

Pharmaceutical Technology Division
Department of Pharmacy
University of Helsinki
Finland

Compression Behaviour and Enteric Film Coating
Properties of Cellulose Esters

Hong Xia Guo

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: Docent Leena Hellén
Orion Pharma
Turku
Finland

Dr. Mervi Niskanen
Orion Pharma
Espoo
Finland

Opponent: Docent Pasi Merkkö
Linnan Apteekki
Turku
Finland

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Abstract

COMPRESSION BEHAVIOUR AND ENTERIC FILM COATING PROPERTIES OF CELLULOSE ESTERS

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The main purpose of this study was to investigate the phenomena related to the compression behaviour and enteric film coating properties of pharmaceutical cellulose esters. The particle deformation in the tablet compression and drug diffusion of film-coated pellets were studied using non-invasive confocal laser scanning microscopy (CLSM).

Autofluorescent riboflavin sodium phosphate (RSP) was used as a model drug for preparing tablets and pellets. Tablets of 1% RSP with two grades of microcrystalline cellulose (MCC) were individually compressed at compression forces of 1.0 kN and 26.8 kN. The matrices were made by direct compression of mixtures of two established enteric cellulose esters, i.e. cellulose acetate phthalate (CAP) and hydroxypropyl methylcellulose acetate succinate (HPMCAS), and MCC. Pellets were made with the extrusion/spheronisation technique. The pellets were film-coated by the air-suspension method with an aqueous dispersion of CAP.

The results suggested that the compression behaviour of both the autofluorescent drug RSP and the non-fluorescent filler MCC can be visualised simultaneously by using fluorescence and reflection modes in CLSM. RSP particles partly dissolved under compression and then recrystallised. In studying the compression of matrix tablets confocal images confirmed the Heckel plot results. CLSM micrographs of the surface of the tablets made from CAP and MCC (1:1) showed more deformation than the one from HPMCAS and MCC (1:1). Slight aggregation of HPMCAS particles may influence their deformation. There were larger voids in the tablets made from cellulose ester and MCC (1:3) mass than in the one made from cellulose ester and MCC (1:1) mass.

A well-behaving enteric film-coating formulation was developed and patented. The coating formulation was based on waxy maize starch (amylopectin) as a co-filler in the pellet cores, and this innovation evidently prevented the premature drug migration from the core into the film coat layer. Confocal images of film-coated pellets at 30% theoretical weight increase showed that the amylopectin-containing pellets had a more appreciable coalescence of the polymer spheres than the respective lactose-containing pellets. The dissolution test was consistent with the confocal microscopy results. Amylopectin as subcoating material can prevent the influx of the dissolution medium into the pellet core, and thus decrease the premature dissolution and release of the drug from the enteric-coated pellets in 0.1 N HCl solution. The drug release mechanism appeared to be osmotically driven release, followed by diffusion through the polymer film. Therefore, particle deformation in the tablet compression, drug migration of enteric-coated pellets and release mechanism can be studied using a non-invasive CLSM technique.

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List of original publications

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

- I. Guo, H. X., Heinämäki, J. and Yliruusi, J., 1999. Characterization of particle deformation during compression measured by confocal laser scanning microscopy. *Int. J. Pharm.* 186, 99-108.
- II. Guo, H. X., Heinämäki, J., Antikainen, O. and Yliruusi, J., 2002. Compression of sustained-release matrix tablets of enteric cellulose esters. *S. T. P. Pharm. Sci.* 12.
- III. Guo, H. X., Heinämäki, J. and Yliruusi, J., 2002. Diffusion of a freely water-soluble drug in aqueous enteric-coated pellets. *AAPS PharmSciTech.* 3 (2) 16.
- IV. Guo, H. X., Heinämäki, J., Karjalainen, M., Juhanoja, J., Khriachtchev L. and Yliruusi, J., 2002. Compatibility of aqueous enteric film coating with pellets containing waxy maize starch and lactose (note). *S. T. P. Pharm. Sci.* 12 (3), 198-200.
- V. Guo, H. X., Heinämäki, J. and Yliruusi, J., 2002. Amylopectin as sub-coating material improves acidic resistance of enteric-coated pellets containing freely soluble drug. *Int. J. Pharm.* 235, 79-86.

1. Introduction

Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules. A simplified flow-chart of the relationship of pharmaceutical dosage forms is shown in Figure 1. These dosage forms are designed either for improving the physical and mechanical properties of materials during manufacture and/or for providing a desired drug delivery system. The tablets and capsules can be made directly from powders or from granules and pellets, or from film-coated multiple units. Tablets are now the most popular dosage form, accounting for some 70% of all ethical pharmaceutical preparations produced (Rubinstein, 2000).

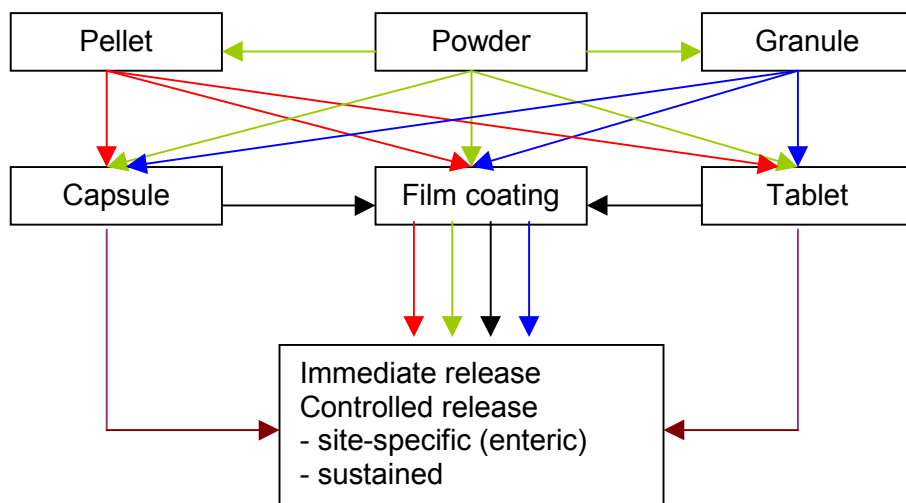


Fig. 1 Relationship of pharmaceutical solid dosage forms.

The great number of materials and the variety of properties of different solid dosage forms may complicate the understanding of phenomena occurring during a pharmaceutical manufacturing process. Solid particles have been compressed into tablets for a very long time, but the underlying theory has proved to be extremely complex. A number of difficulties which arise during compression can be related to the behaviour of particles under the influence of a compressing force (Armstrong, 1982).

Enteric cellulose esters, such as cellulose acetate phthalate (CAP) and hydroxypropyl methylcellulose acetate succinate (HPMCAS), are widely used for film coating of granules, pellets and tablets to obtain controlled site-specific release of drug in the human intestinal tract. Since cellulose esters are chemically close to the direct compression cellulose derivatives, it would be reasonable to assume that these materials can be used as direct compression excipients in matrices for controlled-release applications.

Enteric-coated dosage forms are designed to resist the acidic environment of the stomach and to disintegrate in the higher pH environment of the intestinal fluid. Polymers for enteric coating can be applied to solid dosage forms (i.e. granules, pellets or tablets) from aqueous latex or pseudolatex dispersions, aqueous solutions of alkali salts or organic solvent solutions.

Aqueous polymeric dispersions and solutions of alkali salts have been used extensively for enteric film coating of pharmaceutical solid dosage forms. These coating systems have numerous advantages over e.g. organic solvent-based systems with respect to ecological, toxicological and manufacturing safety concerns. However, the potential limitation related to many aqueous enteric coating formulations is the risk of premature drug release (permeation) through the enteric coat in the stomach. This can be due to an increased permeability of the aqueous film coating (Chang, 1990) or to a high water solubility of the drug (Bianchini et al., 1991). If the active ingredients are freely water-soluble, they may dissolve in the spray mist during the coating process, resulting in active ingredients being included in the film.

