Pharmaceutical Technology Division
Department of Pharmacy
University of Helsinki
Finland

# Studies on Aqueous Film Coating of Tablets Performed in a Side-Vented Pan Coater

by

Mirja Ruotsalainen

Academic Dissertation

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Supervisors: Professor Jouko Yliruusi
Division of Pharmaceutical Technology
Department of Pharmacy
University of Helsinki
Finland

Docent Jyrki Heinämäki
Division of Pharmaceutical Technology
Department of Pharmacy
University of Helsinki
Finland

Reviewers: Dr. Leena Christiansen
Division of Pharmaceutical Technology
Department of Pharmacy
University of Helsinki
Finland

Dr. Pirjo Luukkonen
AstraZeneca R&D Mölndal
Sweden

Opponent: Docent Juhani Posti
Schering Oy
Turku
Finland


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## Abstract

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The main purpose of this study was to investigate and gain understanding about the factors affecting the aqueous film coating of tablets performed in an instrumented and automated side-vented pan coater.

The effects of film coating conditions and storage on surface morphology, moisture content and stability of hydroxypropyl methylcellulose (HPMC) coated tablets containing a moisture-labile drug (acetylsalicylic acid, ASA) were investigated. In addition, the time-dependent dimensional changes of coated tablets and the relevance of these changes to film adhesion were measured. The surface roughness was measured using a non-contacting laser profilometer, an optical roughness analyser and a confocal laser scanning microscope (CLSM). Process automation with an air flow rate measurement system, data storage and monitoring capability was used to control and analyse the film-coating process.

Critical pan coating process parameters that affect the surface morphology and residual water content of the film-coated tablet were inlet air flow rate, inlet air absolute humidity, flow rate of the coating solution, spraying air pressure and pan air temperature. The process conditions influenced coating solution drying and penetration, and thereby the migration of tablet core components into the coating layer. A moisture-labile drug (ASA) appeared relatively insensitive to the aqueous film coating process and subsequent residual water, but during storage the hydrolysis increased due to moisture penetration. The time-dependent dimensional changes and their effect on film adhesion were negligible if the tablet cores were compressed with sufficient compression force. CLSM was well suited for imaging changes in the film-core interface and the surface morphology of the film-coated tablet and consistent with other surface roughness measuring techniques. The uniformity and smoothness of the coating can be improved by more precise control of the coating solution application and water evaporation.

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## List of original pulications

This thesis is based on the following original papers, which are referred to in the text by the Roman numerals I-V.

I Heinämäki, J., Ruotsalainen, M., Lehtola, V-M., Antikainen, O., Yliruusi, J., 1997. Optimization of aqueous-based film coating of tablets performed by a side-vented pan-coating system. *Pharm.Dev.Tech*., 2, 357-364.

II Ruotsalainen, M., Heinämäki, J., Rantanen, J., Yliruusi, J., 2002. Development of an automation system for a tablet coater. *AAPS PharmSciTech*. 3 (2), http://www.aapspharmscitech.com/.

III Ruotsalainen, M., Heinämäki, J., Taipale, K., Yliruusi, J., 2003. Influence of the aqueous film coating process on the properties and stability of tablets containing a moisture-labile drug. *Pharm.Dev.Tech.* (accepted).

IV Ruotsalainen, M., Heinämäki, J., Guo, H., Laitinen, N., Yliruusi, J., 2003. Novel technique for imaging film coating defects in the film-core interface and surface of coated tablets. Submitted for publication.

V Ruotsalainen, M., Heinämäki, J., Antikainen, O., Yliruusi, J., 2002. Time-dependent dimensional changes and film adhesion of coated tablets. *S.T.P. Pharm. Sci*., 12, 385-389.

# 1 INTRODUCTION

Aqueous film coating is applied as a thin polymeric film to the surface of a tablet. Film coating can protect the tablet from light, temperature and moisture, mask undesirable taste or odour, improve the appearance, provide tablet identity, facilitate swallowing and control or modify the release of the drug. Aqueous coating of oral solid dosage forms has rapidly replaced solvent-based coatings for safety, environmental and economic reasons. However, since tablets may contain moisture-sensitive drugs or excipients, the use of water raises concerns about the physical and chemical stability of the coated tablets.

Film-coating of tablets is a multivariate process, with many different factors, such as coating equipment, process conditions, composition of the core tablet and coating liquid, which affect the pharmaceutical quality of the final product. The side-vented, perforated pan-coater is the most commonly used coating device of tablets. Its air flow system through a perforated pan ensures rapid and continuous drying conditions. The low evaporation capacity of water requires high drying efficiency of aqueous film-coating equipment.

Traditionally the level of instrumentation and automation of coating equipment has been low and, subsequently, the coating process difficult to control. To improve the reproducibility and predictability of the coating process and, consequently, the quality and safety of the final coated product, demand for instrumentation and automation of coating equipment in the pharmaceutical industry has increased. Furthermore, the reduction of product costs has become an important factor in the pharmaceutical industry as a requirement for efficient production. An automated film-coating process and a critical process parameter monitoring system would provide a useful tool for controlling the process and for understanding the phenomena during the process.

High-quality aqueous film coating must be smooth, uniform and adhere satisfactorily to the tablet surface and ensure chemical stability of a drug. Critical process parameters, such as inlet air flow rate, spraying air pressure, coating solution flow rate, pan air temperature and rotating speed of the pan, are quite well identified and can greatly affect the spreading, penetration and drying (i.e. water evaporation) of the coating liquid on the tablet surface and, subsequently, the quality of the coated tablet. In the aqueous film coating process, tablets are exposed to wide temperature and humidity variations that may promote undesired water penetration into the tablet core during

coating or storage. Penetrated water can cause changes in the structure of the film-core interface, core expansion and increase the risk of degradation of a moisture-labile drug.

Probably due to lack of effective instrumentation and automation systems, the effects of process conditions on the properties of coated tablets are not very well understood. In determining the effects of the film coating process and storage on the quality of the coated tablet, the relevant parameters are surface roughness, film-core interface, i.e. water penetration into the core, residual moisture content, degradation of moisture-labile drug, dimensional changes of coated tablets and the effect of these changes on adhesion.

# 2 LITERATURE REVIEW

## 2.1 Aqueous film coating of tablets

### 2.1.1 Film formation mechanisms

Aqueous film coating applications are either solutions or dispersions, depending on the water solubility of the film former polymers. Film formation from the polymer solution occurs through a series of phases. When the polymer solution is applied to the surface of a tablet, cohesion forces form a bond between the coating polymer molecules (Banker, 1966). To obtain high cohesion, the cohesive strength of the polymer molecules must be relatively high and continuous surfaces of the film material must coalesce. Coalescence of adjacent polymer molecular layers or surfaces occurs through diffusion. When most of the water evaporates, the viscosity of the solution increases (gelation) and leaves the polymer chains in close proximity to each other (Harris and Ghebre-Sellassie, 1997) and deposited over a previous polymer layer. If there is adequate cohesive attraction between the molecules and sufficient diffusion and coalescence upon the more complete evaporation of the residual water, the individual polymer chains align themselves to form a cohesive film (Harris and Ghebre-Sellassie, 1997).

Film formation from dispersion occurs when polymeric particles coalesce to form a continuous film (Fig.1), making it a more complex mechanism compared to film formation from solution (Obara and McGinity, 1995). Several reports on the mechanism of aqueous polymer dispersion film formation have been presented in the literature (Ortega, 1977; Yang and Ghebre-Sellassie, 1990; Eskersley and Rubin, 1996; Dobler and Holl, 1996; Wheatley and Steuernagel, 1997).

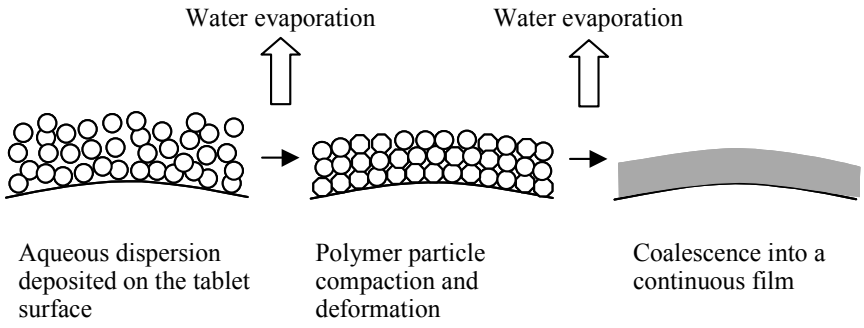



Figure 1. Film formation from aqueous polymer dispersion.

The coalescence of aqueous polymer dispersion deposited on the surface of a tablet into a continuous film is initiated by water evaporation. As water evaporates, dispersed polymer particles are pushed into a closely packed, ordered array with water filling the voids. After the polymer particles come into contact with each other, they must deform and fuse in order to coalesce into a film. Coalescence will occur when the promoting forces are greater than the resistive forces of the particles. The forces promoting particle coalescence include capillary pressure (water-air interfacial tension), as well as particle-air and particle-water interfacial tension. Finally, the coalescence of the polymer particles is further complemented by inter-diffusion of polymer chains (autohesion) occurring through particle interfaces, making the film more homogeneous.

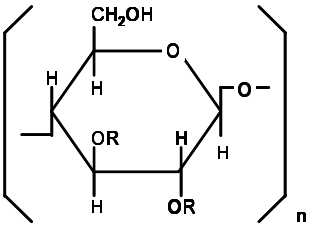
Film formation, i.e. coalescence, is a complex process and dependent on coating and storage conditions, coating polymer, polymer molecular weight and particle size, coating liquid constituents and properties like viscosity and surface tension (Dobler and Holl, 1996; Eckersely and Rubin, 1996; Aulton et al., 1997). Since coalescence only occurs above a minimum film formation temperature (MFT) of coating polymer, temperature and water evaporation are considered to be major process-related factors affecting the properties of coatings (Obara and McGinity, 1995).

### 2.1.2 Film formers

The aqueous-based coating materials of solid dosage forms can be divided into water-soluble, pH-dependent (enteric) and water insoluble (sustained release) materials. The most commonly used water-soluble coating polymers are hydroxypropyl methylcellulose (HPMC), other cellulose derivatives and polyvinylpyrrolidone (Fisher and Rowe, 1976; Okhamafe and York, 1985, 1989; Danserau et al.,1993; Sakellariou and Rowe, 1995; Heng, 1996; Guo et al., 1998; Khan et al., 2001; Rege et al., 2002). Recently, new rapid-release coating materials have been introduced, such as amylose starch (Krogars et al., 2002) and chitosan (Phaechamud et al., 2000). Water-soluble coating materials dissolve completely in the gastrointestinal tract and do not modify the drug release characteristics of the dosage. These polymers are usually applied as aqueous solutions.

