1. INTRODUCTION

1.1. COATING OF SOLID DOSAGE FORMS

Film coating of solid dosage forms is a high sophisticated process, first described in 1930 (Cole, 1995e). Its obvious advantages resulted in a soon replacement of the traditional sugar coating by the emerging technology, thus the first film-coated tablet became commercially available in 1954. The technology advanced with the introduction of the semi-synthetic cellulose derivatives and the synthetic acrylic polymers in the early 1950s (Lehmann, 1989; Savage and Rhodes, 1995).

Film coatings are applied for several reasons (Cole, 1995e; Schmidt, 2000; Seitz, 1988):

- taste masking and moisture- / light protecting coatings
- improved product appearance
- improved mechanical resistance of the coated product (e.g. reduced friability)
- modified drug release (e.g. gastric resistant or extended release coatings)

The properties and performance of the final coat is strongly affected by the polymer properties and the formulation parameters. The coating formulation may contain other major components beside the polymer such as the solvent, plasticisers or pigments (Hogan, 1995a; Porter, 1990). Obviously, they can affect the performance of the coat by changing e.g. the mechanical properties, which will be discussed later.

According to the interesting aspect for the specific use, the polymer may be classified as protective or functional coating. Based on their origin or preparation, natural, semi-synthetic or synthetic polymers are distinguished. Natural polymers are mostly subjected to several purification steps, but without chemical modification. Usually, related to their origin, they are mixtures of different compounds, subjected to a certain variability of their composition and thus the resulting performance (Hogan, 1995a; Specht et al., 1998). Semi-synthetic polymers are derived from a natural substance, receiving its specific property after certain chemical modifications. The cellulose derivatives used for coating are one example of such materials. Synthetic polymers in contrast are fully chemically synthesised, as for example the methacrylic acid copolymers.

1.1.1. Protective coatings

Thin films of water soluble polymers are often applied for taste or odour masking, to improve the stability of moisture sensitive products or for better mechanical resistance of the product during handling (Lehmann, 1994). Such protective coatings need to remain intact for the short time of swallowing the dosage form. Thereafter they should dissolve instantaneously to assure immediate drug release without retardation. Polymers employed for these tasks are mostly water-soluble, such as cellulose ethers (e.g. hydroxypropyl methylcellulose (HPMC)), polyvinyl acetate (PVA) or polyvinyl pyrrolidone (PVP) (Porter and Bruno, 1990). Eudragit® E is a methacrylic copolymer especially designed to be insoluble in the saliva, but should rapidly dissolve in the acidic pH of the stomach. Sometimes also enteric polymers, e.g. shellac are applied at very low coating level. In that case the film thickness is not sufficient to provide gastric resistance and disintegrated in the stomach within 30 min (Lehmann, 1994).

1.1.2. Functional coatings

Film coatings, which are applied to achieve a certain desired release profile of the incorporated drug, are generally called functional or modified-release coatings. Those, intended to protect the drug from the acidic environment of the gastric medium or to prevent the drug release in this part of the GIT, are commonly called enteric coatings. Extended release coatings, in contrast, are requested to control the release of the drug over a prolonged period of time (Porter, 1990).

a. Enteric coatings

Enteric coatings are prepared from gastric resistant polymers. The coatings prepared from such polymers remain intact in acidic environment, but dissolve readily at the elevated pH of the small intestine. This property is related to the chemical structure of the applied polymer. The most effective enteric polymers contain many carboxylic acid groups with a pKa of 3-5

(Lehmann, 1994; Porter, 1990). Therefore they will dissociate and dissolve only when the pH rises above this value.

Before the synthetic polymers were introduced to the market, shellac, a natural polymer, was one of the main polymers used for this purpose (Hogan, 1995b). Cellulose acetate phthalate (CAP) was the first synthetic polymer described in 1937, which gained soon high popularity as a gastric resistant polymer (Malm and Waring, 1937). Later polyvinyl acetate phthalate (PVAP) and hydroxypropyl methylcellulose phthalate (HPMCP) were preferred, due to their lower permeability in the gastric fluid and improved stability against hydrolysis (Porter, 1990). Today the methacrylate copolymers Eudragit®L and S are two of the most widely used polymers for this purpose.

b. Extended release coatings

The patient compliance is strongly decreasing in such cases, when multiple daily administrations are necessary to maintain constant blood levels of the drug. Therefore, extended release polymers were developed, which are able to provide a sustained action by a controlled release over time (Lehmann, 1994; Porter, 1990).

Waxes and some natural polymers were already discovered earlier to be useful to prolong the drug release if coated onto solid dosage forms. Mostly their mechanism of performance is based on slow degradation or erosion.

Polymers for extended release are in general insoluble in water over the entire pH-range (Sakellariou and Rowe, 1995). The drug release is thus controlled by diffusion through the hydrated polymer or through cracks or water-filled pores (Lecomte et al., 2005). There are still only few polymers available on the market for extended release, e.g. cellulose acetate, ethylcellulose or the methacrylic acid copolymers Eudragit®RS, RL and NE (Hogan, 1995a; Savage and Rhodes, 1995). Combinations of ethylcellulose with waxes, water-soluble or enteric polymers were investigated to achieve extended drug release for drug with varying or even pH-dependent solubilities (Chester et al., 1970; Hogan, 1995b; Lecomte et al., 2003).

Synthetic polymers, however, do not fit into the overall product concept of phytopharmaceutical products, or as for nutraceuticals they are even not approved. Therefore several attempts were undertaken to achieve sustained drug release by using only natural polymers. The drug release from silk fibroin coated tablets after cross-linking with a carbodiimide was extended to several hours, though the release of the uncoated tablets was already prolonged over 3 h (Bayraktar et al., 2005).

Shellac is also able to provide prolonged drug release at higher coating levels or as matrix forming material (Pearnchob et al., 2003a; Pearnchob et al., 2003b). However, there is no drug released in the gastric medium for such systems due to the enteric property of shellac.

Zein as a water-insoluble natural polymer is an alternative for extended drug release, especially in combination with an additional enteric topcoat (Mazer et al., 1992).

1.2. ZEIN

Zein is a prolamine gained by hydro-alcoholic extraction from corn and occurs as a by-product during its processing (Evans and Manley, 1941; Swallen, 1941). Prolamines are the alcohol-soluble protein fraction in cereal grains, with their major characteristic of being insoluble in aqueous media. Zein was first isolated in 1821 and was immediately subjected to extensive investigation due to its film-forming properties and solubility behaviour (Osborne, 1897; Reiners, 1973; Swallen, 1941). Commercial use started around 1939 with top market size between 2000 and 7000 tonnes per year. After 1970, zein production decreased again to less than 500 tonnes per year nowadays (Reiners, 1973; Shukla and Cheryan, 2001).

1.2.1. Protein composition and properties

The solubility behaviour of zein is determined by the high hydrophobic amino acid content like e.g. leucine, proline and alanine, and its relative deficiency of basic or acidic amino acid residues (Table 1) (Evans and Manley, 1941; Oh and Flanagan, 2003; Reiners, 1973; Shukla and Cheryan, 2001).

Table 1 Amino acid composition of zein (Freeman Industries LLC, 2005b).

Amino acid	Content, %
Glutamic Acid & Glutamine	20-22
Leucine	17-20
Proline	5-9
Alanine	8-10
Phenylanlanine	4-7
Isoleucine	3-7
Serine	4-6
Tyrosine	3-5
Asparagine	4-5

All others are present < 3%.