In order to understand in greater detail these problems during pharmaceutical manufacturing in terms of particle deformation during compression and premature drug release during aqueous film coating, non-invasive techniques are required. Confocal laser scanning microscopy is a potential technique because of its non-invasive nature and its ability to visualize the internal structure of samples but, so far, it has been used to a minor extent in pharmaceutical solid dosage form research (Cutts et al., 1996; Adler et al., 1999;

Lamprecht et al., 2000). In the present study, the CLSM technique was applied for the first time to investigating the particle deformation under tablet compression, and to determining the drug release mechanisms of enteric-coated dosage forms exposed to an acidic environment.

2. Literature review

2.1 Pharmaceutical powder compression

2.1.1 Particle deformation

The behaviour of powders during tablet compression is often very complicated because air can exist both between and inside particles. The physical nature of a powder column is different from that of a solid body, as powder can flow and have rheological properties of liquids, and the deformation of particles is different in powders (Paronen and Ilkka, 1996). The process by which a particulate solid is transformed by the application of pressure to form a coherent compact or tablet can essentially be divided into two stages, consolidation and bond formation.

When a force is applied in a die, the particles will first undergo rearrangement to form a less porous structure. This will take place at very low forces. Second, the particles will reach a state where further relative movement is impossible. A further increase in the force applied can then induce either particle fragmentation or deformation (or both) (Fig. 2). Deformation of particles includes both elastic deformation and/or plastic deformation. Which process prevails depends on the physical characteristics and structure of the consolidating material (Nesic, 1987). Some materials are brittle and consolidate by brittle fracture or fragmentation, some are ductile and consolidate by plastic deformation, while others consolidate by both fragmentation and plastic flow (Roberts and Rowe, 1987). Plastic deformation usually occurs with powders in which the shear strength is less than the tensile strength, whereas fragmentation becomes dominant with hard, brittle materials in which the shear strength is greater than the tensile strength (Celik and Driscoll, 1993).

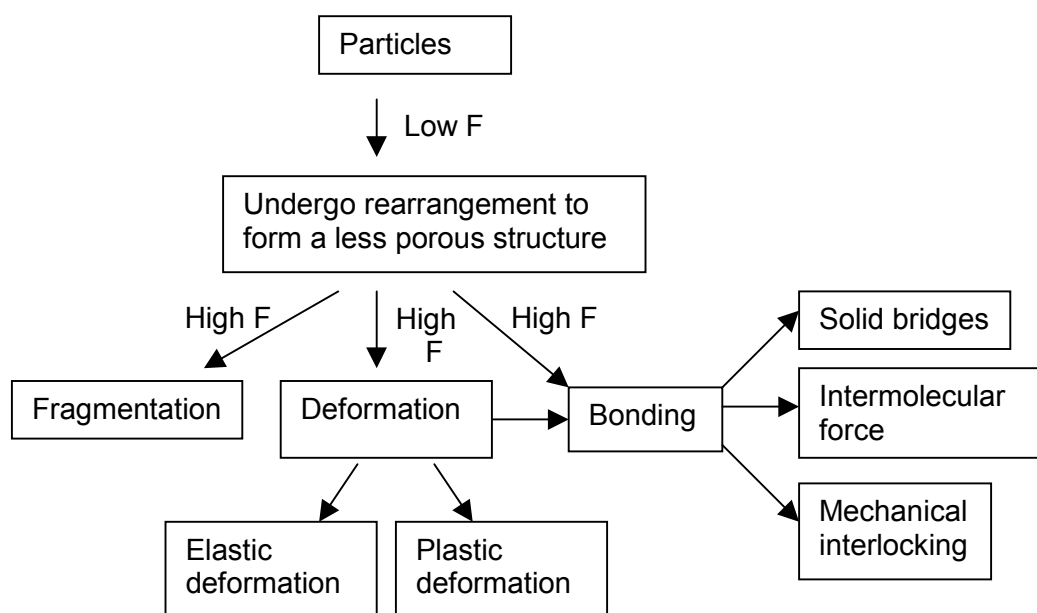


Figure 2. The deformation mechanisms of powder particles under the compression (F = compression force).

There exists no pharmaceutical powder that exhibits only one of the above-mentioned deformation mechanisms, although there is a spectrum of ranges from highly elastically deforming to highly plastically deforming or highly brittle materials. Even for materials that are known to be brittle, smaller particles of these materials may deform plastically (Celik and Driscoll, 1993). Different deformation is crucial in the consideration of tablet formation. A prerequisite for the formation of a coherent compact is that the surfaces deform to such an extent that the combined effects of bonding with intermolecular forces and solid bridges are greater than the elastic component of the material. This can be expressed as the critical compaction pressure needed to form a compact (Karehill et al. 1990).

Most drugs and some excipients show a tendency to fracture on compression. Materials such as sodium chloride, potassium chloride, aspirin and lipids exhibit plastic deformation while starches and celluloses demonstrate elastic behaviour at low pressures and deform plastically at high pressures (Hess, 1978).

2.1.2 Mechanisms of interparticular bonding

As seen in Figure 2, the consolidation of powder into a tablet can be divided into initial packing of the particles and elimination of void spaces in the powder bed. As the applied force rises, elastic deformation, plastic deformation and brittle fracture of the particles occur. At this stage, interparticular bonding takes place, and a coherent mass is formed. Three types of bond applicable to tablets include solid bridges, intermolecular forces and mechanical interlocking (Fuhrer, 1977), but they never act independently (Celik and Driscoll, 1993). Intermolecular forces constitute the dominating bond mechanism for pharmaceutical materials (Nyström et al., 1993). Solid bridges have been defined as areas of physical contact between adjacent surfaces. They can occur due to melting followed by resolidification or by dissolution of solid materials followed by recrystallization (York and Pilpel, 1973). The nature of solid bridges is dependent on the chemical structure of the material (Olsson et al., 1996; Adolfsson et al., 1997). If two surfaces are sufficiently close to each other, they will exhibit mutual attraction. Intermolecular forces include van der Waal's forces, hydrogen bonding and electrostatic forces, created during the plastic deformation or fragmentation of particles (Nyström et al., 1993). The incidence and importance of mechanical interlocking obviously depends on the size and shape of the particles. Smooth spherical particles will have little tendency to interlock, whereas irregularly shaped particles might be expected to do so (James, 1977). Bonding with mechanical interlocking is a bonding mechanism of minor importance for most of the investigated materials with the possible exception of Avicel PH 101 (Nyström et al., 1993).

The mechanism of compaction not only depends on the powder properties (Jones, 1977) but is also affected by particle size (Roberts et al., 1989), shape (Wong and Pilpel, 1990), moisture content (Sebhatu et al., 1997) and experimental conditions, e.g. applied pressure (Holman and Leuenberger, 1988) and velocity of compaction (Roberts and Rowe, 1985). In addition, the properties of the resulting compact can be influenced by the presence of a lubricant and binder (Nyström et al., 1982). Since pharmaceutical materials normally

consolidate by more than one of the mechanisms (Duberg and Nyström, 1986), adequate characterization techniques are needed.

Various techniques have been utilized to determine the extent of consolidation and bonding mechanisms in pharmaceutical powders, such as stress relief under pressure (Shlanta and Milosovich, 1964; Rees and Rue, 1978), three dimensionless tablet indices (Hiestand and Poet, 1974), brittle-fracture index (Lipson and Juvinall, 1963), X-ray diffraction (Muñoz-Ruiz et al., 1996) and multi-compression cycle (Khosravi and Morehead, 1997).

2.1.3 Crystalline aspects of powder during compression

Most drugs and additives are crystalline materials, or they possess a high degree of crystallinity. The frequency of defects (e.g. screw dislocations, lattice vacancies) in crystalline solids can be related to deformation during compression (Hüttenrauch, 1977). The changes can take place in crystal structure and shape. Such structural changes are opposed by intermolecular forces which restore the crystal to its original form, as in the case of elastic materials. If the intermolecular forces are exceeded, plastic or permanent deformation will result and, if the stress is continued, plastic flow will continue (Hess, 1978).

Decreases in crystallinity and order in deformed crystalline materials are thought to produce an unstable activated state, the intensity of which determines the properties of the resulting product. Experiments with lactose demonstrated that its crystallinity decreased as the compaction pressure increased, producing stronger tablets due to the more activated crystals dissipating acquired energy by interparticle bonding (Hüttenrauch, 1977).

