Comprehensive Summaries of Uppsala Dissertations
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New Concepts in Administration of Drugs in Tablet Form

Formulation and Evaluation of a Sublingual Tablet for Rapid Absorption, and Presentation of an Individualised Dose Administration System

BY

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ACTA UNIVERSITATIS UPSALIENSIS
UPPSALA 2003

Dissertation for the Degree of Doctor of Philosophy (Faculty of Pharmacy) in Pharmaceutics presented at Uppsala University in 2003

ABSTRACT

Bredenberg, S., 2003. New Concepts in Administration of Drugs in Tablet Form: Formulation and Evaluation of a Sublingual Tablet for Rapid Absorption, and Presentation of an Individualised Dose Administration System. Acta Universitatis Upsaliensis. *Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy* 287. 83 pp. Uppsala. ISBN 91-554-5600-6.

This thesis presents two new concepts in oral drug administration and the results of evaluation of some relevant formulation factors.

Investigation into improving the homogeneity of mixtures for tableting indicated that it may be possible to obtain interactive dry mixtures of micronised drugs containing drug proportions as low as 0.015% w/w. By studying the relationship between disintegration time and tensile strength, it was found that the microstructure surrounding the disintegrant particles may influence the disintegration process. Therefore, avoidance of excipients which are highly deformable or very soluble in water will result in more rapid disintegration. Further, it is possible to increase the bioadhesive properties of a non-bioadhesive carrier material by forming interactive mixtures containing a fine particulate bioadhesive material.

The new sublingual tablet concept presented is based on interactive mixtures consisting of a water-soluble carrier covered with fine drug particles and a bioadhesive component. With this approach, it is possible to obtain rapid dissolution in combination with bioadhesive retention of the drug in the oral cavity. Clinical data indicate that this allows rapid sublingual absorption while simultaneously avoiding intestinal absorption.

An individualised dose administration system is also presented. This system is based on the use of standardised units (microtablets), each containing a sub-therapeutic amount of the active ingredient. The required dose is fine-tuned by electronically counting out a specific number of these units using an automatic dose dispenser. A patient handling study supported the suggestion that the dosage of some medications can be more easily and safely individualised for each patient with this method than by using traditional methods of mixing different standard tablet strengths or dividing tablets.

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ISSN 0282-7484
ISBN 91-554-5600-6

Printed in Sweden by Uppsala University, Tryck & Medier, Uppsala 2003

Till Lars & Ella

Contents

Papers discussed

This thesis is based on the following papers which will be referred to by the corresponding Roman numerals in the text.

I. Sundell-Bredenberg, S., Nyström, C., 2001. The possibility of achieving an interactive mixture with high dose homogeneity containing an extremely low proportion of a micronised drug. Eur. J. Pharm. Sci., 12, 285-295.

II. Mattsson, S., Bredenberg, S., Nyström, C., 2001. Formulation of high tensile strength rapidly disintegrating tablets - Evaluation of the effect of some binder properties. S.T.P. Pharma Sci., 11, 211-220.

III. Bredenberg, S., Nyström, C., 2003. *In vitro* evaluation of bioadhesion in particulate systems and possible improvement using interactive mixtures. J. Pharm. Pharmacol., 55, 169-177.

IV. Bredenberg, S., Duberg, M., Lennernäs, B., Lennernäs, H., Pettersson, A., Westerberg, M., Nyström, C. *In vitro* and pharmacokinetic evaluation of a new sublingual tablet system for rapid oromucosal absorption using fentanyl citrate as the active substance. Submitted.

V. Lennernäs, B., Hedner, T., Holmberg, M., Bredenberg, S., Nyström, C., Lennernäs, H. Clinical pharmacokinetics and safety of fentanyl following sublingual administration of a rapidly dissolving tablet in cancer patients: a new approach for treatment of incident pain. In manuscript.

VI. Bredenberg, S., Nyholm, D., Aquilonius, S.M., Nyström, C. An automatic dose dispenser for microtablets - A new concept for individual dosage of drugs in tablet form. Submitted.

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Pharmaceutical tablets

Pros and cons compared to other dosage forms

Because oral administration of drugs is simple, convenient and safe, it is the most frequently used route. Over 80% of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms (Rudnic and Kottke, 1996). In the past, it was even thought in some cultures (e.g. China) that the drug effect could only be achieved via the oral route and therefore other dosage forms, such as ointments, were considered ineffective. The oral tablet has a relatively short history, however, and was introduced as late as 1843 by the Englishman Brockedon, who invented the first hand-operated device for compressed pills. Nonetheless, for a long time the tableting machine was not available at pharmacies, and pills, divided powders and capsules, which were made by hand, were more common. With the development of the modern pharmaceutical industry and effective production methods, mass production of tablets became possible and their popularity increased worldwide. The European Pharmacopoeia (2002) defines tablets as "solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated." Despite the long and continuing history of the development of new technologies for administration of drugs, the tablet form remains the most commonly used dosage form. However, advantages and disadvantages associated with this well-established form could be discussed, in order to form the basis for the development of new improved systems for tablet administration.

The tablet as a divided dosage form

The dispensation of drug preparations into single doses, such as divided powders, capsules or tablets, is convenient for the patient. In contrast to drugs dispensed in bulk for self-administration, such as oral liquids and ointments, the divided dosage form provides a well-defined drug dose that is convenient and safe. The change from early hand-made divided powders to the standardised volume-based filling of a die during automatic tableting procedures has resulted in improved homogeneity of drug between dosage units. This is especially important for preparations containing a small amount of a potent drug. However, the use of standardised tablet strengths does compromise the individualisation of doses, since this can only be achieved by dividing the tablets or by combining tablets of different strengths.

Stability

One of the main contributors to degradation of an active drug substance in a pharmaceutical formulation is the presence of moisture. Tablets, which are essentially dry dosage forms containing only minute amounts of water, commonly have a much longer shelf life than other formulations, such as oral and parenteral liquids. Nonetheless, it cannot be taken for

granted that all tablets will have a long shelf life. The choice of excipients, for example, is an important factor in this respect. Some excipients are hygroscopic, and even minute amounts of moisture can decrease the stability of the drug. This is especially important for effervescent tablets; the packaging material plays an important role in the protection of this tablet form from moisture.

Drug release

Before an active substance administered in tablet form can be absorbed into the systemic blood circulation, it has to be broken down to its component molecules. Obviously, the drug will not be released from conventional tablets as fast as from, for example, an injection formulation, which would normally contain the active substance already in molecular form. However, it is now possible to design a range of different release patterns by changing tablet excipients and/or the manufacturing process. The site of absorption is also a factor in this respect; using the oral mucosa as the administration site can improve the speed of both tablet disintegration and drug release and subsequently increase the absorption rate compared with conventional tablets.

Manufacturing

The manufacture of conventional tablets is a cost-effective process. Modern tableting machines are able to cater for large-scale production; a rotary press can output over 10 000 tablets per minute (Alderborn, 2002). This speed of production gives the tablet form its superior edge over other solid dosage forms such as capsules. Additionally, the direct compression process involves only a few steps: one or more dry mixing steps followed by compression of the powder. However, direct compression of a powder mass requires certain properties, such as a low tendency for segregation, good flowability and high compactability. If direct compression is not possible, the formation of aggregates or granules from the drug excipients can improve the tableting properties. Granulation requires a few more steps than direct compression, but it is still a relatively simple process compared with processes like the production of injectable dosage forms.

Compliance

The tablet form is convenient to handle and easy and safe for the patient to take. Since tablets are a well known dosage form for most patients, there will be fewer requirements for explanatory information and compliance is assumed to be better. However, there are also compliance disadvantages; some people, especially the elderly and children, find it difficult to swallow tablets. Further, most people require water to facilitate swallowing tablets. However, several new types of tablets, intended for rapid disintegration and drug release in the oral cavity, have been developed over the last decade. This approach may be useful for increasing patient compliance, since disintegration of the tablet in the mouth facilitates swallowing, and concomitant intake of water can sometimes be omitted.

Tableting excipients

In a tablet formulation, a range of excipient materials is normally required along with the active ingredient in order to give the tablet the desired properties. For example, the reproducibility and dose homogeneity of the tablets are dependent on the properties of the powder mass. The tablet should also be sufficiently strong to withstand handling, but should disintegrate after intake to facilitate drug release. The choice of excipients will affect all these properties.

Filler: Fillers are used to make tablets of sufficient size for easy handling by the patient and to facilitate production. Tablets containing a very potent active substance would be very small without additional excipients. A good filler will have good compactability and flow properties, acceptable taste, will be non-hygroscopic and preferably chemically inert. It may also be advantageous to have a filler that fragments easily, since this counteracts the negative effects of lubricant additions to the formula (de Boer et al., 1978).

Binder: A material with a high bonding ability can be used as a binder to increase the mechanical strength of the tablet. A binder is usually a ductile material prone to undergo plastic (irreversible) deformation. Typically, binders are polymeric materials, often with disordered solid state structures. Of special importance is the deformability of the peripheral parts (asperities and protrusions) of the binder particles (Nyström et al., 1993). Thereby, this group of materials has the capacity of reducing interparticulate distances within the tablet, improving bond formation. If the entire bulk of the binder particles undergo extensive plastic deformation during compression, the interparticular voids will, at least partly, be filled and the tablet porosity will decrease. This increases the contact area between the particles, which promotes the creation of interparticular bonds and subsequently increases the tablet strength (Olsson et al., 1998; Mattson and Nyström, 2000). However, the effect of the binder depends on both its own properties and those of the other compounds within the tablet. A binder is often added to the granulation liquid during wet granulation to improve the cohesiveness and compactability of the powder particles, which assists formation of agglomerates or granules. It is commonly accepted that binders added in dissolved form, during a granulation process, is more effective than used in dry powder form during direct compression.

Disintegrating agent: A disintegrant is normally added to facilitate the rupture of bonds and subsequent disintegration of the tablets. This increases the surface area of the drug exposed to the gastrointestinal fluid; incomplete disintegration can result in incomplete absorption or a delay in the onset of action of the drug. There are several types of disintegrants, acting with different mechanisms: (a) promotion of the uptake of aqueous liquids by capillary forces, (b) swelling in contact with water, (c) release of gases when in contact with water and (d) destruction of the binder by enzymatic action (Rudnic and Kottke, 1995). Starch is a traditional disintegrant; the concentration of starch in a conventional tablet formulation is normally up to 10% w/w. The starch particles swell moderately in contact with water, and the tablet disrupts. So-called superdisintegrants are now commonly used; since these act

primarily by extensive swelling, they are effective in only small quantities (Shangraw et al., 1980; Bolhuis et al., 1982; Pesonen et al., 1989). Cross-linked sodium carboxymethyl cellulose (e.g. Ac-Di-Sol®), which is effective in concentrations of 2-4%, is a commonly used superdisintegrant. Larger particles of disintegrants have been found to swell to a greater extent and with a faster rate than finer particles, resulting in more effective disintegration (Rudnic et al., 1982).

Glidant, antiadherent and lubricant: Glidants are added to increase the flowability of the powder mass, reduce interparticular friction and improve powder flow in the hopper shoe and die of the tableting machine. An antiadherent can be added to decrease sticking of the powder to the faces of the punches and the die walls during compaction, and a lubricant is added to decrease friction between powder and die, facilitating ejection of the tablet from the die. However, addition of lubricants (here used as a collective term, also including glidants and antiadherents) can have negative effects on tablet strength, since the lubricant often reduces the creation of interparticular bonds (e.g. de Boer et al., 1978). Further, lubricants can also slow the drug dissolution process by introducing hydrophobic films around drug and excipient particles (e.g. Westerberg and Nyström, 1991). These negative effects are especially pronounced when long mixing times are required (Bolhuis et al., 1975). Therefore, the amount of lubricants should be kept relatively low and the mixing procedure kept short, to avoid a homogenous distribution of lubricant throughout the powder mass. An alternative approach could then be to admix granulated qualities of lubricant (Johansson, 1984).

Flavour, sweetener and colourant: Flavour and sweeteners are primarily used to improve or mask the taste of the drug, with subsequent substantial improvement in patient compliance. Colouring tablets also has aesthetic value, and can improve tablet identification, especially when patients are taking a number of different tablets.

Some factors affecting mechanical strength of tablets

When the powder is compressed into a coherent compact, the particles bond together. How strong the tablet is going to be is dependent on the properties of the component materials and particles, but the tablet instrument settings can also affect the tensile strength. Tablet strength is important for withstanding handling during coating processes, transport and normal patient use. However, the strength of tablets should not be increased at the expense of rapid disintegration and drug release.

