coated with Eudragit® NE 30 D (neutral polymethacrylate dispersion). Coated pellets on the other hand demonstrate stable release profiles after 1 h of curing at 70 °C [98]. Pellets coated with Eudragit® NE 30 D and kaolin do not show any change in release at room temperature. The authors [108] nevertheless point out that storage at temperatures above 40 °C can lead to unpredictable release profiles.
Storage at 20 °C of non-cured films of silicone latex and 30% PEG 8000 causes a slight but continuous decrease in release in the course of time (up to 45 weeks). In contrast to this, storage at 50 °C causes a marked decrease in release after 15 weeks which stays constant in the following weeks. This indicates complete coalescence after 15 weeks of storage at 50 °C [89]. Coatings made of Eudragit® NE 30 D show progressive film formation of the latex particles during storage at 25 °C and 40% r.h., which leads to reduced release. The release rate becomes constant after one week. But a short term increase in temperature to 40 and 70 °C, respectively, still reduces release [109]. Vecchio et al. [110] investigated the influence of curing with of indobufen pellets coated with Eudragit® RL 30 D/RS 30 D, TEC and Syloid (highly porous silica). Curing in a fluidized bed at 55 °C leads to a slight decrease in release with increasing curing duration. On the other hand, release is strongly decreased after 15 min of curing at 70 °C, but remains unchanged after longer curing times. Additional storage for one month at 40 °C induces only a slight decrease in release rate.

2.3.1.2. Storage humidity

Post-treatment of the films through high temperature alone often does not sufficiently stabilize release. Therefore, in their patent Oshlack et al. [111] state that coated pellets must be cured at temperatures above the Tg of the coating (polymer and additives) and at high relative humidity, i.e. 60 to 100% r.h. Optimal conditions (temperature, relative humidity and time) must be determined for each formulation.
The following studies on films and on coated pellets and tablets concentrate on cured products. The instabilities observed in some cases can be attributed to inadequate curing and the effect of water.
Other than at 97% r.h., drug containing films of Eudragit® NE 30 D show no changes in release after storage at different humidities. In contrast, films made from Eudragit® RS 30 D demonstrate an increase in release rate as well as increased water absorption at increasing relative humidity [112]. The effect of storage humidity on the mechanical properties of poured films of Eudragit® RS 30 D and TEC and ATBC, respectively, was studied in relation to the concentration of plasticizer [57]. The tensile strength of films with 10, 15 or 20% plasticizer increases with increasing relative humidity. Films containing 10% plasticizer become brittle at 0 and 20% r.h. The tensile strength of films with 15 and 20% plasticizer increases with increasing relative humidity due to the plasticizing effect of water. Water absorption of the films (less than 2% at storage up to 75% r.h.) causes significant changes of the mechanical properties.
Tablets coated with Eudragit® NE 30 D and $CaHPO_4$ as pore former show no change in release after 6 months storage at 22 °C and 75% r.h. This observed stability is due to the low hygroscopicity of the pore former. At high relative humidity pore formers such as saccharose and sorbitol develop sticky films and recrystallize on the surface when the humidity conditions change [113]. Theophylline diffusion pellets coated with Eudragit® NE 30 D have been studied by Amighi et al. [105] with respect to their stability after 4 months storage at 25 °C and different humidity conditions. A change of the release profile could not seen

at 0 and 30% r.h. The release rate increases at 50 and 70% r.h., which can be explained by an increase in the water content and hydration of the coating. A transformation of anhydrous theophylline into the monohydrate takes place at 90% r.h. and the release rate decreases slightly. In the case of Eudragit® RS 30 D, this transformation leads to cracks in the coating and increased release rates [87].

Prinderre et al. [113] divided the water absorption of coated granules after storage at high r.h. into three phases:

- adsorption of water molecules on the surface of the film; this is influenced by the surface properties of the granules,
- diffusion of the water molecules through the film,
- desorption on the film granules interphase, where hydrophobic granules make the penetration of water into the interior more difficult.

The rate and extent of the diffusion of water molecules depend on the chemical nature as well as on the permeability properties of the polymer coating. Films consisting of Eudragit® RS 30 D and L 30 D absorb less than 2% water and films consisting of HPMC absorb up to 5% water after 5 days at 20 °C and 100% r.h.

After storage at room temperature, pellets coated with Eudragit® RS 30 D demonstrate various degrees of water uptake depending on the plasticizer used. Hence, the water content of films with PEG 300 increases by 0.6% in comparison to TEC-containing films, which show a decrease of 0.01%. Although the changes in water content are not pronounced, hydrolysis of sensitive active agents can take place [114].

Water can not only be absorbed during the storage, but also desorbed. Coatings have a residual water content after the coating process. Water can theoretically be fully removed if the process temperature lies above the Tg. This is not always possible, since the Tg of the resulting film is usually too high. The water desorption depends on the affinity of water for the polymer and the polymer structure and on the free volume of the polymer, respectively.

When water disappears from the film, a decrease in free volume and an increase of the Tg of the polymer takes place. The water loss during storage often causes changes of the physical properties of the coating as well as changes of release behaviour. Addition of hydrophilic additives causes an increase in absorbed water [115].

2.3.2. Physical aging

Polymers, especially when they are in a metastable state, can show so-called physical aging. This purely physical phenomenon has been described and studied extensively by Struik [116]. Aging effects are thermoreversible, that is heating of the polymer to temperatures above the Tg and further cooling neutralize these effects. Changes during physical aging are caused by a decrease in the free volume of the polymer [116] or by changes of the molecular order and restructuring of the polymer chains, respectively [117]. On the basis of changes in the mechanical properties of polycarbonates caused by physical aging, Bubeck et al. [118] demonstrate that not only a decrease of the free volume of the polymer but also an increase in the order of the polymer chains are very important for the brittleness and hardening of polymer films.