The protein can be separated into two fractions according to the solubility in ethanolic solutions (Esen, 1986; Swallen, 1941). α–zein is soluble in 95% ethanol, whereas β–zein is soluble in 60% ethanol but insoluble in 95% ethanol (Esen, 1986; Reiners, 1973; Shukla and Cheryan, 2001). Today four classes are known as α–, β–, γ– and δ–zein, based on their different

solubility behaviour and sequence (Esen, 1986; Tatham et al., 1993). Commercially available zein contains mostly α–zein, which represents 75-85% of the total zein (Esen, 1986; Reiners, 1973; Shukla and Cheryan, 2001; Tatham et al., 1993). The α–zein is comprised of two major protein groups, each of them consisting of about 210-245 residues, having a molecular weight (Mw) of 23 and 27 KDa (Matsushima et al., 1997; Tatham et al., 1993). Commercially available zein has an average Mw of 35 KDa (Freeman Industries LLC, 2005a), due to its content of the higher molecular weight β–zein fraction, which is assumed to consist of disulfide-linked α–zein (Reiners, 1973; Shukla and Cheryan, 2001). Structural investigations demonstrated that α–zein is an extended rod-like prolate shaped particle in solution. The exact arrangement of the partially repetitive molecular sequences and their symmetry is controversially discusses, but the elongated molecular structure is agreed to be the reason for the film forming capability of the protein (Argos et al., 1982; Tatham et al., 1993). Films cast from ethanolic solution will thereby result in a mixture of α-helical and β-sheet conformation in the unoriented solid state (Kretschmer, 1957). The type of solvent used does not seem to have a major effect on the resulting conformation.

1.2.2. Solvents and stability in solution

Solvents for zein should exhibit combined properties, containing polar as well as nonpolar groups. Solvents with OH-groups, amines, amides and acids can dissolve zein, as long as not all polar groups are linked with hydrophobic side-chains. The length of the lipophilic side-chain decreases the solubilizing capacity, too. The solvents also affect the stability of zein solutions. Gelation of zein in solution may happen easily within a short time, and may lead to

the denaturation of the protein. Water in combination with solvents may promote this reaction, as well as higher temperature, pH and mechanical stress (Evans and Manley, 1941; Osborne, 1897; Shukla and Cheryan, 2001; Swallen, 1941). The process is assumed to be autocatalytic with the denatured insoluble material promoting further gelation of zein (Shukla and Cheryan, 2001; Swallen, 1941).

1.2.3. Preparation processing

The first process to isolate zein on a production scale started with an extraction with 85% isopropanol at 55-60 °C (Swallen, 1942). The extract was mixed with hexane after a cooling and a filtration step. Hexane is a non-solvent for zein and is used to purify it from corn oil and xanthophyll pigments. After separation of the hexane layer zein was precipitated in refrigerated water, washed, dried and ground to receive a fine powder of slightly yellow colour containing 1-4% corn oil (Reiners, 1973; Swallen, 1941; 1942).

A product of less oil-content can be achieved by re-extraction or further washing steps (Shukla and Cheryan, 2001). Further processing is also necessary to diminish the colour, which hindered many potential applications of zein. It is caused by the xanthophyll and carotenoid pigments, which seem to be associated with the hydrophobic protein and are co-extracted with it.

High effort was undertaken over the decades to decolorize zein (Cook et al., 1996; Mason and Palmer, 1934; Morris et al., 1956; Sessa et al., 2003). However, all these steps to decrease the lipid and pigment concentration in the final product increase the operation costs due to the complex solvent recovery systems required. This makes zein a high value product with prices varying from US$ 10-40 per kg, depending on its purity (Shukla and Cheryan, 2001).

1.2.4. Applications of zein

Zein was mainly used in the food industry as a coating polymer for fruits, nuts and candies, to prevent their deterioration or desiccation over storage (Bai et al., 2003; Haralampu et al., 1991; Reiners, 1973). This application was favoured due to the ability of zein to form clear, tough, glossy and grease-proof coatings with an excellent resistance to microbial attack (Reiners, 1973; Shukla and Cheryan, 2001).

Another application area was the coating of paper, where large quantities were consumed to improve grease- and scuff-resistance (Reiners, 1973). A lot of effort was undertaken to develop coatings of increased water resistance for this application (Int Patents Dev Co, 1939; James and Tenafly, 1944; McDowell, 1957). Films of higher water resistance were achieved by mixing zein with hydrophobic substances like e.g. oils and waxes. The enhanced moisture resistance of zein in combination with fatty acids and oil coatings attracted attention to its use as a biodegradable packaging material. Lots of investigations were done for this aim on isolated zein films (Lai and Padua, 1997; 1998; Lai et al., 1997).

The main use of zein today is in the pharmaceutical area (Reiners, 1973). First applications of zein in this field were as protective coatings to improve the appearance of immediate release tablets (Winters and Deardorff, 1958). It is appreciated also as a binder for granulation purposes (Reiners, 1973; Sheth and Leeson, 1979). New interest came up recently for zein as a coating material for taste masking (Meyer and Mazer, 1997). Combinations with oil or wax were used once more to effectively suppress the release of the active substance from the encapsulated particles and thereby mask the unpleasant taste of the drug.

1.2.5. Zein for controlled release

Due to its insolubility in water, zein implies the potential to sustain the release of an active drug. However, only few attempts were undertaken up to now to extend drug release by the use of zein. Sustained release was first claimed by its use as a matrix polymer, where the

drug was dispersed in. The formed mix contained 20-45% zein and was either extruded to cylindrical pellets or granules for tabletting (Rosenthal, 1959). Similar processes were later described again with granulation and subsequent compression to obtain controlled release matrix tablets of zein (Beatty and Boettner, 1984; Sheth and Leeson, 1979). Alternatively, the drug was dissolved in 70% v/v ethanol together with zein and spray-dried. The received powder was then compressed to tablets (Katayama and Kanke, 1992). The drug release of paracetamol containing tablets could be retarded by the application of an aqueous pseudolatex of zein (O´Donnell et al., 1997). However, all these formulations were highly susceptible to degradation by proteolytic enzymes. In simulated gastric medium in the presence of pepsin, the former sustained drug release broke down to less than 4 h (Katayama and Kanke, 1992; O´Donnell et al., 1997). A delivery in the intestinal tract of the active substance was achieved by zein coatings with an additional topcoat of a gastric resistant polymer (Mazer et al., 1992). This delivery system is especially useful to limit the exposure time of the drug to the acidic environment of the stomach.

The positive toxicological status of zein (GRAS-listed) is of substantial advantage for its use in the pharmaceutical area (CDER, 1996; FDA, 2004). It is approved by the FDA for marketed products for oral formulations for sustained release tablets and as a coating material.

1.3. SHELLAC

1.3.1. General overview

Shellac is a natural polymer obtained by refining the resinous secretion of the insect Kerria lacca, commonly known as 'lac' (Hogan, 1995a; Specht et al., 1998; Vasavada, 1994). It consists mainly of a mixture of polyesters, basically composed of shellolic and alleuritic acid, which are responsible for its gastric resistant properties. It possesses outstanding film forming properties, despite of its comparatively low molecular weight of around 1 KDa (Penning, 1990). However, as a product of natural origin it is subjected to batch-to-batch variation of the quality in dependence of the purification process and the resulting content of wax, colouring material and other impurities (Hogan, 1995a; Specht et al., 1998; Vasavada, 1994). Basically, the refining process can be performed by physical purification (e.g. by heat or solvents extraction) or by a chemical process based on bleaching (Sturm, 2005). The solvent extraction process starts with the dissolution of seedlac in 96% v/v ethanol, where after a filtering step a decolourization is performed with activated carbon. After the solvent removal dewaxed and decolourized shellac is obtained in a purity suitable for pharmaceutical and cosmetic use.

