A INTRODUCTION

Coating of solid oral dosage forms is a common technique in order to protect the active pharmaceutical ingredient (API) against environmental impact and the body fluids or rather to protect the body against adverse effect of the API. The origin of the coating technology of the modern times is the coating process based on organic polymer solutions which have been replaced gradually by aqueous dispersions in order to avoid the disadvantages of organic solvent based processes like toxicity and environmental pollution [60, 68]. However aqueous dispersions have the disadvantage that the energy input to evaporate the dispersion medium water is high due to the high latent heat of evaporation [84]. Also slow spraying rates must be employed to prevent water from penetrating the surface of the substrate enhancing processing time [33]. Furthermore, the API may interact with the water and i. e. hydrolysis may occur.

A further development of the coating technology is the coating without the uses of organic solvent respectively water, namely the dry coating process, where polymer powder particles and liquid plasticizer are layered on the pellet. This innovative alternative is still in the stage of development and needs further optimization and characterization. Different interpretations of the process are performed and introduced in literature [31, 101, 107-109, 153], however, little information about the coating mechanism and the storage stability of the coated oral dosage form is documented [125]. A certain drawback of the dry coating process is that its coating efficiency is below the coating efficiency of the conventional coatings.

The process is composed of two phases, applying in the first phase the coating material, and curing the coated oral dosage form in the second phase. It is assumed that the critical phase for the coating efficiency is the coating phase whereas the curing phase is decisive for the film formation occurring mainly during this phase. This is in contrast to conventional coating where material application and film formation takes place concurrently. Several parameters are influencing the process which have to be characterized since they differ from the key parameters of the conventional coating like the minimum film formation temperature [77]. As dry coating polymer powders are applied to the dosage form, interparticle forces will take place during the coating phase of the process. Their influence has to be regarded assuming that high interparticle forces will lead to an increase of the coating efficiency. Furthermore, due to the absence of a dispersion media, film formation differs considerably from film formation of aqueous dispersion based processes. Thus, the film formation mechanism needs to be analyzed and the key parameters have to be identified.

First, investigations with respect to the functionality of the film and the storage stability of the dry coated dosage form were used to characterize the process. Drug loaded pellets were coated with micronized polymer powders and liquid plasticizers by the dry coating technique. The drug release of the coated pellets was investigated in order to evaluate the functionality of the film, and the storage stability was investigated by monitoring the drug release after different storing times. Different formulations were composed and compared to each other.

Afterwards the formulations were used for characterizing the two phases of the process. Contact angle measurements and atomic force microscopy gave information about the interparticle forces occurring during the coating phase. Further, thermal analysis was used to describe the coating material with regard to the glass transition temperature. With respect to the film formation it is expected that the Tg affect film formation of the polymer particles. In order to define the curing temperature, which is needed for film formation the pellets are cured at different temperatures. Scanning electron microscopy gave information about the morphology of the film.

After the key parameters of the dry coating process have been determined with regard to the coating efficiency and the functionality of the film, the process parameters of the equipment were characterized using a factorial design. This elucidated the critical factors of the process and lead to an optimization of the process settings. Finally, the process was transferred on larger coating equipment in order to demonstrate the suitability of this innovative coating technology.

1 Aim of film coating

Early in the history the first steps of coating technology is passed on from the 9th century B.C. when the Egyptians began to coat hand-shaped spheres using beside talc and gelatin, silver and gold as coating material demonstrating affluence and political reputation. Coating with honey and sugar was further developed in order to mask the unpleasant and bitter taste encountered as the pill was taken into the buccal cavity and swallowed. In the 19th century, sugar became a major ingredient for coating candy products, which were also used for pharmaceutical coatings. Other natural products such as shellac, zein, and gum arabic were commonly used in the pharmaceutical industry. However, such materials were replaced predominantly by semi- or fully-synthetic substances last century, which are available on the market today. In 1954 Abbott Laboratories produced the first commercially available film coated tablet, although the first film coating appeared in 1930. Compared to sugar coating, film coating provides more flexibility with the ability to coat a variety of substrates [9, 33, 146]. Today the pharmaceutical development and production of solid dosage forms is inconceivable without film coating.