Physical aging can also be described as a time dependent relaxation of the polymer structure. Due to relaxation, curing below the Tg leads to structural changes in the case of polyvinylchloride (PVC), which are due to a decrease of the free volume [119].

The presence of free volume results from a need for space caused by chain segment mobility, which develops above the Tg. This free volume remains when there is rapid cooling below the Tg. Since this state is thermodynamically unstable, the more stable state is reached in the course of time in different ways depending on the ambient temperature. The macromolecules are arranged in a more space saving manner. This temporal decrease of the enthalpy at a temperature below the Tg is called enthalpy relaxation. The nearer the curing or storage temperature lies too the Tg, the faster does enthalpy relaxation takes place [16, 120].

In the literature, it is often stated that, when using thermal analysis, enthalpy relaxation develops as an endothermic peak above the Tg [16, 119–121] and is a measure for the changes of the state during curing or storage [119]. Other authors [122] describe this endothermic peak as being a result of an orientation of the polymer chains during aging and as a structural reorganization of amorphous polymers after storage at temperatures near the Tg, a result of slow cooling in the glass transformation interval [123].

Guo [124] studied the effect of physical aging on the water vapor permeability of ethylcellulose and cellulose acetate films, the mechanical properties of ethylcellulose and the dissolution rate of HPMCP films. Before the measurements the films were cured for 15 min above the Tg and were then put into cold water and stored at temperatures below the Tg. The water vapor permeability and dissolution rate decrease as the aging time increases. The effect of physical aging on the water vapor permeability can be described by a double logarithmic relationship between permeability and aging time. Creep measurements on films prepared from ethylcellulose dispersions show a decrease in stretching when the aging time increases [125]. This can be explained by a decrease in the free volume and further coalescence of the latex particles. Physical aging also leads to a time-dependent decrease in the dissolution rate of HPMCP in phosphate buffer. This decrease reaches a certain level, which depends on the density and structure of the polymer in the glassy state [126].

List et al. [16] also explain the decrease in water vapor permeability of films consisting of Eudragit® L 30 D after storage at temperatures just below the Tg as being caused by enthalpy relaxation of the film. Eudragit® L films made from organic solutions with a Tg well above the storage temperature show almost no relaxation.

Sinko et al. [127] discuss the physical aging of polymers from the pharmaceutical point of view. Aging can have a negative influence on the film properties, if the Tg of the polymer is near the storage temperature. The closer the temperature is to the Tg, the stronger is the effect of physical aging. Storage at temperatures near the Tg can "overage" the polymer and can lead to a slower release than in the case of lower storage temperatures. With cellulose acetate, storage at temperatures of 45 °C below the Tg for 1 month led to a decrease in the permeability, comparable to one calculated for a storage time of 10^5 years at RT (90 °C below Tg). It is advisable to store films made of cellulose acetate 60 °C below the Tg to minimize the effects of physical aging.

Hancock et al. [128, 129] studied the molecular mobility of amorphous pharmaceutical substances below and above their Tg with respect to predicting their relative stability. In general, one can expect significant molecular mobility at temperatures up to 50 °C below the Tg of the substances. When polymers are stored at temperatures above

this limit (less than 50 °C below the Tg), orientation and relaxation of the polymer chains take place, depending on time and temperature [130]. Adam and Gibbs [131] describe the temperature dependence of the relaxation behaviour within the region of the Tg by a theory of molecular kinetics.

2.3.3. Development of cracks in the coating

Apart from crack formation in the film, which is caused by ineffective plasticizing (see chapter 2.2.1.) or by coating at temperatures below the MFT (see chapter 2.2.2.) as well as lack of curing (see chapter 2.2.3.), it can also take place by processes characterized by strain induced formation of cracks [132]. This is a purely physical process, in which time dependent diffusion and swelling processes play an essential role. Thus, the literature states that paracetamol tablets coated with Surelease® and pectine and cured for 1 h at 70 °C show a drastic increase in amount of drug released after 6 h as a result of destruction of the coating. This crack formation could result from swelling of the core during curing (thickness of the tablets increases from 4.86 to 4.99 mm), which causes strains within the film [133]. Similar crack formation is observed due to expansion of the core of theophyllin diffusion pellets at high r.h., caused by the formation of theophyllin hydrate [87].

2.3.4. Migration and evaporation of plasticizers

An important condition for the stability of a coating is the persistence of the plasticizer in the film. Numerous publications report a loss of plasticizer when spraying the dispersion, when curing and during storing. The loss mainly takes place by evaporation of the plasticizer or by migration into the core. In the following paragraphs, the effects following loss of plasticizer are summarized with respect to the properties and stability of the coating.

2.3.4.1. Coating process

As early as during spraying of plasticizer-containing ethylcellulose dispersions a loss of almost 60% of DEP at a bed temperature of 53 °C has been reported. In contrast to this, DBP is not prone to volatilize out of coatings [66]. Large losses of propyleneglycol (20–35%) can also be observed during the coating process [55]. Propyleneglycol can act as a plasticizer for a certain period of time, but much of it evaporates during the coating processes. A loss of propyleneglycol has also been observed by other authors [134, 135]. The evaporation of different plasticizers is described by Frohoff-Hülsmann [66].