1.3.2. Applications of shellac

The industrial large scale application started 1860 with the use of shellac as a coating for ship floors to improve their resistance against sea water (Stroever Schellack Bremen). Up to the 1950s it was widely used for gramophone records with peak sales up to 50,000 tonnes per year, but declined after 1958 when shellac was replaced by plastic records to approximately 8,000 tonnes per year nowadays. The majority of it is still used for technical purposes such as wood coatings and varnishes (Sturm, 2005).

In the pharmaceutical area it was the most important polymer for enteric coating in the past (Hogan, 1995b; Johnston et al., 1966; Signorino, 2003). However, due to its high pKa of

6.9-7.5 the dissolution in the intestine is only slow and unreliable (Hogan, 1995b). Moreover, stability problems upon storage mostly can cause a hardening of the coating and prolong the disintegration times (Johnston et al., 1966; Vasavada, 1994). This fact is related to a self-polymerization of shellac by cross-linking dependent on the purification process and the system used for the application of the coat (Signorino, 1973; Specht et al., 1998).

Today it is still used in many marketed products as an ingredient for enteric coating and extended release and is approved as a food additive (CDER, 2006; Vasavada, 1994). At higher coating levels, e.g. >20%, shellac is able to retard the drug release, but these formulations lack of drug release in the gastric environment (Pearnchob et al., 2003a). Mixtures with water-insoluble polymers such as ethylcellulose are also suitable for sustained release coatings (Jan et al., 2001). However, these coatings do not fit to a phytopharmaceutical or nutraceutical product due to the mixture with a synthetically modified polymer.

The dissolution behaviour of shellac is better predictable, if the acid number of the mixture is exactly specified (Signorino, 2003). Additionally, the disintegration in the intestinal pH-range can be improved by addition of small molecular weight organic acids, which enhance its dissolution at higher pH (Pearnchob et al., 2004b). The stability on storage can be enhanced by a thermal treatment (Johnston et al., 1966), or by changing the coating system from organic to aqueous application (Signorino, 2003; Specht et al., 1998). Improvements of the disintegration and stability of storage combined with its positive regulatory status are good perspectives for its ongoing use.

1.4. ETHYLCELLULOSE

1.4.1. General overview

Ethylcellulose is a cellulose ether, soluble in many organic solvents but insoluble in water at any pH. Therefore it is widely used as an extended release polymer, as well as a matrix former or as a coat.

Large scale production of ethylcellulose starts by preparing alkali cellulose from cellulose and sodium hydroxide of concentrations of at least 50% w/w. The reaction of alkali cellulose with ethyl chloride follows at 90-150 °C for several hours. The product is subsequently rinsed with water to remove the resulting sodium chloride and finally dried (DOW, 2004; Rekhi and Jambhekar, 1995).

Its physical properties are mainly determined by the degree of substitution (DS) of the hydroxyl groups per glucose unit by ethyl-residues, whereby DS can reach a maximum of 3 if all available positions are substituted. Commercial products usually have an average DS of 2.2.-2.6, corresponding to an ethoxyl content of 44.5% up to 49% (DOW, 2004; Rekhi and Jambhekar, 1995). Different viscosity grades are available, which reflect the molecular weight. With increasing chain length of the polymer the mechanical strength of the resulting films are enhanced, too. Special grades are offered for pharmaceutical use (DOW, 1998). Micronized fine powders for direct compression are commercially available with a mean particle size of 10-45µm, depending on the viscosity grade (DOW, 1996a). Aqueous ethylcellulose dispersions with solid contents of 25-30% are commercially available. Aquacoat® is an unplasticised aqueous dispersion, imparting more flexibility in the choice of plasticiser type and amount. Surelease® is a fully developed aqueous pseudo-latex containing already a suitable amount of DBS or MCT as plasticiser being therefore ready to use (Colorcon, ; FMC, 1996).

1.4.2. Applications of ethylcellulose

In pharmaceutical formulations ethylcellulose is used as a binder for granulation, coating polymer or for microencapsulation (Aqualon, 2002; DOW, 2004). Sustained release is achieved with ethylcellulose as a matrix forming polymer by granulation (Majid Khan and Bi Zhu, 1998). Improved compactability allows its use for direct compression of tablets as well (Durig et al., 2003). In combination with additives even the pH-dependent release of weakly basic drugs can be overcome (Streubel et al., 2000). Mostly, however, it is used as coating material for extended release (Bartholomaeus and Ziegler, 2002; Bodmeier et al., 1997; Ozturk et al., 1990; Rekhi et al., 1995). Strong retardation is achieved already at low coating level, thus water-soluble pore former (such as HPMC or PVP) are often added to enhance the drug release (Bodmeier et al., 1997; DOW, 2004). Combinations with waxes are also able to sustain the drug release, whereas the wax to ethylcellulose ratio is adjusted according to the drug solubility (Chester et al., 1970). For more versatile drug release profiles also in dependence of the solubility properties of the drug, ethylcellulose mixed coatings with enteric polymers were recently investigated (Lecomte et al., 2003). Compression coating of tablets was examined as an alternative to solvent or aqueous based systems (Lin et al., 2001). Improved film formation and resulting prolonged lag time was observed with decreasing particle size of the used ethylcellulose powder.

Dry powder coating is an innovative solvent and water free coating process for solid dosage forms. Application of ethylcellulose for this coating process is possible, however curing at elevated temperature and up to 24 hours is required to achieve extended drug release (Pearnchob and Bodmeier, 2003a; b).

The release mechanism from ethylcellulose coated dosage forms is increasingly discussed, with more and more evidence that the drug is mainly released through micro-sized cracks and water-filled pores (Lecomte et al., 2004; 2005).

1.5. COATING PROCESSES AND FORMULATION PARAMETERS

1.5.1. Organic coating

Film coating in the early 1950s was performed by applying the polymers dissolved in organic solvents (Porter, 1990; Porter and Bruno, 1990; Savage and Rhodes, 1995). The use of such polymer solutions benefits of several advantage:

-highly reduced processing time, due to the rapid evaporation of the solvent

-possibility to prepare thin, smooth continuous coatings

-water-free process, reducing the risk of hydrolysis of any compound

The film formation is rather simple: the evaporation of the solvent leads to an up-concentration of the polymer solution, which will finally resemble a gel (Lippold and Monells Pages, 2001). A thin film of the polymer remains on the substrate surface upon complete evaporation of the solvent (Bauer et al., 1988). A key role for the quality of the resulting film plays the capability of the polymer solution to spread on the surface of the solid dosage form, which is dependent on the viscosity and contact angle of it. High attention needs to be paid on the exact formulation and process parameters to avoid defects of the resulting coating due to picking, orange peel, cracking or other reasons (Porter, 1990; Porter and Bruno, 1990). Then, thin films with a very smooth surface can be achieved, in contrast to the systems, which apply the polymer as a particulate matter (Schmidt, 2000).

Coating with organic polymer solutions however decreased in popularity related to the upcoming restrictions concerning the use of organic solvents (Lehmann, 1994). Most of the organic solvent used before are highly toxic or even cancerogenic and were not acceptable for further use. On the other hand side, environmental concerns were leading to requirements for solvent recovery systems, which increased the productions costs. Also the risk of explosion needed to be minimized by improvements in the equipment design.