Volume reduction mechanisms for pharmaceutical powders during compression
During compression of powders, the force applied increases as a function of reduced distance between the punches while the powder bed decreases in volume. The volume reduction mechanism that dominates during compression is dependent on the properties of the component materials. In fact, there is usually more than one mechanism involved (Duberg and Nyström, 1985). Under initial low pressures in the die, the powder particles

rearrange to form a more closely packed structure, the voids between the particles are reduced in size, and the porosity of the tablet unit decreases. The degree of particle slippage and rearrangement is dependent on the particle size and surface roughness (York, 1978). Subsequently, after an initial elastic (reversible) deformation, the materials undergo plastic (irreversible) deformation and eventually, if the applied stress is high enough, fragmentation (Nyström et al., 1993). Pharmaceutical materials, which mainly consist of organic compounds with complex particle structures, sometimes undergo limited initial elastic/plastic deformation and then extensive particle fragmentation at low pressures, followed by a second deformation process, involving the newly formed smaller particles, at higher loads (Duberg and Nyström, 1982; 1986). This is especially pronounced for pharmaceutical materials composed of aggregates of primary particles or highly porous particles, which after the initial fragmentation undergo plastic or elastic deformation at higher compaction loads (Duberg and Nyström, 1986). After the maximum load has been reached, the compaction pressure is gradually released. If the material has undergone extensive elastic deformation, the tablet will expand, which can cause breakage of interparticulate bonds and possibly capping of the tablet.

Bonding mechanisms

The particles in pharmaceutical compacts or tablets are thought to be held together by three dominating bonding mechanisms: weak distance forces, interparticular solid bridges and mechanical interlocking (Führer, 1977).

Distance forces

Intermolecular forces or bonding forces acting over some distance between atoms, molecules or surfaces primarily comprise van der Waals forces, hydrogen bonds or electrostatic interactions. Van der Waals forces are attraction forces between ions, molecules or particles and can occur in vacuum, gas and liquid environments. They primarily act over distances of 1-100 nm with strengths dependent on the distance between the surfaces (Israelachvili, 1992). Since the hydrogen atom is small in size, electronegative atoms or molecules can approach closely, with the formation of relatively strong electrostatic attractions, so-called hydrogen-bonding interactions (Israelachvili, 1992). Electrostatic forces may arise during the handling process, e.g. during mixing and tableting, from triboelectric charging. These forces are considered not to make any significant contribution to the mechanical strength of pharmaceutical tablets since they are neutralised rather quickly over time (Nyström et al., 1993).

Solid bridges

During powder compression, it is possible that the particles come into such close contact, i.e. at an atomic level, that solid bridges are formed. These solid bridges are considered to be relatively strong, and they can contribute substantially to the mechanical strength of the tablets (Führer, 1977, Nyström et al., 1993). There are several possibilities for the mode of formation of these solid bridges, including melting (if high temperatures arise as a result of friction between particles at their contact points during compaction) diffusion of atoms between surfaces, and recrystallisation of soluble materials (Shotton and Rees, 1966;

Führer, 1977). The nature of the solid bridge is dependent on the chemical structure of the material (Adolfsson and Nyström, 1996). It is primarily materials with a simple crystal structure that form solid bridges, which necessarily excludes many pharmaceutical materials (Führer, 1977). Adsorption of moisture at particle surfaces may also contribute to the formation of solid bridges (Ahlneck and Alderborn, 1989).

Mechanical interlocking
This bonding mechanism involves the hooking or twisting together of the particles (Führer, 1977). Particles with irregular shapes, e.g. needle forms, and/or with a rough surface texture can hook or twist together during compaction (Nyström et al., 1993). However, materials forming compacts predominantly by this bonding mechanism often require high compression forces and the resultant tablets have low tablet strength, high friability and long disintegration times (Führer, 1977).

Particle size
Generally, tablet strength increases with decreased initial particle size of the compacted material (Shotton and Ganderton, 1961; Alderborn and Nyström, 1982a; McKenna and McCafferty, 1982; Vromans et al., 1985a; Leuenberger et al., 1989). The effect of particle size is dependent on the volume reduction mechanism of the compressed material (e.g. Alderborn and Nyström, 1982a). For materials with a high fragmentation tendency, the effect of initial particle size is more limited. For these materials, the large particles fragment into smaller particles, creating larger surface areas and increasing the number of interparticulate contact points, which promotes the creation of interparticulate bonds. For materials which deform during compaction, the effect of particle size may be more pronounced. For these materials, the surface area partitioning in the bonding structure is not changed to a large extent during compaction and therefore the effect of initial particle size is more pronounced. The dominating bonding mechanism of the material may also be important. Alderborn and Nyström (1982a) found that the tensile strength of the tablet increased with increases in the particle size of sodium chloride. This material bonds predominantly by solid bridges (e.g. de Boer et al., 1978; Alderborn and Nyström, 1982a; Adolfsson et al., 1998) and since the contact points between the particles are fewer for larger particles, increasing the applied stress increases the probability of strong bridges. However, the effect of particle size on tablet strength is also dependent on the compression speed (Sheikh-Salem and Fell, 1982). Particle shape and surface texture can also influence powder compactability (e.g. Alderborn and Nyström, 1982b; Alderborn et al., 1988; Wong and Pilpel, 1990).

Solid state structure
The bonding properties of a material are dependent on differences in the physical and chemical properties, i.e. the solid state structure, of the material. Analyses of the relationships between crystalline (ordered) or disordered structures of substances and their mechanical properties can be found in the literature (e.g. York, 1983, for review). Generally, compacts containing amorphous materials result in stronger tablets. This has been explained by the higher degree of plastic deformation seen with these materials, which

results in an increased ability to form interparticulate bonds (e.g. Hüttenrauch, 1977). Lactose, a commonly used filler which is available in several crystalline forms and in an amorphous form, has been widely studied (e.g. Hüttenrauch, 1977; Vromans et al., 1985a, b; Sebathu and Alderborn, 1999). Tablets of the anhydrate form of lactose have higher tensile strengths than tablets of the monohydrate form (Vromans et al.,1985a; b), the amorphous form resulted in stronger tablets than the crystalline form (Sebathu and Alderborn, 1999) and the strength of tablets of alpha-lactose monohydrate increased with decreases in crystallinity (Hüttenrauch, 1977). However, Hancock et al. (2002) did not find any differences in tensile strength between crystalline and amorphous states of active pharmaceutical substances, although they did find that the amorphous form had a higher propensity for fracture when controlled flaws were introduced into the tablet before measurement of the radial tensile strength. Further, during compression of the powder and after mechanical activation (such as grinding), energy is transformed into the material (Hüttenrauch et al., 1985). This can cause disordering of the crystal lattice of the material, which could influence the tablet strength.

Compression speed

Generally, higher compression speeds result in tablets with lower tensile strength (Fell and Newton, 1971; Sheikh-Salem and Fell, 1982). The effect of compression speed on the tablet tensile strength is dependent on the volume reduction mechanism of the compressed material (Sheikh-Salem and Fell, 1982; Roberts and Rowe, 1985; Armstrong and Palfrey, 1989; Olsson, 2000). For materials undergoing plastic deformation during compression, e.g. sodium chloride, the compression speed will have a greater effect (Sheikh-Salem and Fell, 1982; Roberts and Rowe, 1985; Armstrong and Palfrey, 1989; Olsson, 2000). Since the deformation process is more or less time dependent, the particles flow more effectively at slower compression speeds, which creates larger contact areas for bonding; at higher compression speeds, the time for plastic flow is limited. For materials undergoing fragmentation during compaction, the effect of compression speed is not as pronounced as for the more deformable materials (Armstrong and Palfrey, 1989; Olsson, 2000).

Some factors affecting drug release

Before an active substance administered in tablet form can be absorbed into the systemic blood circulation it must be transformed to its molecular form. The potential rate limiting steps for this process involve wetting of the tablet, penetration of liquid into the tablet structure, disintegration of the tablet and drug dissolution. For sparingly soluble, orally administered drugs, the dissolution rate can often be the rate-limiting step in drug absorption. Therefore, it is important to identify and learn how to influence the factors affecting the processes of drug release, so that improved tablet designs for instant release and absorption of drug can be developed.

Wetting
Acceptable wetting is normally obtained simply by using filler, binder or disintegrant excipients that also have hydrophilic properties. Hydrophobic lubricants and antiadhesives, such as stearates, may pose a problem, however (Levy and Gumtow, 1963; Ragnarsson et al., 1979; Lerk et al., 1982). With these materials, the use of brittle excipients, such as crystalline lactose, sugar alcohols and inorganic salts, can be advantageous (Alderborn et al., 1985a; Duberg and Nyström, 1986). Because of partial fragmentation of the excipient particles, new surfaces that are not coated by lubricant are exposed, thereby increasing the fraction of hydrophilic solid surface (de Boer et al., 1978).

Water penetration
Liquid penetration is enhanced by improving wetting (lowering the contact angle), increasing the surface tension, keeping the viscosity of the penetrating liquid low, and increasing the average pore diameter (Washburn, 1921; Nogami et al., 1963). After applying these factors in relation to wetting, any unnecessary surfactants should be removed from the formulation (Nogami et al., 1963). Gelling polymers should also be avoided, to keep the viscosity of the penetrating liquid as low as possible. Finally, the pore structure could be affected by the choice of excipient. Liquid penetration is thought to be influenced by the porosity of the tablets, which is determined by such factors as compaction load and the properties of the constituent materials (Shangraw et al., 1980).

Disintegration
A thorough understanding of the properties of the tablet and its constituents is required before speedy disintegration can be achieved. Numerous studies have investigated the disintegration processes (e.g. Kanig and Rudnic, 1984; Caramella et al., 1986). Various mechanisms of action have been proposed for the disintegrants used (e.g. Shangraw et al., 1980; Kanig and Rudnic, 1984). The main processes involve swelling of the disintegrant particles which rupture the tablet, and disintegrants which facilitate water uptake through capillary action or wicking, i.e. the disintegrant draws water up into the porous network of the tablet which reduces the physical bonding forces between particles (Shangraw et al., 1980; Kanig and Rudnic, 1984). Other mechanisms mentioned in the literature include deformation of disintegrant particles, which recover in contact with water, and particle repulsion (Kanig and Rudnic, 1984). However, disintegrants do not act by one single mechanism; the dominant mechanism is mainly determined by the choice of disintegrant in combination with the characteristics of the other tablet materials (e.g. Lowenthal, 1972; Kanig and Rudnic, 1984). Wetting and rate of liquid penetration into the pores within the tablets will influence the disintegration time. Water penetration and subsequent swelling of the disintegrant have been related to the development of a disintegrating force within the tablet (Caramella et al., 1986). A high water penetration rate facilitates the disintegrating force of the swelling disintegrant, especially in less water soluble tablet matrices. In more water soluble matrices, the disintegrant is not always able to develop its maximum swelling force because of continuous dissolution (Caramella et al., 1986).

Dissolution
It does not necessarily follow that if a tablet disintegrates quickly into smaller fragments and particles, the drug will automatically dissolve quickly. The main prerequisites for rapid dissolution of the drug are a large surface area of the drug exposed to the dissolving liquid (Noyes-Whitney, 1897) and drug dissolution unhindered by slow diffusional transport due to thick, stagnant hydrodynamic boundary layers (e.g. Nyström et al., 1985; Bisrat et al., 1992). The main method of increasing the exposure of drug particle surface area is to use very finely divided grades of drug while making sure that the added excipients do not separate the dissolving liquid from the drug particles. To this end, water-soluble excipients can be used; alternatively, freeze-drying, a well-known principle used to obtain highly porous tablets, promotes rapid exposure of the drug phase and thus drug dissolution (e.g. Corveleyn and Remon, 1998). Other approaches include the use of ordered mixtures (Westerberg, 1992) or solid dispersions (Sjökvist Saers, 1992), as discussed below.

Optimised tablet systems for instant drug release

As described above, finely divided drug particles can be used to improve drug dissolution since the particle surface area exposed to the solvent is increased. However, this often results in agglomeration of the particles with a subsequent decrease in effective dissolution surface area. To prevent this, ordered mixtures or solid dispersions can be used.

Ordered mixtures for low drug content
Ordered mixtures are commonly used to improve the content uniformity of low dose preparations (Hersey, 1975). To achieve ordered mixtures in practice, coarse carrier particles are mixed with a fine drug component for a relatively long time so that the fine drug particles adhere to the surface of the carrier particles by adhesion forces, with resultant improved exposure. Additionally, any tendency towards agglomeration of drug particles, corresponding to a strongly reduced effective dissolution surface area, is counteracted with this technique (Nyström and Westerberg, 1986). Ordered mixtures have also been used to promote the dissolution of drugs with low aqueous solubility (Westerberg, 1992). When the freely soluble carrier particles rapidly dissolve, the drug is released as discrete, primary particles, thus increasing the dissolution rate. Westerberg and Nyström (1993) found that by using ordered mixtures with a low surface area coverage of the carrier particle, the dissolution rate of the drug was greatly increased, even more than from well-dispersed suspensions.