2.3.4.2. Curing

Hutchings et al. [136] report on the different behaviour of plasticizers after curing diffusion pellets coated with ethylcellulose dispersions. When using DBS at a concentration of 30%, curing at high temperature or over a long period of time causes an increase in the release.
In contrast to this, coatings that contain TBC at a concentration of 25% as plasticizer show a slowing down of release after curing. The increase in release rate for DBS-containing coatings shows that the plasticizer is present in excess and it can evaporate during the curing. The higher the temperature or the longer the curing time, the more noticable is the migration of the plasticizer to the surface of the coating. Additionally, sticking problems can develop, which can cause destruction of the coatings. Furthermore, the drug, propranolol HCl, can dissolve in the plasticizer DBS at high temperatures. This contradicts the results of Ozturk et al. [137], which show only slight solubility for a similar substance, phenylpropanolamine-HCl, in DBS. The decrease in release rate with TBC is explained by further coalescence of the film that seems to be complete after approximately 3 h.
Different volatility behaviour is associated with DBS, depending on the type of ethylcellulose dispersion used. Films made of Surelease® show fundamental changes in mechanical properties after 16 h of curing at 90 °C, that can be explained by the evaporation of the plasticizer DBS at high temperatures [138]. Thermogravimetric studies of Aquacoat® films with DBS as plasticizer show no loss of volatile substances after coating and 24 h curing at 60 °C [70].
Studies on isolated Aquacoat® films with 20 and 30% TEC as plasticizers [58] show minimal changes in mechanical properties after curing, although a decrease in the TEC-content can be observed with increasing curing temperature and time. This loss is attributed to evaporation or decomposition of the plasticizer. It is also reported that there is a loss of TEC and TA when using cellulose acetate latex [139]. Curing of tablets with coatings made of silicone and PEG 8000 as pore formers at temperatures above 60 °C causes melting of the PEG (melting range 60–63 °C). The amount of PEG migrated must be very small, as curing at temperatures above and below the melting point of PEG causes similar release profiles [90].

2.3.4.3. Storage

After studies on the storage of phenylpropanolamine-HCl pellets, coated with Aquacoat® with different plasticizers (DBS, TEC, TBC, ATBC) in a concentration of 30%, the following conclusions were drawn [92]: Diffusion pellets that contain DBS, TBC or ATBC as plasticizer, show the lowest release rate after production. Storage at 35 °C causes an increase in release rate after 3 months, which stays constant for the following 3 months. This increase in release cannot be explained by loss of plasticizer during storage or by increasing film porosity. These results show, that it is not only the drug that migrates to the surface of the ethylcellulose film, but also that the plasticizers are able to dissolve the drug and therefore contribute to an increase in the release rate. TEC-containing coatings show a slowing down of release after 3 months storage at RT and 35 °C. This decrease in release rate can be explained by incomplete coalescence due to inadequate curing. In contrast to this, stable release profiles can be observed after the third and sixth month. On the other hand, determination of the plasticizer content of diffusion pellets coated with Aquacoat® and 30% TEC shows a loss of TEC of 8% at RT and 18% at 35 °C after 6 months storage.
Migration of PEG in the coating during storage can be observed with PEG 400-containing capsules coated with Eudragit® L 30 D-55. It causes changes in the mechanical properties of the film and an increase in the stickiness of the coating [140]. Films made of Aquacoat® with 30% plasticizer (DBS, TBC, ATBC), stored at high temperature and relative humidity, were examined with respect to changes in their mechanical properties [59]. The results show an increase in tensile strength after storage at 45 and 60 °C at high r.h. and a decrease after storage at 80 °C

and ambient humidity. The former is explained by volatility of the plasticizer at high temperatures. The plasticizer loss was confirmed by the loss in weight of the films at 80 °C.
With stored enteric-coated preparations, inadequate strength results from decomposition of the plasticizer (hydrolysis of triacetin) or its volatilisation (TA, TEC) [55, 141]. The migration of the plasticizer into the core can also be observed during storage [141].

2.3.5. Incompatibility and interactions between pore formers and coatings

Too slow a release rate from coated slow release preparations can be accelerated with the aid of pore formers. During film formation from aqueous dispersions, the additives are incorporated between the polymer particles. The process of film formation can be disrupted by adding high concentrations of pore formers [93]. The distribution of pore formers at the end of film formation is more or less heterogeneous [25]. The additives incorporated are often not in thermodynamic equilibrium, and they try to separate and diffuse to the surface. The kind of changes in the release and mechanical properties of the coating which can be caused by these substances during storage are rarely discussed in the literature. It is to be expected that, as with films made of organic solvents (ethylcellulose coatings with PEG 1500 [3]) (see chapter 1.) or HPMC films with PEG additives [142], pore formers, which are not compatible with the film coating, will cause phase separation. This process is similar to the separation of emulsifiers (see chapter 2.3.6.). Incompatibilities have been observed between Eudragit® RS 30 D and PEG 6000 and polyvinyl pyrrolidone. These films are not permeable after curing. DSC-measurements help to identify incompatibilities [87].