However, organic coatings experience a revival today, as they are less problematic concerning stability on storage. Residual solvent or chemical or structural changes are the few reasons for possible instabilities from organic solvent based coatings, whereas coatings

applied from aqueous dispersions often reveal changes in the release profile upon storage due to incomplete film formation during processing (Lippold and Monells Pages, 2001).

1.5.2. Aqueous coating

a. Solutions

For the application of polymers from aqueous solutions a pre-requirement is that the polymer is soluble in water. The major application of such systems is for protective coatings, as they will result in water-soluble films without retarding effects (Porter and Bruno, 1990). Hydrophilic polymers used are mainly water-soluble cellulose derivatives, such as HPMC, however PVP, PVA and PEGs are suitable, too. Moreover, small molecular weight polymers are preferred, in order to optimize the solid content to viscosity ratio of the coating formulation (Lehmann, 1994; Porter and Bruno, 1990). Optimal interaction of the polymer is obtained by the use of water-soluble plasticisers, generally being glycerol, propylene glycol or triacetin.

b. Dispersions

Aqueous polymer dispersions replaced organic polymer solutions to a wide extent in coating of water-insoluble polymers, as increasing concerns about the toxicity of the used solvents, environmental pollution and related cost-intensive solvent recovery systems made their use unattractive. Polymer lattices were already developed in the 1930s for applications as technical coatings for papers, textiles, food packaging and as paintings (Dillon et al., 1951; Lehmann, 1997). The size of the polymer particles in these two-phase systems is in general in the colloidal range, with the upper limit around 1µm, to assure stability on storage without sedimentation. The prominent characteristic of aqueous colloidal dispersions is their low viscosity despite their high solids content, which may reach up to 30% of the total formulation. In this case water serves only as a dispersing medium, as the polymer is insoluble in water (Harris and Ghebre-Sellassie, 1997).

A major problem related to aqueous coating systems was initially the prolonged processing time, related to the higher heat of vaporization of water in contrast to organic solvents (539 kcal/kg for water vs. 204 kcal/kg for ethanol) (Cole, 1995c; Nagai et al., 1997). However, improvements in the equipment design soon overcame these concerns. The development of side-vented perforated coating pans and fluidized bed equipment highly increased the drying efficiency during the coating process (Cole, 1995b; Mehta, 1997). Moreover, process automation and the concept of qualification and validation resulted in a strong increase of productivity, exceeding by far the formerly dreaded drawbacks (Cole, 1995a; d; Sathayé, 2002).

The film formation from aqueous colloidal dispersions is a complex, multi-step process (Keddie et al., 1995; Voyutsskii, 1958). The polymer particles are closely packed upon up-concentration of the dispersion due to water evaporation. In this ordered arrangement the polymer particles come the first time into contact with each other. Further water loss goes along with a deformation of the particles to a dense array. Dry sintering and capillary forces were discussed as possible mechanisms for the particle deformation and will be discussed in detail later on (Brown, 1956; Dillon et al., 1951). Finally, in the last stage of film formation the individual particles will loose their identity after the polymer chains diffuse through the boundary and form a continuous film with adequate mechanical properties. The performance of the resulting film is highly affected by the temperature during film formation. The formation of a thin surface layer of coalesced particles is assumed, through which the residual water needs to diffuse during the progress of drying (Sheetz, 1965). Above the boiling temperature of water the vapour pressure during film-formation may be sufficient to burst the surface film layer and cause voids and pinholes (Guo et al., 1993). These imperfections may be responsible for higher water vapour permeabilities or enhanced drug release.

c. Redispersible powders

Redispersible powder formulations were initially developed for enteric polymers with the introduction of aqueous polymer dispersions. Enteric polymers are mostly esters, thus possibly subjected to hydrolysis if stored in aqueous media (Porter and Bruno, 1990). Therefore, redispersible dry powder formulations were introduced to the market, being prepared for coating by dispersing the powder in water just prior to their use. Examples are Aquateric, the commercial redispersible powder of cellulose acetate phthalate (CAP), or redispersible EudragitL, a methacrylic acid copolymer with enteric properties. General advantages of redispersible powders were recognized later and initiated the development of such formulations for other polymers, too (Bodmeier, 1999).

Special advantages of redispersible powder formulations are reduced storage and shipping cost as well as enhanced microbiological stability. Additionally, the polymer powders are less prone to flocculation or coagulation if being exposed to high shear forces or temperature changes as heat or freezing, which otherwise limit the shelf life of aqueous polymer dispersions to a still acceptable performance and is generally a maximum of one year (Bodmeier, 1999).

Redispersible polymer powders are usually prepared from aqueous polymer dispersions through drying mainly using freeze- or spray drying processes. Thereby it is important that the properties of the original polymer dispersions are regained after the redispersion of the polymer powder in water. It is especially important that the original particle size distribution is retained as especially an increase in the particle size, e.g. by the formation of agglomerates, would affect the coalescence and film formation negatively.

1.5.3. Dry coating

a. Compression coating

After the introduction of compressed tablets as a superior dosage form compared to pills, compression coating was introduced in 1858 as an alternative to the traditional sugar coating, although it major use was delayed until the 1950s (Buerki and Higby, 1993; Cole, 1995e).

The principle of manufacturing is very simple: usually half of the polymer powder intended for the coat (containing possible additives or actives) is filled into a die of the tabletting machine. The core tablet is placed in the centre onto the powder and the remaining coat powder added on the top. The overall combination is then compressed into a single tablet. The advantage of this type of coating process is that it is completely free of the use of any solvent or water. Beside that, no additional coating equipment is necessary, as only a tablet press is needed, why still a lot of investigation focuses on this type of preparation of coated tablets (Fukui et al., 2000; Lin et al., 2001; Waterman and Fergione, 2003).

The compression process however, bears several risks, especially when too high compression forces are applied the inner core tablet could be damaged (Cole, 1995e). In case that the applied pressure is too low, the adhesion of the coat and its mechanical performance may not be sufficient. Therefore compressibility and compaction of the coating material are the two most important parameters (Lin et al., 2001). From the process point of view, it is very difficult to achieve appropriate automation for such a process, where careful placement of the inner core is required to obtain symmetrical thickness of the coating. Equipments developed for this purpose only have a low output of around 1000 tablets per minute, compared to the ten times higher output of a regular tabletting machine (Cole, 1995e). Therefore, possibilities to improve the manufacturing process of compression-coated tablets are still investigated (Hariharan and Gupta, 2002).

The coat properties are not homogeneous throughout the coating due to an uneven force distribution during the compression process. This leads to a less dense compaction on the

lateral region, often resulting in a rupture of the coat into two halves after a certain lag time (Lin et al., 2001). This results in a pulsatile release of the drug, which may be intended for certain chronotropic applications, but is unsuitable, if extended release is aimed.

b. Coating with micronized polymer powders

Dry polymer powder coating is an innovative coating technique first described for the preparation of enterically coated solid dosage forms (Maruyama et al., 1998; Obara et al., 1999). The method involves the use of the coating polymer as a dry powder, fed directly into the coating chamber with the simultaneous application of the plasticiser. Thereby, the particles size of the polymer is crucial. To achieve reasonable film formation, micronized polymer powder should be used. Obara et al. reported that a curing step was further necessary to achieve film formation, which involved also the application of a small amount of water. Even though only a small amount of water was involved, the process was criticized not to be really 'dry'. Later it was demonstrated, that depending on the polymer properties and processing conditions, film formation can be achieved without any application of water.

Meanwhile dry polymer powder coating is enjoying increased popularity with in depth investigation of different polymers, formulation parameters and coating processes.