HPMC is a cellulose derivative in which some of the hydroxyl groups are substituted with methyl and hydroxypropyl groups (Fig. 2). HPMC has many of the desired coating polymer properties: it forms a transparent, tough and flexible film that protects fragile tablets, masks the unpleasant taste of a drug and improves the appearance. HPMC is stable in the presence of heat, light, air and moisture in room

conditions, although it is moderately hygroscopic. Aqueous film coating using HPMC, however, has proven complex and more sensitive to changes in the process compared to those of organic solvent coating (Nagai et al., 1997). In aqueous coating the water evaporation capacity is lower, which requires compensating adjustments to other coating parameters, such as air temperature, flow rate of coating solution and spraying air pressure. The increased use of aqueous-based film coating has clearly increased the amount of coating defects (Rowe, 1997). If the coating conditions during aqueous film coating using HPMC were better characterized, these problems could be avoided.




R = -H, -$CH_3$, -$CH_2CH(OH)CH$

Figure 2. Chemical structure of hydroxypropyl methylcellulose (HPMC), (modified from Nagai et al., 1997).

The enteric coating materials today include cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate (HPMCP) (Baudoux et al., 1990; Edgar et al., 2001) and methacrylic acid copolymers (Gutierrez-Rocca and McGinity, 1993; Thomaa and Bechtoldb, 1999) which persist in the stomach and only disintegrate in the higher pH environment of the intestinal fluid. The widely used water-insoluble polymers, ethyl cellulose (Yang and Ghebre-Sellassie, 1990; Ozturk et al., 1990) and polymethacrylate copolymers (Ghebre-Sellassie et al., 1987; Petereit and Weisbrod, 1999) control the rate of drug release by swelling in water and forming a permeable membrane. Since polymers for enteric and sustained-release formulations are practically insoluble in water, they are usually applied as aqueous dispersions.

### 2.1.3 Other constituents

Film coatings prepared from pure polymers tend to be brittle and crack upon drying. The addition of plasticizers to the coating liquid decreases the intermolecular forces along the polymer chains by relieving molecular rigidity. Plasticizer molecules interpose

themselves between the individual polymer chains, thus breaking down polymer-polymer interactions, making it easier for the polymer chains to move past each other. The plasticizer improves the flexibility and reduces the brittleness of the film coating and makes it more resistant to mechanical stress during the coating process. Typical plasticizers of aqueous HPMC coating formulations are glycerol, propylene glycol, polyethylene glycol and triacetin (Johnson et al., 1991; Heinämäki et al., 1994; Heng et al.,1996). Titanium dioxide and polydextrose can be added in the coating liquid to increase adhesion as difficulties can sometimes arise with the satisfactory adhesion between the HPMC film and tablet surface (Lehtola et al., 1995a).

A distinctive colour is often used in film coatings primarily for tablet identification. Typically these are aluminium lakes, titanium dioxide and iron oxides or natural colours such as riboflavin and carotenoids. Opacifiers, like titanium dioxide, iron oxides and other pigments with high refractive indices, can be included in film coatings to protect light-sensitive drugs (Sakellariou and Rowe, 1995). Talc or colloidal silicon dioxide can be used to minimize tackiness between coated tablets.

### 2.1.4 Design of an automation and measurement system for a tablet pan coater

Film coating of tablets is a complex and multivariate process and, consequently, a rather sensitive manufacturing technique. Thus the pharmaceutical quality of the final film-coated product is difficult to control, which can influence the reproducibility of the batches. In the pharmaceutical industry, aqueous-based film coating of tablets is performed by using either an air-suspension (fluid-bed) coating apparatus or, today more often, by different kinds of perforated pans (Fig. 3). The side-vented perforated pan coating technique has been designed for rapid and efficient production of aqueous film-coated tablets. In a side-vented pan coater the air current passes through a perforated pan to ensure continuous and consistent drying conditions. The construction of the rotating pan ensures complete mixing of the tablets. The aqueous coating liquid is commonly applied by pneumatic (air) spray systems, where the pressure of the spraying air disperses the coating liquid as appropriately sized droplets.

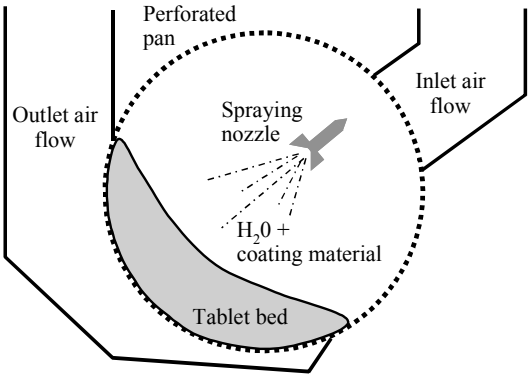



Figure 3. Side-vented perforated pan coater.

Only a limited number of reports are available on the aqueous-based film coating process using a side-vented pan coater (Rowe et al., 1978a; Kara et al., 1982; Leaver et al., 1985; Danserau et al., 1993; Poukavoos and Peck 1993a, 1993b, 1994; Twitchell et al., 1995a, 1995b; Khan et al., 2001; Rege et al., 2002). Based of these papers, the critical aqueous film coating process parameters of the pan coater are generally quite well identified. However, due to lack of effective instrumentation and automation systems, the effects of individual process variables on the coated tablet properties are not very well characterized and understood. Therefore, specialized instrumented coating equipment and optimally controlled process conditions would be beneficial.

Instrumentation and automation includes measuring, monitoring and controlling critical process parameters such as properties of process air (temperature, humidity, flow rate), flow rate of coating liquid, spraying air pressure and rotating speed of pan. With an instrumented and automated coater system, the desired conditions can be reliably maintained constant during coating, thus improving the reproducibility and efficiency of the process and ensuring the high quality and safety of the final product. A critical process parameter monitoring system would provide a useful tool for controlling the process and understanding the phenomena during the process.

Traditionally coating equipment has not been instrumented or automated, but the demand for automated systems has increased in pharmaceutical manufacturing during recent years. Nevertheless, only few previous reports have been published on the instrumentation and automation of pan coaters (Cole et al., 1983; Yokam and Cambell, 1984; Le Floc'h ,1996). Development of computer capacity, supervisory control and data

acquisition systems enables reliable monitoring and control of the measured coating parameters (Rantanen et al., 2000). The measured and logged coating parameter data is important for further observation and analysis and to meet the high requirements for process control documentation of today.

### 2.1.5 Process parameters

Many quality aspects of the final coated product are greatly influenced by the combined effect of process parameter values used in aqueous film coating. Coating process parameters affect the spreading, penetration and drying (i.e. evaporation of water) of the coating liquid on the tablet surface and, subsequently, the surface roughness and the residual moisture of the coated tablets (Twitchell et al., 1995b; Obara and McGinity, 1995).

#### 2.1.5.1 Air flow rate

Although process air is an essential element in the manufacture of pharmaceutics, earlier studies of pan coaters have not put much emphasis on the effects of air flow rate on the coating process. To our knowledge there is only one previously published report on a precise process air measurement system used in pharmaceutical manufacturing (Rantanen et al., 2000). In papers published on the air flow of a perforated pan coater, the air flow is reported to affect the drying efficiency of the coating unit and, subsequently, the quality of the coated tablets (Cole et al., 1983; Yoakam and Campbell, 1984). Franz and Doonan (1983) found that an increase of the inlet air flow rate causes a linear increase in the tablet bed temperature, increasing the evaporative capacity of the coating unit and eliminating overwetting problems of tablets. However, Rege et al. (2002) did not find the inlet airflow to affect the content uniformity of the coating composition or coating efficiency.

#### 2.1.5.2 Absolute humidity of inlet air

Although the aqueous film coating process of tablets has been studied extensively, there are virtually no reports in the literature on the effects of the absolute humidity of the coating process air on the properties of the film-coated tablet. It is obvious that the humidity of the coating process air is an important factor affecting the penetration and evaporation of water on the tablet surface. The water removal efficiency of the coating process is linearly correlated with the residual moisture content, tensile strength and porosity of the coated core tablet (Pourkavoos and Peck, 1994).

#### 2.1.5.3 Spraying air pressure

The spraying air pressure disperses the coating liquid into droplets and affects the droplet size distribution and, subsequently, the droplet spreading and penetration on the tablet surface. For the formation of an adequate and adhesive film coat, the atomised droplets have to spread completely over the surface of the tablet and only limitedly penetrate into the tablet core. Increasing the spraying air pressure to form smaller droplets and to increase the droplet velocity and momentum increases the extent of droplet spreading and therefore the rate of droplet drying and could thus reduce the degree of solution penetration into the substrate (Juslin et al., 1995; Twitchell et al., 1995a; Khan et al., 2001).

In general, increasing the spraying air pressure decreases the surface roughness of coated tablets and produces denser and thinner films (Twitchell et al., 1995a, 1995b; Tobiska and Kleinebudde, 2003). If spraying air pressure is excessive, the spray loss is great, the formed droplets are very fine and could spray-dry before reaching the tablet bed, resulting in inadequate droplet spreading and coalescence (Tobiska and Kleinebudde, 2003). If spraying air pressure is insufficient, the film thickness and thickness variation are greater possibly due to change in the film density and smaller spray loss. In addition, with low spraying air pressure big droplets could locally overwet the tablet surface and cause tablets to stick to each other. Wetting effects of spraying air pressure were found to have a minor effect on the adhesion of HPMC-film to the core tablet (Khan et al., 2001), because the interactions between film additives and tablet surface will become important only as the film coating liquid dries.

#### 2.1.5.4 Flow rate of coating solution

During a successful aqueous film coating process, the flow rate of the coating liquid is equal to the rate of water evaporation from the coated tablet's surface. Increasing the flow rate allows a greater number of droplets to be sprayed onto the tablet bed per time unit and increases the droplet size (Juslin et al., 1995). The flow rate is an important parameter since it impacts the moisture content of the formed coating and, subsequently, the quality and uniformity of the film (Franz and Doonan, 1983; Obara and McGinity, 1995; Porter et al., 1997). A low coating liquid flow rate causes incomplete coalescence of polymer due to insufficient wetting, which could result in brittle films (Obara and McGinity, 1995). A high coating liquid flow rate may result in overwetting of the tablet surface and subsequent problems such as picking and sticking (Franz and Doonan, 1983; Obara and McGinity, 1995). If the flow rate is high and the tablet surface temperature is

low, films are not formed during the spraying but the postdrying phase, and rapid drying often produces cracks in the films (Obara and McGinity, 1995).