2.3.6. Separation of emulgators

Depending on the compatibility between polymer and emulsifier, the emulsifiers can separate during film formation or during storage of the film. The surface of the (pseudo-)latex particles is obviously more hydrophilic than the inner area of the particles [143]. They consist of a polymer core and a hydrophilic membrane [27]. Not only hydrophilic polymer groups but also emulsifiers concentrate at the particle surface. An incompatible emulsifier is squeezed out to the surface during the progressive coalescence of the film, or it is found in isolated pools at the interface between the polymer particles [31, 144–146]. Compatible emulgators, on the other hand, distribute in the polymer and are able to act as plasticizers [31]. Emulsifiers can also migrate to cavities inside pigment clusters in pigment-containing dispersions [144].
Ethylcellulose dispersions (Aquacoat®) contain sodium laurylsulfate and cetylalcohol as emulsifiers. These two emulsifiers are squeezed out of the film during storage [67].
The superior mechanical properties of Surelease® compared to Aquacoat® are explained by the different emulsifiers. Surelease® contains ammonium oleate as an ionic emulgator, that changes to oleinic acid during the drying process and acts as a plasticizer [58]. Poured films made of cellulose acetate latex show a separation of the sodium laurylsulfate stabilizer in the form of small islands during film formation. This phase separation at concentrations above 0.5% leads to changes in the structure, mechanical properties and permeability of the film [147, 148].
Eudragit® NE 30 D contains a water soluble emulgator of the nonoxinol type [73]. This emulsifier separates from the polymer phase after storage at RT. In the presence of the drug clenbuterol in the matrix, the emulsifier crystallizes in the form of needles [149]. Studies by Haubitz [109] with free polymer films made of Eudragit® NE 30 D, confirm this. Depending on the storage time (at 40 °C and up to 40% r.h.) the crystallinity of the emulsifier increases. This effect is reversible by heating the polymer film over 70 °C (melting temperature of the emulsifier) and it obviously does not influence release from the diffusion pellets.

2.3.7. Chemical aging processes

Here, processes that change the chemical composition, the molecule structure and/or the molecule size of the polymer are summarized. Chemical aging of solid polymers due to the environment, that is oxygen, light and heat, can often mean: crosslinking, depolymerisation, hydrolysis and decarboxylation. The following changes in polymer coatings from aqueous dispersions are described with respect to their pharmaceutical use:

2.3.7.1. Polymerisation/depolymerisation

Fokkens et al. [150] report on the change of intrinsic viscosity and molecular weight of neutral polymethacrylate (Eudragit® NE 30 D), caused by heat and light. An increase in temperature leads to an increase in these values due to polymerisation. However the polymer is depolymerized under the influence of light.

2.3.7.2. Hydrolysis

In the presence of humidity, cellulose acetate phthalate (CAP) is able to hydrolize and loose its resistance to gastric juice (see chapter 1.). Hard gelatine capsules coated with Aquacoat® show a reduction in release after 3 months storage at RT, which is caused by the reaction of gelatine with CAP or its decomposition products. Gelatine then becomes insoluble [151].

2.3.7.3. Decarboxylation

In the case of enteric coatings, which were extensively studied by Thoma et al. (see chapter 1.), there is a risk of loss of gastric juice resistance by decarboxylation in the course of time.

2.3.8. Migration of drugs into and through coatings

Drug diffusion from the core through the coating during storage may result in a sublimate on the inner surface of the container, e.g. coated guaiphenesine pellets [152]. Different authors [134, 153–155] have observed drug dependent changes in coated preparations. REM-photographs show the appearance of ibuprofen crystals on the surface of EC-diffusion pellets of this drug [97]. The drug may also diffuse into the core if it is incorporated in the coating [156].

2.4. Summary of aspects affecting stability

The stability of a formulation chosen for the production of coated slow release preparations with aqueous polymer dispersions is very hard to be predicted precisely. There-

fore, in many cases stability has to be optimized empirically. The use of expert systems [157] and computer simulations [158] during the development of such dosage forms gives a new perspective on stability prediction and identification of problems [159]. Independent of this, the following aspects should be considered when striving for stable coatings from aqueous dispersions.

The *choice of plasticizer* should depend on its compatibility with the polymer. The compatibility limit relates to the maximum amount of plasticizer that is miscible with the polymer. Furthermore, it should be effective, in other words, the Tg and/or MFT should be clearly diminished. The plasticizer should remain in the coating until release of the drug takes place. Evaporation and migration of the plasticizer often cause instability or non-reproducible release profiles. This phenomenon is not restricted to storage, but can also be observed during coating or curing. The necessary concentration of plasticizer, which decreases the MFT sufficiently and which gives the resulting coating enough flexibility, is of course dependent on the dispersion used.

The *incorporation of the plasticizer* in the dispersion is very important in the case of lipophilic plasticizers, for they take a longer period of time to distribute into the polymer particles. If this plasticizing time is not long enough, sticking problems during the coating as well as unreproducible release profiles of different batches or changes in release in the course of time may occur due to further distribution of plasticizer droplets in the polymer film.

Apart from plasticizers, other additives such as *pore formers*, antitacking agents or pigments are added to the dispersion or they are already incorporated, e.g. *emulsifiers*. They must be compatible with the polymer. Comparable changes and instabilities to those associated with plasticizers, can occur when using these additives. In particular, the phase separation of pore formers and emulgators has to be considered. The use of aqueous dispersions without emulgators avoids the above problems.

The *bed temperature* during the coating process should of course lie above the MFT of the additive-containing dispersion. The temperature that is to be used depends on many factors and has to be empirically defined depending on the apparatus, dispersion and spraying parameters. The temperature, the spraying rate and the air flow have to be mutually adjusted in such a way that film formation takes place rather than spray drying. At too low a temperature or too high a humidity a significant migration of the drug can take place.

Curing of the coatings in an oven or fluidized bed after the production of the diffusion pellets is in most cases a necessity, because the film formation is not always optimal. It takes place at temperatures above the Tg of the polymer and it usually leads to a slowing down of release and to changes in the film structure. How long the curing period should be, depends on the effectiveness and concentration of the plasticizer and on the temperature used. An essential factor is the relative humidity, that contributes to the complete coalescence and allows a shorter curing time and lower curing temperature. The cooling process after curing should also be considered, since high cooling rates can create metastable conditions. The use of slow cooling rates results in a thermodynamic stable state, so that no enthalpy relaxation can take place. Optimal curing conditions (temperature, relative humidity and time) must be defined for every formulation.