The process is very versatile concerning the use of equipment type, as e.g. rotor-granulator, rotor-fluidized bed, pan coater or regular fluidized bed can be utilised (Cerea et al., 2004; Engelmann, 2004; Kablitz et al., 2006; Obara et al., 1999; Pearnchob and Bodmeier, 2003c).

Technical solutions are necessary for the simultaneous, but spatial separation of the polymer and the plasticiser during application. This is possible by the use of particularly designed three way nozzles, which on the other hand implies the risk of sticking of the pellets due to the close proximity of the polymer powder and the plasticiser during spraying.

More elegant solutions enable the application of the polymer and the powder through two different nozzles, as for example in a ball coater (Fig.1).

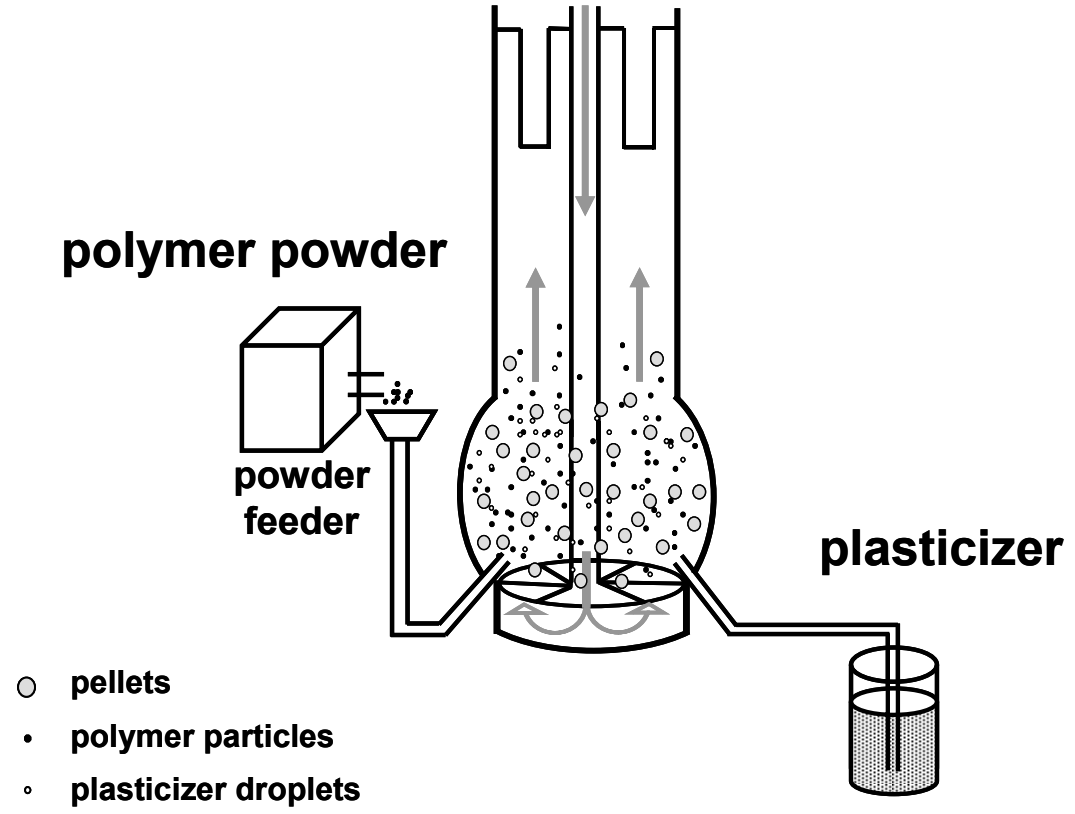

Figure 1 Setup for dry powder coating in a fluidized bed ball coater

However, when using fluidized bed equipments, the air flow should be reduced, to avoid extensive loss of powder over the filter system (Obara et al., 1999). Tablets or pellets are both able to be processed.

The dry powder coating process was first described by using HPMCAS, an enteric polymer (Obara et al., 1999). HPMCAS has a high Tg of ~120°C (Engelmann, 2004; Kablitz et al., 2006), thus the first results gave rise to the conclusion, that it is not possible to achieve film formation without the use of a small amount of water for curing. The authors pointed out, that heating alone was not sufficient to achieve film formation (Obara et al., 1999). Several factors may explain this result, as later coalescence and film formation was obtained with the same polymer (Kablitz et al., 2006).

One crucial difference described was the particle size, which was approximately half as big as in the first report (10 µm vs. 5.4 µm). Concerning the mechanism of film formation, the

particle size is one of the major parameters affecting the deformation and resulting coalescence of polymer particles, as will be discussed in more detail in the next chapter.

Moreover, in the first investigations the temperature during curing was kept around 40 °C, assuming to be sufficient based on the minimum film-forming temperature (MFT) of an aqueous HPMCAS-dispersion of 23 °C. However, film formation from aqueous dispersions at the MFT is only possible due to the additionally acting capillary forces of the evaporating water plus some plasticising effect. This additional impact is missing during dry powder coating, and therefore film formation will not take place below the Tg. The Tg of a polymer is in general higher than the MFT (here: 23 °C vs. 42.5 °C), thus film formation could be achieved as the curing temperature was risen above the Tg to 53-55 °C, without additional use of water.

The Tg influences many physical properties of the polymer, especially e.g. the elasticity and viscosity, two relevant parameters for coalescence. Polymers with higher Tg thus require higher temperatures during curing to sufficiently lower the viscosity of the polymer.

Similar results were reported for Eudragit® E, Eudragit® RS, shellac and ethylcellulose (Cerea et al., 2004; Pearnchob and Bodmeier, 2003a; b; c). Uncured pellets coated by dry powder coating resulted in porous, inhomogeneous films with fast drug release. Neither extended release nor gastric resistance or taste masking could be achieved even for drugs of low or moderate solubility (e.g. theophylline and propranolol HCl) without a thermal after-treatment (curing) at elevated temperatures (Cerea et al., 2004; Kablitz et al., 2006; Pearnchob and Bodmeier, 2003a; c). Coalescence was easily achieved for the polymers with low Tg without curing or at mild curing conditions (Eudragit® E, Eudragit® RS, shellac), whereas thermal after-treatment at elevated temperature for prolonged time periods was necessary for ethylcellulose (80°C/24h).

1.5.4. Theory of coalescence and film formation

The question of the mechanism of film formation from particulate polymeric matter arose simultaneously with the increased use of aqueous polymer dispersions for coating. Obviously, the process of film formation is different and more complicated than from organic solutions, were the polymer is in a dissolved state, whereas in aqueous dispersions it is present as a solid of small particle size.

Basically, the process can be subdivided in several stages (Fig.2). Water starts to evaporate after deposition of the aqueous dispersion on the surface of the substrate. Further up-concentration leads to an orderly packed array of the particles followed by a deformation of the particles. Finally, coalescence of the particles results in film formation (Keddie et al., 1995; Wheatley and Steuernagel, 1997).