#### 2.1.5.5 Pan air temperature

It is important that the pan air temperature is monitored, because the spray-tablet core interface is where problems manifest during aqueous film coating (Franz and Doonan, 1983). The spray rate of coating solution, inlet air flow rate and inlet air temperature have a significant effect on the tablet bed surface temperature, whereas spraying air pressure and pan speed do not (Franz and Doonan, 1983). During the coating process, the initiation of the spraying causes a rapid drop in the pan air temperature until an equilibrium is attained (Franz and Doonan, 1983; Okutgen et al., 1991b). The pan air temperature affects the drying efficiency (i.e. water evaporation) of the coating pan and the uniformity of coatings (Porter et al., 1997). High inlet air temperature increases the drying efficiency of the aqueous film coating process and a decrease in the water penetration into the tablet core decreases the core tablet porosity, tensile strength and residual moisture content of coated tablets (Pourkavoos and Peck, 1994; Porter et al., 1997). Excessive air temperature increases the premature drying of the spray during application and, subsequently, decreases the coating efficiency (Porter et al., 1997; Rege et al., 2002). Measuring the pan air temperature helps to control the optimum conditions during the coating process and, consequently, enables predicting possible drying or overwetting problems which may result in poor appearance of the film or may have detrimental effects on the moisture- and heat-sensitive tablet cores (Okutgen et al., 1991b).

#### 2.1.5.6 Rotating speed of the pan

It is well recognised that increasing the rotating speed of the pan improves the mixing of tablets (Kara et al., 1982; Porter and Saraceni, 1988; Porter et al., 1997; Rowe 1997; Tobiska and Kleinebudde, 2001; Rege et al., 2002). The pan speed affects the time the tablets spend on the spraying zone and, subsequently, the homogeneous distribution of the coating solution on the surface of each tablet throughout the batch. Increasing the pan speed decreases the thickness variation and improves the uniformity of coatings (Skultety et al., 1988; Porter et al., 1997; Wilson and Crossman 1997; Rowe, 1997; Rege et al., 2002). Too rapid a rotating speed of the pan will cause the tablet to undergo excessive attrition and breakage.

## 2.2 Adhesion of coating polymer

For aqueous film coating to be successful, the film must adhere satisfactorily to the tablet surface. When a polymeric solution is applied to a tablet surface, an internal stress inevitably develops within the film coating. The total internal stress (Eq. 1) within the film is influenced by (1) the effect of coating conditions on the shrinkage of the film due to evaporation of water, (2) differences in the thermal expansion of the film and the tablet core and (3) volumetric changes due to tablet core or polymer swelling during coating or storage and (4) the elasticity of the polymer (Okutgen et al., 1995; Felton and McGinity, 1999).

$$P = \frac{E}{3(1-v)}\left[\frac{\Phi s - \Phi r}{1-\Phi r} + \Delta\alpha_{(cubic)}\Delta T + \frac{\Delta V}{V}\right] \qquad (1)$$

Where $P$ is the total internal stress in the film, $E$ the elastic modulus of the film, $v$ the polymer's Poisson ratio, $\Phi s$ the volume fraction of the solvent at the solidification point of the film, $\Phi r$ the volume fraction of the solvent remaining in the dry film at ambient conditions, $\Delta\alpha_{(cubic)}$ the difference between the cubical coefficient of thermal expansion of the film coat and the substrate, $\Delta T$ the difference between the glass transition temperature of the polymer and the temperature of the film during manufacture and storage, $\Delta V$ the volumetric change of the tablet core and V the original volume of the tablet core.

Adhesion is influenced by the strength of interfacial bonds between the polymeric film and the surface of tablets and the internal stresses (Eq. 1) within the film coating (Felton and McGinity, 1999). Poor adhesion may result in peeling of the coating from the tablet surface, which could significantly reduce the film functionality. Loss of adhesion may compromise the mechanical protection that the film coating provides to the tablet and may lead to an accumulation of moisture at the film-tablet interface, affecting the stability of moisture-labile drugs (Okhamafe and York, 1985). Several researchers have investigated variables such as composition of the tablet core, compression force of the tablet i.e. surface roughness, coating formulation, coating conditions and ageing, which influence the adhesion (Nadkarni et al., 1975; Fisher and Rowe, 1976; Rowe, 1977, 1978b, 1983; Okhamafe and York, 1985; Okutgen et al., 1991a,1995; Lehtola et al., 1995a, 1995b; Felton and McGinity, 1996, 1997; Khan et al., 2001). In addition, dimensional changes in the tablet core will influence the internal

stresses (Eq. 1) within the film of the final coated tablets, and may ultimately affect polymer adhesion (Okutgen et al., 1991a, 1995). However, the significance of dimensional changes occurring in tablet cores after coating and its effects on film adhesion is not understood well enough.

## 2.3 Film coating morphology and defects

For aqueous film coating to be successful, the film must be smooth and uniform. When the main function of the film coating is to control the drug release from the tablet and to protect the drug from moisture ingress or light degradation, uniformity of the coating is of primary importance (Yang and Ghebre-Sellassie, 1990; Fourman et al., 1995; Sakellariou and Rowe, 1995; Porter et al., 1997; Mowery et al., 2002). In addition, the appearance of the coating is very important to the customers who usually identify and evaluate the tablet according to the coating quality.

The coating liquid application conditions, like atomization and drying, roughness of the core tablet and the properties of coating formulation can affect the coating morphology and surface roughness (Aulton and Twitchell, 1995). Smoother coatings could be produced by increasing the spraying air pressure, decreasing the spray rate of the coating solution, decreasing the distance of the spray gun from the tablet bed, or reducing the concentration of HPMC (i.e. viscosity) in the coating solution (Rowe 1978a; Porter et al., 1997; Obara and McGinity, 1995; Twitchell et al., 1995a). If coating spray droplets dry prematurely due to too effective drying conditions or excessive atomization, the droplets subsequently become too viscous to spread on the tablet surface and coalesce into a continuous film, resulting in a rough coating. If the drying is ineffective, the coalescence of coating polymers slows and could penetrate into the core, resulting in a rough coating.

Overwetting and water penetration into the tablet core during the coating could affect the water-soluble components of the tablet core migrating to the film coating (Okhamafe and York, 1989; Yang and Ghebre-Sellassie, 1990; Masilungan et al., 1991; Dansereau et al., 1993; Guo et al., 2002b, 2002c). The flow rate of the coating liquid and inlet air temperature (i.e. the rate of water evaporation) during the coating process affect the migration, whereas atomization air pressure does not (Yang and Ghebre-Sellassie, 1990; Dansereau et al., 1993). Therefore, by controlling the process conditions it is possible to control the core components' migration into the film coating. The migration of a tablet core component into the film coating could, for example, alter its adhesion

properties and seriously interfere with the film formation mechanism, making the film less continuous and porous and increasing the drug release rates of coated tablets (Okhamafe and York, 1989; Yang and Ghebre-Sellassie, 1990; Dansereau et al., 1993, Guo et al. 2002b). In addition, overwetting of the tablet bed during the coating process may cause picking and sticking of tablets, which greatly affects the surface morphology (Obara and McGinity, 1995).

High internal stresses (Eq.1) within the film coating may cause many coating defects such as cracking, peeling, bridging and edge chipping (Rowe, 1997). Shrinkage of the coating due to evaporation of water or different expansion characteristics of the core and the coating cause stresses in coatings and may result in cracking of coatings (Rowe, 1981; Okutgen et al., 1991a, 1991c, 1995). Also too rapid drying often produces cracks in the films (Obara and McGinity, 1995). In addition, excessive amount of pigment in coatings can promote crack initiation, which can lead to crack propagation (Rowe and Roberts, 1992a, 1992b; Rowe, 1997; Plumb et al., 2002). The addition of plasticizer, use of higher molecular weight polymer and larger particle size pigment were found to alleviate the problems of cracking. Edge chipping or erosion of tablets can be caused by excessive rotating speed of the pan, low tablet hardness, low spray rate of the coating solution and low mechanical strength of the coating (Porter, 1981, Porter and Saraceni, 1988). These defects can be avoided by reducing the internal stresses in coatings by decreasing the pan speed, improving the mechanical strength of the core by increasing the compression force, increasing the spray rate and polymer content of the coating liquid and improving the plasticizing characteristics of the coating liquid.

## 2.4 Moisture interaction with core tablet and coating during coating and storage

In aqueous film coating, tablet cores may greatly interact with moisture during the spraying and drying phase of the film coating process and subsequent storage (Fig. 4). Penetration of water into the outer layers of the tablet surface is inevitable. Although new approaches, such as the use of coating equipment with increased drying efficiency and optimized processes, have tended to increase the stability of sensitive tablet cores, answers to the question of moisture penetration from the applied coating solution into the tablet core remain speculative (Pourkavoos and Peck, 1993b). During coating, water penetration into the tablet core depends on a complex set of interacting factors related to the coating conditions, the formulation of the coating liquid (e.g. viscosity) and the tablet

core, including pore structure and surface roughness (Twitchell et al., 1995a). The effects of process parameters on the coating liquid penetration and drying on the tablet surface and, subsequently, the quality of the coated tablets are discussed in Section 2.1.5 Process parameters.

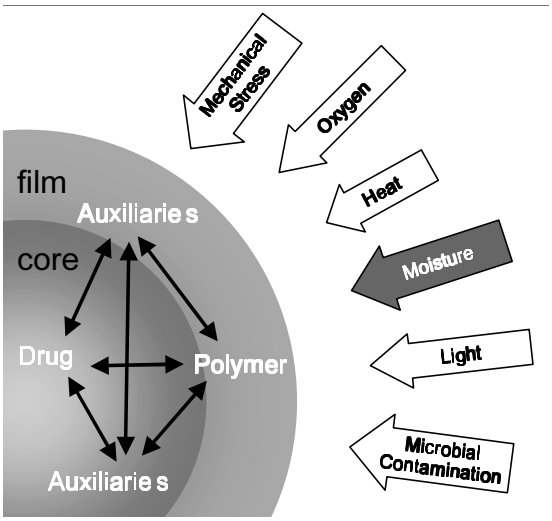



Figure 4. External and internal interactions of the film-coated tablet (modified from Petereit and Weisbrod, 1999).