Release instabilities during storage can mainly be attributed to inadequate curing, but they can also be caused by too high a *water absorption*. Changes of the physico-chemical state of the core and the coating may be the consequence of this.

References

1 Spitael, J.; Kinget, R.: Pharm. Acta Helv. **55**, 157 (1980)
2 Banker, G. S.: J. Pharm. Sci. **55**, 81 (1966)
3 Lippold, B. C.; Förster, H.: Pharm. Ind. **44**, 735 (1982)
4 Thoma, K.; Gröning, R.; Zimmer, T.: Acta Pharm. Technol. **32**, 137 (1986)
5 Chetty, D. J.; Dangor; C. M.: Drug Dev. Ind. Pharm. **20**, 993 (1994)
6 Munday, D. L.; Fassihi, A. R.: Proc. 5th Int. Conf. Pharm. Technol., Vol. II, p. 55, Paris 1989
7 Munday, D. L.; Fassihi, A. R.: Drug Dev. Ind. Pharm. **17**, 2135 (1991)
8 Okhamafe, A. O.; York, P.: Int. J. Pharm. **39**, 1 (1987)
9 Okhamafe, A. O.; York, P.: Pharm. Res. **2**, 19 (1985)
10 Okhamafe, A. O.; York, P.: J. Pharm. Sci. **77**, 438 (1988)
11 Thoma, K.; Heckenmüller, H.: Pharmazie **42**, 837 (1987)
12 Thoma, K.; Heckenmüller, H., Pharmazie **42**, 832 (1987)
13 Thoma, K.; Oschmann, R.: Pharmazie **47**, 595 (1992)
14 Thoma, K.; Oschmann, R.; Piringer, O.: Pharmazie **47**, 355 (1992)
15 Delporte, J. P.: Pharm. Ind. **41**, 984 (1979)
16 List, H.; Kassis, G.: Acta Pharm. Technol. **28**, 21 (1982)
17 Gutierrez-Rocca, J. C.; McGinity, J. W.: Drug Dev. Ind. Pharm. **19**, 315 (1993)
18 Gutierrez-Rocca, J. C.; McGinity, J. W.: Proc. 11th Pharm. Technol. Conf., p. 190, Manchester 1992
19 Bianchini, R.; Rescinti, M.; Vecchio, C.: Drug Dev. Ind. Pharm. **17**, 1779 (1991)
20 Hoblitzell, J. R.; Thakker, K. D.; Rhodes, C. T.: Pharm. Acta Helv. **60**, 28 (1985)
21 Lalla, J. K.; Bhat, S. U.: J. Pharm. Sci. **82**, 1288 (1993)
22 Beckett, A. H.; Samaan, S. S.: J. Pharm. Pharmacol. Suppl., 69P (1978)
23 Lindholm, T.; Juslin, M.; Kekäläinen, S.: Pharm. Ind. **47**, 1093 (1985)
24 Liebowitz, S. M.; Ichizuka, K.; McGinity, J. W.; in: Rubinstein, M. H. (Ed.), Pharmaceutical Technology, Controlled drug release, Vol. 1, p. 9, Ellis Horwood, Chichester 1987
25 Porter, S. C.; Ghebre-Sellassie, I.; in: Ghebre-Sellassie I. (Ed.): Multiparticulate oral drug delivery, p. 217, Marcel Dekker, New York 1994
26 Bindschaedler, C.; Gurny, R.; Doelker, E.: Labo-Pharma-Probl. Tech. **31**, 389 (1983)
27 Chevalier, Y.; Pichot, C.; Graillat, C.; Joanicot, M.; Wong, K.; Maquet, J.; Lindner, P.; Cabane, B.: Colloid Polym. Sci. **270**, 806 (1992)
28 Dobler, F.; Pith, T.; Lambla, M.; Holl, Y.: J. Coll. Interface Sci. **152**, 1 (1992)
29 Dobler, F.; Pith, T.; Lambla, M.; Holl, Y.: J. Coll. Interface Sci. **152**, 12 (1992)
30 Keshikawa, T.; Nakagami, H.: Chem. Pharm. Bull. **42**, 656 (1994)
31 Vanderhoff, J. W.: Br. Polym. J. **2**, 161 (1970)
32 Winnik, M. A.: Current Op. Col. Int. Sci. **2**, 192 (1997)
33 Wicks, Z. W.: J. Coat. Technol. **58**, 23 (1986)
34 Hahn, K.; Ley, G.; Oberthür, R.: Colloid Polymer Sci. **266**, 631 (1988)
35 Hahn, K.; Ley, G.; Schuller, H.; Oberthür, R.: Colloid Polymer Sci. **264**, 1092 (1986)
36 Yoo, J. N.; Sperling, L. H.; Glinka, C. J.; Klein, A.: Macromol. **23**, 3962 (1990)
37 Wang, Y.; Winnik, M. A.: Macromol. **23**, 4731 (1990)
38 Winnik, M. A.; Wang, Y.; Haley, F.: J. Coat. Technol. **64**, 51 (1992)
39 Millili, G. P.; Wigent, R. J.; Schwartz, J. B.: Drug Dev. Ind. Pharm. **16**, 2383 (1990)
40 Rowe, R. C.; in: Florence, A. T. (Ed.): Materials used in pharmaceutical formulation, p. 1, Blackwell Scientific Publications, Oxford 1984
41 Guo, J.-H.: Drug Dev. Ind. Pharm. **19**, 1541 (1993)
42 Guo, J.-H.: Drug Dev. Ind. Pharm. **20**, 1883 (1994)
43 Guo, J.-H.: J. Pharm. Sci. **83**, 447 (1994)
44 Guo, J.-H.; Robertson, R. E.; Amidon, G. L.: J. Pharm. Sci. **82**, 1229 (1992)
45 Wang, C.-C.; Zhang, G.; Shah, N. H.; Infeld, M. H.; Malick, A. W.; McGinity, J. W.: Int. J. Pharm. **152**, 153 (1997)
46 Heaps, J. M.; in: Ritchie, P. D. (Ed.), Plasticisers, stabilisers, and fillers, p. 50, Iliffe Books, London 1972
47 Lin, S.-Y.; Lin, Y.-Y.; Cheng, C.-L.: Pharmazie **50**, 801 (1995)
48 Sutter, B.; Lippold, B. H.; Lippold, B. C.: Acta Pharm. Technol. **34**, 179 (1988)
49 Hancock, B. C.; York, P.; Rowe, R. C.: Int. J. Pharm. **148**, 1 (1997)
50 Sakellariou, P.; Rowe, R. C.; White, E. F. T.: Int. J. Pharm. **31**, 175 (1986)