In the literature, there is a great number of studies concerning changes in the crystal form of drug by compression. For example, the effects of tablet compression mechanical energy (Otsuka et al., 1989), compressional force (Ghan and Lalla, 1991; Pirttimäki et al.,

1993) and temperature (Matsumoto et al., 1991; Otsuka and Matsuda, 1993) on the polymorphic transformation or transition of drugs were reported. The crystal habit can also influence the ease of compression of a tablet (Florence and Attwood, 1998). Considerable research efforts have been made to optimize crystals for compression (Shekunov and York, 2000).

2.1.4 Mathematical models of powder compression

Most of the equations on the characterisation of powder properties relate to volume reduction under pressure (Heckel, 1961; Kawakita and Ludde, 1970; Macleod, 1983; Lippmann et al., 1997; Masteau and Thomas, 1999; Narayanasamy and Ponalagusamy, 2000). Many authors have used the Heckel equation to describe the compaction behaviour of materials, but it seems that it should be used with caution. The Heckel plot obtained for materials depends on the experimental techniques used (York, 1979). Some limitations of the Heckel relation in predicting the deformation mechanisms of powders were reported (Rue and Rees, 1978). Elastic deformation causes positive deviations in the Heckel plot, and therefore leads to a yield strength that is lower than the true value (Sun and Grant, 2001). The numerous models proposed did not give a satisfactory description of reality (Bockstiegel, 1966) or limited practical relevance in pharmaceutical development and quality control (Sonnergaard, 2001). Attempts have been made to describe the entire compression profile by several equations (Holman, 1991) or with several coefficients (Chen and Malghan, 1994). These are also of limited practical value. For practical purposes it is important to predict the strength of the resulting compact (Sonnergaard, 1999).

Sonnergaard (2000) investigated the compaction profiles of 17 materials with different molecular structures and particle densities. The influence of density is demonstrated by non-linear regression on the Heckel equation where the optimal particle density is estimated. The parameter in the Kawakita equation is not influenced to any greater degree by variation in the initial volume.

Equations describing volume reduction under pressure:

$$dD/dP = K (1-D) \quad (1)$$

[Heckel, 1961].

By integration equation (1) gives

$$\ln [1/(1-D)] = K P + A \quad (2)$$

where D is the relative density of the powder compact, P is the applied pressure and A is a constant. Equation (1) assumes that the rate of change in density with respect to pressure is directly proportional to the remaining porosity.

$$V_0 - V/V_0 = abP / 1 + bP \quad (3)$$

[Kawakita and Lüdde, 1970]

where V_0 is the initial apparent volume, V is the powder volume under applied pressure P , and a and b are constants. This equation describes the relationship between the relative change in volume and pressure.

$$V_0 - V/V_0 - V_\infty = a_1 \exp (-k_1/P) + a_2 \exp (-k_2/P) \quad (4)$$

[Cooper and Eaton, 1962]

where V_∞ is the powder volume at pressure $P \rightarrow \infty$, and a_1 , a_2 , k_1 , and k_2 are constants. Cooper and Eaton (1962) claimed that the compaction of powders takes place in two stages. If a non-porous powder column is produced under infinite pressure, the sum of a_1 and a_2 equals unity. If the sum is less than unity, other processes must be involved. The two terms on the right-hand side of the equation are related to the slippage of particles at early stages of compaction and to the subsequent elastic deformation, respectively.

2.1.5 Compaction properties of microcrystalline cellulose (MCC)

Microcrystalline cellulose is one of the most commonly used filler-binder in direct compression. Its popularity in direct compression is due to the extremely good binding properties as a dry binder. It exhibits the highest capacity and compressibility of all known direct compression excipients. However, its flow properties are relatively poor. It exhibits low bulk densities (Bolhuis and Chowhan, 1996). At low compression forces, stress relief is dominated by a slight elastic phase (Aulton et al., 1974). This has been explained by its hollow microfibrillar structure (Marshall et al., 1972). At higher forces it exhibits either further deformation (Hüttenrauch and Jacob, 1970) or permanent deformation by non-specific plastic flow (Reier and Shangraw, 1966). Mechanical interlocking is believed to be an important method of bonding in microcrystalline cellulose (Nyström et al., 1993).

Maganti and Celik (1993 and 1994) applied the Heckel equation to data obtained for the compacts of MCC powder and pellets as well as uncoated and coated pellet formulations. The slopes of the linear portion of the Heckel plots differed for the powder and pellet forms, suggesting that changing the shape, size and surface properties of MCC particles may have affected the compaction properties (e.g. degree of bonding) of this material.

Temperature may change during tableting. The temperature rise of the tablets with MCC was probably due to non-homogeneous particle shape and plastic deformation instead of fragmentation of MCC (Ketolainen et al., 1993). The thermophysical properties of MCC in tablet compression have also been investigated (Ketolainen et al., 1995) in the literature.

2.2 Aqueous enteric film coating

Film coating can be applied to solid dosage forms (i.e. granules, pellets or tablets) for protecting ingredients from the environment, particularly light and moisture, or masking unpleasant taste. Functional film coatings are used to impart site-specific (enteric) or controlled-release properties to the coated dosage form.

The advantages of an aqueous-based coating system have been recognized. This is derived from the drawbacks of organic solvents, including pollution, explosion hazards and solvent toxicity. Especially, there are risks for operators. For these reasons, water-based systems are now gradually being applied instead of organic coating systems. There are, however, also problems associated with aqueous film coating, e.g. poor volatility of water, migration of drug to the film coating or water into the core, microbial growth in aqueous dispersions, and instability of the colloidal dispersions (Baudoux et al., 1990).

Enteric-coated dosage forms are designed to resist the acidic environment of the stomach and to disintegrate in the higher pH environment of the intestinal fluid. The reasons for using an enteric coating are to protect the stomach wall from the effect of the drug contents in a dosage form or to protect the drug contents in a dosage from the harmful effect of the gastric contents. Enteric coating can also be used to deliver the active ingredients to a particular region of the intestine, e.g. the upper part of the small intestine, so as to enhance the bioavailability of the drug.

Aqueous enteric film coatings have been used widely in recent years. Many of these systems are pseudolatex dispersions of polymers such as CAP, latex dispersions of methacrylic acid copolymers and aqueous solutions of alkali salts. Finely divided colloidal polymer dispersions are classified as true latexes or pseudolatexes largely on the basis of the technique of production (Wheatley and Steuernagel, 1997). Aqueous solutions of alkali salts can be prepared using neutralization of enteric polymers of cellulose ester containing carboxylic groups with a base such as ammonium.

2.2.1 Cellulose esters

The most commonly used pH-sensitive enteric polymers today include cellulose esters such as cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate (HPMCP) and methacrylic acid copolymers. The general chemical structures of pharmaceutical cellulose esters are shown in Figure 3 (Baudoux et al., 1990). In gastric fluid these polymers are protonated and therefore insoluble in the low pH of the stomach, but ionize and become soluble in the higher pH of the small intestine.

The CAP and CAT are prepared by dissolving cellulose acetate in acetic acid. Phthalic or trimellitic anhydride is added to the solution and heated to allow for transesterification of the phthalic or trimellitic acid onto the cellulose backbone in the presence of basic catalysts.

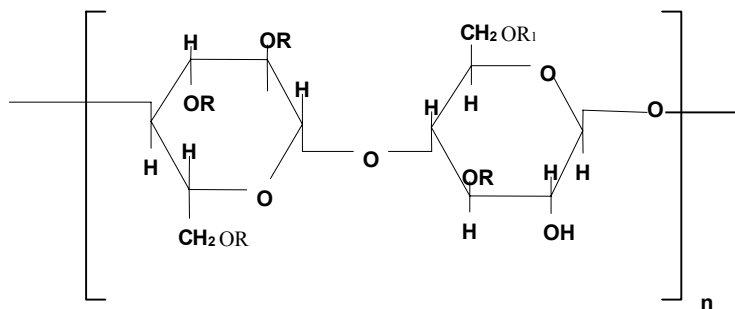
The polymer properties, e.g. molecular weight of the polymer, degree of substitution of acidic functional groups and pKa value determine the applicability of an enteric coating polymer. The mechanical strength of an enteric coating is a function of the molecular weight of the polymer. The pH-dependent solubility is mainly determined by the degree of substitution of acidic functional groups and the pKa value. The CAT film dissolved completely at pH 5.5, but CAP at pH 6.5. The difference in the pKa values may account for the difference of the dissolution characteristics of these two polymers (Wu et al., 1997).