### 2.4.1 Effect of moisture on the physical properties of tablets

In the aqueous film-coating process, tablets are exposed to wide temperature and humidity variations that may promote significant changes in the tablets. Water penetration into the tablet core is directly linked to the hydrophilic nature of excipients present in the tablet formulation (Ahlneck and Alderborn, 1988; Pourkavoos and Peck, 1993b; Faroongsarng and Peck, 1994; Dalton and Hancock, 1997). During aqueous film coating under normal coating conditions water penetrates from the film coating solution into tablets containing disintegrants and microcrystalline cellulose, and the penetration is not restricted to the tablet surface (Pourkavoos and Peck, 1993a). The penetration of water promotes the hydration of disintegrants, widening the pore structure of the coated core tablets and causing the tablets to swell and expand. The penetration of water during coating may result in significant changes in other physical properties of coated tablets, such as residual water content, glass transition temperature and tensile strength (Pourkavoos and Peck, 1993a, 1993b, 1994). Residual water has significant effects on a variety of physical and chemical properties, such as chemical stability of solids, crystal

structure, polymer film permeability and dissolution rate (Zografi, 1988; Ahlneck and Zografi, 1990; Angberg et al., 1991).

### 2.4.2 Effect of moisture on the chemical stability of a moisture-labile drug

Water in the tablet core increases the risk of undesirable degradation of a moisture-labile drug (Fig. 4). However, very little is known about the effects of the aqueous film coating process on the activity and stability of moisture-labile drugs. The degradation rate of acetylsalicylic acid (ASA) during storage at elevated conditions may be directly associated with the influence of formulation excipients due to their water adsorption characteristics (Mitrevej and Hollenbeck, 1983; Ahlneck and Alderborn, 1988; Patel et al., 1988). Hygroscopic excipients may also enhance drug stability by binding moisture, thus making the dosage form less susceptible to effects of moisture during manufacture or storage (Ahlneck and Alderborn, 1988; Heideman and Jarosz, 1991). The rate of ASA degradation is a slow process and accelerates with time (Snavely et al., 1993; Nagai et al., 1997). By controlling the coating conditions and selecting the excipient that is most resistant to moisture interaction it is possible to reduce the amount of adsorbed water and the degradation of a moisture-labile drug (Cunningham and Kinsey, 2001).

### 2.4.3 Effect of moisture on dimensional changes and coating structure

During a simulated coating process the nature of tablet excipients causes either contraction or expansion of the tablet (Okutgen et al., 1991a). Exposure to different temperatures and relative humidities were found to influence the magnitude and rate of these changes in tablets, due to water adsorption and evaporation (Okutgen et al., 1991a, 1991c). The most significant and important dimensional changes of tablets occur at the completion of the coating process and a few hours later (Okutgen et al., 1991a, 1991c). Dimensional changes occurring in tablet cores create high internal stresses (Eq. 1) within the film coat which consequently may cause major defects such as cracking or peeling of the film coat and may affect the film adhesion (Aulton et al., 1973; Rowe 1983; Okutgen et al., 1991a, 1991c; Pourkavoos and Peck, 1993b). However, there is insufficient understanding of the significance of tablet composition and compression force on the dimensional changes of coated tablets and their effect on film adhesion.

During storage at elevated humidity, adverse changes in the film structure have been reported to result from adsorbed water plasticizing the polymer and inducing increased polymer chain mobility, deformation, elasticity and flexibility (Okhamafe and York, 1986; Gutierrez-Rocca and McGinity, 1993; Felton et al., 1996). The swelling of

the film and tablet core, as water penetrates during storage, causes the formation of new stresses within the film coating and weakens the film-core interface and results in a decrease of adhesion (Okhamafe and York, 1985; Felton and McGinity, 1997, 1999). The strength of the coated tablet decreases due to adsorbed moisture from the environment (Riepma et al., 1992; Felton and McGinity, 1997).

## 2.5 Characterization of coated tablets

### 2.5.1 Surface roughness and morphology

The roughness of tablet surface has been traditionally determined using a contacting stylus instrument that scans a line from which the roughness parameters are calculated (Nadgarni et al., 1975; Rowe 1978a, 1978b). In a previous study, a light-section microscope was used to measure the roughness of coated tablets without contacting them and calculating the roughness parameters (Twitchell et al.,1995b). Non-contacting laser profilometry has been previously used to provide very accurate determination of the roughness parameters of tablets (Healy et al., 1995; Riippi et al., 1998). In this method, a line or an area of the tablet surface is evaluated to obtain a three-dimensional surface profile. During measurement the surface remains undamaged because the technique is non-contacting and repeat measurements can be made on the same surface.

The surface roughness measurements of coated tablets are of great importance in the development of an optimal coating. The roughness parameters enable comparison of numerical values of the tablet surface (Fig. 5) which are relevant and valuable for tablet surface texture and structure characterization. The roughness parameters are well standardized and they have been used for a long time (Cielo, 1987; Healy et al., 1995; Riippi et al., 1998). The most widely used parameter of surface roughness is the arithmetic average of the absolute values of all points of the profile (Ra):

$$R_a \approx \frac{1}{n}\sum_{i=1}^{n} |y_i| \qquad (2)$$

Where $R_a$ is the roughness average, $n$ the number of measurement points and $y_i$ the $i^{th}$ point.

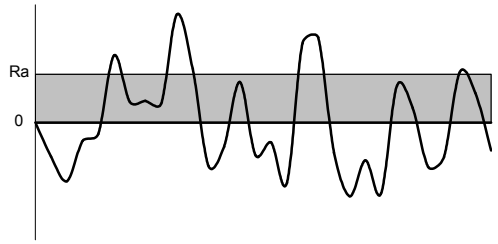



Figure 5. Roughness parameter, Ra, calculated from the tablet surface profile line.

The other surface roughness parameters used are the root mean square of all values of all points of the profile (Rq), the maximum distance between the highest point and the mean line of the profile (Rp), the maximum distance between the highest and the lowest mean line of the profile (Rt) and the arithmetic average of the five highest profile points and five lowest profile valleys (Rz).

Scanning electron microscopy (SEM) is a commonly used technique to examine the surface morphology of tablets and to visually support other qualitative and quantitative results (Porter and Saraceni, 1988; Poukavoos and Peck, 1993b; Lehtola et al., 1995b; Felton and McGinity 1996, 1997; Riippi et al., 1998; Guo et al., 1999). Atomic force microscopy (AFM) is used to observe the surface topography and morphology of coating dispersions, and to measure film roughness, polymer particle deformation and the degree of coating flattening during film formation (Lin and Meier, 1995; Gilicinski and Hegedus, 1996; Pérez and Lang, 1999; Tang et al., 2001). Also environmental SEM (ESEM) (Keddie et al., 1995; Royall and Donald, 2001), cryogenic scanning electron microscopy (Cryo-SEM) (Sutanto et al., 2001) and small-angle neutron scattering (SANS) (Eu and Ullman, 1996; Yoo et al., 1990) have been used to study the polymer particle deformation mechanisms during film formation.

### 2.5.2 Film-core interactions

Coating liquid and core tablet interactions, such as droplet spreading, wetting and penetration tendencies, are commonly characterized by contact angles (Nadkarni et al., 1975; Lehtola and Yliruusi, 1994; Lehtola et al., 1995b; Twitchell et al., 1995a; Felton and McGinity 1996, 1997). The contact angle is the angle of a tangent drawn along the edge of the drop from the point where solid, liquid and vapour contact. These tests provide fundamental information about film-core interactions (processing conditions aside), but do not reflect what may occur in practice when droplets of coating

formulation impinge on a surface during the coating process (Twitchell et al., 1995a; Khan et al., 2001). Therefore it would be important to clarify the behaviour of the coating liquid at the film-core interface during coating and find techniques for acquiring exact information of coating liquid penetration into the tablet core.

Confocal laser scanning microscopy (CLSM) has been previously used to investigate the deformation of particles during compression (Guo et al., 1999), the drug permeability and release mechanisms within controlled-release and enteric-coated pellets (Cutts et al., 1996; Guo et al., 2002a) and the diffusion of water-soluble drug from the pellet cores into the film layer (Guo et al., 2002b). CLSM is a non-invasive technique producing high-resolution 2-D images, but also 3-D visualization of the surface or internal structure of the samples.

### 2.5.3 Dimensional changes

In earlier studies, dimensional changes of tablets were measured by a free-armature transducer rig, with the tablet placed underneath the rig (Okutgen et al., 1991a, 1991c). This method measures by contact and there is a risk that the surface of the tablet is damaged during the determination. As previously mentioned (2.5.1. Surface roughness and morphology), a non-contacting laser profilometer has been used for the surface roughness study of tablets, leaving the samples undamaged.

### 2.5.4 Adhesion

Adhesion measurements are useful during preformulation studies of film-coated tablets, as they provide information on the relationship of the polymeric coating formulation and composition of the tablet core to the strength of the film-core interfacial bond. Adhesion could be measured by several adhesion testing methods, for example, with tensile strength testers (Fisher and Rove, 1976; Okhamafe and York, 1985), with a Lloyd LRX materials testing machine (Lehtola et al., 1995a, 1995b) and with a Chatillon digital force gauge (Felton and McGinity, 1996, 1997). This method determines the force required to remove the entire film from the surface of the tablet.

# 3 AIMS OF THE STUDY

The main aim of the present study was to gain understanding about the factors affecting the aqueous film coating of tablets performed in a side-vented pan coater. Hydroxypropyl methylcellulose (HPMC) was used as a film-forming agent.