The purpose of film coating can be categorized into three main groups examining it from three different points of view. The first group regards film coating from the point of the patient and stands for safety due to easy identification and for compliance due to visual attractiveness as well as for taste masking which enhances palatability describing the possible reasons why people started to coat oral dosage forms in earlier centuries. The pharmaceutical aspects are found in the second group which results in the increase of the stability of an active drug substance during exposure to light, moisture and atmospheric oxygen and the increase of the mechanical integrity of the oral dosage form during manufacturing and packaging. Additionally, it is possible to avoid incompatibility of active drug substances by physical separation of the incompatibles into the core and coat. Biopharmaceutical rationales display the third group where enteric coatings, sustained release coatings or osmotic pump systems are used to modify the drug release profile. Furthermore, side effects of the active drug substance can be avoided as preventing gastric irritation by employing an enteric polymer coating [9, 16, 33, 124]. Considering these aspects it is self-evident that the development of coating processes and coating materials continues consequently.

2 Coating processes

The early coating techniques were extemporaneous and rather crude often performed on individual pills by picking them up one at time, either on the point of a needle or with a pair or forceps, and dipping them into a coating solution [5]. In the last century, the first steps of liquid coating development were performed using organic solvents. Solutions of polymeric coating material were sprayed onto pellets and the solvent was evaporated subsequently. Later on the organic solvent-based processes have been replaced by aqueous coatings applying aqueous based solutions respectively dispersions onto the pellets. In order to overcome the time consuming processes due to the evaporation of the media the development of new coating technologies proceeds constantly resulting in coating techniques conducted without any media named dry coating or rather dry powder coating.

2.1 Solution based coatings

Film coating in the early 1950s coatings was performed by applying polymers dissolved in organic solvents [119]. The use of such polymer solutions benefits of several advantages like short processing times due to the rapid evaporation of the solvent. Furthermore, the possibility to produce thin, smooth continuous films with 5% - 30% coating material based on weight of the core was an innovation compared to sugar coatings where 50% - 150% coating material had to be applied [8].

Film formation using organic polymer solutions is easily achieved due to the dissolved polymer that after deposition builds the film on the substrate surface by undergoing sol to gel transition as the organic solvent evaporates [86]. Upon evaporation, the polymer molecules approach each other and finally form a homogenous film with a high degree of polymer chain interpenetration [81] (Figure 1). However, the use of organic solutions holds various disadvantages, such as that the toxicity of the solvent requires its recovery combined with high costs and environmental concerns. Nevertheless, organic coatings experience a revival today due to their less problematic stability on storage. Residual solvent or chemical respectively structure changes are few reasons for instabilities of the API whereas coats applied from aqueous dispersions often reveal changes in the drug release after storage due to incomplete film formation during the process [87].

Figure 1: Film formation of solution based coatings

An alternative coating technology is the aqueous solution based coating where water-soluble polymers are applied on solid dosage forms [96]. The major application of such systems is for protective coatings as the films will be water soluble without any functional effect. The coating process is similar to the organic based process; however, the high energy demand of the process has to be considered. Higher coating temperatures and lower spraying rates due to the relatively high latent heat of vaporization of water (540 kcal/g for water vs. 204 kcal/g for ethanol) [84] must be employed to ensure sufficient evaporation of solvent. The low polymer concentration, which is limited by the viscosity of the solution, extends the process time which is disadvantageous for both, the organic and the solvent based coatings. Therefore, the improvement to coat oral dosage forms with polymer dispersions was a major step in the history of coating technology.