Most of the studies on cellulose esters in the literature concerned their permeability properties, such as the water vapor transmission through free films of cellulose esters as a function of temperature and film thickness (Patel et al., 1964), the influence of plasticizers on the water vapor transmission through free films of CAP (Lachman and Drubulis, 1964), the effect of an increasing concentration of plasticizer and pigment on the permeability to both water vapour and simulated gastric juice of CAP (Porter and

Ridgway, 1982) and the permeability coefficients of CAP (Raffin et al., 1996). Except for the permeability properties, the monomolecular film properties of cellulose esters have been studied at the air-water interface (Zatz and Knowles, 1970) and thermal, mechanical and functional properties of CAP were also investigated from neutralized aqueous solutions (Bécharde et al., 1995). Both CAP and HPMCP have been successfully applied in ammoniated aqueous solutions, but this approach has not been used commercially due to the difficulty of quantitatively removing ammonia from the final film (Edgar et al., 2001).

Many of the aqueous enteric coating systems are pseudolatex dispersions of polymers such as CAP and latex dispersions of methacrylic acid copolymers. Aquateric is a pseudolatex based on CAP polymer spray-dried into a chemically stable powder. This powder is reconstituted in water by mild agitation to the original colloidal or near-colloidal size. The dispersion is manufactured by an emulsion process in which the CAP polymer is converted into a latex. The liquid product is then converted into a spray-dried powder with the aid of a barrier dispersant (McGinley and Tuason, 1985). A barrier dispersant is necessary in the manufacture of this aqueous enteric polymer dispersion because without it when CAP latex is spray-dried the particles would coalesce into a continuous film of CAP polymer.

In addition to use as an enteric coating material, cellulose esters can be used in preparing matrix tablets. Modified-release matrix tablets may be produced by compressing material made by spray drying theophylline slurried in an aqueous solution of enteric polymers of cellulose ester (e.g., CAP) (Wu et al., 1997).



	R	R ₁
CAP	$\text{---CH}_3\text{---C(=O)---}$	
CAT	$\text{---CH}_3\text{---C(=O)---}$	
HPMCP	---CH_3 Or $\text{---CH}_2\text{---CH(OH)---CH}_3$	 Or

Figure 3. Chemical structures of pharmaceutically used cellulose esters (Baudoux et al., 1990).

2.2.2 Film formation of aqueous enteric polymer dispersions

Since polymers for enteric coating are insoluble in water, they are usually applied as aqueous dispersions. The mechanism of film formation from an aqueous polymeric dispersion is more complex than that from an aqueous or organic solution (O'Donnell and McGinity, 1997) because the polymeric particles dispersed in the water must coalesce to form a continuous film (Fig. 4).

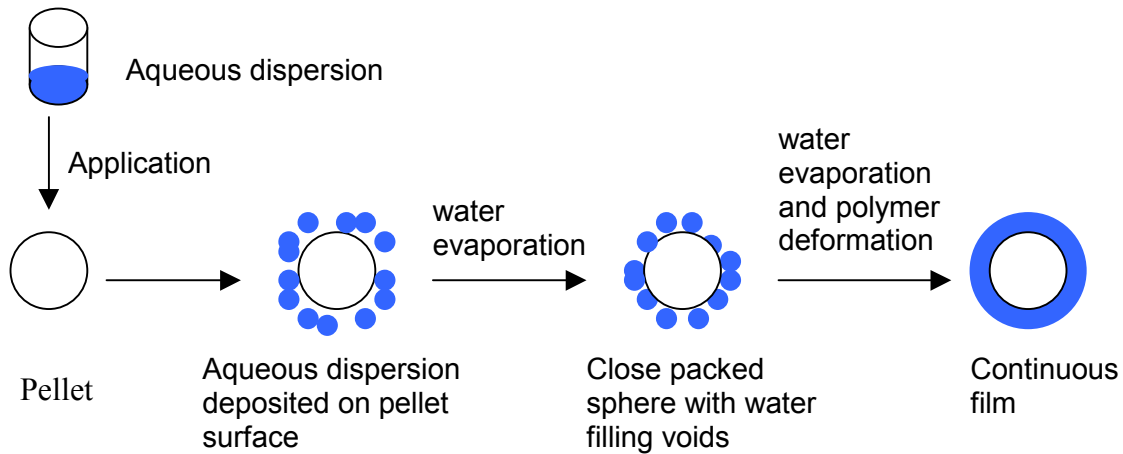


Figure 4. Film formation from aqueous polymer dispersion (Wheatley and Steuernagel, 1997).

An aqueous polymer dispersion is deposited from aqueous polymer spheres and coalesce into a continuous film by water evaporation. As water evaporates, interfacial tension between water and polymer pushes particles into a closely packed ordered array. Capillary force caused by the high interfacial surface tension of water provides the driving force to fuse the polymer spheres, facilitating coalescence and reducing minimum film formation temperatures (MFT) (Wheatley and Steuernagel, 1997). Several studies have been reported on the mechanisms of film formation in the literature (Ho and Suryakusuma, 1988; Eckerssley and Rudin, 1990; Roulstone et al., 1991; Chevalier et al.,

1992; Winnik and Wang, 1992). An important factor for film formation is the driving force that causes the coalescence of polymeric particles that results from water evaporation or capillary force. Since coalescence occurs only above a certain temperature, i.e., MFT, temperature and water evaporation are considered to be major factors that affect the film properties of coating materials (O'Donnell and McGinity, 1997). With dispersions it is particularly important to avoid sedimentation or coagulation of the film-former and incomplete film formation (Lehmann, 1982). The volatility of plasticizers in water vapour during the coating process can cause problems in film formation from aqueous dispersions (Nakagami et al., 1991).

2.2.3 Limitations of aqueous enteric film coating

A potential problem associated with enteric-coated formulations made of aqueous disperse systems or solutions is the lack of resistance against gastric fluid. According to Chang (1990), enteric films prepared from organic-solvent-based solutions showed considerably lower permeability to a basic drug, theophylline, than films prepared from aqueous latex and pseudolatex dispersions. Heinämäki et al. (1994) reported that the diffusion of a water-soluble drug was faster through films prepared from ammoniated aqueous solutions than through films prepared from organic-solvent-based (acetone) solutions. More recently, as different aqueous enteric coating systems were evaluated, tablets coated with aqueous enteric dispersions exhibited good performance in the USP dissolution test when a water-insoluble drug was used (Bianchini et al., 1991). With a water-soluble substance, however, enteric-coated tablets did not pass the USP test unless the tablet cores were insulated by sub-coating barriers or were coated with double amounts of the coating. Also a number of other studies (Chang, 1990; Plaizier-Vercammen and Suenens, 1991) have shown that the enteric-coated formulations made of aqueous film-coating systems gave poor gastric fluid resistance. The premature drug release (permeation) through the enteric coat in the stomach can be due to an increased permeability of aqueous film coating (Chang, 1990) or to a high water solubility of the drug (Bianchini et al., 1991).

According to the literature, dissolution of a small amount of drug from the core tablet to the aqueous film may occur during the coating process (Dansereau et al., 1993; Yang and Ghebre-Sellassie, 1990). The higher release rates of coated pellets were attributed primarily to drug diffusion into the film layer during the coating process (Yang and Ghebre-Sellassie, 1990). The undesired presence of a drug or an excipient in an applied film coating substantially alters the mechanical adhesion and permeation characteristics of the coating (Okhamafe and York, 1989). If the active ingredients are freely water-soluble, they may dissolve in the spray mist during the coating process, resulting in active ingredients being included in the film. Although a suitable method to prevent this phenomenon completely has not yet been found, a fairly effective method is to keep the droplet size of the spray mist small and to use a low spray rate (Nagai, 1997). Recently, Guo et al. (2000) reported that the pellet core containing amylopectin as a co-filler provides considerably low premature permeability to a freely water-soluble active agent in the acidic environment of the simulated gastric fluid. Cunningham et al. (2001) investigated the combination of excipients in a tablet core that would be suitable for use in an aqueous enteric film-coating process.