The specific aims were:

- to utilize and test a novel instrumentation and automation system for a side-vented pan coater of tablets

-to investigate the effects of film coating process conditions on the surface morphology and moisture content of film coated tablets

- to study the effects of the film-coating process and storage on the stability of tablets containing a moisture-labile drug

- to examine confocal laser scanning microscopy (CLSM) as a novel technique for imaging the film-core interface and the morphology of coated tablets

- to investigate the time-dependent dimensional changes of coated tablets and the relevance of these changes to film adhesion

# 4 EXPERIMENTAL

## 4.1 Materials

### 4.1.1 Tablet cores

For preparing tablet cores, caffeine (Ph.Eur) (I), ibuprofen (Ph.Eur) (II), acetylsalisylic acid (ASA) (Ph.Eur) (III, IV) and ibuprofen 50 (Boots Co. Ltd., UK) (V) were used as model drugs. Lactose monohydrate (Lactose NF Tablettose, Meggle, Germany) (I, II), (Pharmatose 80, DMV International, the Netherlands) (III-V), microcrystalline cellulose (MCC, Emcocel 90M, Edward Mendell, USA) (I, II), (Avicel PH-102, FMC International, Ireland) (III, IV) and pregelatinized starch (Starch 1500, Colorcon, UK) (V) were used as fillers. Magnesium stearate (Ph.Eur) (I-IV) and talc (Ph.Eur) (III, IV) were used as lubricants. Purified water (Ph.Eur) and ethanol (Ph.Eur) were used as granulation liquid (V).

### 4.1.2 Coating solution

The coating solution was prepared from Opadry OY-GM-22902 (Colorcon, UK) dry power (I, II) or HPMC (Hypromelloc E5, Dow Chemical, USA) (III-V). Opadry consists of HPMC, polyethylene glycol (PEG), polydextrose, titanium dioxide and riboflavin. Purified water (Ph.Eur) was used as the coating liquid (I-V). Glycerol (Fluka Chemie AG, Switzerland) (III, IV) and polyethylene glycol (Polyethylene glycol 400, Fluka Chemic AG, Switzerland) (V) were used as plasticizers. Glycerol was used in the coating solution if the core tablet included ASA because PEG is incompatible with ASA. Riboflavin sodium phosphate (Ph.Eur) was used as the color and autofluorescent agent (III, IV).

## 4.2 Preparation of film-coated tablets

### 4.2.1 Preparation of tablet cores

The compositions of core tablets used in the coating experiments are presented in the original papers (I-V). The tablets were compressed with a rotating tablet machine (Kilian & Co., GmbH, Germany) (I, II) or with an eccentric tablet machine (Korsch EK-0, Erweka Apparatebau, Germany) (III, IV). The tablets were compressed to a constant breaking strength of 60 N (I, III, IV) and 95-100 N (II) using 11-mm biconvex punches. The average weight of the tablets was 500 mg.

The granules were produced in an oscillating sieve (1000 µm) granulating machine (Erweka GmbH, Germany) (V). The tablets weighing 300 mg each were compressed to the breaking strengths of 25 N, 45 N and 65 N (S.D. ± 2 N) with an instrumented eccentric tablet machine (Korsch EK-0, Erweka Apparatebau, Germany) using 9-mm flat-faced punches (V). The tablets were stored after compression in controlled conditions (22°C/50% RH) for at least five days (I-V).

To compare the expansion (i.e. water penetration) of microcrystalline cellulose (MCC) and direct-compression powder mixture (PM), containing ASA, lactose monohydrate, MCC, talc and magnesium stearate, two types of tablet cores were prepared for surface profile examination (Fig. 6, IV). The inner part of tablet A consisted of PM and the outer part of MCC. In tablet B, the order of the masses was reversed. The inner compact was loosely compressed to a constant breaking strength of 20 N using 5-mm flat-faced punches. The inner compact was placed in the middle of the lower part of a 13-mm flat-faced punch and the tablet mold was manually filled with the outer mass. The tablet was compressed to a constant breaking strength of 60 N. After compression the tablets were stored for four days at two different relative humidity conditions of 22°C/50% RH and 22°C/95% RH to examine the water penetration into different parts of the tablet.

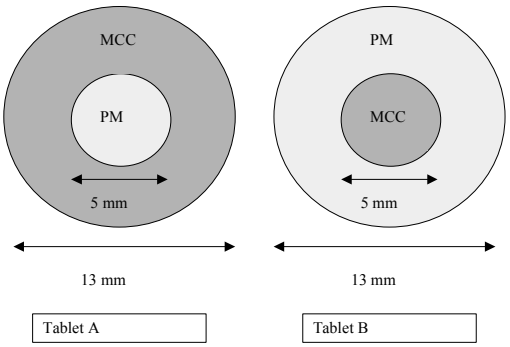



Figure 6. Schematic diagram of the experimental tablet preparations used in the surface profile examination. The inner part of tablet A consists of the basic direct compression powder mixture (PM) and the outer part microcrystalline cellulose (MCC). In tablet B, the order of the masses was reversed.

### 4.2.2 Film coating of tablets

The tablets were film-coated using a pilot-scale side-vented, perforated pan coating apparatus (Thai Coater, Model 15, Pharmaceuticals and Medical Supply Ltd. Partnership, Bangkok, Thailand) (I) which was instrumented and automated (II-V). The architecture of the present pan coater automation system was based on a previous automated system (Rantanen et al. 2000) (II). Process parameters describing the state of the coating process were measured and monitored, and the information was logged. The flow rate and temperature of the process air were PID (Proportional-Integral-Derivative) controlled. InTouch version 7.0, part of FactorySuite 2000 (Wonderware Corporation, Irvine, CA, USA), was used as the user interface for controlling the process parameters.

The process parameters studied and the user-controllable constant setting ranges are presented in Table 1. The 5 g/m$^3$ and 12 g/m$^3$ absolute humidities of inlet air are representative of low (winter) and high (summer) humidity conditions in Northern Europe. Each coating batch comprised 2.5 kg (I) or 1.0 kg (II-V) of tablets. The amount of coating solution applied was 300 g (I-IV) or 340 g (V). The tablets were preheated for 5 min (I-IV) or 10 min (V), and dried for 15 min (I) or 5 min (II-V) after spraying. After film coating, the tablets were stored in closed glass bottles at controlled conditions of 25°C/60% RH or 40°C/75% RH for three months (III, IV).

Table 1. User-controllable process parameter ranges in the original papers (I - V).

| Process parameter | I | II | III | IV | V |
|---|---|---|---|---|---|
| Pan air temperature (°C) | - | 40 | 35 - 55 | 40 | 40 |
| Inlet air temperature (°C) | 55, 75 | - | - | - | - |
| Spraying air pressure (kPa) | 150, 350 | 300 | 100 - 500 | 100, 500 | 300 |
| Flow rate of coating solution (g/min) | 2.4 - 8.5 | 4.6 | 2.2 - 7.8 | 5.7 | 3.5 |
| Outlet air flow rate (l/s) | - | 12 - 24 | 18 | 18 | 18 |
| Rotating speed of pan (rpm) | 4 - 11 | 7 | 7 | 7 | 7 |
| Absolute humidity of inlet air (g/m$^3$) | - | - | 5, 12 | 12 | - |
| Pan air pressure (Pa) | - | -5 | -5 | -5 | -5 |

The coating solution was prepared by dissolving film former in purified water at 20ºC using magnetic mixing. Opadry 10% w/w (I, II), HPMC 8% w/w (III, IV) and HPMC 10% w/w (V) coating liquids were prepared. Plasticizer 20% w/w of polymer weight (III-V) and riboflavin sodium phosphate 0.5% of solution weight (III, IV) were added after the polymer had dissolved. Riboflavin sodium phosphate is an autofluorescent agent which was included in the coating solution (i.e. fluorescent coating) to provide good contrast against the non-fluorescent core material when studied with confocal laser scanning microscopy (IV). The coating solution was kept in a refrigerator (+8ºC) overnight and used the next day for preparation.

## 4.3 Evaluation of film-coated tablets

### 4.3.1 Surface morphology and film-core interface

#### 4.3.1.1 Laser profilometry (II-IV)

The surface roughness of tablets was measured using a non-contacting laser profilometer (UBM Microfocus Measurement System, UBM Messtechnik GmbH, Ettlingen, Germany) similar to that described by Healy et al. (1995) and Riippi et al. (1998). An area of 3 x 3 mm was scanned from the surface of ten (II) or three (III, IV) randomly sampled film-coated tablets. The roughness parameters were calculated from data measured with 125 pixels/mm x-y resolution and 0.1 μm z resolution. The surface profiles of the two tablet core types (MCC and PM) were measured by scanning an area of 8 x 8 mm (IV). The roughness parameters were calculated from data measured with 50 pixels/mm x-y resolution and 0.1 μm z resolution. The frequency of all measurements was 120 pixels/s.

The roughness parameters calculated were the arithmetic average of the absolute values of all points of the profile (Ra) and the maximum distance between the highest point and the mean line of the profile (Rp). The image data was transferred to Mathematica software (Wolfram Research Inc., USA) which was used to draw 2-D surface plots.

#### 4.3.1.2 Optical roughness analysis (IV)

The tablet surface roughness was measured also using an optical instrument, introduced by Krogars et al. (2002). A scheme of the imaging system used is presented by Laitinen et al. (2002). The following setup was used: light source power supply voltage 5 V, distance of the light sources to the sample 10 cm, illumination angle 58° and a dimmer

set to 8 and a 50-mm lens objective with a 40-mm extension tube (focal length 1.3). Ten images of a surface area of 6.2 x 4.7 mm of three randomly sampled tablets were taken with a resolution of 600 x 800 pixels. The roughness was determined from parallel profile line measurements using Mathcad 2001 Professional software (MathSoft Inc., USA). Roughness is the arithmetic average of the absolute values of all points (pixels) of the profile.

#### 4.3.1.3 Confocal laser scanning microscopy (IV)

The surface morphology and film-core interface of the film-coated tablets were examined using confocal laser scanning microscopy (CLSM). Observations were made with a Bio-Rad Lasersharp MRC-1024 (Bio-Rad, UK) attached to a microscope (Axiovert 135M, Zeiss, Germany) using a Zeiss Plan-Neofluar 10x/0.30 NA air lens. A 488-nm line of a krypton-argon laser and a laser power of 0.15 mW were used. The iris, black, gain control and all other settings were kept constant during all experiments. Kalman for N=6 frames per Z level was set prior to initiation of the Z series. Images were recorded at intervals of 5 µm in the Z direction. The confocal aperture setting was 1.1 mm. The figures were maximum projection.

The images were measured by comparing the fluorescence intensity of riboflavin sodium phosphate in the coating with that of the core tablet (non-fluorescent area). Each stack of pictures was evaluated using an image analysis system (ImageSpace, Molecular Dynamics, Inc., USA.). The confocal image area was 7578 µm x 7578 µm. The 3-D plots were calculated based on quantified riboflavin intensity values and they represent the same surface areas as the corresponding confocal images.