Solid dispersions for medium/high drug content
When the amount of drug in a tablet is medium to high, ordered units cannot be used since the surface area coverage of the carrier would be much higher than unity. This will result in slowed dissolution of the carrier particles for hydrophobic drugs, thus preventing the liberation of discrete, primary drug particles (Westerberg and Nyström, 1993). Agglomeration of the fine drug particles would probably also occur, along with decreased exposed particle surface area. Solid dispersions are prepared by melting (dispersing,

dissolving or melting the drug in the carrier), dissolving (both drug and carrier are dissolved in a common solvent) or a mixture of both (e.g. Chiou and Riegelman, 1971; Ford 1986). The use of solid dispersions in fast release formulations has been studied extensively (e.g. Sjökvist Saers, 1992). To obtain rapid drug dissolution, the carrier particle should be freely soluble in water and preferably be able to increase the solubility of the drug. If the dissolution rate from solid dispersions decreases with increasing amounts of incorporated drug, probably because of the hydrophobic nature of the drug, the addition of a surfactant could help. If the dispersion is to be used for tablets, it is important to incorporate an effective disintegrating agent, and probably also to avoid carrier excipient materials of extremely deformable nature, frequently used in preparing solid dispersions. Instead, sugar alcohols, such as xylitol can optionally be used (Sjöqvist and Nyström, 1991).

Modified release tablets

In contrast to conventional tablets or tablets for instant release, modified release tablets can provide a range of release patterns (extended, delayed or repeated release) resulting in deposition of the drug in varying positions within the gastrointestinal tract. Several alternative terms are used to describe extended release systems, such as controlled release, prolonged release and sustained release (Collet and Moreton, 2002). The release rate and/or time to release onset differ among the modified release tablet systems, but the main common objective is to control the release of the drug from the dosage form. The main mechanisms that can be controlled are the dissolution of the active substance and the diffusion of the dissolved drug within the tablet (Collet and Moreton, 2002). There are several techniques available to accomplish this. A dissolution controlled release system can be obtained by covering the readily soluble drug particles and or the tablet with a slowly soluble coating. It is also possible to modify the structure of the active substance to reduce its solubility, resulting in a slower dissolution rate. The diffusion can be controlled by the addition of an insoluble membrane surrounding the drug particles or the tablet or by forming matrix tablets. In the latter, the active substance dissolves within the tablet and diffuses through the membrane or matrix. The drug can also be incorporated into an eroding matrix; the drug is then released as the matrix erodes and also by a diffusion process within the matrix.

Using the tablet form for a rapid onset of action

Parenteral dosage forms are most suitable if an instant effect is desired, because of their rapid onset of action and avoidance of the first pass effect. However, these formulations are not always convenient for the patient and can have relatively short shelf lives; thus, a tablet with similar fast-acting properties would be of great interest.

Oromucosal drug delivery

Oromucosal delivery, especially that utilising the buccal and sublingual mucosa as the absorption site, is a promising drug delivery route which promotes rapid absorption and high bioavailability, with subseqent almost immediate onset of pharmacological effect. These advantages are the result of the highly vascularised oral mucosa through which drugs enter the systemic circulation directly, thus bypassing the gastrointestinal tract and the first pass effect in the liver (Moffat, 1971). The sublingual mucosa has been used for fast absorption of drugs such as nitroglycerin in the treatment of acute angina pectoris for over 100 years (e.g. Fusari, 1973; Zhang et al., 2002). However, not all drugs can be efficiently absorbed through the oral mucosa, because of enzymatic breakdown or large molecule size (Zhang et al., 2002). Further, if the sublingual route is to be used for instant release and absorption of a drug, some formulation aspects of the dosage form must be taken into consideration. If a tablet formulation is used, the disintegration time should be short to facilitate exposure of the particles to dissolution by dissolving fluids in the oral cavity. The parent drug has to be soluble, stable and able to easily permeate the mucosal barrier at the administration site.

Another problem associated with sublingual tablet formulations is that there is always a risk that the patient will swallow part of the dose before the active substance has been released and absorbed locally into the systemic circulation. This could result in intestinal absorption, an unwanted prolongation of the pharmacological effect and high inter- and intra-individual variability of plasma concentrations and, consequently, of effect. Addition of a bioadhesive component is a well-known method of increasing the possibility of a more site-specific release. However, this concept is normally applied to non-disintegrating tablets or discs to achieve extended release of the active substance and, consequently, such a system will not be suitable for a fast acting formulation. Therefore, it would be of interest to study a disintegrating tablet which releases the drug quickly, but which also has bioadhesive properties which could prevent the drug from being swallowed.

The design of a sublingual tablet with rapid oromucosal absorption for administration of a potent drug

As mentioned above, some formulation aspects must be taken into consideration when designing a sublingual tablet. For a tablet containing a potent drug, three formulation aspects are of special interest. Firstly, incorporation of the necessarily small amounts of a very potent drug could result in poor dose homogeneity, especially if direct compression is desired. Secondly, disintegration should be fast to facilitate rapid drug dissolution. Thirdly, some bioadhesive properties are desirable to avoid swallowing the drug. However, these bioadhesive properties should not hinder the fast drug release.

Dry mixing of low proportions of drugs

In mixtures in which the particles are randomly distributed, the drug homogeneity will depend on the sample size and the number of particles of the mixed components in each sample. To obtain a random mixture, the component particles should be free-flowing and of similar size, density and shape. However, in practice, the components of tablets often vary in size. If the drug particles are small, they will normally be cohesive. In contrast to random mixtures, ordered mixtures consist of ordered units of coarse carrier particles mixed with a fine drug component. The homogeneity of an ideal ordered mixture (consisting of identical ordered units) will be greater than that of a random mixture (Hersey, 1979; Egermann, 1980a). In an ideal ordered mixture, the standard deviation (a measure of dose hetergeneity) will also be independent of the sample size, provided that the sample size exceeds at least one ordered unit, and will approach zero (Hersey, 1979).

However, in practice, the heterogeneity of powder mixtures containing micronised drugs is almost invariably far greater than that predicted for an ideal ordered system and is also dependent on sample size (Egermann, 1980b). This has been attributed to such variables as the agglomeration tendencies and wide particle size distributions of the fine cohesive drug component of the mixture (Nyström and Malmqvist, 1980; Malmqvist and Nyström 1984a). Further, if the carrier has a wide particle size distribution, the different size ranges of the carrier particles could segregate. Since, ideally, the weight of drug particles adhering to a carrier particle is proportional to the surface area of the carrier particle, segregation of the carrier particles will result in segregation of the drug, so-called ordered unit segregation (Yip and Hersey, 1977).

It is also probable that the number or the weight of drug particles adhering to the surfaces of a carrier particle will in practice not be consistent, and that can explain why an ideal ordered mixture is difficult to obtain by conventional dry mixing processes. It appears that, even if monodispersed carrier and drug particles are used, the amount of drug per carrier unit will vary (Egermann, 1980b). This effect is especially important if the mixture contains a very potent drug. According to Egermann (1980b; 1985a), this variation in the number or weight of drug particles on each carrier unit should be regarded as a random process and ideal ordered mixtures cannot be achieved in practice. Ordered mixtures are thus termed interactive mixtures in this thesis (adhesive interactive mixtures in paper I).

Disintegration of tablets

Disintegration is an important factor affecting drug release, absorption into the systemic circulation, and subsequent pharmacological effects. While it is important that tablets disintegrate swiftly, it is also desirable that they retain adequate tensile strength. Normally, this is obtained by adding specific binder excipients. However, the bond promoting properties of these binders may counteract rapid tablet disintegration. Addition of a binder often decreases the porosity of the tablet and, according to the Washburn equation, any decrease in average pore diameter results in decreased liquid penetration, which probably slows the disintegration time (Washburn, 1921; Groves and Alkan, 1979). However, a relatively low porosity has been shown to be most effective for the action of some

disintegrants (Khan and Rhodes, 1975; Shangraw et al., 1980; Ferrari et al., 1995). Conversely, high porosity would allow fast liquid penetration if the dominant disintegration mechanism was rupture of the bonds by the liquid. Sugimoto et al. (2001) utilised the good compactability of amorphous sucrose to prepare tablets with high porosity for rapid disintegration in the mouth. After storage, sucrose recrystallised with subsequent increase in tensile strength, and the previously short disintegration time was only slightly extended. Further, Kanig and Rudnic (1984) suggested that the effect of a disintegrant could be dependent on the deformability of the matrix of the tablet. If the excipients create a ductile environment, the disintegration force of the disintegrant can be counteracted, resulting in slow disintegration. However, hitherto there is no experimental evidence to support their suggestion.

During the last decade, several new types of tablets intended for rapid disintegration and drug release in the oral cavity have been reported, especially in the patent literature. The oral cavity has often been used as the site for disintegration and/or dissolution but, in most tablet systems reported, the active substance is not intended to be absorbed there, i.e. it is intended that absorption still takes place in the gastrointestinal region. Sublingual formulations such as these could be used to increase patient compliance, but could also be used to optimise the disintegration or dissolution times. The freeze-drying technique could be applied here; the resultant tablets, sometimes also denoted "fast-melting tablets" because of their high porosity, provide instant dissolution of the tablet matrix and subsequent rapid exposure of the drug. A recent pending patent, WO 0051539 from R P Scherer, describes such a matrix system. This is purported to also provide a rapid onset of action by utilising so-called "pre-gastric" absorption. Another example of an orally disintegrating tablet formulation is OraSolv® from CIMA, described in patent WO 0009090, where the tablet rapidly disintegrates in the oral cavity and thereafter forms a viscous slurry containing microcapsules or microparticles which are easy to swallow. Another fast disintegrating tablet formulation which consists mainly of small particles of sugar alcohol or saccharides has been described in patent EP 0914818 from Kyowa Hakko. Since most of these systems are not designed to directly expose the active substance in its molecular form, they are not primarily intented to give a rapid onset of effect, but rather to accelerate the disintegration or dissolution step.

Bioadhesion of tablets, powders and interactive mixtures

Bioadhesion is usually defined as the bond formed between two biological surfaces or between a biological and a synthetic surface. The term mucoadhesion is used when the mucus or mucosal surface is involved in these adhesive bonds (Chickering and Mathiowitz, 1999). Bioadhesive materials increase the contact time of the dosage form at the absorption site, resulting in site-specific drug absorption. However, incorporation of bioadhesive materials into a tablet formulation often results in slow release of the drug. This is mainly because these materials often have long polymeric chains that can create a viscous layer surrounding the fluids, thus hindering drug dissolution.

Bioadhesion mechanisms
The mucus layer is often involved in the adhesion of a bioadhesive polymer and is present as either a gel layer adhering to the mucosal surface or a solution or suspension of various substances (Smart, 1999). The mucus layer mainly consists of mucin glycoproteins, inorganic salts, proteins, lipids and water, with the composition varying depending on its source (Smart, 1999). The most common theories of bioadhesion mechanisms have been reviewed by Chickering and Mathiowitz (1999). The electronic theory involves an electronic transfer between the two materials causing a double layer of electrical charge, which results in attraction forces. The adsorption theory involves adhesion between the mucosa and the adhesive material by van der Waals interactions, hydrogen bonds and related forces. The wetting theory involves interfacial tensions between the two materials. Penetration of polymer chains into the mucus network and vice versa, causing a mechanical bond, is referred to as the diffusion theory. The importance of water content and movement of water into the bioadhesive material from the mucosa, i.e. dehydration of the mucosa, has also been suggested as a mechanism for adhesion (Duchêne et al., 1988; Mortazavi and Smart, 1993).

Evaluation of the bioadhesive properties of a material
One common in vitro method of evaluating bioadhesion is based on the fracture approach, i.e. directly evaluating the force required to separate the formulation from the mucosa, after keeping them in contact under a specified force for a specified time. The tensile stress can then be determined by dividing the maximum force of detachment by the total surface area involved in the adhesive interaction (Chickering and Mathiowitz, 1999). This method has been used for evaluating the bioadhesive properties of both pure materials and formulations (e.g. Ponchel et al., 1987; Tobyn et al., 1997). Tablets were most often used in these studies (Ponchel et al., 1987; Tobyn et al., 1997) but individual microspheres and powders have also been investigated (Chickering and Mathiowitz, 1995; Mahrag Tur and Ch'ng, 1998). Robert et al. (1988) used a method for assessing bioadhesion similar to that used in this thesis. They suggest that using powders provides a simple, rapid method of measuring the adhesive properties of a material. However, they do not appear to have performed any comparative experiments using other specimen types (such as tablets) to evaluate the influence of specimen type on the bioadhesive results.