2.3 Confocal laser scanning microscopy (CLSM)

Confocal laser scanning microscopy (CLSM) is widely used in cell biology and medicine but also in material science where it has become a recognized part of paper science research (Moss, 1998). In material science, CLSM has been applied widely in the study of a variety of materials and processes such as phase separation in binary polymer mixtures, fracture toughness in alloys and in microvisualization of corrosion (Tata and Baldev, 1998). It can generate high-resolution images, as out-of-focus interference is essentially absent from confocal images, and also visualize structures in three dimensions through materials. Thus, it allows profiling of the surfaces of 3-D objects and multi-layer structures (Sheppard and Shotton, 1997). CLSM offers several advantages: (i) It allows information to be collected from a defined optical section. (ii) Out of focus fluorescence can be virtually eliminated, which results in an increase in contrast, clarity and detection.

(iii) The technique circumvents artifacts by permitting immediate investigation of the sample, thereby avoiding any fixation procedure.

The basic principle of confocal microscopy is shown in Figure 5. The details are described in I. The key feature of confocal imaging is that only what is in focus is detected. The image produced was a thin section of precisely those structures that were in focus. The Z series was an automatically collected series of optical sections through the tablets, which was saved as a single multi-image file. By projecting the Z series the images from different sections were subsequently combined. The images from the horizontal section (xy) have a better resolution than those from the vertical section (xz).

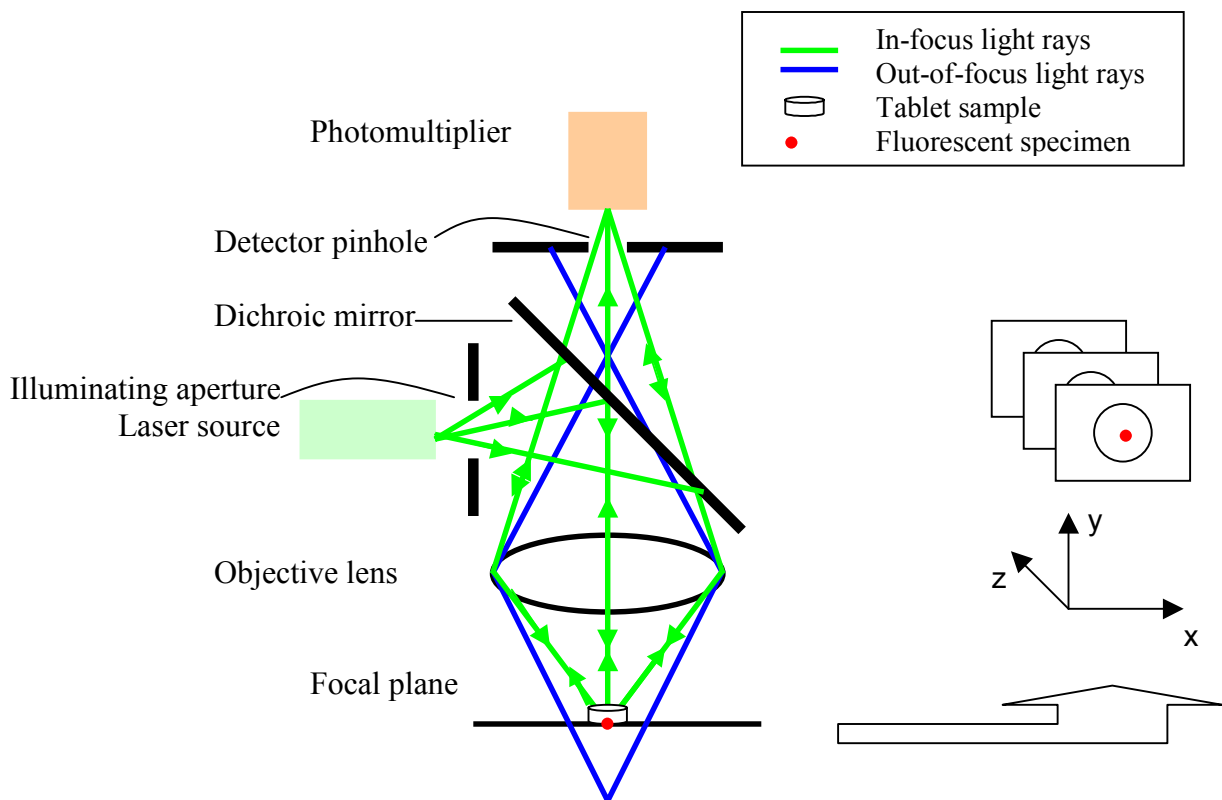


Figure 5. Schematic diagram of the confocal laser scanning microscopy (CLSM) principle.

3. Aims of the study

The main objective of the present study was to investigate and gain understanding of the compression behaviour and enteric film coating properties of pharmaceutical cellulose esters. The particle deformation in the tablet compression and drug diffusion of film-coated pellets were studied by using non-invasive confocal laser scanning microscopy (CLSM).

The specific aims of the study were:

1. to investigate an application of CLSM as a non-invasive method in studying phenomena related to pharmaceutical tablet compression and aqueous film coating,
2. to evaluate the underlying deformation mechanisms of powder particles in direct compression of tablets under the influence of different compression forces,
3. to study the compaction and consolidation behaviour of enteric cellulose esters and to estimate their value as direct compression excipients for sustained-release matrix tablets,
4. to image and quantify the migration and release of a freely water-soluble drug in aqueous enteric-coated pellets by using a CLSM technique and
5. to study the effect of amylopectin (waxy corn starch) as a non-traditional filler and subcoating material on the gastric resistance and dissolution of enteric-coated pellets.

4. Experimental

4.1 Materials

Riboflavin sodium phosphate (RSP) (Ph. Eur.) was used as a model drug (I-V). Two grades of microcrystalline cellulose (MCC), Avicel PH-102 (FMC Int., Ireland.) (I, II) and Avicel PH-101, were used as direct compression fillers. Acetone (E. Merck, Germany) was used for preparing the lubricant suspension for tablet compression (I, II). Two kinds of cellulose esters, cellulose acetate phthalate (CAP), (Aquateric, FMC Corporation, Philadelphia, USA) and hydroxypropyl methylcellulose acetate succinate (HPMCAS), (HF grade, Shin-Etsu, Japan) were used as tableting polymers (II).

For preparing pellets, MCC (Emcocel[®], type 90M, E. Mendell, Nastola, Finland) and lactose monohydrate (Pharmatose[®], type 80M, DMV International, Veghel, Netherlands) were used as excipients (III, IV, V). Waxy maize starch (amylopectin, Amioca[®], National Starch & Chemical GmbH, Neustadt, Germany) (Fig. 6) was applied as a co-filler in preparing pellet cores (III, IV) or as a subcoating material (V). Purified water was used as a granulation liquid. HPMC (Methocel E5[®], Dow Chemical, USA) was used as a reference sub-coating material (V). CAP, (Aquateric, FMC Corporation, Philadelphia, USA) was used as an aqueous enteric coating material (III, IV, V) or tableting excipient (II). As a plasticizer and surfactant for enteric coatings, triacetin (Fluka Chemie AG, Buchs, Switzerland) and Tween 80 (Fluka Chemie AG, Buchs, Switzerland) were used, respectively.