51 Entwistle, C. A.; Rowe, R. C.: J. Pharm. Pharmacol. **31**, 269 (1979)
52 Hutchings, D.; Nicklasson, M.; Sakr, A.: Pharmazie **48**, 912 (1993)
53 Rowe, R. C.; Kotaras, A. D.; White, E. F. T.: Int. J. Pharm. **22**, 57 (1984)
54 Sakellariou, P.; Rowe, R. C.; White, E. F. T.: Int. J. Pharm. **31**, 55 (1986)
55 Nakagami, H.; Keshikawa, T.; Matsumura, M.; Tsukamoto, H.: Chem. Pharm. Bull. **39**, 1837 (1991)
56 Gutiérrez-Rocca, J. C.; McGinity, J. W.: Int. J. Pharm. **103**, 293 (1994)
57 Obara, S.; McGinity, J. W.: Int. J. Pharm. **126**, 1 (1995)
58 Bodmeier, R.; Paeratakul, O.: Pharm. Res. **11**, 882 (1994)
59 Hutchings, D.; Clarson, S.; Sakr, A.: Int. J. Pharm. **104**, 203 (1994)
60 Sinko, C. M.; Amidon, G. L.: Int. J. Pharm. **55**, 247 (1989)
61 Lehmann, K.: Acta Pharm. Technol. **32**, 146 (1986)
62 Bodmeier, R.; Paeratakul, O.: Int. J. Pharm. **152**, 17 (1997)
63 Monells Pagés, R.; Lippold, B. C.: Proc. 14th Pharm. Technol. Conf., Vol. 1, p. 104, Barcelona 1995
64 Zerbe, H.; Luckow, V.; Cawello, W.; Cordes, G.: Pharm. Res. **2**, 30 (1985)
65 Bodmeier, R.; Paeratakul, O.: Int. J. Pharm. **103**, 47 (1994)
66 Frohoff-Hülsmann, M.: Wäßrige Ethylcellulosedispersionen mit Hydroxypropylmethylcellulose als Überzugsmaterial für Arzneistoffpellets; Dissertation, Düsseldorf 1997
67 Lippold, B. C.; Lippold, B. H.; Sutter, B. K.; Gunder, W.: Drug Dev. Ind. Pharm. **16**, 1725 (1990)
68 Lippold, B. H.; Sutter, B. K.; Lippold, B. C.: Int. J. Pharm. **54**, 15 (1989)
69 Maul, K.: Perlglanzpigment- und Weichmachereinfluß auf die Wirkstoff-Freisetzung aus überzogenen Pellets; Dissertation, Tübingen 1994
70 Iyer, U.; Hong, W.-H.; Das, N.; Ghebre-Sellassie, I.: Pharm. Technol. **14**, 68 (1990)
71 Siepmann, J.; Paeratakul, O.; Bodmeier, R.: Int. J. Pharm. **165**, 191 (1998)
72 Parikh, N. H.; Porter, S. C.; Rohera, B. D.: Pharm. Res. **10**, 525 (1993)
73 Lehmann, K. O. R.; in: McGinity, J. W. (Ed.): Aqueous polymeric coatings for pharmaceutical dosage forms, p. 101, Marcel Dekker, New York 1997
74 Yang, S. T.; Ghebre-Sellassie, I.: Int. J. Pharm. **60**, 109 (1990)
75 Rekhi, G. S.; Porter, S. C.; Jambhekar, S. S.: Drug Dev. Ind. Pharm. **21**, 709 (1995)
76 Lorck, C. A.; Grunenberg, P. C.; Jünger, H.; Laicher, A.: Eur. J. Pharm. Biopharm. **43**, 149 (1997)
77 Schmidt, P. C.; Niemann, F.: Drug Dev. Ind. Pharm. **19**, 1603 (1993)
78 Watano, S.; Harada, T.; Terashita, K.; Miyanami, K.: Chem. Pharm. Bull. **41**, 580 (1993)
79 Watano, S.; Takaya, H.; Wada, I.; Miyanami, K.: Chem. Pharm. Bull. **42**, 2338 (1994)
80 Watano, S.; Wada, I.; Miyanami, K.: Chem. Pharm. Bull. **43**, 877 (1995)
81 Watano, S.; Yoshikawa, K.; Miyanami, K.: Chem. Pharm. Bull. **42**, 663 (1994)
82 Arwidsson, H.: Acta Pharm. Nord. **3**, 223 (1991)
83 Gilligan, C. A.; Li Wan Po, A.: Int. J. Pharm. **73**, 51 (1991)
84 Mehta, M.: Pharm. Technol. **12**, 46 (1988)
85 Ghebre-Sellassie, I.; Iyer, U.; Kubert, D.; Fawzi, M. B.: Pharm. Technol. **12** (9), 96 (1988)
86 O'Donnell, P. B.; McGinity, J. W.; in: McGinity, J. W. (Ed.): Aqueous polymeric coatings for pharmaceutical dosage forms, p. 517, Marcel Dekker, New York 1997
87 Monells Pagés, R.; Steuerung und Stabilität der Arzneistofffreisetzung aus Diffusionspellets überzogen mit der wäßrigen Polymethacrylatsäuredisper-sion Eudragit® RS 30 D, Dissertation, Düsseldorf 1999
88 Guma, N. C.; Kale, K.; Morris, K. R.: J. Pharm. Sci. **86**, 329 (1997)
89 Li, L. C.; Peck, G. E.: Drug Dev. Ind. Pharm. **15**, 499 (1989)
90 Dahl, T. C.; Sue, I. T.: Drug Dev. Ind. Pharm. **16**, 2097 (1990)
91 Milojevic, S.; Newton, J. M.; Cummings, J. H.; Gibson, G. R.; Botham, R. L.; Ring, S. G.; Stockham, M.; Allwood, M. C.: J. Controlled Rel. **38**, 75 (1996)
92 Wheatley, T. A.; Steuernagel, C. R.; in: McGinity, J. W. (Ed.): Aqueous polymeric coatings for pharmaceutical dosage forms, p. 1, Marcel Dekker, New York 1997
93 Porter, S. C.: Drug Dev. Ind. Pharm. **15**, 1495 (1989)
94 Sheen, P.-C.; Sabol, P. J.; Alcorn, G. J.; Feld, K. M.: Drug Dev. Ind. Pharm. **18**, 851 (1992)
95 Dyer, A. M.; Khan, K. A.; Aulton, M. E.: Drug Dev. Ind. Pharm. **21**, 1841 (1995)
96 Goodhart, F. W.; Harris, M. R.; Murthy, K. S.; Nesbitt, R. U.: Pharm. Technol. **8** (4), 64 (1984)
97 Bodmeier, R.; Paeratakul, O.: Drug Dev. Ind. Pharm. **20**, 1517 (1994)
98 Christensen, F. N.; Bertelsen, P.: Proc. Int. Symp. Controlled Release Bioact. Mater. **17**, 124 (1990)