#### 4.3.1.4 Optical and electron microscopy (I, II, IV, V)

The physical appearance (film quality) was characterized with a microscopy image analyzer (Leica MZ 6, Leica Imaging Ltd, Germany) (II) and by stereomicroscopic inspection with Nikon SMZ-10 (Nikon, Japan) (I). The surface morphology, film adhesion and dimensional changes of the coated tablets were studied by scanning electron microscopy (SEM) (JEOL JSM-820, Japanese Electron Optical Ltd., Japan) (I), (Zeiss DSM-962, Carl Zeiss, Germany) (IV, V).

### 4.3.2 Moisture content (I, III)

The weight increase of 20 tablets was determined by weighing the tablets before and after the coating (I, III). Tablet weight increase is caused by both the residual water and

applied polymer and therefore also process data on water evaporation (difference between absolute humidity of outlet and inlet air) was used to determine the moisture content of coated tablets (III). The moisture content of three coated tablets was determined with a moisture analyzer by measuring the loss of weight (Sartorius Thermo Control, Sartorius GmbH, Germany) (I). The three crushed coated tablets were heated up to 100ºC during 10 minutes.

### 4.3.3 Hydrolysis of moisture-labile drug (III)

ASA hydrolyses into salicylic acid (FSA), which was quantified by using a UV spectrophotometer (Ultrospec III, UK) at a wavelength of 540 nm. The coated tablet was crushed and dissolved in purified water (Ph.Eur). The colour reagent was ferrichloridum solution ($FeCl_3$, 0,1M $HNO_3$). The remaining amount of ASA in the tablet was calculated from the measured amount of FSA in the tablet. Random sample of six coated tablets from each batch were analyzed.

### 4.3.4 Dimensional changes (V)

The time-dependent dimensional changes of film-coated tablets were determined with a non-contact laser profilometer (UBM Microfocus Measurement System, UBM Mebtechnik GmbH, Ettlingen, Germany). A random sample of six tablets from each batch was mounted under the laser profilometer in a mould holding the tablets immobile during the measurements. A line of 7.0 mm (x traverse) was scanned from the centre of the top surface of the tablet. The profile line scanning was performed with 1000 pixels/mm x resolution, the z resolution was 0.1 µm and the measurement frequency was 120 pixels/s. The surface profile line measurement of core tablets and film-coated tablets was performed in two phases during 24 hours. The first measurements of the core tablets started five days after the tablets had been compressed and stored in closed glass containers in controlled conditions (22°C/50% RH) and continued for six hours. The first measurements of coated tablets started immediately after the coating process and continued for six hours. The second measurements of the cores of 45 N breaking strength and coated tablets were made at 22, 23 and 24 hours after the beginning of the measurements. The profile lines of the tablet surface were measured from exactly the same location. The ambient conditions were controlled (22°C/50% RH). The method used to calculate the dimensional changes of the tablet with profile line measurements at different points of time was demonstrated in the original Paper V (Figs. 1 and 2).

### 4.3.5 Adhesion and mechanical strength (I, II, V)

A Lloyd LRX materials testing machine (Lloyd Ltd., England) was used to measure the adhesion strength between the film coat and the tablet surface (V). Adhesive tape was attached around the sides of the tablet cores before coating to prevent film formation on the sides. After coating the tape was carefully removed. The tablet was mounted onto the lower grip of the materials testing machine with a piece of double-sided adhesive tape. A fixed force of 3.0 N was applied to obtain a firm contact between the upper grip with a piece of adhesive tape and the tablet coat. The film was removed from the tablet surface by lifting the upper grip. Measurements were performed using a 50-N load cell and a cross-head speed of 7.5 cm/min and repeated six times.

The breaking strength of ten tablets was measured with a Schleuniger-2E tester (Schleuniger GmbH, Germany) (I) and 20 tablets with an Erweka Multicheck tester (Erweka Multicheck, GWB, Germany) (II).

# 5 RESULTS AND DISCUSSION

## 5.1 Development of an automation and measuring system for a tablet coater

An instrumentation and automation system for a side-vented pan coater with a novel air flow rate measurement system covered 13 different coating-process parameters that were continuously measured, monitored and controlled (Fig. 7; II). The process information was logged and the most significant parameters were analysed using common statistical software. The process air flow was measured from the off-line calibrated flow tubes. Accurate control of process air is a requirement for reproducible coating conditions.

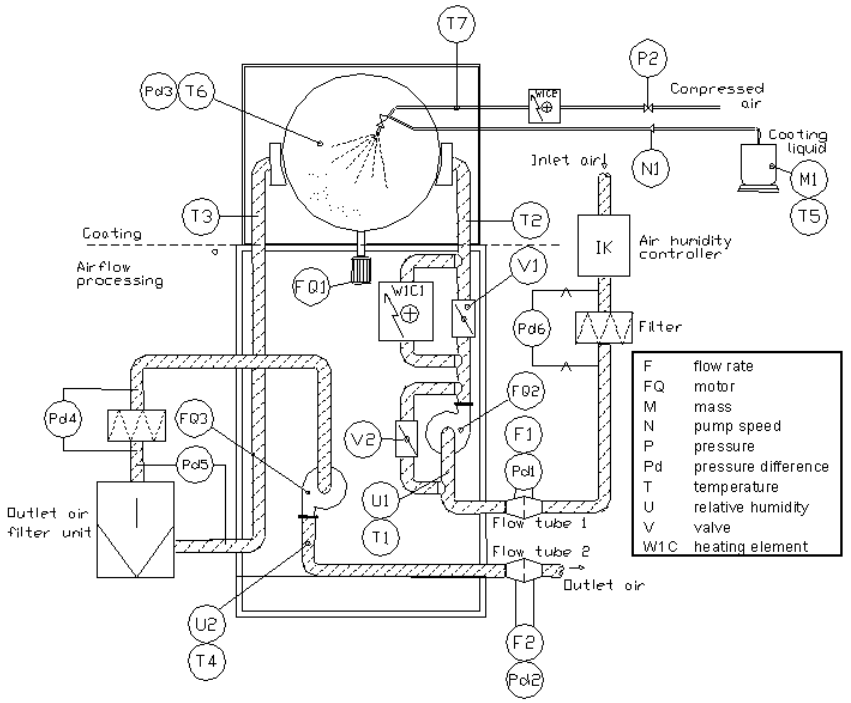



Figure 7. Instrumentation of the tablet pan coater.

The instrumentation and automation system provided comprehensive and quantitative process information on the behaviour of the most important parameters during each coating experiment (II). The process information proved that the coating process is reproducible and that the air flow rate measurement system operated reliably

(II, Figs. 3-9; III, Fig. 1). In addition, the variation of the evaluated tablet responses after the repeat coating experiments was negligible and demonstrated the homogeneity and reproducibility of the coating process (II, Table 3).

A fully automated system and historical data storage of critical process parameters provides an excellent tool for controlling, analyzing and characterizing the film coating process. Process automation and monitoring of critical process parameters can be used to increase overall process efficiency and predictability, and to improve the reproducibility of the coated tablet batches.

## 5.2 Effect of coating process on the properties of film coated tablets

### 5.2.1 Surface morphology and film-core interface

#### 5.2.1.1 Air flow rate (II)

The inlet flow rate of process air (F1) influenced the coating process and the subsequent quality of the coated tablets (II). An increase in F1 increased the amount of heat in the incoming process air, and because the tablet bed temperature (T6) was set as constant, the heat increase was compensated by decreasing the temperature of inlet air (T2), as shown by the process information (II, Figs. 7-9). In addition, an increase in F1 decreased the outlet air absolute humidity due to an increased amount of air molecules in proportion to water molecules (II, Figs. 7-9). Increasing the F1 clearly increased the drying efficiency of the coating pan and accelerated the drying of the tablet surface. This result is in agreement with Franz and Doonan (1983) who reported that the increase of inlet air flow rate causes a linear increase in the tablet bed temperature.

At maximum F1 level (16 l/s) the surface of coated tablets was rough and uneven, the roughness between tablets varied greatly and the film quality was considered unacceptable (II, Fig.10B, Table 5). At high F1 the coating solution dries so rapidly that the polymer does not coalesce properly and the film deforms. In addition, too rapid drying of the coating solution spray may make the droplets too viscous to spread evenly over the tablet surface. At minimum (6 l/s) and medium (10 l/s) F1 levels the surface roughness was small, the batches were homogeneous and the film quality was satisfactory (II, Fig. 10A, Table 5). Earlier studies on the effect of air flow are not fully consistent, as air flow has been reported to affect the quality of the coated tablets (Cole et al., 1983; Yoakam and Campbell, 1984), but Rege et al. (2002) did not find the inlet air flow to affect the content uniformity of the coating composition or coating efficiency.

A reliable air flow rate measurement system enables more conclusive determination of the optimal air flow rate with regard to film drying and quality.

#### 5.2.1.2 Absolute humidity of air (II, III)

Coating performed with the higher (12 g/m³) inlet air absolute humidity (AH1) resulted in a clearly rougher and more unhomogeneous coating surface than with lower (5 g/m³) AH1 (III, Figs. 2 and 3, Table 2). The process information provided evidence that higher AH1 decreased the magnitude of drying (i.e. water evaporation) from the tablet surface (III, Fig. 1 A and B), which probably slowed the coalescence of the coating polymer and subsequently increased the surface roughness. The changes in AH1 not only alter the temperature of the spray but also influence the amount of water evaporated before the spray reaches the tablet bed. Pourkavoos and Peck (1994) reported that the water removal efficiency (evaporation of water) of the coating process linearly correlates with the residual moisture content, tensile strength and core porosity of coated tablets.

Water evaporation from the tablet surface during coating must be adequate to ensure high-quality coatings. Absolute humidity of the outlet process air (AH2) was a more reliable indicator of water evaporation during the coating process and an indicator of drying end point (II, Fig. 5) than relative humidity (U2) (II, Fig. 6). The absolute humidity of the outlet and inlet air at the drying phase of coating was used as an indicator of the drying end point. The drying end point occurred where the steepest decrease of AH2 in the drying phase ended and reached the same value as in the preheating phase. It is more difficult to determine the drying end point from U2 which does not provide a reference point for the level that drying should reach.