Individual dosage

In the development of new drugs, the recommended dosages are generally based on mean results from large patient populations. However, the advantages of individualised dosage regimens are becoming increasingly apparent. Individualised dosages are able to reflect interpatient differences such as gender, age, weight, ethnicity and environment, as well as details such as genetically controlled drug metabolising enzymes (Sjöqvist, 1999). Further, the administration of the right drug at the wrong dosage could result in adverse effects or decreased efficacy, especially for drugs with narrow therapeutic indices. Fredholm and

Sjöqvist (2001) claim that these problems have increased rather than decreased over recent years and that it should be possible to avoid adverse effects by using individualised dosages. For example, Evans et al. (1998) demonstrated that individualising the dosages of methotrexate in children with B-lineage acute lymphoblastic leukaemia significantly improved outcomes without increasing toxicity. It is believed that, in future, molecular diagnostics will be used to identify genetic polymorphisms in drug-metabolising enzymes, transporters and receptors in order to individualise, and thereby optimise, drug therapy (Evans and Relling, 1999).

Current options for obtaining a more individualised dosage regimen

Tablets

Although the tablet form has many advantages, it has not always been suitable for the fine-tuning of doses to individual patients. Normally, there are only a limited number of standard tablet strengths. Combining tablets containing different amounts of the active substance has been one method of achieving a more individualised dose. However, this approach is not very convenient for the patient, who has to handle several different tablet containers and take different numbers of tablets that may be confusingly similar in dimension and shape. Further, it is not cost effective for the manufacturer to produce a wide range of tablets containing differing doses. Dividing tablets is also a common and simple technique of obtaining smaller doses, but some patients, e.g. those suffering from movement disorders and elderly people, could have difficulties with this. Breaking tablets by hand can also decrease dose uniformity, which could cause problems for some patients, especially those using drugs with narrow therapeutic indices (Teng et al., 2002). Despite these drawbacks associated with combining tablets of different strengths or splitting tablets containing standard doses, these approaches are often applied because of a lack of more effective alternatives.

Other dosage forms

Before the modern pharmaceutical industry was developed, the pharmacist divided drugs, or drug triturations, in powder form in individualised different weights *ex tempore* for each patient as prescribed by the physician. However, such an expensive approach would be impractical today, since the vast majority of pharmaceutical preparations are manufactured industrially on a large scale. Like the oral powders, powders for inhalation can be divided into different doses. Dosage forms for use in an inhaler consist of a number of blisters, each containing a small volume of powder, and individual dosages are obtained by inhaling different numbers of these small doses (Brindley et al 1995; Fuller 1995). Parenteral injections also allow adjustment of the dose, although this dosage form is not as convenient for the patient as oral dosage forms. Oral liquid dosage forms may therefore be a better alternative, and these are often used to individualise doses, especially when medication for children needs to be adjusted to their body weight. One of the main disadvantages of liquid oral and parenteral dosage forms is that the chemical stability of most drugs is rather limited as solutions or suspensions. This can be overcome by using powders and granules

that are dissolved immediately before use. However, unless each powder dose is individually predispensed, the patients have to make the solution or suspension themselves, with the associated inconvenience and risks that this entails. While transdermal preparations such as creams and ointments can also be divided into individual doses, effective systemic absorption of these preparations requires that the active substance has specific physicochemical properties at low dosage.

Aims of the thesis

The main objective of this thesis was to present and study two new concepts in oral drug administration and to evaluate them both in vitro and in vivo. In the design of new drug preparations, especially if new mechanisms, materials or processes are being developed, it is crucial to evaluate critical formulation factors in relation to the required behaviour of the final dosage form. The factors under study for the new tablet concepts investigated in this thesis included high dose homogeneity, rapid disintegration, sufficient tensile strength and bioadhesive properties. These areas have been well covered in the pharmaceutical literature, but some aspects still require more detailed investigation. For the papers included in this thesis the detailed aims were:

- To evaluate the possibility of achieving homogeneous mixtures containing a fine particulate potent drug and coarse carrier particles and to compare experimental results with theoretical data for ordered, interactive and random mixtures. Also, to study how the number of drug particles *per se*, or relative to the number of carrier particles, influences homogeneity of the mixtures (paper I).
- To study properties which could affect rapid disintegration of tablets while maintaining high tensile strength and to investigate binder properties which could affect the functionality of a superdisintegrant (paper II).
- To evaluate the biadhesion of powder and tablet specimen forms of certain materials and to investigate the possibility of increasing the bioadhesive properties of coarse, nonadhesive carrier particles by coating them with fine particulate bioadhesive materials, i.e. by forming interactive mixtures (paper III).
- To present a new sublingual tablet concept which should provide a rapid and reproducible onset of action while also offering convenience for the patient. Further, to investigate whether rapid disintegration and dissolution of the new tablet form in vitro would result in improved drug bioavailability, especially regarding absorption rate, and to investigate the importance of addition of a bioadhesive component in order to avoid swallowing the active ingredient (papers IV-V).
- To present and evaluate a new drug administration concept including an electronic automatic dose dispenser for adjustable individualised delivery of a specific number of microtablets. Also, to test this dispensing device in patients with Parkinson's disease and obtain their opinion of the concept and its ease of use (paper VI).

Materials and methods

Drug substances

- Sodium salicylate was milled in a mortar grinder (Retsch, Germany) and three particle size fractions were subsequently obtained. Two size fractions were then prepared by air classification (100 MZR, Alpine, Germany) while the third was used as obtained after milling. The samples were used as a model of a fine particulate drug substance in paper I.
- Fentanyl citrate was milled in a mortar and used in papers IV and V.
- Levodopa and carbidopa were used as supplied in paper VI.

Model compounds (paper II)

The term compound is used in this thesis for models of either drugs or excipients other than binders or disintegrants.

- Mannitol (granulated quality) (250-425 μm).
- DCP (90-180 μm).
- Sodium chloride (355-500 μm).

The different size fractions were obtained by dry sieving (Retsch, Germany).

Carrier materials in interactive mixtures

- Mannitol (granulated quality) was used as a carrier material in two size fractions: 250-425 μm (paper I) and 180-355 μm (paper III) and was used as supplied in papers IV and V.
- Dibasic calcium phosphate dihydrate (DCP) was used as a carrier material in paper III (180-355 μm).

The different size fractions were obtained by dry sieving (Retsch, Germany).

Excipients

Binders and fillers

Paper II

- Microcrystalline cellulose (MCC; Avicel PH105 (20 μm); referred to hereafter as MCC105).
- Polyethylene glycol (PEG 3000; <20 μm),
- Crystalline lactose (α-lactose monohydrate; <20 μm)
- Partially crystalline lactose (prepared by freeze drying crystalline α-lactose monohydrate; Virtis, Gardiner, USA)

- Amorphous lactose (prepared by spray drying crystalline α-lactose monohydrate; Niro Atomiser, A/S Niro, Denmark)

These materials were used as binders in paper II. The size fractions of PEG 3000 and crystalline lactose were obtained by air classification (100 MZR, Alpine, Germany). PEG was milled in a pin disc mill (160Z, Alpine, Germany) before air classification. MCC105 was used as supplied and amorphous lactose was used as prepared. Freeze dried lactose was ground in a mortar with a pestle for five minutes.

Papers IV-VI

- Silicified microcrystalline cellulose (SMCC; ProSolv SMCC® 90) was used as a binder as supplied in papers IV-V.
- Microcrystalline cellulose (MCC; Avicel® PH 101; referred to hereafter as MCC101) and crystalline lactose (α-lactose monohydrate) were used as fillers as supplied in paper VI.
- Polyvinylpyrrolidone (PVP) was used as a binder as supplied in paper VI.

Disintegrants

- Cross-linked carboxymethyl cellulose sodium (Ac-Di-Sol®) (paper II).
- Cross-linked polyvinylpyrrolidone (Kollidon CL®) (papers IV-V).

These materials were used as supplied.

Materials tested for their bioadhesive properties (paper III)

- Sodium alginate (viscosity 400-600 mPas for a 1% solution) was used as supplied
- Kollidon CL to represent materials with potential bioadhesive properties; used as supplied.
- Ac-Di-Sol was used both as supplied and in finer particle sizes obtained by milling in a mortar grinder (Retsch, Germany) followed by air classification (100 MZR, Alpine, Germany) for two of the three finer particle sizes.
- Micronised cross-linked polyvinylpyrrolidone (Kollidon CLM®) was used as supplied.
- DCP and mannitol were used as nonadhesive materials in the baseline bioadhesion studies with the size fraction 180-355 μm, which was obtained by dry sieving (Retsch, Germany).

The three particle sizes of Ac-Di-Sol were also mixed with mannitol and DCP to form interactive mixtures. Kollidon.CLM was mixed with DCP to form interactive mixtures.

Other excipients

- Ethanol (95% w/w) was used as granulation liquid in paper VI.
- Magnesium stearate was used as a lubricant in papers II-VI.

Storage conditions for materials

All powders were stored at room temperature and 40% relative humidity (RH), except partially crystalline and amorphous lactose which were stored at 0% RH, for at least 48 hours before characterisation, mixing and compaction. However, in papers IV and V the materials were stored at room temperature and without control of relative humidity before mixing and compaction.

Primary characterisation of materials

Density
The apparent particle densities (B.S. 2955,1958) of all pure materials (papers I-VI) and mixtures (papers II and III) were assessed using a helium pycnometer (AccuPyc 1330 Pycnometer, Micromeritics, USA). In papers IV-VI the apparent particle densities of the mixtures were calculated according to Jerwanska et al. (1995) (Table 1).

External surface area
The external surface area of materials with a coarse size fraction (>90 μm) was determined using Friedrich permeametry (Eriksson et al., 1990). Blaine permeametry (Kaye, 1967) was used to determine the external surface area of all other powders. The surface area of materials with a small particle size was corrected for slip flow (Alderborn et al., 1985b), (Table1).

Particle size
In paper I, the size of the particles in the three fractions of sodium salicylate was estimated using laser diffraction analysis (LS 230, Coulter, USA). Since sodium salicylate is highly soluble in water, cyclohexane was used as the dispersion medium (Table 1).

Amorphous content
The degree of disorder of the different forms of lactose, used in paper II, was investigated using a 2277 Thermal Activity Monitor (TAM; Thermometric AB, Sweden). The measurements were performed according to the miniature humidity chamber technique (Angberg et al., 1992). The experimental temperature was 25 °C and a saturated salt solution (sodium bromide) was used to obtain a relative humidity of 57%. An empty, freshly sealed glass vessel was used as reference. DSC (Mettler DSC 20 TC10A/TC15, Switzerland) was also used to characterise the degree of amorphous content. The samples were scanned over a temperature range of 30-250 °C at a rate of 10 °C/minute. For both techniques the area under the recrystallisation peak was integrated and normalised for sample weight. The degree of disorder in the sample was calculated from these normalised values, assuming amorphous lactose as the amorphous standard (Sebhatu et al., 1994).

Table 1. *Primary characteristics of test materials (data from papers I-VI).*

Material		Paper	Particle size[a] (μm)	Apparent particle density[a] (g/cm^3)	External specific surface area[a] (m^2/g)
Fentanyl citrate		IV-V	-	1.282	2.3
Levodopa		VI	-	1.503	1.3
Carbidopa		VI	-	1.466	8.5
Sodium salicylate	A	I	87 (22, 150)[b]	1.563[c]	0.77
	B		15 (5.0, 27)[b]	1.563[c]	2.6
	C		3.6 (2.0, 6.0)[b]	1.563[c]	4.3
Mannitol		IV-V	-	1.481-1.486[c]	0.024
		III	180-355	1.481-1.486[c]	0.029
		I-II	250-425	1.481-1.486[c]	0.023-0.024
Sodium chloride		II	355-500	2.155	0.0066
DCP		II	90-180	2.884-2.920[c]	0.065
		III	180-355	2.884-2.920[c]	0.044
Crystalline lactose		II	<20	1.536	0.85
Partially crystalline lactose		II	-	1.528	0.27
Amorphous lactose		II	-	1.527	0.24
MCC101		VI	-	1.564	0.33
MCC105		II	-	1.569	0.72
PEG 3000		II	<20	1.220	0.98
SMCC		IV-V	-	1.578	0.35
Kollidon CL		III-V	-	1.224	0.42
Kollidon CLM		III	-	1.212	3.3
Ac-Di-Sol		II-III	-	1.604-1.607[c]	0.24-0.26
Coarse		III	>5	1.604-1.607[c]	0.32
Medium		III	-	1.604-1.607[c]	0.64-0.67
Fine		III	<5	1.604-1.607[c]	1.3
Sodium alginate		III	-	1.717	0.20

[a] A range is given for measurements of more than one batch.

[b] Median values by weight. The size limits for which the cumulative amounts (by weight) from undersize distribution were equal to 10 and 90%, respectively, are given in parentheses.

[c] The value was characterised for the material as supplied and used for all size fractions.