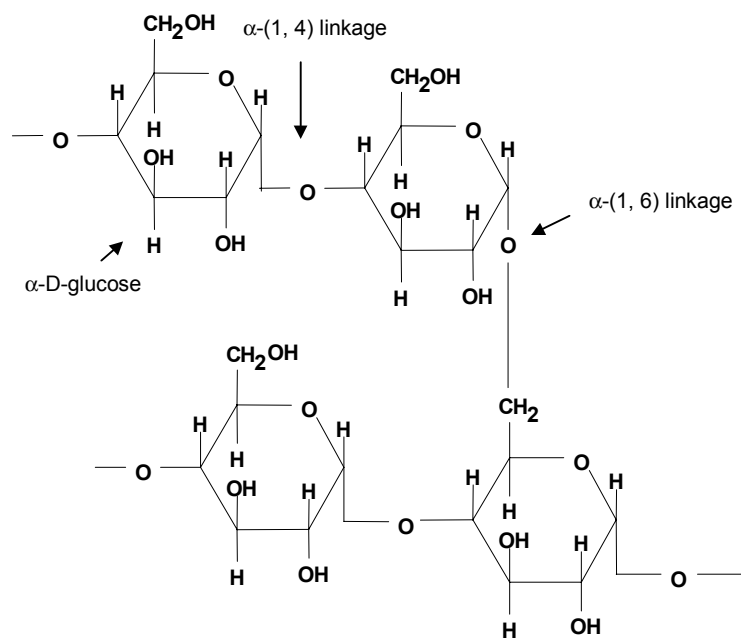


Figure 6. Chemical structure of waxy maize starch (amylopectin).

4.2 Methods

4.2.1 Preparation of solid dosage forms

4.2.1.1 Tableting

Tablets of 1% RSP with two grades of MCC (I) and matrix tablets (II) were individually obtained by direct compression in a Korsch EK-0 single-punch tablet machine fitted with strain gauges. The upper punch, the lower punch and the die were lubricated with 5% magnesium stearate-acetone solution. The press was operated at a speed of 35 rpm (I, II). The tablet height under load was held constant at 3.0 mm. The depth of filling was held constant (II).

4.2.1.2 Pelletisation

Pellets were made with the extrusion/spheronization technique (Nica M6L mixer/granulator; Nica E170 extruder; Nica S320 spheronizer; Nica System AB,

Möln dal, Sweden). Pellets were dried for 24 h in a drying oven at 32°C. The dried pellets were sieved manually, and those between 0.71-1.0 mm in diameter were selected for subsequent film coating (III, IV, V).

4.2.1.3 Film coating of pellets

Subcoating

Aqueous amylopectin coating solution was prepared in a thermal and pressure reactor equipped with a blade mixer (VTT Automation, Espoo, Finland). Five percent HPMC solution was used as a subcoating reference (V).

Enteric coating

The composition of the aqueous enteric coating dispersion was as follows: Aquateric 11%, triacetin 3.9%, Tween 0.10% and purified water 85% (III, IV, V). The pellets were coated using an Aeromatic air-suspension film coater (Aeromatic Strea-1, Aeromatic AG, Muttenz, Switzerland). Each coating batch comprised 300 g pellets. The pellet cores were pre-heated for 10 min. The inlet air temperature was adjusted to 40 ± 2 °C and the outlet air temperature to 30 ± 2 °C for the Aquateric film coating. The pneumatic spraying pressure was 1.6 bar and air flow rate was 100 m³/h. The pump rate of the coating solution was 3.4 g/min until a 2% increase in coating weight was obtained, then proceeding at a pump rate of 6.8 g/min to complete the coating run. After spraying, the same elevated temperature was maintained for another 10 minutes in the drying phase to avoid the sticking problem.

4.2.2 Characterisation of solid dosage forms

4.2.2.1 CLSM and image analysis

Observations were made with a Bio-Rad Lasersharp MRC-1024 (Bio-Rad, UK) attached to a microscope (Axiovert 135M, ZEISS, Germany) using Zeiss Plan-Neofluar 10×/0.30 N.A. (I, III, V) and 40×/0.75 (II) N.A. air lenses. 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 were set prior to initiation of the Z series. Images were recorded at intervals of 5 µm in the Z direction (I, II, III, V).

Each stack of pictures was evaluated using an image analysis system (ImageSpace, Molecular Dynamics, Inc., U.S.A). An area of about 0.01 mm² of the image was measured by determination of mean fluorescence intensity of RSP in the film. Exactly the same size of image was determined for images at different distances (III, V).

4.2.2.2 Dissolution tests (II, III, V)

The *in vitro* release tests were performed using a USP apparatus I (basket method) (III, V) and USP apparatus II (paddle method) (II). The dissolution medium was 500 ml of 0.1N hydrochloride acid and SIF without enzyme (pH 7.4, USP) maintained at 37 ± 0.5 °C. Samples were assayed by UV spectrophotometry (PERKIN ELMER, Bodenseewerk, Perkin-Elmer GmbH, Uberlingen, Germany) at 444 nm for RSP (II, III, V). n = 6 (II, III) and 5 (V).

4.2.2.3 Powder and matrix tablet characterisation (II)

The particle size distribution was determined by the laser diffraction method (Malvern 2605 LC Droplet and Particle Size Analyser, Malvern Instruments Ltd., Malvern, UK). The true densities of the powders were determined by a difference pressure pycnometer

(micromeritics, multivolume pycnometer 1305, NORCROSS, USA) using helium as an inert gas. Bulk and tap densities were determined in triplicate in a 250 ml cylinder using a volumeter (Erweka SWM-1 DW, Erweka GmbH, Heusenstamm, Germany). The poured density and tapped density of powder were determined according to USP. The moisture content of powders was measured as a loss of weight by an infrared apparatus (Sartorius thermol control, Sartorius GmbH, Göttingen, Germany). All measurements were made in triplicate.

The weight, thickness and breaking strength of 20 tablets were determined with a tablet multi-tester (ERWEKA GmbH, Heusenstamm, Germany). The friability of the tablets was measured using a friabilator (SOTAX, CH-4123 Allschwil, Basel, Switzerland).

4.2.2.4 Scanning electron microscopy (I, II, IV)

For scanning electron microscopy the pellets were fixed on double-sided carbon tape and coated with 20 nm platinum with a sputter coater (Agar sputter coater B7340, Agar Scientific Ltd,UK). The micrographs were taken with a Zeiss DSM-962 (Carl Zeiss, Oberkochen, Germany) scanning electron microscope (I, II, IV).

4.2.2.5 Wide-angle X-ray scattering (WAXS) and Raman spectroscopy (IV)

Both the coated and uncoated pellets and the pure materials in the pellets were measured by means of wide-angle X-ray scattering (WAXS). The Raman spectra were recorded using a single-stage spectrometer (Acton SpectraPro 5001) in a low-resolution mode (6 cm^{-1}) equipped with a 1024×256 pixel CCD camera (Andor InstaSpec IV).

5 Results and discussion

5.1 Particle deformation in direct compression (I)

The RSP powder was composed of spherical particles which cohere, forming aggregates of different shapes (I, Figs. 2-3). A new shape of crystals has been formed after pure RSP powder was manually compressed without a die under a high compression force (I, Fig. 5A). The same phenomenon also appeared in mechanical compression of pure RSP with a compression force of 23.0 kN (I, Fig. 5B). This phenomenon can probably be explained by recrystallization and/or sintering phenomena.

The images in Figure 7 showed how RSP particles deformed in a tablet under a high compression force and oriented in different layers. As regards the compression behaviour and deformation of RSP combined with two grades of MCC, at a lower compression force the original shapes of Avicel PH-101, Avicel PH-102 and RSP particles could be clearly distinguished (I, Fig. 6A and 6C). Distinct recrystallised areas in the RSP particles were observed in both grades of tablets (I, Fig. 7-8). The upper surface of the tablet showed a small area of spotted crystals (I, Fig. 7A) as a result of recrystallisation. No recrystallisation was observed on the lower surface of the same tablet (I, Fig. 7B). The particles on the lower surface had more voids than those on the upper surface, obviously due to the fact that the compression force obtained by the lower punch is always less than that applied by the upper punch (Armstrong, 1982). At a higher compression force, MCC and drug particles were deformed and lost their individuality (I, Fig. 6B and Fig. 6D). The recrystallisation of RSP was more extensive on the upper surface of the Avicel PH-102 tablet than in the Avicel PH-101 tablet (I, Fig. 9A and Fig. 10A). In the case of Avicel PH-101 tablets, a recrystalline structure was formed to a smaller extent on the upper surface of the tablet (I, Fig. 10A). This is obviously due to the elastic recovery of Avicel PH-101 at the higher compression force (>10 kN) (Szabo-Revesz et al., 1996) and the more porous structure of Avicel PH-101 (Landin et al., 1993), which may somewhat impede some recrystallization of RSP.