#### 5.2.1.3 Spraying air pressure (III, IV)

The effects of the spraying air pressure on the film surface are illustrated in CLSM images (Fig. 8). With the lower spraying air pressure (100 kPa), clear film defects and roughness were observed compared to the higher spraying air pressure (Fig. 8; III, Table 2; IV, Tables 1 and 2). The CLSM images show relatively large gaps (i.e. non-fluorescent areas) on the coating surface (Fig. 8A). Some component(s) from the core, probably the water-soluble lactose, migrated into the coating during the coating process (Fig. 8). With the lower spraying air pressure, larger droplets were formed, allowing water to penetrate into the tablet core, and increased the migration of the component into the coating. The low spraying air pressure decreased the magnitude of drying (i.e. evaporation of water) (III, Fig. 1B), prolonging the drying of the coating solution and

increasing the surface roughness. It has been reported earlier that coating conditions can affect water penetration into the substrate (i.e. the rate of water evaporation) during the coating process and, subsequently, the migration of water-soluble components of the tablet core into the film coating (Yang and Ghebre-Sellassie, 1990; Danserau et al, 1993). If the component of the core migrates into the film layer during the early stages of the coating process, it could lead to unhomogeneous film formation (Yang and Ghebre-Sellassie, 1990).

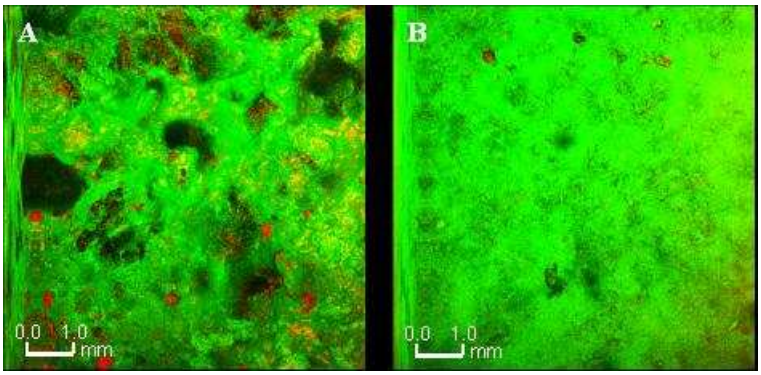



Figure 8. Confocal images of the HPMC film coating immediately after coating. The coatings were applied with spraying air pressures of 100 kPa (A) and 500 kPa (B). The coating appears green (fluorescent material) and red indicates components migrated from the tablet core (reflective material).

The 3-D plots (Fig. 9) illustrate the film-core interface and represent the same surface areas as the corresponding confocal images (Fig. 8). With the lower spraying air pressure (100 kPa) the applied film coating solution was unevenly distributed and the thickness varied in different parts of the film (Fig. 9 A1). The aqueous coating solution penetrated significantly into the inner regions of the tablet core and formed “valleys” on the core surface (Fig. 9 A2). Variation in film thickness, due to coating solution penetration and surface roughness, may be important when the properties of the film coat are dependent on the thinnest part of the coating, especially in case of modified drug release coatings (Yang and Ghebre-Sellassie, 1990; Fourman et al., 1995; Sakellariou, and Rowe, 1995; Twitchell et al., 1995a; Porter et al., 1997; Mowery et al., 2002).

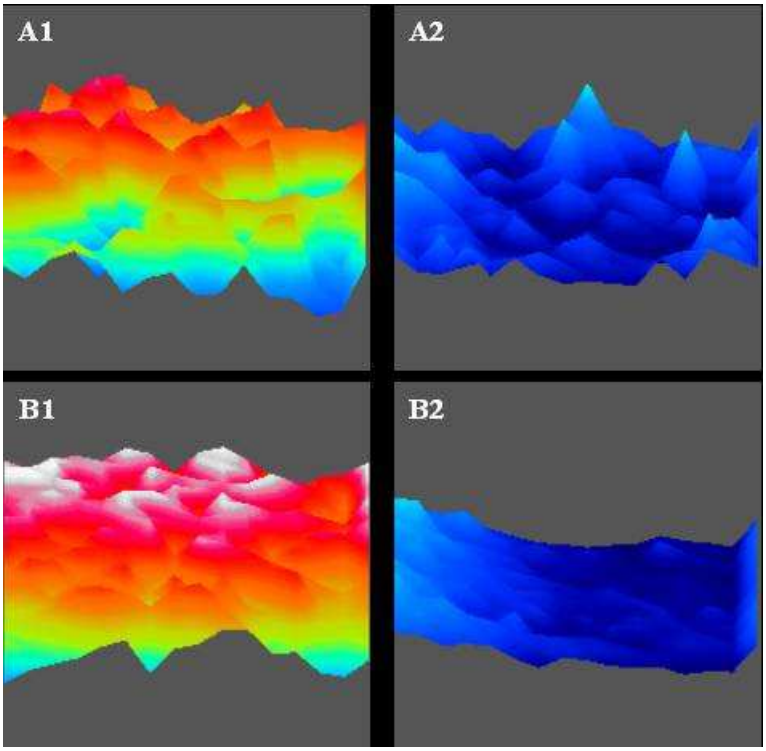



Figure 9. 3-D plots of the HPMC film coating (1) and tablet core (2) immediately after coating. The coatings were applied with spraying air pressures of 100 kPa (A) and 500 kPa (B). The red colour indicates the topmost coating layer, green the coating layer near the tablet core and blue the non-fluorescent tablet core.

With the 500 kPa spraying air pressure, the coating surface was significantly ($p < 0.05$) more uniform and smooth compared to the lower spraying air pressure (Fig. 8; III, Table 2; IV, Tables 1 and 2). The migration of the core component into the coating was minimal (Fig. 8B). The film coating solution was homogeneously distributed onto the tablet core (Fig. 9 B1). The solution did not penetrate perceivably into the core, as evidenced by the even surface of the core (Fig. 9 B2). With the higher spraying air pressure, fine droplets were formed, thus improving the spreading and water evaporation of the film (III, Fig. 1B), which reduced the degree of solution penetration into the tablet core and produced smoother and denser films. These results are in agreement with Twitchell et al. (1995a, 1995b) who reported that when the atomizing air pressure increases, the surface roughness of the coated tablets decreases.

CLSM is a suitable method for studying the film-core interface and surface defects, as it can visualize simultaneously both fluorescent (in this case coating) and reflective (non-fluorescent) materials (in this case core material particles migrated into the coating). The results obtained by CLSM and the other two surface roughness measuring techniques, laser profilometry and optical roughness analysis, were comparable (Figs. 8 and 9; IV, Tables 1 and 2). The images produced by the CLSM method are supported by the results of the numerical roughness measurements.

#### 5.2.1.4 Flow rate of coating solution (I, III)

The appearance of the film coating clearly improved with reduction in the coating solution flow rate (I, III). With the lower flow rate (2.2 g/min) of coating solution, the coated tablet surface was particularly smooth (III, Table 2). With the higher flow rate (7.8 g/min), the moisture in the tablet surface increased compared to the lower spraying rates, because the proportional magnitude of drying was smaller (III). The drying of the coating solution was prolonged and, subsequently, the surface was significantly ($p < 0.05$) rougher compared to the lower spray rate (III, Table 2). The results are consistent with Franz and Doonan (1983) and Obara and McGinity (1995) who reported that a high spraying rate of coating solution could cause overwetting of the tablet surface and an uneven film to form during the drying phase. Increasing the flow rate increases the droplet size (Juslin et al., 1995), prolonging the spreading and drying of the coating solution and increasing the surface roughness.

#### 5.2.1.5 Pan air temperature (III)

With the lower pan air temperature (35$^{o}$C), the surface of the coated tablets was rougher compared to those coated with the higher (55$^{o}$C) pan air temperature (III, Figs. 2 and 3, Table 2). The process information proved that the higher pan air temperature increased the degree of drying (III, Fig. 1C) and coalesced the coating polymer into a homogeneous film. These findings support previous studies that have stated more generally that inlet air temperature affects the uniformity of coatings (Pourkavoos and Peck, 1994; Porter et al., 1997; Rege et al., 2002).

#### 5.2.1.6 Rotating speed of the pan (I)

By increasing the rotating speed of the pan the appearance of the film coatings clearly improved (I). The rotating speed between 8.5 and 10.0 rpm gave a satisfactory film appearance, except at low flow rate of coating solution (I, Figs. 1 and 2). Increasing the rotating speed of the pan improves the mixing of the tablets and distribution of the

coating solution onto the tablet bed. This results in reduced thickness variation and improves the uniformity of the coating (Skultety et al., 1988; Porter et al., 1997; Wilson and Crossman, 1997; Rowe, 1997; Tobiska and Kleinebudde, 2001; Rege et al., 2002).

### 5.2.2 Mechanical properties and moisture content

Tablets coated with the higher inlet air absolute humidity (AH1) were heavier than those coated with the lower AH1 (III, Table 3). The higher AH1 also decreased the drying from the tablet surface (III, Fig. 1A and B). Decreased drying with the higher AH1 means that a relatively higher proportion of the tablet's weight increase must be due to penetrated water, i.e. high AH1 increases the moisture content of tablets. In general, the drying efficiency of the coating process is linearly correlated with tablet residual moisture (Poukavoos and Peck, 1994).

The increase in inlet air temperature significantly decreased the moisture content ($p < 0.01$) and weight increase ($p < 0.05$) of coated tablets, but its effect on the breaking strength was negligible (I). With the lower pan air temperature the degree of drying decreased (III, Fig. 1C), indicating high degree of water penetration into the tablet core. High inlet air temperature has been reported to decrease the porosity of coated core tablets, tensile strength and residual moisture content of coated tablets (Pourkavoos and Peck, 1994). High inlet air temperature prevents the overwetting problem that may have a detrimental effect on the moisture-sensitive tablet cores (Okutgen et al., 1991b).

The spraying air pressure (150 - 350 kPa) did not affect the moisture content, weight increase or breaking strength of coated tablets (I). This was contrary to expectations, as the coating solution was unevenly distributed with low (100 kPa) spraying air pressure, as evidenced by relatively large gaps on the coating surface, and the coating solution had obviously penetrated into the tablet core more than with the high (500 kPa) spraying air pressure (III, IV). The more narrow spraying air pressure range used and not instrumented coating pan (I) may explain the lack of efficacy of air pressure on the measured responses. Earlier studies indicate that by increasing the spraying air pressure the degree of solution penetration into the substrate could be reduced, producing denser and thinner films (Twitchell et al., 1995a; Khan et al., 2001).