99 Harris, M. R.; Ghebre-Sellassie, I.; Nesbitt, R. U.: Pharm. Technol. **10**, 102 (1986)
100 Chang, R.-K.; Hsiao, C.-H.; Robinson, J. R.: Pharm. Technol. **11** (3), 56 (1987)
101 Dressman, J. B.; Derbin, G. M.; Ismailos, G.; Jarvis, C.; Ozturk, A.; Palsson, B. O.; Wheatley, T. A.: J. Controlled Rel. **36**, 251 (1995)
102 Bodmeier, R.: Int. J. Pharm. **70**, 59 (1991)
103 Lippold, B. C.; Gunder, W.; Lippold, B. H.: Eur. J. Pharm. Biopharm. **47**, 27 (1999)
104 Amighi, K.; Moes, A. J.: Eur. J. Pharm. Biopharm. **42**, 29 (1996)
105 Amighi, K.; Moes, A. J.: S.T.P. Pharma Sci. **7**, 141 (1997)
106 Kuhnert-Brandstätter, M.: Pharmazie **51**, 443 (1996)
107 Bianchini, R.; Bruni, G.; Gazzaniga, A.; Vecchio, C.: Drug Dev. Ind. Pharm. **19**, 2021 (1993)
108 Ghebre-Sellassie, I.; Gordon, R. H.; Nesbitt, R. U.; Fawzi, M.B.: Int. J. Pharm. **37**, 211 (1987)
109 Haubitz, H.: Entwicklung eines prozeßgesteuerten Labor-Rotor-Wirbelschichtgranulators zur Herstellung von Retardpellets; Dissertation, Berlin 1993
110 Vecchio, C.; Fabiani, F.; Sangalli, M. E.; Gazzaniga, A.: Drug Dev. Ind. Pharm. **23**, 345 (1997)
111 Oshlack, B.; Pedi, F.; Heights, Y.; Chasin, M.: Stabilized controlled release substrate having a coating derived from an aqueous dispersion of hydrophobic polymer; US-Patent 5,273,7601993 (1993)
112 Bodmeier, R.; Paeratakul, O.: Int. J. Pharm. **59**, 197 (1990)
113 Bodmeier, R.; Paeratakul, O.: Pharm. Res. **8**, 355 (1991)
114 Prinderre, P.; Cauture, E.; Piccerelle, P.; Kalantzis, G.; Kalaoustian, J.; Joachim, J.: Drug Dev. Ind. Pharm. **23**, 817 (1997)
115 Ghebre-Sellassie, I.; Nesbitt, R. U.; Wang, J.; in: McGinity J.W. (Ed.): Aqueous polymeric coatings for pharmaceutical dosage forms, p. 267, Marcel Dekker, New York 1997
116 Struik, L. C. E.: Physical aging in amorphous polymers and other materials; Elsevier, Amsterdam 1978
117 Haward, R. N.; Hay, J. N.; Parsons, I. W.; Adam, G.; Owadh, A. A. K.; Boxnyak, C. P.; Aref-Azaf, A.; Cross, A.: Colloid Polym. Sci. **258**, 643 (1980)
118 Bubeck, R. A.; Bales, S. E.: Polym. Eng. Sci. **24**, 1142 (1984)
119 Illers, K.-H.: Makromol. Chem. **127**, 1 (1969)
120 Her, L.-M.; Nail, S. L.: Pharm. Res. **11**, 54 (1994)
121 Lovrecich, M.; Nobile, F.; Rubessa, F.; Zingone, G.: Int. J. Pharm. **131**, 247 (1996)
122 Holsworth, R. M.: J. Paint Technol. **41**, 167 (1969)
123 Ali, M. S.; Sheldon, R. P.: J. Appl. Polym. Sci. **14**, 2619 (1970)
124 Guo, J.-H.; Robertson, R. E.; Amidon, G. L.: Pharm. Res. **8**, 1500 (1991)
125 Guo, J.-H.; Robertson, R. E.; Amidon, G. L.: Pharm. Res. **10**, 405 (1993)
126 Sinko, C. M.; Yee, A. F.; Amidon, G. L.: Pharm. Res. **7**, 648 (1990)
127 Sinko, C. M.; Yee, A. F.; Amidon, G. L.: Pharm. Res. **8**, 698 (1991)
128 Hancock, B. C.; Shamblin, S. L.; Zografi, G.: Pharm. Res. **12**, 799 (1995)
129 Hancock, B. C.; Zografi, G.: J. Pharm. Sci. **86**, 1 (1997)
130 Foltz, C. R.; McKinney, P. V.: J. Appl. Polym. Sci. **13**, 2235 (1969)
131 Adam, G.; Gibbs, J. H.: J. Chem. Phys. **43**, 139 (1965)
132 Schreyer, G.: Konstruieren mit Kunststoffen; p. 1, Carl Hanser Verlag, München 1972
133 Wakerly, Z.; Fell, J. T.; Attwood, D.; Parkins, D.: Int. J. Pharm. **153**, 219 (1997)
134 O'Donnell, P. B.; Wu, C.; Wang, J.; Wang, L.; Oshlack, B.; Chasin, M.; Bodmeier, R.; McGinity, J. W.: Eur. J. Pharm. Biopharm. **43**, 83 (1997)
135 Osterwald, H.; Eisenbach, C. D.; Bauer, K. H.: Acta Pharm. Technol. **28**, 34 (1982)
136 Hutchings, D.; Kuzmak, B.; Sakr, A.: Pharm. Res. **11**, 1474 (1994)
137 Ozturk, A. G.; Ozturk, S. S.; Palsson, B. O.; Wheatley, T. A.; Dressman, J. B.: J. Controlled Rel. **14**, 203 (1990)
138 Arwidsson, H.; Hjelstuen, O.; Ingason, D.; Graffner, C.: Acta Pharm. Nord. **3**, 65 (1991)
139 Kelbert, M.; Béchard, S. R.: Drug Dev. Ind. Pharm. **18**, 519 (1992)
140 Felton, L. A.; Shah, N. H.; Zhang, G.; Infeld, M. H.; Malick, A. W.; McGinity, J. W.: Int. J. Pharm. **127**, 203 (1996)
141 Bechtold, K.; in: Gröning, R; Schmidt, P.C. (Hrsg.): Entwicklungen in der pharmazeutisch-technologischen Arzneimittelforschung, p. 1, DAV, Stuttgart 1999
142 Aulton, M. E.; Abdul-Razzak, M. H.: Drug Dev. Ind. Pharm. **7**, 649 (1981)
143 Distler, D.; Kanig, G.: Colloid & Polymer Sci. **256**, 1052 (1978)
144 Bondy, C.; Coleman, M. M.: J. Oil Colour Chem. Assoc. **53**, 555 (1970)
145 Bradford, E. B.; Vanderhoff, J. W.: J. Macromol. Chem. **1**, 335 (1966)
146 Vanderhoff, J. W.; Bradford, E. B.; Carrington, W. K.: J. Polym. Sci.: Symp. **41**, 155 (1973)