2.2 Dispersion based coatings

Organic solution based coatings of water-insoluble polymers were predominately replaced by aqueous dispersion based coatings. The use of aqueous polymer dispersions is of interest due to the high amount of polymer in the dispersion resulting in shorter process times compared to aqueous solution based processes. The dispersion with up to 30% (w/w) solids including the polymer with a colloidal size is sprayed on the cores similar to the coating solution, however, the film formation differs completely since water-insoluble solid polymer particles are used. The mechanism is a complex process [75] and is still discussed in literature [137].

The film formation of aqueous polymer dispersions using latex or pseudolatex polymer materials is driven by the evaporation of water and subsequent coalescence of the polymer particles [45]. The process of film formation using aqueous polymer dispersions is usually divided in three phases [3, 137]. Phase I is the evaporation of water. The density of the dispersion increases until the colloidal particles come into contact with each other and, subsequently, form close-packed arrays. The particles then undergo deformation to polyhedra [103] without interparticle spaces in phase II, induced by an increase in temperature above the minimum film formation temperature (MFT), one of the most important parameters of film formation from aqueous dispersion based coatings. It is

defined to be the minimum temperature at which a cast film becomes crack-less and clear [40]. Below this temperature, the dried dispersion appears opaque and powdery [45]. Increasing the temperature above the glass transition temperature (Tg) in stage III, the boundaries between the particles disappear through interdiffusion of polymer chains developing a continuous film without distinguishable particles [114]. The micromechanical process of the coalescence is still not completely analyzed, however, several models are discussed. Dillon et al. [36] explained the film formation mechanism introducing the dry sintering hypothesis which postulates that the surface tension of the polymer is the driving force accompanied by viscous flow and particle deformation. An analogous mechanism based on the polymer-water interfacial tension was suggested by Vanderhoff et al. [69] known as wet sintering. An alternative theory was developed by Brown et al. [20] termed the capillary theory. Capillary forces exerted by the liquid facilitate the deformation of the particles in the interstitial capillary system between particles during drying.

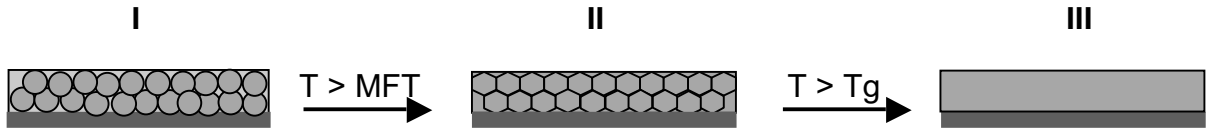

Figure 2: Film formation of aqueous dispersion based coatings

Film formation of aqueous polymer dispersions usually takes several minutes up to hours depending on film thickness and environmental conditions [152]. Temperature has an important effect on the rate of polymer diffusion and film formation [17, 103] and is highly affecting the quality of the resulting film. Recently Siepmann et al. reported that additionally to heat, humidity enhances film formation of HPMCAS coatings. Furthermore film formation was shown to be dependent on the particle size of the polymer. Additionally, it is described in the literature that film formation begins at the upper surface of the coating and proceeds from top to bottom progressively during drying or rather curing [57]. 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 [132].

Like organic based processes aqueous based process exhibit several disadvantages. Since water is used as dispersion media it has to be evaporated which is time and energy consuming. A simple way to shorten coating time is to use a coating dispersion of higher concentration, but this approach is limited by the risk of spray nozzle blocking caused by agglomerated particles, which can be transported to the nozzle. Furthermore, nozzle blocking is caused by premature coalescence of the polymer in the dispersion. Hence, the use of dry powders as coating material is a new challenge of the coating technology.

2.3 Dry coating

Initially, redispersible powders were developed for the preparation of aqueous polymer dispersions. Enteric polymers contain esters in their chemical structure which may be hydrolyzed if stored as aqueous dispersion. Thus, redispersible dry powders were offered by the manufacturers in order to be dispersed in the dispersion media prior to the application [120]. These redispersible powders were adopted to develop new coating technologies.