Preparation of mixtures

In paper II, mixtures of compounds, binders and the superdisintegrant were prepared in different combinations and amounts. The powders were mixed in glass jars in a tumbling mixer (Turbula mixer T2F, W.A. Bachofen AG, Switzerland) at 120 rpm for 100 min. The weight of the mixtures was held constant at 25 g. In papers I, III, IV and V, the drug or

bioadhesive substance was added to the carrier material and mixed in glass jars or a teflonized metal jar (papers IV and V) in a Turbula mixer (Turbula mixer T2F, W.A. Bachofen AG, Switzerland) at 90 or 120 rpm for 24-72 hours. The weights of the mixtures were 64.65 g and 226.28 g in paper I, 10 g in paper III and 59.6 g in papers IV and V. In papers IV and V, Kollidon CL and SMCC were also added and mixed at 30 rpm for an additional 30 minutes. In this thesis, the surface area coverage of the carrier particles is defined as the surface area ratio (Nyström et al., 1982a).

Determination of mixture homogeneity

In paper I, the relative standard deviation of the content of sodium salicylate was used to express the quality (i.e. heterogeneity) of the mixtures (Williams 1968/69). Samples of each mixture weighing 25, 45 and 110 mg (30 of each) were withdrawn with the aid of sample thieves. The amount of sodium salicylate in the samples was measured spectrophotometrically (U1100, Hitachi Ltd, Japan and UV4-100, Unicam Ltd, U.K.) at a wavelength of 295 nm. To eliminate the effect of variations in sample weight between the individual samples, the sodium salicylate content was normalised for each respective mean sample weight before calculation of the relative standard deviation. The standard deviations were assumed to follow a χ^2-distribution and the confidence limits were calculated for the 95% probability level (Valentin, 1967).

Theoretical models for prediction of mixture homogeneity

Three theoretical models were used in paper I to compare the experimental values of the sodium salicylate mixtures. Firstly, the concept of a random distribution of the components was applied, assuming that no interactions or adhesive forces were developed between the two components (random mixtures). Secondly, the mixtures were assumed to be capable of forming ideal ordered mixtures, with stable interactions and an identical amount of drug component or number of drug particles attached to each individual carrier particle (ordered mixtures). Thirdly, the mixtures were assumed to develop interactive forces, but the drug amount adhering to carrier units was assumed to be random, as suggested by Egermann (1980a) and Egermann and Frank (1992) (interactive mixtures).

Random mixtures

The homogeneity, expressed in terms of variance (σ^2), of a theoretical random distribution of sodium salicylate and mannitol can be calculated according to Lacey (1943):

$$\sigma^2 = \frac{p \cdot q}{N_p + N_q} \qquad (1)$$

where σ is the population standard deviation, p and q are the proportions of sodium salicylate and mannitol, respectively, and N_p and N_q are the numbers of particles of sodium salicylate and mannitol, respectively. Thus, $(N_p + N_q)$ is the total number of particles per

sample and p+q=1. This equation, which is valid for mixtures containing monodispersed components, has been further developed by Poole et al. (1964) to include polydispersed materials:

$$\sigma^2 = p \cdot q / \left[\frac{M}{p \cdot \overline{w}_q + q \cdot \overline{w}_p} \right] \qquad (2)$$

where M is the weight of the mixture sample, p and q are the proportions by weight of the two components and $\overline{w}_p$ and $\overline{w}_q$ are the mean particle weights, expressed in terms of weight (see below), of the two components. The mean particle weights were calculated according to Poole et al. (1964) and are denoted $\overline{w}$ in eq. 3 to indicate that the method of calculation is identical for sodium salicylate ($\overline{w}_p$) and mannitol ($\overline{w}_q$). Thus:

$$\overline{w} = \sum \left[f_r \cdot \alpha_v \cdot \rho_s \left(\frac{d_{r1}^3 + d_{r2}^3}{2} \right) \right] \qquad (3)$$

where α_v is the volume shape factor (Heywood, 1954), ρ_s is the apparent particle density of the material, d_{r1} and d_{r2} are the lower and upper limits, respectively, of particle diameter in size class r, as measured by laser diffraction data for sodium salicylate and dry sieving for mannitol, and f_r is the fraction of material in size class r, expressible in terms of number or weight of particles. Consequently, the mean particle weights ($\overline{w}_p$ and $\overline{w}_q$) can be defined as number based or weight based. In eq. 2, mean particle weights expressed in terms of weight rather than in terms of number should be used (Kristensen, 1981). The standard deviation was divided by p and multiplied by 100 to achieve the relative standard deviation as a percentage (σ_{rel}). This theoretical value represents the most homogeneous mixture possible, assuming no adhesive interactions between drug and excipient particles and no tendency for the two types of particle to segregate.

Ordered mixtures
For an ideally ordered state, the theoretical value of the standard deviation is 0 %, presuming that the two components exist as identical perfectly monodispersed units and that the sampling and analytical errors are zero. This model assumes that an identical number or weight of drug particles are attached to all carrier units.

Interactive mixtures
The relative standard deviation for these mixtures can be calculated using Johnson's equation (Johnson, 1972) as modified by Egermann (1980b and 1985b):

$$\sigma_{rel} = 100 \cdot \sqrt{\frac{\overline{w}_p}{G}} \qquad (4)$$

where G is the mean weight of drug per sample, i.e. p · M, and $\overline{w}_p$ is the mean particle weight, expressed in terms of weight, of a drug in monodispersed form. Later this equation was suggested to be valid also for polydispersed drug particles and monodispersed carrier units (Egermann, 1985a). The particles were divided into a number of size fractions, the particle weight for each fraction was calculated and the mean particle weight ($\overline{w}_p$) was obtained as in eq. 3.

Calculation of relative and absolute numbers of drug particles

Calculation of particle number ratios in mixtures

The number of particles of each respective material, i.e. $\overline{N}_p$ and $\overline{N}_q$ in a sample (of weight M) was calculated according to:

$$\overline{N}_p = \sum \left[\frac{f_r \cdot p \cdot M}{\overline{w}_{p,r}} \right] \qquad (5)$$

$$\overline{N}_q = \sum \left[\frac{f_r \cdot q \cdot M}{\overline{w}_{q,r}} \right] \qquad (6)$$

where f_r is the fraction of material in size class r (as in eq. 3) and $\overline{w}_{p,r}$ and $\overline{w}_{q,r}$ represent the mean particle weights within each respective size class r. Since f_r in eq. 5 and 6 can be expressed in terms of either particle number or weight, the corresponding mean particle numbers, $\overline{N}_p$ and $\overline{N}_q$ can also be expressed either by particle number or by weight. Again, in eq. 2, for calculation of the theoretical random distribution in binary mixtures, the mean particle weights must be defined by weight and thus the mean number of particles must be defined as the mean particle number by weight. However, in reality, the actual number of particles will obviously correspond to the mean particle weights by number (Nyström et al., 1982b). In eq. 1, neither N_p nor N_q need to be defined as mean values because, since the two materials are inherently defined as monodispersed, only one expression for particle number is possible.

For polydispersed materials, however, the mean number of particles must be clearly defined. In this study, the particle number for sodium salicylate was calculated as described in eq. 5, with two results (using weight and number). Mannitol, however, has a rather narrow distribution of particle sizes and, subsequently, the number of particles in the number fraction will be similar to the number in the weight fraction. Therefore, since f_r in eq. 6 was defined using only the weight fraction, there was only one particle number for mannitol. In contrast, the particle number ratio $\overline{N_p} / \overline{N_q}$ was calculated in terms of both number and weight for sodium salicylate as a way of expressing the relative amounts of the two materials.

Calculation of number of drug particles in samples
The particle number ratio, i.e. an expression characterising a property of the mixture without taking into account any effect of sample size, could function as a predictor of the homogeneity of an ideal ordered mixture. For such a mixture, the existence of identical or nearly identical ordered units means that only the relative number ratio will be important, since the mixing quality is expected to be independent of sample size. However, if the number of drug particles attached to the carrier particles varies, e.g. in a random fashion, the sample size must also be taken into account. For this reason, the absolute number of particles in the sample tested was also calculated. Thus, the number of salicylate particles by weight in each sample was calculated using eq. 5.

Preparation of granules for microtablets

Levodopa (25.0 grams), carbidopa (6.25 grams) and MCC 101 (28.75 grams) were mixed in a glass jar in a tumbling mixer (2L Turbula mixer, W.A. Bachofen AG, Basel, Switzerland) at 120 rpm for 5 min. Ethanol containing 10% w/w PVP (30 ml) was added during stirring and the granulation mass was pressed through a 500 μm sieve (Retsch, Germany). The granulate was dried at room temperature for 48 hours. The dry granules were then sieved (300 μm), magnesium stearate powder (0.5% w/w) was added and the combination was mixed in glass jars in the tumbling mixer for 2 min. For the clinical study, placebo tablets were prepared in the same way except that they contained lactose (12.0 grams) and MCC101 (48.0 grams) instead of levodopa and carbidopa.

Compaction of tablets

In papers II-V, the tablets were made in a single punch press (Korsch EK0, Germany), which was instrumented in papers II and III with maximum upper punch pressures of 200 MPa (paper II) and 100 MPa (paper III). In papers II-III, 1.13 cm flat-faced punches and in papers IV-V 6 mm flat bevel edged punches were used. In paper VI, a single punch press (Diaf, Denmark) and 3 mm flat-faced punches were used. In papers II and III, the upper punch pressure was obtained by keeping the distance between the punches constant (3 mm at zero pressure) and varying the amount of powder in the die, while in papers IV-VI the

amount of powder was held constant. In papers II and III, the powder was weighed on an analytical balance and manually filled into the die, while in papers IV-VI a hopper shoe was used to fill the die. In paper II, the surfaces of the die and punches were lubricated with magnesium stearate powder before each compaction and in papers III-VI the magnesium stearate powder (0.5% w/w) was added to the powder in a tumbling mixer (Turbula mixer, 2L, W.A. Bachofen, Switzerland) and mixed at 30 rpm or 120 rpm for 2 min.

Characterisation of compaction behaviour

Deformation properties

In paper II, the deformability of the materials was evaluated from Heckel plots (Duberg and Nyström, 1985) and determined by recording the upper punch pressure and the height of the tablets every millisecond during the compression and decompression cycles (in-die). The tablets were compressed at a maximum upper punch pressure of 200 MPa and the porosity of the resultant tablets was obtained from the tablet heights and apparent densities of the materials. The apparent yield pressure of the materials was calculated from the reciprocal of the slope of the linear part of the Heckel plot (Duberg and Nyström, 1985). Since the measurements were made in-die, the yield pressure was assumed to reflect the total deformation of the material, i.e. including both plastic and elastic deformation (Duberg and Nyström, 1986; Paronen, 1986; Olsson et al., 1998). Out-of-die measurements were also made, i.e. the binders were compressed at different maximum compaction loads (30-200 MPa) and the porosity of the tablets was calculated from the tablet dimensions after compaction and the apparent density of the powder. An out-of-die yield pressure was calculated from the reciprocal of the slope of the linear part of the corresponding Heckel plot. It was assumed that this yield pressure value reflected the degree of plastic deformation of the material (Paronen, 1986). The axial elastic recovery was calculated from the relative difference between minimum (during compaction) and maximum (after 48 hours of storage) tablet heights (Armstrong and Haines-Nutt, 1972).

Fragmentation tendency

Tablets of the compounds and binders were compressed by hand at different compaction loads in a specially constructed die using an instrumented single punch press (Korsch EK0, Germany). The specific surface area of the tablets was determined using Blaine permeametry and the surface area was corrected for slip flow (Kaye, 1967; Alderborn et al., 1985b). The degree of particle fragmentation during compaction was evaluated by plotting the tablet specific surface area as a function of compaction load as described by Alderborn et al. (1985a).

Characterisation of tablets

In papers II, III and VI, all tablets were stored at 40% RH, except tablets containing partially crystalline and amorphous lactose which were stored at 0% RH, for at least 48 hours before characterisation.

Porosity
The porosity of the tablets was calculated from their weights and dimensions and the apparent particle density of the material or mixture.

Tensile strength
A diametral compression test (Holland C50, UK, M39K Lloyd Instruments, UK or Kraemer HC97, Kraemer Elektronik GmbH, Germany) was performed. In papers II and VI the radial tensile strength of the tablets was calculated according to Fell and Newton (1970).

Friability
The friability of the tablets was measured using the Roche friabilator. In paper IV, twenty tablets and, in paper VI, forty-one tablets corresponding to a weight of approximately 0.5 grams were weighed before and after rotating for 4 minutes at a speed of 25 rpm, and the weight loss was calculated (n=3).

Disintegration
In paper II, the disintegration time of the tablets was measured in deionised water (37 °C) according to the USP XXII disintegration test (without discs) (Pharmatest PTZ-E, Germany). In paper IV, the disintegration time of the tablets was measured in water according to European Pharmacopoeia (1997), as measured both with and without the use of discs (Kraemer DES-1, Kraemer Elektronik GmbH, Germany).