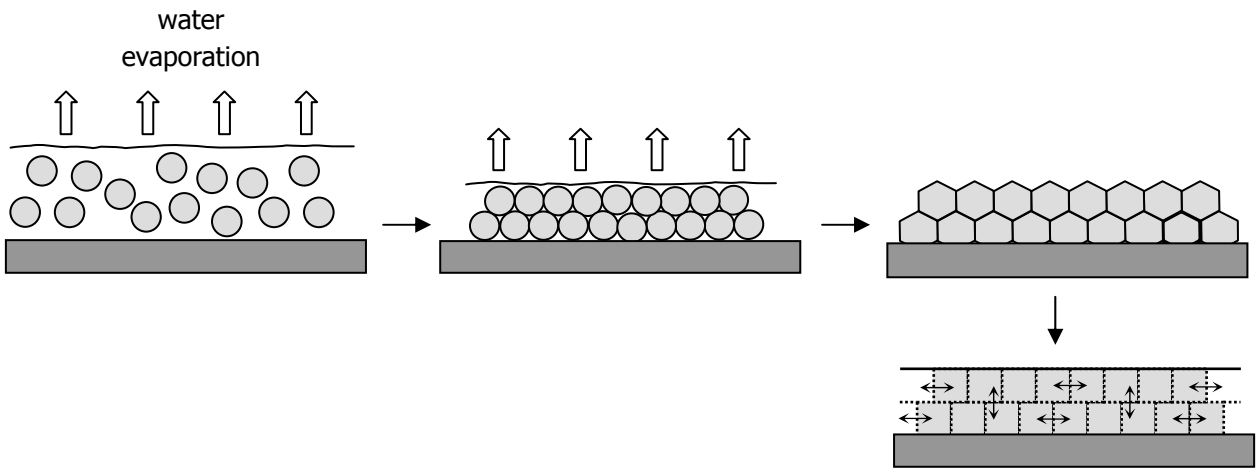

Figure 2 Process of film formation from aqueous colloidal dispersions

The *dry sintering theory* was the first mechanism suggested for the film formation from colloidal latices. It was described based on observations in the use of polymer powders for coating in the metallurgy (Dillon et al., 1951). According to this theory, the mechanism of coalescence of latex particles is based on the viscous flow of the polymer.

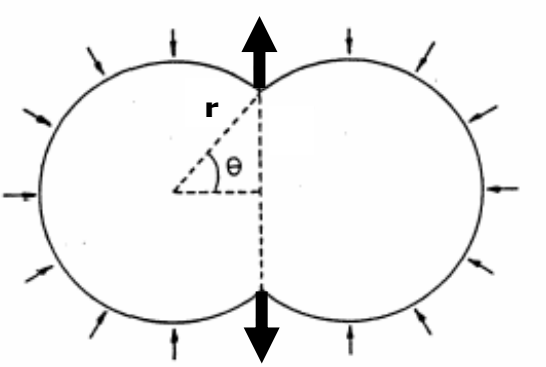

Figure 3 Shear stress favouring the coalescence of two polymeric particles

The driving force for the viscous flow is the shear stress, to which the polymer particles are exposed to (Fig.3). The polymer surface tension γ_p tends to minimize the surface area to reduce the surface free energy. The differential pressure P, which is acting over the circle of junction, can be calculated by:

$$P = \frac{2 \cdot \gamma_p}{r} \qquad (1)$$

with: γ_p: surface tension of the polymer

r: particle radius

For a typical latex this pressure may be up to 100 atm.

The time-dependent coalescence of spheres by purely viscous flow follows the relationship proposed by Frenkel:

$$\theta^2 = \frac{3\gamma_p}{2 \cdot \pi \cdot \eta \cdot r} \cdot t \qquad (2)$$

with: θ: half-angle of contact (according Fig.1)

γ_p: surface tension of the polymer

r: particle radius

η: polymer viscosity

The time t, necessary for complete coalescence was calculated to be between less than one second and a few hours, depending on the viscosity of the particles (Frenkel, 1945).
Improved coalescence results in an increase of the angle θ (Fig.3). From equation (1) it can be derived, that θ increases with increasing polymer surface tension γ_p or a decrease of the viscosity η or the particle size r. The addition of a plasticiser or the application of heat will both decrease the viscosity of the polymer and thus will result in a more complete coalescence in a given time (Dillon et al., 1951).

The mechanism of film formation from aqueous dispersions by purely viscous flow was criticised in several points (Brown, 1956):

1. according to experimental observations the film formation from aqueous polymer dispersions occurs concurrently with the evaporation of water, being completed when the water evaporation is complete. Thus, the polymer-water interfacial tension is assumed to be the driving force for coalescence, which in general may be lower than the polymer surface tension.
2. the rate of water removal determines the extent of coalescence, as demonstrated experimentally
3. porous, incompletely coalesced films are obtained, if the temperature during water evaporation is kept below a critical value
4. continuous films can be formed from emulsion polymers in spite of being slightly cross-linked. Purely viscous flow and interpenetration is hereby assumed to be hindered due to the cross-linking.

Therefore, Brown developed an alternative *capillary theory*. He considered the capillary forces developed by the evaporation of water from the aqueous dispersions to be the main reason for coalescence of the polymeric particles (Fig.4).

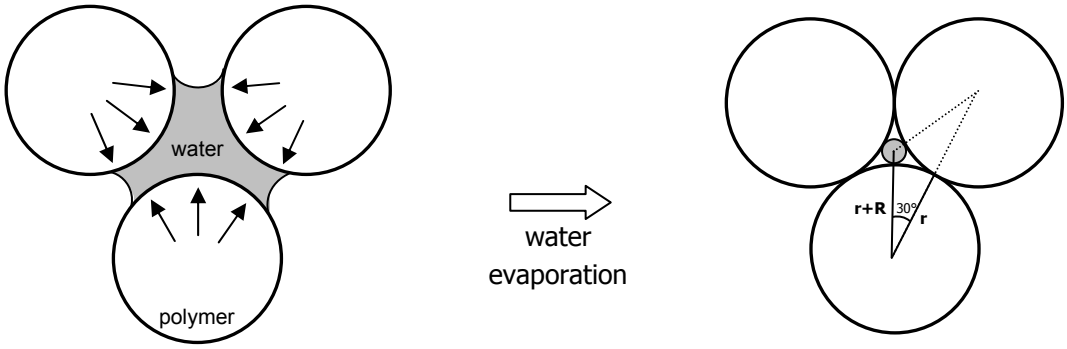

Figure 4 Capillary forces acting on polymeric particles during the evaporation of water

There are several forces promoting and hindering the coalescence of adjacent particles, however many of them have only a minor effect, and were considered to be negligible. The two forces competing with each other are finally F_c and F_G. F_c is thereby the capillary force resulting from the negative curvature of the water surface present in the interstitial capillary during water evaporation. F_G on the other hand denotes the resistance of the polymer sphere to deformation. The following inequality needs to be fulfilled for coalescence to occur:

$$F_c > F_G \qquad (3)$$

Thereby the capillary pressure, arising from the concave water surface (Fig. 4), exerts a force normal to the water-particle interface, deforming the particles and initiating coalescence. However, a polymer of sufficient rigidity will resist deformation by the capillary forces and water will evaporate without particle coalescence. On the other hand side, if viscous flow is possible, the particles will undergo stress relaxation and deformation, with the required stress being a function of the complex modulus of the polymer.

Based on the considered geometrical array r/(r+R) = cos 30 ° with r as the radius of the polymer particle and R the radius of the capillary (Fig.4).

The capillary pressure with respect to the radius of the polymer particles results in:

$$P_c = \frac{12.9\gamma_w}{r} \qquad (4)$$

with: γ_w: surface tension of water in the capillaries.