147 Bindschaedler, C.; Gurny, R.; Doelker, E.: J. Appl. Polym. Sci. **34**, 2631 (1987)
148 Bindschaedler, C.; Gurny, R.; Doelker, E.: J. Appl. Polym. Sci. **37**, 173 (1989)
149 Göpferich, A.; Lee, G.: J. Controlled Rel. **18**, 133 (1992)
150 Fokkens, J.; Gorissen, H.: Drug Dev. Ind. Pharm. **22**, 335 (1996)
151 Murthy, K. S.; Enders, N. A.; Mahjour, M.; Fawzi, M. B.: Pharm. Technol. **10** (10), 36 (1986)
152 Sutter, B. K.: Wäßrige Ethylcellulosedispersionen zur Herstellung von Mikrokapseln mit gesteuerter Arzneistofffreisetzung; Dissertation, Düsseldorf 1987
153 Bodmeier, R.; Wang, J.: J. Pharm. Sci. **82**, 191 (1993)
154 Jenquin, M. R.; Liebowitz, S. M.; Sarabia, R. E.; McGinity, J. W.: J. Pharm. Sci. **79**, 811 (1990)
155 Miller, R. A.; Vadas, E. B.: Drug Dev. Ind. Pharm. **10**, 1565 (1984)
156 Aulton, M. E.; Richards, J. H.; Abdul-Razzak, M. H.; Hogan, J. E.: Proc. 3rd Int. Conf. Pharm. Vol. III, p. 154, Paris 1983
157 Rowe, R. C.: Pharm. Ind. **55**, 1040 (1993)
158 Rowe, R. C.: S.T.P. Pharma Sci. **7**, 189 (1997)
159 Rowe, R. C.; Rowe, M. D.; Roberts, R. J.: Pharm. Technol. **18** (10), 132 (1994)

Received July 28, 2000
Accepted August 10, 2000

Prof. Dr. B. C. Lippold
Institut für Pharmazeutische Technologie
Heinrich-Heine-Universität Düsseldorf
Universitätsstr. 1
D-40225 Düsseldorf