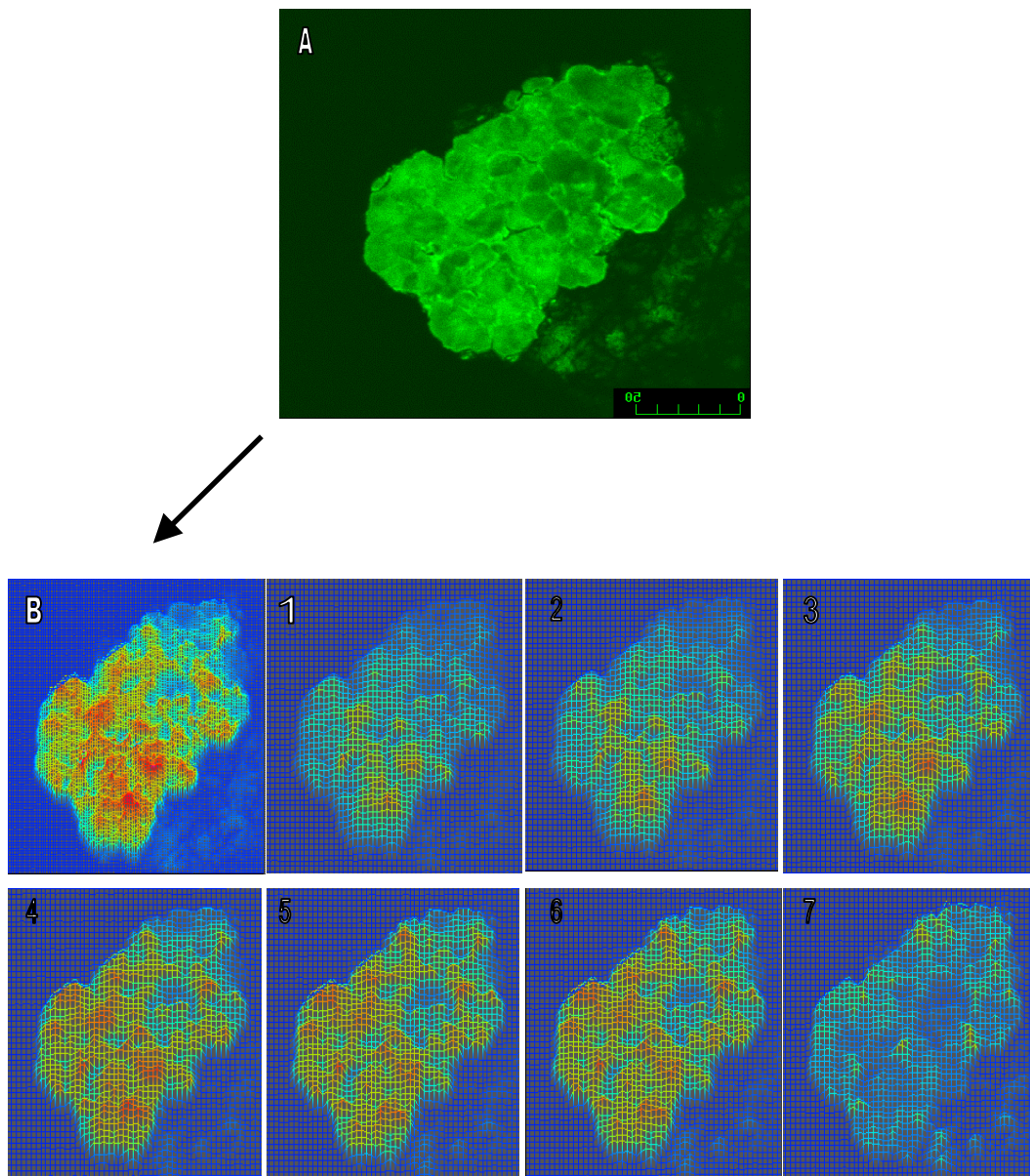


Figure 7. Confocal image of RSP particle deformation (A) in an Avicel PH-102 tablet and its 3-D deformation (B) in different layers (1-7) under a high compression force.

The plastic deformation properties of both MCC grades reduced the fragmentation of RSP particles. When compressed with MCC, RSP behaved as a plastic material. The RSP particles were more tightly bound on the upper surface of the tablet than on the lower surface, and this could also be clearly distinguished by CLSM. Drug deformation could

not be visualized by other techniques. CLSM provides valuable information on the internal mechanisms of direct compression of tablets.

5.2 Compression behaviour of cellulose esters (II)

The particle sizes and shapes of HPMCAS and CAP (II, Fig. 1 and Table II) are different. Both the particle size and the shape of the binder had a significant effect on the tablet strength (Nyström et al., 1980; Wong and Pilpel, 1990). A higher tensile strength was obtained for the HPMCAS-containing tablets (6.3 MPa) than for the respective CAP-containing tablets (1.3 MPa). CAP exhibited more elastic recovery than HPMCAS. The more cellulose ester a formulation contained, the larger were the values of elastic recovery. Too high an elastic recovery is likely to result in weak tablets and, under some conditions, will give rise to capping. This is perhaps the reason why the pure CAP caused capping under mechanical compression.

In the literature (Hersey and Rees, 1971), the reciprocal of k was defined as the mean yield pressure, P_Y , in order to study whether the fragmentation of particles was the predominant compaction mechanism of powders. The lower yield pressure values indicate that the material has a good compressibility behaviour (Yang et al., 1996). The CAP and MCC (1:1) mixture has a tendency to plastic deformation and good compressibility behaviour compared with other mixture ratios (II, Table IV).

Confocal images confirmed the results obtained from the Heckel plot (II, Fig. 3). Internal images of a tablet made from CAP and MCC (1:1) (II, Fig. 3A) showed higher deformation than that made from HPMCAS and MCC (1:1) (II, Fig. 3C). Slight aggregation of HPMCAS particles (II, Fig. 3C and 3D) may influence their deformation. When more MCC is included in the formulation, larger MCC particles may prevent the deformation of smaller particles of HPMCAS.

5.3 Dissolution of cellulose ester matrix tablets (II)

Both the compression force and the proportion of CAP and MCC can affect the drug release rate of matrix tablets (II, Fig. 4). Increasing the compression force or the 1:1 ratio of CAP and MCC in the formulation decelerated the rate of drug release in the acid phase. When the proportion of CAP and MCC was 1:1, the release profile of the drug was sustained. Decreasing the CAP and MCC ratio in the formulation accelerated the rate of drug release. The tablets did not disintegrate and kept intact during 0.1N HCl dissolution tests (II, Fig. 6B), which may account for the significantly decreased release rate of the tablet. Dissolution profiles of matrix tablets in SIF also showed sustained release profiles (II, Fig. 5). Inversely, the size of tablets in SIF decreased significantly (II, Fig. 6C).

5.4 Enteric film coating of cellulose esters (III, IV, V)

5.4.1 Diffusion of drug in enteric-coated pellets

To investigate the enteric quality of the film-coated pellets, a dissolution test was performed in 0.1N HCl for one hour, and subsequently in simulated intestinal fluid without enzymes. The results showed that pellets containing waxy maize starch had a good acidic resistance in 0.1N HCl solution for at least one hour while the lactose-containing enteric pellet formulations studied failed the test (III, Figs 1 and 2).

Waxy maize starch contains almost entirely amylopectin, with no amylose. Amylopectin is a branched D glucose (α 1-6) chain. This chain also contains α 1-4, one of the two polysaccharides that make up a starch (Fig. 6). Obviously this large branched molecule of waxy maize starch is able to better control premature RSP release from the enteric-coated pellets than lactose as a co-filler. The reasons mentioned above explain why lactose-containing pellet cores dissolved faster and, consequently, were poorer candidates for substrates for enteric coating than respective waxy corn starch pellets.