The resistance to deformation is dependent on the time-related elastic shear modulus G_t of the polymer, and was determined to be:

$$P_G = 0.37 \cdot G_t \qquad (5)$$

As the pressures P_c and P_G were assumed to be proportional to the forces F_c and F_G , they can be applied in equation (3) and result in:

$$G_t < \frac{35 \cdot \gamma_w}{r} \qquad (6)$$

Brown stated, that at the minimum temperature required for film formation, the modulus G_t will be less than the calculated maximal value, such that film formation can occur. Equation (6) also reveals, that at a given temperature, which affects the modulus of the polymer, coalescence is only possible up to a certain particle size.

However, it was assumed, that the coalescence of particles may take place even in the absence of water, as a result of the surface tension of the particles, although this might be much slower than in the presence of water (Brown, 1956).

Later, Voyutskii commented to the mechanisms proposed by Dillon and Brown, that the physical contact of two polymer particles, irrespective of resulting from viscous flow or capillary forces, is not sufficient to assure a stable film formation. Moreover, it is necessary, that segments of the polymer chains diffuse through the boundary from one particle to another, resulting thus in an interpenetrating network (Voyutsskii, 1958). Only such a strong linkage is able to impart sufficient mechanical strength to the formed film, allowing it to swell, but not to redisperse upon contact with water.

These proposed mechanisms gave reason for much discussion about the role of viscous flow and capillary forces for the film formation (Dobler et al., 1992; Keddie et al., 1995). Finally, experimental proof was presented in so far as capillary forces alone are insufficient to

explain the film formation, but the combination with the interfacial driving force facilitates coalescence (Eckersley and Rudin, 1990). Moreover, film formation from aqueous colloidal dispersions can take place even under conditions, where water is not evaporating, that means, without acting capillary forces (Dobler et al., 1992). However, it takes place faster under wet conditions, confirming the role of the capillary forces, whereas coalescence may occur even under completely dry conditions, proving the basic role of the viscous flow of the polymer (Lin and Meier, 1996).

A deviating mechanism of particle coalescence and film formation was already discussed for an aqueous dispersion of HPMCAS. The polymer in the reported system has a significantly higher particle size of about 5 µm compared to the usual 200-400 nm for colloidal aqueous dispersions. It was suggested, that upon the evaporation of water the plasticiser separates. As plasticisers are solvents for the polymers they plasticise, they are able to dissolve or gel the HPMCAS particles, such as the polymer particles are able to fuse together (Nagai et al., 1997).

The drug release from dry polymer powder coated dosage forms are further proofs for film formation due to viscous flow. In the first experiments small amounts of water were necessary to achieve film formation (Obara et al., 1999). Proper adjustment of the formulation and process parameters finally resulted in film formation without the use of water (Kablitz et al., 2006). Hence, capillary forces could not act in that setup, but still film formation was possible.

The film formation during dry polymer powder coating was suggested according the following mechanism (Fig.5) (Pearnchob, 2003):

First, the polymer particles needed to adhere to the surface of the dosage form. This was enhanced by heating and simultaneous spraying of an aqueous 10% w/w HPMC-solution emulsified with the plasticiser. The HPMC was used to act as a binder, promoting the adhesion of the polymer to the substrate surface (Pearnchob and Bodmeier, 2003c). The softening of the polymer particles was further facilitated by the elevated temperature and

plasticiser uptake. However, according to the proposed mechanism, the coalescence did not take place during the coating process, but during a subsequent curing step.

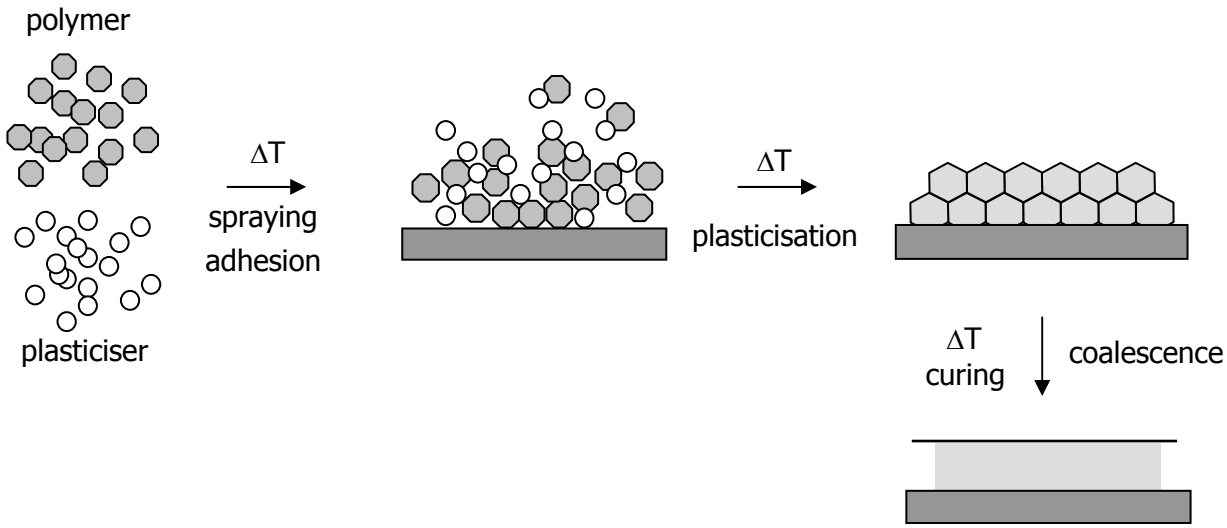

Figure 5 Polymer powder deposition and film formation from dry polymer powders (Pearnchob, 2003)

For the described coating process with the corresponding formulation parameters this mechanism is reasonable. However, with optimized formulation and process parameters, adherence of the polymer to the substrate surface can be achieved without the use of a binder (Cerea et al., 2004; Engelmann, 2004; Kablitz et al., 2006).
Moreover, coalescence and film formation can occur already during the coating process, superseding the use of additional water or a curing process.

Film formation by dry powder coating differs in some aspects more, beside the absence of water, if compared to the process from aqueous colloidal dispersions. More basically, the plasticiser is applied simultaneously with the polymer. Therefore, the polymer is not homogeneously plasticised at the time point it hits the surface of the dosage form. However, as a solvent for the polymer, it will be able to soften or even dissolve the surface of the

polymer particles. The viscosity and modulus of the polymer is thus decreased, enhancing the deformation of the particles, as a softer polymer is able to deform and flow easier than a harder one (Keddie et al., 1995). The particles identity vanishes in a much shorter time for softer polymers, too. In order that this process can take place rapidly, the polymer should be heated well above its Tg, which in general means 10-50 °C more (Cerea et al., 2004; Engelmann, 2004; Kablitz et al., 2006; Pearnchob and Bodmeier, 2003a; b; c).

Additionally, the concurrent application of the plasticiser with the polymer facilitates the adhesion of the polymer to the surface of the substrate during coating.

1.5.5. Formulation and process parameters

a. Plasticisers

Polymers used for coating often result in brittle films, which may lead to crack formation, being responsible for the failure of the functionality of the coating (O´Donnell and McGinity, 1997; Rowe and Forse, 1981; Sakellariou and Rowe, 1995; Sinko and Amidon, 1989). Plasticisers are added to avoid the internal strain leading to these defects and to insure appropriate film properties (Seitz, 1988; Wu and McGinity, 2001).