The flow rate of the coating solution did not significantly affect the moisture content of the coated tablets, but it appeared to have a positive influence on the breaking strength (I). However, with the higher coating solution flow rate, the moisture of the tablet surface increased compared to the lower spraying rates (III). A high coating liquid

flow rate may result in overwetting of the tablet surface (Franz and Doonan, 1983; Obara and McGinity, 1995). A low coating liquid flow rate could decrease the breaking strength by causing internal stresses during polymer coalescence due to insufficient wetting. It has been reported earlier that a low flow rate of coating solution could result in brittle films (Obara and McGinity, 1995).

Rotating speed of the pan decreased the moisture content ($p < 0.10$), weight increase ($p < 0.05$) and breaking strength ($p < 0.05$) of the coated tablets (I). Increasing the rotating speed improves the distribution of the coating solution. According to some earlier reports, a higher rotating speed of the pan resulted in low thickness variation and improved the uniformity of the coatings (Skultety et al., 1988; Porter et al., 1997; Wilson and Crossman, 1997; Rowe, 1997; Rege et al., 2002).

## 5.3 Effect of short-term storage on the properties of film-coated tablets

### 5.3.1 Surface morphology (III, IV)

The surface roughness of coated tablets clearly increased and the internal structure of the film coating deteriorated after storage for three months at 25°C/60% RH and especially at 40°C/75% RH (III, Figs. 2 and 3, Table 2; IV, Figs. 2-5, Tables 1 and 2). The coating sprayed with the higher (500 kPa) air pressure remained clearly more homogeneous and smooth than the coating sprayed with the lower air pressure (IV, Fig. 5, Tables 1 and 2). The impaired film structure and increased surface roughness of the coated tablets were mainly caused by the expansion of the tablet core due to MCC hydration during storage (IV). This was evidenced by the fact that the presence of MCC in the outer or inner part of the tablet led to tablet surface profile expansion (i.e. water penetration) of these regions already at 50% RH (IV, Fig. 6) and the surface roughness of the core tablets clearly increased during storage (IV, Table 1). It has been shown earlier that MCC absorbs water and expands very rapidly (Angberg et al., 1991; Faroongsarng and Peck, 1994; Dalton and Hancock, 1997).

The expansion of the tablet core increased the internal stress in the films and subsequently deteriorated the film structure. Adverse changes in film structure during storage at high humidity have been reported to result from absorbed water acting as a plasticizer, which induces swelling, increases polymer chain mobility, deformation and flexibility (Okhamafe and York, 1986; Felton et al., 1996).

In tablets containing moisture-labile ASA in the tablet core, needle-like crystals appeared on top of the film coating within three months of storage at 40°C/75% RH (IV, Figs. 4 and 7). This is due to the migration of salicylic acid into the applied film coating occurring during storage at elevated humidity (Okhamafe and York, 1986). The present stress storage conditions accelerated the hydrolysis of acetylsalicylic acid to salicylic acid and acetic acid.

### 5.3.2 Hydrolysis of moisture-labile drug (III)

The aqueous film coating parameters studied did not affect the amount of hydrolysis of ASA; during the coating processes only a minor quantity of ASA hydrolysed (ASA remaining 99.2 ± 0.4%) (III, Fig. 4). This is obviously due to the fact that chemical hydrolysis of ASA is a slow process. Hence the exposure time of tablets to high-humidity conditions during the coating process is too short to induce any significant decomposition of the drug.

The hydrolysis of ASA was observed after storage for one month (ASA remaining 98.2 ± 0.6%) and three months (ASA remaining 97.5 ± 0.3%) at 25°C/60% RH (III, Fig. 4 A1, B1). When stored at 40°C/75% RH, the hydrolysis of ASA had clearly increased during the storage period of one month (ASA remaining 92.5 ± 1.4%) and further increased during the storage of three months (ASA remaining 90.0 ± 2.3%) (Fig. 4 A2, B2). It appears, however, that the process conditions and subsequent residual water did not affect the chemical hydrolysis of ASA during storage, and the hydrolysis of ASA increased more due to moisture penetration into the tablet core during storage. In an earlier study it was shown that there seems to be a direct relation between the degradation rate of ASA and the amount of water in the tablet due to the tendency of MCC to absorb water during storage (Ahlneck and Alderborn, 1988).

### 5.3.3 Dimensional changes (V)

The measurement of dimensional changes of film-coated tablets was started immediately after the coating process. The film-coated ibuprofen/pregelatinized starch tablets expanded for four hours (V, Fig. 3). The expansion of the tablets was evidently caused by the hygroscopic ingredients taking up water during and after the coating, which resulted in tablet swelling and volume increase. The coated ibuprofen/pregelatinized starch tablets compressed to the lowest breaking strength of 25 N expanded clearly more (25 μm) than those compressed to the higher breaking strengths of 45 N and 65 N (approximately 3 μm), i.e. using higher forces. The dimensional changes of the tablets

compressed with the lowest force correspond to a relative expansion of 0.6%, with higher forces to less than 0.1%. The tablets compressed with the lowest force were more porous and could absorb more water and, subsequently, expand more than tablets compressed with higher forces.

The film-coated ibuprofen/lactose tablets of all compression forces were dimensionally stable or contracted very little during two hours after the coating (less than 3 μm) and remained stable or expanded only a little during the subsequent four hours (V, Fig. 4). The dimensional changes of the coated tablets correspond to a relative contraction of approximately 0.1%. The contraction is probably due to thermal contraction of the ibuprofen/lactose formulation after coating. The ibuprofen/lactose tablets were less sensitive to temperature and humidity variations than the ibuprofen/pregelatinized starch tablets, because evidently lactose absorbed less water. This is supported by a previous study where different tablet ingredients exhibited opposite dimensional behaviour during cooling after simulated coating (Okutgen et al., 1991a).

The expansion of the ibuprofen/pregelatinized starch tablets (6 μm) and the contraction of the ibuprofen/lactose (1 μm) tablets compressed to the breaking strength of 45 N, measured 22-24 hours after coating, confirmed that no additional dimensional changes of tablets occurred after six hours. It can be concluded that it takes no more than six hours for these tablets to attain their final dimensions after coating. The results obtained through the coating process and using film-coated tablets would corroborate the findings of a previous study on the dimensional instability of tablet cores using simulated coating conditions and tablet cores (Okutgen et al., 1991a, 1991c).

### 5.3.4 Adhesion (V)

Immediately after the coating film adhesion was slightly better for the ibuprofen/pregelatinized starch tablets than for the ibuprofen/lactose tablets (V, Figs. 5 and 6). This may be explained by the fact that the ingredients in the tablet formulation significantly affect the formation of hydrogen bonds between the polymer and the tablet ingredients. The adhesion was significantly higher for both types of tablets compressed to the breaking strength of 25 N than for tablets compressed to 45 N ($p < 0.05$). Increasing the compression force (i.e. the breaking strength of tablets) from 45 N to 65 N did not significantly affect the adhesion. According to the literature, compressing tablets with high forces resulted in lower adhesion due to decreased roughness of the tablet

surface and, subsequently, decreased interaction area (Nadkarni et al., 1975; Fischer and Rowe, 1976; Rowe, 1977, 1978b; Felton and McGinity, 1996). It has also been assumed that high-viscosity solutions do not penetrate easily into small pores on the surface of the tablets, and adhesion decreases (Lehtola et al., 1995b).

The adhesion of both tablet formulations tended to decrease when the coated tablets were stored for 24 hours (V, Figs. 5 and 6). The decrease was significant ($p < 0.05$) only for the ibuprofen/pregelatinized starch tablets compressed to the breaking strength of 25 N. As described previously (5.3.3 Dimensional changes), the dimensional changes were greatest for the same tablet. Adhesion appears to depend on the magnitude of the time-dependent dimensional changes of the coated tablet. Dimensional changes occurring in tablet cores create high internal stresses within the film coat which consequently may cause major defects such as cracking or peeling of the film coat and may affect the film adhesion (Aulton et al., 1973; Rowe, 1983; Okutgen et al., 1991a, 1991c; Pourkavoos and Peck, 1993b).

After four weeks of storage the adhesion decreased for both tablet types (V, Figs. 5 and 6). The adhesion of the ibuprofen/pregelatinized starch tablets decreased significantly ($p < 0.05$ or $p < 0.001$) with all compression forces (V, Fig. 5) and the ibuprofen/lactose tablets with the breaking strengths of 25 N ($p < 0.01$) and 45 N ($p < 0.05$) (V, Fig. 6). However, after four weeks of storage there were no differences in the adhesion between tablets of different compression forces or types. The diminished adhesion during storage is attributed to increased swelling-induced stresses at the film-tablet interface due to accumulation of moisture (Okhamafe and York, 1985). During ageing the ibuprofen/pregelatinized starch tablets could have picked up more water than the ibuprofen/lactose tablets. This would agree with the above-mentioned measurements of dimensional changes (5.3.3 Dimensional changes).

Scanning electron micrographs of the interface of the film and tablet core showed minor gaps or voids after four weeks of storage (V, Fig.7). These findings indicate increased volume of the tablet core and reduced adhesion after four weeks of storage. Similar findings have been reported previously on ibuprofen tablets (Aulton et al., 1973).

# 6 CONCLUSIONS

On the basis of the present results, the following can be concluded:

1. An instrumented and automated pan coating system of tablets, including historical data storage capability and a novel air flow rate measurement system, provides an effective tool for controlling, analysing and characterising the film coating process. Process automation and monitoring of critical process parameters increase the overall process efficiency and predictability and improve the homogeneity and reproducibility of the tablet batches.

2. Inlet air flow rate, inlet air absolute humidity, flow rate of the coating solution, spraying air pressure and pan air temperature are critical process parameters affecting the surface morphology and the residual water content of HPMC film-coated tablets.

3. The chemical stability of a moisture-labile drug (ASA) is relatively insensitive to the aqueous film coating process and subsequent residual water. The hydrolysis of ASA is increased due to moisture penetration into the tablet core during storage.

4. The confocal laser scanning microscopy (CLSM) is a powerful tool for imaging changes at the film-core interface, i.e. changes caused by water penetration into the tablet core and surface defects of film-coated tablets.

5. The extent and rate of dimensional changes in tablets can be determined accurately by using a laser profilometer. If the tablet cores are compressed with sufficient compression force, the time-dependent dimensional changes and their effect on film adhesion are negligible. Film adhesion appears to depend greatly on the magnitude of the dimensional changes of the tablet core.

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