Assay of drug content
In paper IV, the content of fentanyl in ten tablets was analysed using reversed-phase high-performance liquid chromatography (RP-HPLC) with UV detection. The mobile phase consisted of phosphate buffer (pH 2.8) with 35% acetonitrile. The analyses were performed according to the European Pharmacopoeia and by Quintiles AB, Sweden. In paper VI, the content of levodopa and carbidopa in twenty microtablets was analysed using RP-HPLC with electrochemical detection (ESA 5100A). The method is a modification of one previously reported (Bredberg et al., 1993). The mobile phase consisted of 0.05 M phosphate buffer (pH 2.8) with 10% methanol. The HPLC system was equipped with a 5A5 Hypersil C18 reversed-phase column (150 x 4.6 mm, 5 μm). The oxidation potential for detector one was 0 V and for detector two + 0.4 V; the flow rate was 1 ml min^{-1}. The analyses were performed by Quintiles AB, Sweden.

Drug dissolution
Dissolution tests were performed according to a modified European Pharmacopoeia paddle method (Prolabo dissolutest, Germany). The paddle rotation rate was 50 rpm and the dissolution medium was water (volume: 300 ml; temperature 37°C). Samples were collected after 1, 3, 5, 7 and 10 minutes. The amount of fentanyl was determined using liquid chromatography (LC) with Shimadzu SPD-10A vp detector. The mobile phase consisted of 65% phosphate buffer (pH 2.8) and 35% acetonitrile. The LC system was equipped with an Aquasil C18 column (250 x 4.6 mm, 5 μm). The analysis was performed by Mikro Kemi AB, Sweden. The percentage of dissolved drug was calculated in relation to the maximum amount detected (=100%) and the data were presented in the dissolution rate profiles as a function of time.

Bioadhesion measurements (paper III)

Materials and characterisation of the mucosa
Fresh pig intestine was collected at a slaughterhouse (Swedish Meat AB, Uppsala, Sweden) and used fresh or was frozen until required. Before use, the frozen intestine was thawed in buffer solution at 4°C overnight. The buffer solution used was Krebs-Ringer Bicarbonate with a pH of 7.4.

To test the quality of the mucus layer and the effect of handling the mucosa, four representative tissue specimens were stained with Alcain blue, partly according to the method by Corne et al. (1974). Both fresh and frozen tissues were then soaked for two hours in TRIS (TRIZMA Hydrochloride) buffered sucrose solution with Alcian blue 8 GX (1mg/ml). The tissues were rinsed in TRIS/sucrose buffer and visually studied.

Adhesion test
A TA-HDi texture analyser (Stable Micro Systems, Haslemere, UK) with a 5 kg load cell and associated software was used for the bioadhesion studies. The pig intestine was cut into approximately 2 cm^2 pieces and placed in a tissue holder. Either a tablet (using a cyanoacrylate adhesive) or powder (using double-sided tape) was attached to the upper probe. The powder was applied by immersing the probe into a powder bed and gently shaking it to remove any excess, so as to achieve a monolayer of particles, which was visually validated. After spreading 30 μl of buffer onto the mucosa with a pipette to standardise hydration, the tablet or powder was brought into contact with the mucosa under a force of 0.5 N over 30 seconds. The probe was then raised at a constant speed of 0.1 mm/s and the detachment force was recorded as a function of displacement. The detachment force was measured at a sampling rate of 25 measurements/second throughout the measuring cycle. The maximum force monitored, i.e. the fracture force, was determined using the computer software Texture Expert Exceed (Stable Microsystems, Haslemere, UK).

Normally, for the type of bioadhesive measurements used in this study, a contact time of around 300 s has been used (e.g. Ponchel et al., 1987; Tobyn et al., 1997). However, a

shorter duration of contact (30 s) was chosen for these studies, mainly because of the intention to reflect a quickly disintegrating system, such as tablets for sublingual administration, as mentioned in the introduction, but also since the mechanism of water movement is believed to occur very rapidly (Mortazavi and Smart, 1993). This shorter contact time has also been used previously by other workers (Reich et al., 1984, Robert et al., 1988). The removal speed of the probe was 0.1 mm/s, as has been used for similar measurements by others (Ponchel et al., 1987; Tobyn et al., 1995). The tensile stress for the adhesive alone (no sample) was 0.22 N/cm^2. This indicated that the adhesive could not substantially have contributed to the bioadhesive effect of the materials, since both lower and higher values were obtained for the powders and mixtures.

Clinical studies

Pharmacokinetic evaluation of the sublingual tablet (Papers IV and V)

Patients

Eleven patients with cancer (4 women and 7 men, age 34-75 years) gave their written informed consent to participate in the pharmacokinetic study. Patients were recruited from the out-patient clinic at the department of oncology, Sahlgrenska Academy, Gothenburg University, Sweden. Eight patients completed the whole study; withdrawal was not associated with the study drug. All patients had metastatic malignant disease and they were all receiving treatment for pain with continuous opiate medication; however, none were receiving a pharmaceutical product containing fentanyl.

Study design

The study was conducted as a double blind crossover trial, consisting of three treatment periods. The patients received fentanyl doses of 100, 200 and 400 μg, respectively, as a single dose in the form of a sublingual tablet. The doses were given in random order and were separated by wash-out periods of at least 3 days. Blood samples (n=16, 7 ml each) for determination of fentanyl in plasma were collected at 0-600 minutes. Tolerability parameters such as blood pressure, heart rate and oxygen saturation were followed during the complete study day. Adverse events were continuously monitored throughout the study. A safety follow-up, including physical examination, routine haematology and clinical chemistry was performed 2-5 days after the last dose. The study was approved by the Ethics committee of the Medical Faculty, Gothenburg University, Sweden, and the Medical Product Agency, Sweden.

Sample analysis

Fentanyl was separated from plasma samples by liquid/liquid extraction, using n-heptan containing 3% 2-butanol at pH>12. After evaporation, the residue was dissolved in 5mM formic acid solution. The amount of fentanyl was determined using RP-HPLC with liquid chromatography – tandem mass spectrometry (LC-MS/MS) detection. The mobile phase consisted of acetonitrile:water (18:82) containing 5mM formic acid. The analysis was performed by Quintiles AB, Sweden.

Handling study for the administration device (Paper VI)

Patients

Twenty patients with Parkinson's disease (PD) (7 women and 13 men, age 49-79 years) gave their written informed consent to participate in the usability study. The patients had had PD for a mean of 8.5 (range 0-26) years and had been exposed to levodopa for a mean of 7.2 (range 0-24) years. Patients were recruited consecutively at the Uppsala University Hospital neurology clinic and the only exclusion criterion was dementia.

Testing procedure

Patients were characterised according to medication, concomitant diseases and severity of PD. The unified PD rating scale (UPDRS), parts I (mentation, behaviour and mood), II (activities of daily living) and IV (complications of therapy) were applied along with the Modified Hoehn and Yahr scale for staging of disease severity, scored from 1 to 5 (Fahn et al., 1987).

All patients were instructed once on how to use the dispensing device. After the demonstration, the patients were asked to operate the dispenser themselves. Any additional instructions were recorded. Patients were asked to start the dispenser, to set the dose to 65 mg (from a default dose of 20 mg), to confirm the dose and to release 13 microtablets into a glass. The patients were also asked to pick up five microtablets from the table. These tests were observed by the investigators, who recorded the outcomes. After the tests, all patients answered 15 questions on their impressions of the method. Placebo microtablets were used for the tests and patients did not ingest any microtablets. The study was approved by the ethics committee of Uppsala University.

Evaluation of factors affecting the formulation of interactive mixtures containing a low proportion of drug

Paper I investigated the possibility of achieving homogeneous mixtures containing a fine particulate potent drug and coarse carrier particles. Micronised materials are normally cohesive and, thus, adhesive forces can arise between the coarser component and the drug, resulting in so-called ordered units. To investigate the presence of adhesive forces between the particles, the distribution of the drug in the withdrawn mixture samples was measured and these standard deviation values were compared with calculated values from theoretical models for random, interactive and ordered mixtures.

Effect of particle and sample size

Mixtures of 0.15 and 0.015% sodium salicylate containing three different particle sizes (A, B and C or large, medium and small particles, as outlined in Table 1) were prepared and samples of three different sizes were withdrawn from each. The effect of particle size was pronounced in mixtures containing both proportions of sodium salicylate (Fig. 1). However, a strong agglomeration tendency was seen with the intermediate-size particles of sodium salicylate, as in sample B, in combination with a low drug proportion, resulted in standard deviations much higher than expected (sample B10). The relative standard deviations for this sample were closer to those obtained for sample A10 than to those for sample C10, as would have been expected from the relative sizes of the sodium salicylate particles (Table 1). The effect of particle size on the homogeneity of mixtures and tablets has also been studied by Sallam and Orr (1986), who concluded that both particle size and agglomeration tendency will affect the homogeneity of formulations containing minute amounts of a potent drug.

The effect of sample size was generally less pronounced than the effect of particle size. However, the effect of sample size was not negligible, and the relationship between the size of the sample and the homogeneity of the mixture is particularly relevant for evaluation of the dominant mechanism of drug distribution in a mixture. Fig. 2 shows the homogeneity values related to the size of the mixture sample, expressed as the reciprocal of the square root of sample size. A linear relationship which intersects origo would be expected for a random mixture (Williams 1969/70). This means that, if the particles are randomly distributed in the mixture, the probability of removing a homogeneous sample will increase with the size of the sample. A linear relationship like this has also been suggested for interactive mixtures (Egermann, 1985b), as seen in eq. 4 and Fig. 2. The homogeneity of an ordered mixture, in contrast, would not be affected by the size of the sample, provided that it exceeded one ordered unit (Hersey, 1979). Therefore, the effect of sample size on the standard deviation could be used to differentiate between a truly ordered state and random or interactive states in a mixture.

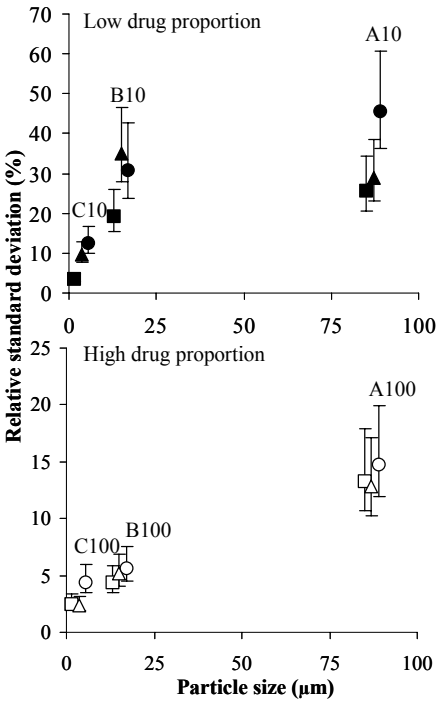

Figure 1. *The effect of drug particle size on the quality of mixtures containing 64.65 g carrier (mannitol) and 10 mg (low drug proportion) or 100 mg (high drug proportion) of sodium salicylate. The figure shows three different size fractions of sodium salicylate particles (A-C), and three different sample sizes (Tables 3 and 4). The samples are separated on the x-axis for clarity: the large sample size is moved to the left by 2µm (■ and □), the small sample size is moved to the right by 2µm (● and ○), and the medium sample size is in the correct position (▲ and Δ). Confidence intervals for p=0.05 are shown where they exceed the dimensions of the symbol.*

The results showed that in order to obtain a homogeneity resembling an ideal ordered mixture (small effect of sample size corresponding with low standard deviation) the highest drug proportion (0.15%) and the finest particles of sodium salicylate (sample C100) had to be used. However, even for this mixing system, the effect of sample size was not entirely negligible. It was thus generally observed (Fig. 2) that the use of coarser drug particles and lower proportions of added drug decreased the likelihood of obtaining mixtures with a degree of homogeneity close to that expected for an ordered distribution of the components. This result was also apparent when the sample size was decreased to the lowest level

(approximately 25 mg), as demonstrated with sample C (Fig. 2c). These collective results indicate that the binary mixtures tested demonstrated properties with some contribution from a random process. Since the relatively fine particles of sodium salicylate used would be expected to develop interactive forces, interactive mixtures were probably formed. It was thus assumed that the distribution of the drug particles adhering to the surfaces of the carrier particles was non-uniform for all the mixtures tested in this study.

With smaller sample sizes, the probability of finding uncoated carrier particles also increased with decreasing proportions of drug, thus resulting in a random distribution of coated and uncoated or less coated carrier particles. This pronounced non-uniform distribution could further be explained by the fact that granules of mannitol have a porous and irregular surface texture, and sodium salicylate particles could accumulate in these pores and irregularities (Staniforth et al., 1981). Since the presence of these pores and irregularities varies among the carrier particles, the accumulation of fine drug particles on the carrier particles will also be non-uniform.

Comparison of theoretical predictions of a random distribution and an interactive distribution

Fig. 2 demonstrates that the calculated predictions for a random distribution of drug (eq. 2) and for an adhesive interactive distribution (eq. 4) are very similar. This similarity increased with an increase in particle size, so that the theoretical values for mixture A were almost identical, while significant differences were obtained for mixture C. In the latter case, equation 4 resulted in almost zero values, especially for mixtures containing 0.15%, whereas the random distribution model (eq. 2) resulted in significant values for the predicted relative standard deviation.