In the film-coated waxy maize starch pellets (Fig. 8A and III, Fig. 3B), appreciable coalescence of the polymeric spheres was formed on the pellet surface (dark network areas). No fluorescence of riboflavin sodium phosphate (i.e. drug diffusion) could be seen surrounding the pellet core. The respective uncoated lactose pellets had a rougher surface (III, Fig. 3C). In the film-coated lactose-containing pellets, the film was not formed by well-defined and discrete polymeric beads (Fig. 8B and III, Fig. 3D). The fluorescence drug of RSP has diffused into the film coat and concentrated in the surface of the pellet. CLSM images showed relatively large non-fluorescence areas in the lactose pellets (III, Fig. 3C and 3D).

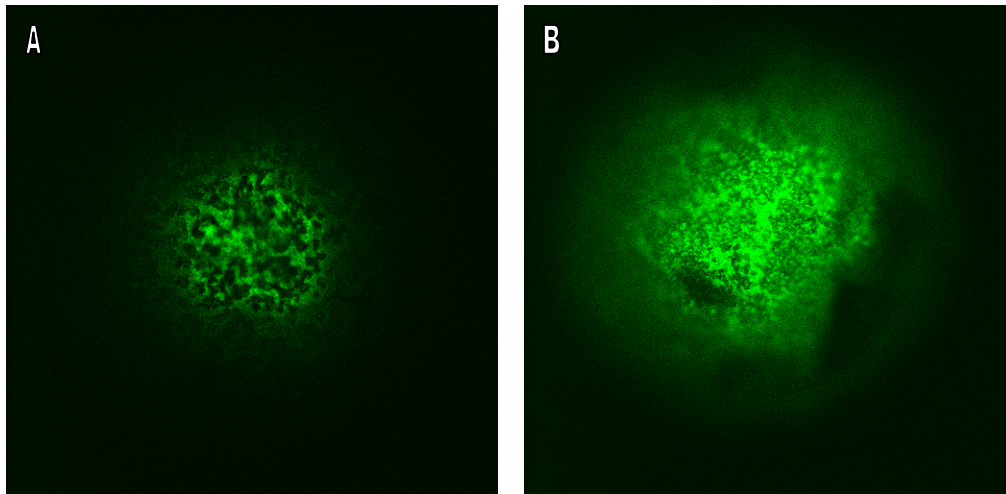


Figure 8. Boundary sections between film layer and pellet core of pellets containing waxy maize starch (A) and lactose (B).

To confirm the observations on the CLSM images, 3-D plots were taken (III, Fig. 4) from film coat to pellet core and the fluorescence intensity of riboflavin sodium phosphate in the sections was quantified (III, Fig. 5). The higher fluorescence intensity in the film coat of the lactose pellets provides an evidence of a greater extent of diffusion than that observed with the pellets containing waxy maize starch as a co-filler.

As seen in SEM micrographs, there were crystallites of various sizes in the film coat of the pellets after application of aqueous enteric coating dispersion (IV, Fig. 1). More and

smaller crystallites are seen in the film coat of lactose pellets (IV, Fig. 1 down) than in the respective film coat of waxy maize starch pellets (IV, Fig. 1 up) suggesting potential drug and/or filler migration to the film and recrystallisation. Thus, the film of lactose-containing pellets did not form an ordered structure like the one of pellets containing waxy maize starch.

Study on crystallinity using a WAXS technique showed that the crystallinity of lactose pellets was higher than that of waxy maize starch pellets, and the film coating decreased the crystallinity in both types of pellets. The crystallinity decreased more in waxy maize starch pellets than in lactose pellets, and this might be due to the migration of lactose to the film coat. This observation was further identified by WAXS, and the diffraction patterns of coated lactose pellets showed strong reflections of the lactose feature.

According to the literature, changes in the degree of crystallinity can greatly affect the physical and pharmaceutical properties of the film coat. An increased degree of film crystallinity reduced the diffusivity of gases in polyethylene films (Michaels and Bixler, 1961). Incorporation of lactose in polyvinyl alcohol films produced a stiffening effect as demonstrated by increased glass transition temperature and crystallinity (Okhamafe and York, 1989). The crystallites in the film probably can to some extent prevent the migration of water-soluble drug from pellet cores. However, due to the water-soluble nature of lactose, its parallel migration to the film coat is probably one of the major reasons causing dissolution failure of the respective enteric-coated pellets in an acidic environment. The Raman data showed that the migration seemed to be stronger for pellets containing lactose as a co-filler (IV, Fig. 3)

5.4.2 Dissolution of enteric-coated pellets

Dissolution profiles of amylopectin-subcoated and subsequently enteric-coated pellets were shown to improve the acidic resistance in 0.1 N HCl medium and dissolve at SIF in less than 10 minutes (V, Fig. 1). Increasing the amount of amylopectin subcoating could delay the drug release in 0.1 N HCl medium (V, Fig. 2). The branched structure of

amylopectin with all its attached chains yields a much larger molecule (Fig. 6). Consequently, amylopectin is better at building viscosity, and high viscosity may contribute to good adhesion of the film coat to the pellet core. The branched amylopectin gives steric hindrance and therefore can prevent riboflavin sodium phosphate migration during the coating process. Amylopectin-subcoated pellets had a more distinct acidic resistance than HPMC-subcoated pellets (V, Fig. 1).

Drug release mechanisms of amylopectin-subcoated pellets were studied by confocal images and corresponding fluorescence intensities of RSP from the pellet coat surface to the pellet core (V, Fig. 3). It is likely that the dissolution medium (0.1 N HCl) first permeated and expanded the film coatings (V, Fig. 3a). In the literature (Thoma and Bechtold, 1999; Thoma and Kräutle, 1999), tablets coated with an aqueous dispersion of cellulose acetate phthalate (CAP) showed massive swelling due to penetration of test medium into the core when acid permeability was evaluated in a 2-hour resistance test in 0.1 N hydrochloric acid. At this point, the mechanism of drug release was primarily induced by osmotically driven release because of the influx tendency of the medium. This is consistent with the coated pellets with a membrane of ethylcellulose and hydroxypropyl methylcellulose. The more soluble salts induced a higher osmotic influx rate of water into the pellet. At the same time they generated a more rapid expansion of the surrounding membrane (Thoma and Bechtold, 1999).

After the inflow medium had dissolved the drug in the core, diffusion appeared to be the major mechanism of drug release (Fig. 3b and Fig. 3c). These confirm well the release from phenylpropanolamine (PPA)•HCl pellets coated with an ethylcellulose-based film, which appeared to be a combination of osmotically driven release and diffusion through the polymer and/or aqueous pore (Ozturk et al., 1990). The confocal image (Fig. 3b) shows that the amylopectin subcoating can prolong medium influx to the core due to its high viscosity and hydrophobic properties.

6 Conclusions

Based on the present studies, the following can be concluded:

1. Confocal laser scanning microscopy (CLSM) is a non-invasive technique that can be used in characterising the behaviour and deformation of drug particles (i.e. autofluorescence drug) and excipients (i.e. MCC and other cellulose derivatives) in tablet compression.
2. In direct compression of tablets, individual powder particles of a freely soluble drug can partly dissolve or melt under the compression pressure, and subsequently recrystallise.
3. Cellulose esters without any co-diluent (MCC) are not able to produce satisfactory direct compressed tablets either because of capping or poor flowability during mechanical compression. Binary mixtures of CAP and MCC (1:1) have a tendency to plastic deformation and, consequently, a good compression behaviour, and the present formulations have potential for sustained-release applications.
4. With pellets containing enteric-coated waxy maize starch (amylopectin), a more appreciable coalescence of the coating polymer spheres can be observed than with respective lactose-containing pellets resulting in less premature drug release from the enteric-coated pellets in acidic medium.
5. Amylopectin used as a co-filler in the pellet cores can prevent drug diffusion from the core into the enteric film coat layer. Application of amylopectin as a subcoating in the pellets subsequently film-coated with aqueous enteric CAP dispersion efficiently prevents premature release of freely water-soluble drugs in acidic medium.

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