Coating with polymer powders is an innovative and promising alternative to the conventional coating technology with organic polymer solution or aqueous polymer dispersion. Conducting organic solvent based processes the solvent needs to be recovered due to environmental pollution. Coating processes with aqueous dispersions are very time and energy consuming [148] caused by the low concentration of coating polymer and large amounts of water which need to be evaporated. Compared to both the dry coating method is favourable regarding environmental friendliness and safety. It is a coating process without any use of water or organic solvent. Because of their absence, water or organic solvent do not need to be evaporated which leads to shorter processing times. It might be a very suitable coating method in order to coat drugs which are sensitive to organic solvents or water.

Different variations of the dry coating process have been developed layering polymer powder particles on the pellet or tablet surface by simultaneously feeding/spraying polymer powder and plasticizer followed by a curing phase at increased temperatures. By using a CF granulator (centrifugal coater) tablets were coated by adding polymer powder and plasticizer composition separately by a powder feeder and a spray nozzle. The powder is dosed onto the tablets and the liquid is sprayed. Afterwards film formation was induced by spraying a small amount of water on the coated beads and by increasing the temperature facilitating coalescence. The tablets were cured in an oven [101]. In an other study, pellets were coated with polymer powder and plasticizer mixed to an emulsion with HPMC solution using a Wurster insert with a powder feeder and separate spray nozzle [108, 109]. However, these processes do not meet exactly the conditions of the dry coating process using a small amount of water. It was demonstrated that dry powder coating compared to aqueous coating procedures generally required higher coating levels, higher plasticizer concentrations, and higher processing temperatures. Recently, soft-gelatin capsules were coated applying the dry powder and the liquid plasticizer separately but simultaneously meeting the process conditions of the dry coating process [30] without any use of water.

An alternative was performed by Zhu et al. conducting the dry coating process in a patented electrostatic pan coater achieving powder adherence due to the electrostatic charging without any water [154]. Furthermore, tablets were coated with polymer powder which prior to the coating process had been preplasticized by mixing polymer powder with plasticizer and sieving afterwards [31] or rather by a hot-melt extrusion process of polymer, plasticizer and thermal lubricant followed by cryogenically grinding of the extrudate [147, 153]. Sauer et al. coated tablets containing a highly water soluble drug applying primers before the powder coating in order to achieve better adhesion of the polymer powder [125]. The disadvantages of these processes are the small batch size of 50 g and the need of additional processing time and equipment for preparation of the coating material. Moreover, prolonged-release microparticles were developed composed of core particles with multi-layer coat of binder, drug and polymeric nanopowder using a high-speed elliptical-rotor powder mixer [65]. Recently, Ando et al. examined the use of a different approach to the making of compressed tablets containing pellets. A double-structure punch (center punch and outer punch) compressed and dry coated the pellets in a single run [2].

In contrast to the research work in literature, in this study the dry coating process is carried out applying the dry powder using a rotary fluid bed equipment. The polymer is passed as dry powder via a powder feeder to the three way nozzle which is able to transport separately but closely together the plasticizer composition and the dry powder into the pellet bed [71]. This method secures an efficient application of the coating material onto the pellets compared to separate addition which was performed by Obara et al. and Pearnchob et al. [101, 109] and does not require any addition of water. Additionally, the dense spiral movement of the fluid bed enhances the layering of the polymer particles by clinging them tightly to the pellet, which minimizes the loss of powder. Furthermore, it does not need any pre-steps as hot-melt extrusion.

First steps of process optimization of the dry coating process is described in the literature by Genovesi et al. who demonstrated that lower feeding/spraying rates results in an increase in coating uniformity not defining if the uniformity between complete batches or the uniformity of the pellets' film is meant [53]. Generally, process optimization can be performed using factorial designs. The significant process parameters and interactions between them can be determined and consequently used to optimize ad scale up process [79, 97]. With respect to the production of pellets in the rotary fluid bed, there is one study describing the optimization of a process using factorial design [19]. The results indicated that the pellet mean particle size was negatively affected by the rotor speed, while the binder spray rate had a positive effect on size; pellet flow properties were enhanced by