The approach suggested by Egermann thus seems to predict the best obtainable low-dose interactive mixtures reasonably well. Predicted standard deviations for mixtures containing fine drug particles will generally be close to zero, i.e. the mixtures will approach ordered mixtures. However, as demonstrated here, the use of eq. 4 will reveal any sensitivity to parameters such as sample size, which would reflect the influence of random attachment of drug particles onto the carrier particles. Nonetheless, equation 4 is less reliable for prediction of the homogeneity of interactive mixtures containing a larger proportion of coarse carrier particles and a small proportion of coarser drug particles (although these would still adhere to a certain extent). This was demonstrated here with mixtures A10 and A100. At the 95% probability level, only one sample (Fig. 2a, A10 low proportion, medium sample size) had an experimental standard deviation significantly lower than predicted; however, there was a tendency towards lower values for both A10 and A100 than predicted from eq.4.

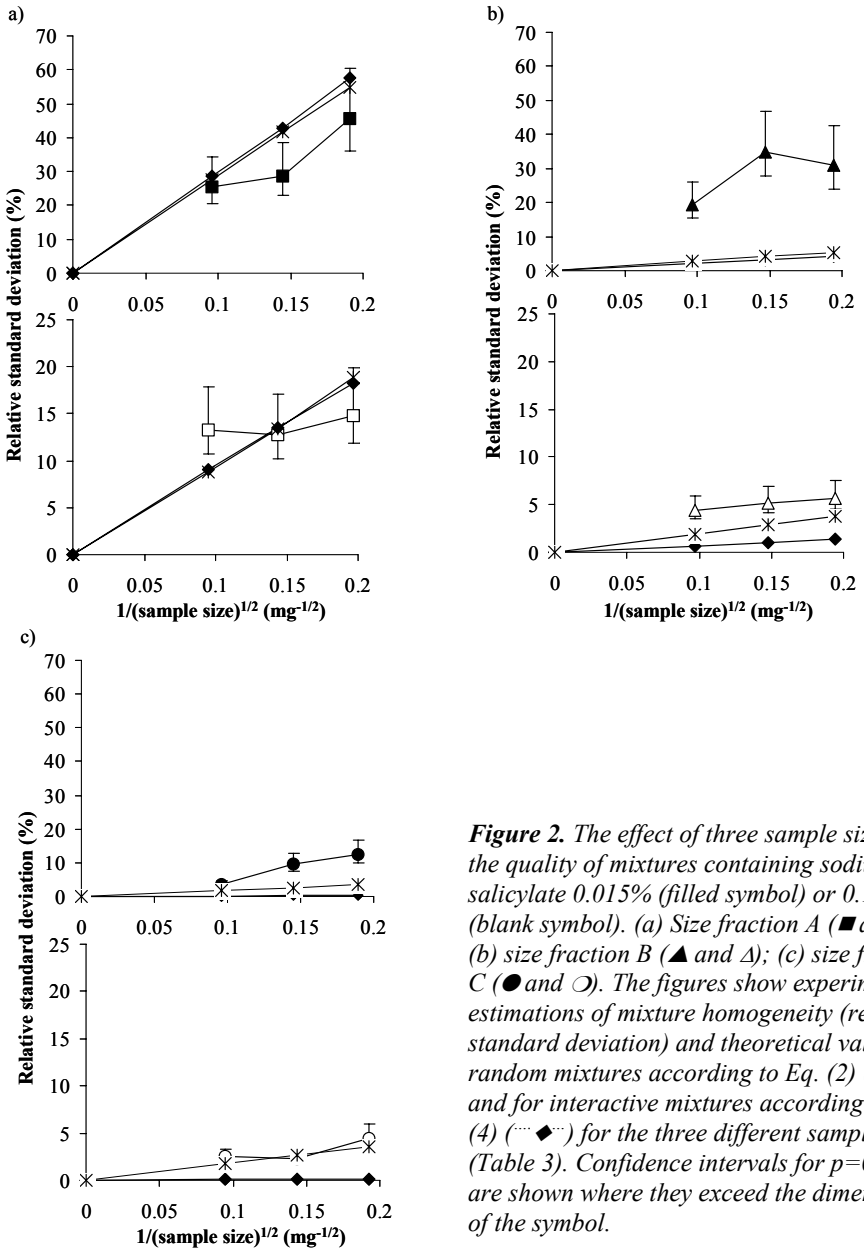

Figure 2. *The effect of three sample sizes on the quality of mixtures containing sodium salicylate 0.015% (filled symbol) or 0.15% (blank symbol). (a) Size fraction A (■ and □); (b) size fraction B (▲ and Δ); (c) size fraction C (● and ○). The figures show experimental estimations of mixture homogeneity (relative standard deviation) and theoretical values for random mixtures according to Eq. (2) (--✳--) and for interactive mixtures according to Eq. (4) (···◆···) for the three different sample sizes (Table 3). Confidence intervals for p=0.05 are shown where they exceed the dimensions of the symbol.*

Table 2. *Summary of mixture characteristics (data from paper I).*

Size fraction of sodium salicylate	Amount sodium salicylate added to 64.65 g mannitol (mg)	Surface area ratios[a] (%)	Ratio of particle numbers[b] $\bar{N}_p / \bar{N}_q$ by weight (-)	by number (-)
A	100	1.29	1.2	4000
B	100	4.34	110	6200
C	100	7.16	2300	6300
A	10	0.129	0.12	400
B	10	0.434	11	620
C	10	0.716	230	630

[a] Ratio of projected external surface area of sodium salicylate to the total external surface area of mannitol, calculated according to Nyström et al. (1982b).

[b] Number of sodium salicylate particles divided by the number of mannitol particles. The number of particles was calculated from size distributions by weight and number for sodium salicylate and by weight for mannitol, according to eq. 4 and 5.

Particle number ratios

The particle number ratios describe the number of particles that can theoretically adhere to one carrier particle (Table 2). Thus, the particle number ratio will increase if the proportion by weight of drug is increased or the size of the drug particles is decreased. An ordered mixture can in theory be reached only when each carrier particle is an "ordered unit", i.e. has at least one drug particle adhered to it (a particle number ratio of at least 1). In practice, however, the particle number ratio (Figs. 3a and 3b) will need to be much higher than 1 in order to obtain a mixture with a standard deviation as low as that expected for an ordered or apparently ordered mixture.

The two different types of number ratios (by weight or by number) could result in quite different characterisations of a mixture. The coarser drug particles are obviously more important when the relative particle numbers are based on weight data (mean particle weights by weight) compared to number data (mean particle weights by number) and likewise a particle number ratio estimated by number will always be higher than the corresponding particle number ratio estimated by weight. A large difference between the two types of particle number ratios indicates a wide particle size distribution.

Figs. 3a and 3b show a general tendency for an increasing particle number ratio to lead to a decreasing relative standard deviation, but the particle number ratio by weight seems to have the best correlation with homogeneity as expressed by the relative standard deviation. This is not surprising, since the homogeneity data are based on variations in drug amounts between mixture samples, where the amounts are characterised in terms of weight

proportions. This is, in fact, also the basis for the derivation of the equation proposed by Poole et al. (1964), where mean particle weights should be defined on a weight basis, as described in detail by Kristensen (1981).

The collective results from this study thus indicate that, for predicting the possibility of obtaining a robust interactive mixture of high quality, the particle number ratio by weight (Fig. 3b) has the best correlation with the relative standard deviation. This is especially based on the following experimental observations. Firstly, only for mixture C100 were homogeneity values close to those of an apparently ordered mixture; all the other mixtures were less homogeneous or had a pronounced sensitivity for e.g. sample size. Secondly, for mixtures containing drugs with a wide particle size distribution, as exemplified by A100, the use of particle number ratios by number resulted in erratic predictions of the achievable homogeneity. Consequently, it appears from Fig. 3b that a high quality mixture should contain more than 500 drug particles (by weight) per carrier particle. Obviously, a more fundamental prerequisite is also that the drug particles are fine enough to develop adhesive interactions with the carrier and do not have a tendency to create strong agglomerates.

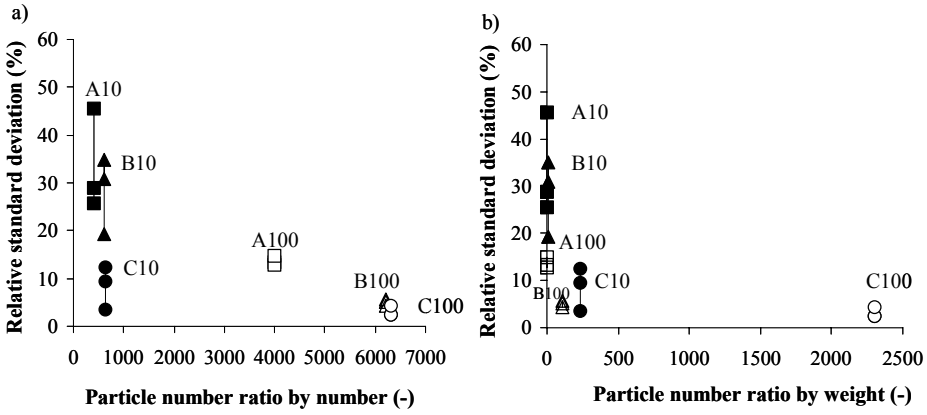

Figure 3. *Mixture homogeneity, expressed as relative standard deviation, as a function of particle number ratio by number (a) and particle number ratio by weight (b). Three sample sizes and two weight proportions of sodium salicylate are presented (symbols as in Fig. 2).*

Absolute particle numbers by weight

The results can be normalised for the effect of sample size by calculating the actual number of drug particles by weight in the sample. This gives a more precise estimate of the mixture homogeneity than using the particle number ratios. It can be seen from Fig. 4 that the relative standard deviation approaches the low values expected for ordered or nearly

ordered mixtures (i.e. the determined relative standard deviation has contribution only from errors in sampling, analytical procedure etc. (Malmqvist and Nyström, 1984b) only when the number of drug particles is very high (>10^6).

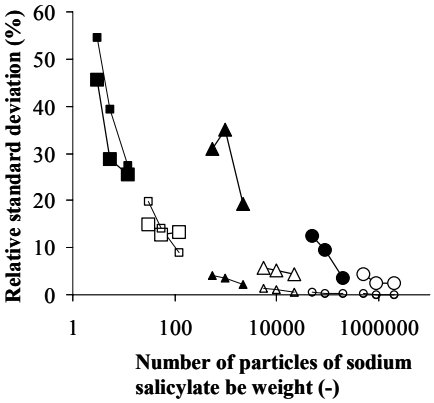

Figure 4. *Mixture homogeneity, expressed as relative standard deviation, determined experimentally (——) and using theoretical values for interactive mixtures according to Eq. (4) (·····) as a function of the absolute number of sodium salicylate particles by weight (symbols as in Fig. 2). Three sample sizes and two weight proportions of sodium salicylate are presented.*

Evaluation of formulation factors required for rapidly disintegrating tablets

In paper II, disintegration, tensile strength and porosity of tablets were studied using different combinations of compound, binder and a superdisintegrant (Ac-Di-Sol). The rate of disintegration affects the dissolution of tablets and therefore could affect the absorption and pharmacological effect of the drug. However, a rapidly disintegrating tablet is often associated with low tensile strength.

Characteristics of the test materials

The chosen study materials had a range of solubilities and volume reduction mechansims. Mannitol and sodium chloride are freely soluble in water while DCP is practically insoluble in water (Wade and Weller, 1994). DCP represented a very brittle material and sodium

chloride represented a more ductile material while mannitol possessed intermediate properties (Table 3). Data for sodium chloride are not explicitly presented in the result section below, but reference is made to details in paper II.

Table 3. *Deformability characteristics of test materials (data from paper II).*

Material	Yield pressure		Minimum porosity during compression	Elastic recovery[c]	Fragmentation tendency[d]
	in-die[a] (MPa)	out-of-die[b] (MPa)	(%)	(%)	($(cm^2/g)*MPa^{-1}$)
Compounds					
Sodium chloride	107 (±1.2)	*	5.4 (±0.1)	4.5 (±0.3)	0.828
Mannitol	187 (±8.8)	*	12.0 (±0.6)	1.5 (±1.8)	159
DCP	637 (±14)	*	35.1 (±0.2)	5.4 (±0.3)	682
Binders					
Crystalline lactose	190 (±1.2)	277	10.9 (±0.0)	5.2 (±0.4)	79.2
Partially crystalline lactose	168 (±2.9)	282	8.2 (±0.2)	6.7 (±0.3)	81.1
Amorphous lactose	182 (±1.6)	212	11.3 (±0.2)	4.8 (±1.1)	1.84
MCC105	87.6 (±0.3)	138	4.9 (±0.1)	10.1 (±0.2)	201
PEG 3000	35.2 (±2.6)	52.1	-0.35 (±0.2)[e]	8.4 (±0.4)	*[f]

[a] Obtained from the reciprocal of the slope of the linear part of an in-die Heckel plot, thus including both plastic and elastic deformation (Duberg and Nyström, 1986). Mean values (± s.d.), n=3.