In general plasticisers are low Mw non-volatile liquids at room temperature with a high boiling point and mostly insoluble in water (Bauer et al., 1988; Osterwald et al., 1982; Sakellariou et al., 1986; Wheatley and Steuernagel, 1997). The right choice of plasticiser and the adequate concentration are very important for the resulting film properties of the coating (Lippold and Monells Pages, 2001). The amount added should be sufficient to reduce the brittle character of the polymer, but not to be as much to cause sticking of the coated product while processing or storage (Morflex Inc., 1993; O´Donnell and McGinity, 1997; Porter and Ghebre-Sellassie, 1994). Plasticisers are mostly used in concentrations between 5-30% w/w based on the dry polymer weight (Lehmann, 1994; Morflex Inc., 1997; Rekhi and Jambhekar, 1995), dependent on the type of plasticiser, the polymer to be plasticised, as well as on the system applied e.g. organic solution or aqueous dispersion.

Solubility of the polymer in the plasticiser is a pre-requirement, to assure the necessary compatibility of the two components (Bauer et al., 1988; Rekhi and Jambhekar, 1995; Wheatley and Steuernagel, 1997). In general effective plasticiser resemble in their chemical structure the polymer they plasticise (Aulton, 1995; Banker, 1966; Hogan, 1995a; Sakellariou and Rowe, 1995). The plasticiser increases the molecular mobility of the polymer by interpenetrating with the polymer chain segments (Bauer et al., 1988; Dillon et al., 1953; Entwistle and Rowe, 1979; Okhamafe and York, 1988; Rowe et al., 1984). This decreases the cumulative intermolecular forces along the polymer chains, leading to a reduction in cohesion and a more open structure of the polymer (Banker, 1966; Dillon et al., 1953). The

superior mechanical properties of the film are the result of the reduced brittleness and improved flexibility (Wheatley and Steuernagel, 1997). The effectiveness of the plasticiser can be quantified by the decrease of the tensile strength and modulus as well as the reduction of the glass transition temperature (Tg) (Banker, 1966; Bauer et al., 1988; Lippold and Monells Pages, 2001; Wheatley and Steuernagel, 1997; Zosel, 1996). Moreover, the viscous flow will be enhanced due to a decrease of the viscosity (Dillon et al., 1951; Zosel, 1996).

b. Mechanical properties

Appropriate mechanical properties are crucial for the performance and stability of the coated dosage form during manufacturing, transport, storage and administration (O´Donnell and McGinity, 1997). Brittle films are exposed to high levels of internal stress, ultimately resulting in the premature failure of the coating e.g. by crack formation (O´Donnell and McGinity, 1997; Porter, 1990; Rowe et al., 1984; Sakellariou and Rowe, 1995; Sinko and Amidon, 1989). Improvement of the mechanical properties, e.g. by the addition of plasticisers, reduces the risk of such problems. Plasticisers will strongly affect the mechanical properties of the polymeric films by decreasing the tensile strength, increasing the elongation and decreasing the elastic modulus (Hogan, 1995a).

The measurement of the mechanical properties of isolated polymer films helps to estimate the performance of the resulting coatings on the final dosage form (Bodmeier and Paeratakul, 1994). Load vs. displacement curves are recorded for the film specimen and the data used to calculate parameters such as the tensile or puncture strength, elongation and elastic modulus (ASTM D882-01, 2001; Radebaugh et al., 1988). These parameters are indicative for the toughness and elasticity of a polymeric film.

However, polymers are viscoelastic materials (Eckersley and Rudin, 1990; O´Donnell and McGinity, 1997; Radebaugh et al., 1988), and therefore these measurements can supply only rough information. The application of a sinusoidal stress as used in dynamic mechanical analysis (DMA) allows to resolve the response of the polymer sample into the in-phase

elastic component and the out-of-phase energy dissipative component, which is related to the viscous property of the polymer (Lafferty et al., 2002; Rowe et al., 1984). This enables the calculation of the storage (elastic) and loss (viscous) modulus and tan δ (ratio of loss and storage modulus). The measurements can provide crucial information about the more predominant property (with increasing tan δ the viscous part is more pronounced), and the change of the properties in dependence of the temperature, especially suitable to determine the Tg.

c. Curing

Coalescence is the pre-requirement for film formation from aqueous polymer dispersion. The distinct polymer particles deposited on the product surface will form thereby a continuous film. In order to accelerate the coalescence, an after-treatment of the coated dosage form at elevated temperature can be performed. This process, called curing, facilitates the film formation and may prevent changes in drug release on storage (Bodmeier et al., 1997).

The curing process is essentially comparable to the sintering. The elevated temperature applied, which should be above the Tg of the polymer, induces a sintering of adjacent polymer particles by viscous flow of the polymer and an interdiffusion of the polymer chains (Li and Li, 1996).

The appropriate temperature conditions are hereby crucial, as well as the surrounding relative humidity (r.h.) as water as a plasticiser may tremendously affect the success of the curing process (Williams and Liu, 2000).

The physical properties of the drug and its compatibility with the polymer are further essential parameters for the resulting effect. A drug possessing a low melting point close to the applied curing temperature may melt and migrate through the polymer coat, leading to enhanced drug release in spite of a more complete coalescence (Bodmeier et al., 1997).

Storage at elevated temperature of dosage forms coated with organic solutions may also be reasonable to reduce the amount of residual solvent (Lippold and Monells Pages, 2001).

1.6. RESEARCH OBJECTIVES

1.6.1. Natural polymers for extended release or protective coatings

a. Pure zein coatings

Zein as a water-insoluble polymer implied to potential to retard the drug release if used as coating for solid dosage forms. Zein from organic solution was investigated with the specific objectives to determine the optimal plasticisers, to evaluate the release properties and the stability on storage of zein-coated pellets, and to investigate the effect of different parameters such as drug solubility, coating level and the release media on the drug release of zein-coated pellets.

Protective coatings of zein at low coating level for immediate release formulations were examined for moisture protection and taste masking purpose.

As an alternative to organic solutions aqueous zein dispersions were investigated with the specific aims to investigate suitable preparation methods for aqueous zein dispersions, to evaluate the drug release pattern from pellets coated with aqueous zein dispersions, and to improve the stability of aqueous zein dispersions with higher polymer concentration. Therefore the effect of different additives and preparation conditions were examined.

b. Zein-shellac combinations

Zein-shellac mixed coatings were investigated to reduce the rapid drug release of pure zein coated pellets in pH 1.2. The objectives were to investigate the influence of the coating composition (zein to shellac ratio) on the drug release and the mechanical properties of the mixed films. The effect of curing was evaluated to overcome the stability problems known for shellac and to result in stable release profiles on storage.

Shellac topcoats over basic zein coats were examined as an alternative system with the objective to achieve extended drug release over the entire pH-range. The topcoats were expected to limit the rapid release at low pH but to dissolve in the intestinal medium, where the basic zein coat would further control the release. The effect of additives in the topcoat to alter the permeability was examined with the purpose, to achieve gradually decreasing drug release related to the coating level to obtain better predictable product properties.

1.6.2. Dry powder coating: critical parameters for film formation

To determine the crucial parameters for the film formation from dry polymer powder coatings the particular objectives of this part of the study were:

- to evaluate the effect of plasticiser type and amount on the thermal and mechanical properties of the polymer to optimise the polymer-plasticiser interaction.
- to study the role of water and its necessity for the film formation during curing.
- to investigate further key parameters such as the polymer viscosity or thermal after-treatment (curing) to achieve film formation and extended drug release.

The investigations were completed by the elucidation of the effect of other formulation parameters such as the drug solubility or the use of additives (e.g. pore formers).

Pre-plasticised micronised ethylcellulose powder was used with the aim:

- to evaluate the effect of pre-plasticisation on coalescence and film formation in comparison to the simultaneous application of the plasticiser during coating.
- to compare the film formation of ethylcellulose powders prepared by different pre-plasticisation processes.