[b] Obtained from the reciprocal of the slope of the linear part of an out-of-die Heckel plot, thus including only plastic deformation (Paronen, 1986).

[c] Defined as the relative difference between minimum and maximum tablet heights (Armstrong and Haines-Nutt, 1972). Mean values (± s.d.), n=3.

[d] The slope of the graph of the specific tablet surface area vs compaction load.

[e] Densification of the solid structure during compression resulted in an apparently negative minimum porosity, n=3.

[f] PEG 3000 was not measured because the very high ductility of this material resulted in compacts that were too dense.

* Not determined.

The studied binders were also classified regarding some material properties. PEG 3000 was the most ductile material. Three lactose samples, crystalline lactose, partially crystalline lactose and amorphous lactose, were used. These three lactose samples were generally similar to mannitol, i.e. they were moderately ductile and had an intermediate tendency to fragment. Amorphous lactose was the least brittle and gave the lowest out-of-die yield

Table 4. *Degree of disorder of the different forms of lactose as evaluated by two thermoanalytical techniques (data from paper II). Mean values (± s.d.), n=3.*

Material	DSC		Microcalorimetry	
	Heat of crystallisation (J/g)	Degree of disorder (%)	Heat of crystallisation (J/g)	Degree of disorder (%)
Crystalline lactose	0	0	0	0
Partially crystalline lactose	23 (±4.0)	23	9.1 (±2.1)	29
Amorphous lactose	100 (±5.5)	100	31 (±5.2)	100

pressure value, indicating that it had a more plastic nature than the other two lactose samples (Table 3). The differences in the tableting behaviour of the three lactose samples was explained by differences in the proportion of disordered (amorphous) solid-state structure (Table 4). MCC105 had more complex volume reduction behaviour, due to its aggregated nature (Ek et al., 1994). The relatively pronounced increase in surface area reflected rather extensive fragmentation of MCC105 aggregates (Nyström et al., 1993), while the Heckel data indicated that MCC105 was relatively ductile (Table 3) (Heckel 1961a; b). However, the plasticity seemed to be limited, as reflected by both a relatively high out-of-die yield pressure value. The existence of a relatively pronounced elastic component was confirmed both by the direct evaluation of elastic recovery and a relatively large difference in data between in-die and out-of-die experiments (Table 3).

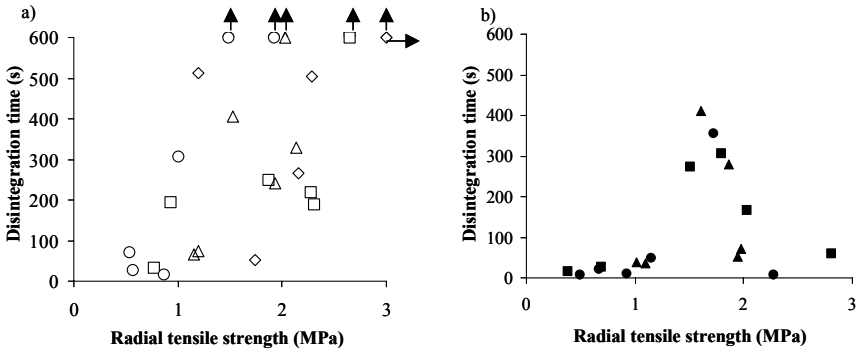

Figure 5. *Disintegration time as a function of radial tensile strength for tablets made of pure binders, pure compounds and mixtures. a) With binder and without superdisintegrant (unfilled symbols) and b) with binder and superdisintegrant (filled symbols). Systems containing sodium chloride (□, ■), dibasic calcium phosphate dihydrate (O, ●), mannitol (Δ, ▲) and pure binders (◊). Disintegration times exceeding 3600 s are shown as 600 s and tensile strength of 12.9 MPa is shown as 3 MPa, with an arrow indicating the higher values.*

The effect of addition of binders with different properties on tablet strength and disintegration time

Generally, a high tablet strength was associated with an extended disintegration time when no superdisintegrant was present (Fig. 5a). However, addition of a superdisintegrant resulted in a short disintegration time simultaneously with a high tablet strength (Fig. 5b). The results indicated no general relationship between porosity and disintegration time of the tablets, since other properties of the binder and compound, e.g. solubility and bonding ability, also influenced the disintegration.

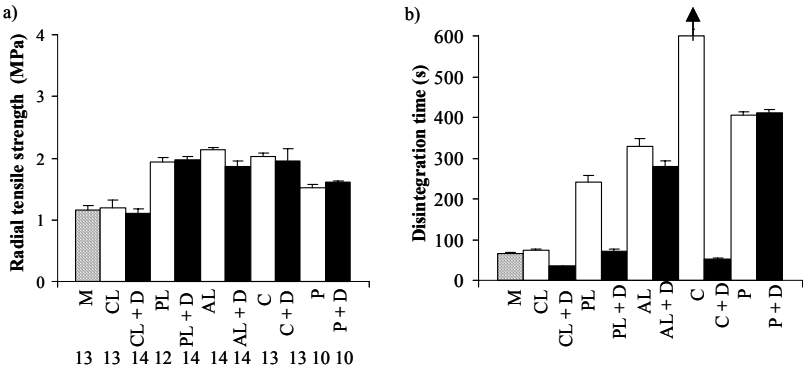

***Figure 6**. a) Radial tensile strength and b) disintegration time of tablets containing mannitol (M) and mixtures with binder, with or without superdisintegrant. In a), the porosity (%) is shown below the denominations. Disintegration time exceeding 3600 s is shown as 600 s with an arrow indicating a longer disintegration time. AL=amorphous lactose; C=microcrystalline cellulose; CL=crystalline lactose; D=Ac-Di-Sol; M=mannitol; P=PEG 3000; PL=partially crystalline lactose. Confidence intervals for p= 0.05 are shown.*

Pure DCP gave tablets with higher porosity, slightly lower tensile strength and similar disintegration times compared to tablets of pure mannitol. When 20% w/w of the binders were added to the compounds, the tablet strength generally increased for both compounds (Figs. 6a and 7a). The strength of tablets containing PEG 3000 and the processed forms of lactose was probably enhanced by the relatively high degree of deformability of these materials. For MCC105, the increase in tensile strength was more related to the high inherent strength (high compactability) of this substance (Olsson et al., 1998; Mattsson and Nyström, 2000; Mattsson and Nyström, 2001). Crystalline lactose has relatively poor

bonding properties (i.e. low compactibility) and a low degree of deformability and therefore it did not contribute to an increase in tensile strength for the compounds.

The addition of a binder also affected (generally increased; Figs. 6b and 7b) the disintegration time. MCC105 has frequently been observed to enhance disintegration when included in a formulation, because of its ability to draw water into the tablet (Khan and Rhodes, 1975; Bolhuis et al., 1979; Lerk et al., 1979). However, in this study a relatively large amount of MCC105 was added and the disintegration behaviour resembled that of pure MCC105, i.e. the disintegration was not completed within 600 seconds. The disintegration time was also prolonged when PEG 3000 was incorporated into a tablet, probably because of impaired water penetration into the tablet. This may be explained by the increased viscosity of water when PEG is dissolved in it. Further, it appears that a water-insoluble substance (e.g. DCP) in combination with a binder with viscosity enhancing properties impairs disintegration of tablets, even when the porosity of the tablets is high. Of the tablets containing the different lactose samples, amorphous lactose usually gave the strongest tablets with the longest disintegration time.

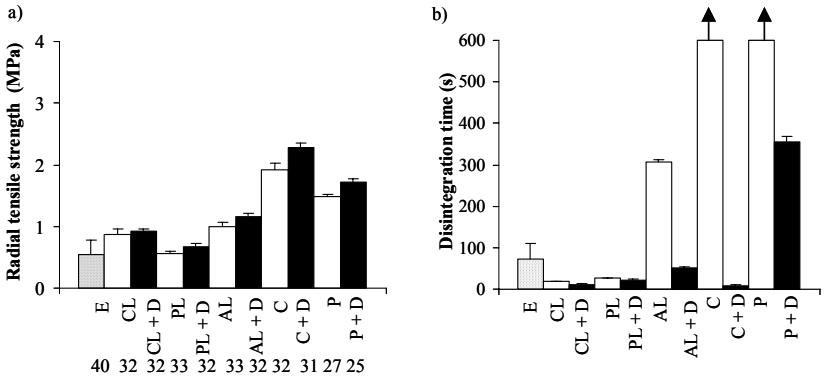

Figure 7. *a) Radial tensile strength and b) disintegration time of tablets containing dibasic calcium phosphate dihydrate(E) and mixtures with binder, with or without superdisintegrant. In a), the porosity (%) is shown below the denominations. Disintegration times exceeding 3600 s are shown as 600 s with an arrow indicating a longer disintegration time. AL=amorphous lactose; C=microcrystalline cellulose; CL=crystalline lactose; D=Ac-Di-Sol; E=dibasic calcium phosphate dihydrate; P=PEG 3000; PL=partially crystalline lactose. Confidence intervals for p= 0.05 are shown.*

Addition of a superdisintegrant and the influence of binder properties on its efficacy

Generally, addition of the superdisintegrant (Ac-Di-Sol) did not affect the tensile strength and porosity of the tablets to a large extent (Figs. 6a and 7a). Disintegration of the tablets was improved for all compounds and most of the mixtures (compound and binder) on addition of the superdisintegrant (Figs. 6b and 7b). The pronounced effect of the disintegrant on DCP tablets was perhaps unexpected, since studies have been reported where high tablet porosity was observed to decrease the effect of the swelling of the superdisintegrant (Ferrari et al., 1995). However, the effect may have been caused by rapid water penetration through the highly porous tablet in combination with the very high swelling capacity of the disintegrant. For the mixtures containing MCC105, there was a substantial reduction in disintegration time when Ac-Di-Sol was added.

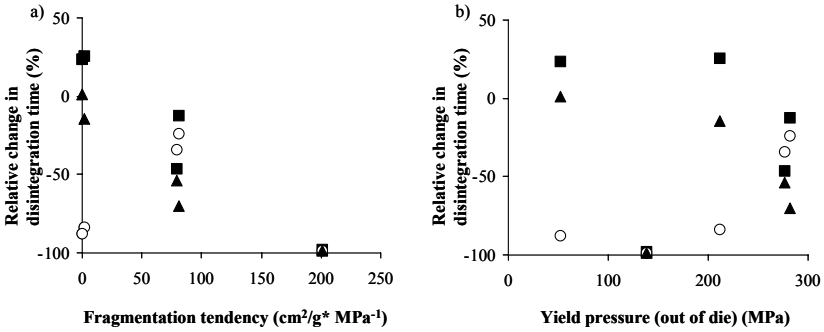

Figure 8. *Relative change in disintegration time following the addition of a superdisintegrant to the mixtures containing compound and binder as a function of a) fragmentation tendency (the slope of the graph of the specific tablet surface area vs compaction load) and b) yield pressure (out-of-die). Systems containing sodium chloride (■), dibasic calcium phosphate dihydrate (○) and mannitol (▲).*

In tablets containing a binder which mainly deforms plastically and does not fragment to a large extent (such as PEG 3000 or amorphous lactose) together with mannitol, the superdisintegrant had little or no effect on disintegration time (Fig. 8). This was probably because the deformability of the binder created a ductile environment, which counteracted the disintegration force of the superdisintegrant. When the superdisintegrant swells, the force that normally causes the bonds to break is instead "absorbed" by the deformable structure of the ductile binder. However, when these binders were added to compounds resulting in tablets with high porosity (such as DCP), the importance of the volume reduction mechanism of the binder seemed to be reduced. Tablets containing binders that fragmented to a larger extent (such as MCC105 and crystalline lactose) were more susceptible to the addition of a superdisintegrant, regardless of the compound.

When a soluble binder or compound is used and especially when two such components are combined, the effectiveness of the superdisintegrant may be reduced (Ferrari et al., 1995; Johnson et al., 1991). The rationale behind this effect is, as discussed above, that a soluble component might increase the viscosity of the penetrating liquid and thus reduce the penetration rate into the tablet (e.g. Washburn, 1921). Further, rapid binder/compound dissolution within the tablet might result in instant widening of voids and pores. Such an initial increase in porosity and pore size might counteract the effect of a superdisintegrant, where swelling and mechanical expansion are the dominant disintegration mechanisms. However, it seems probable, especially considering the results generated for the different lactose samples, that the deformability/plasticity of the binder may be equally important to any effect that binder solubility might have on liquid viscosity and pore widening.

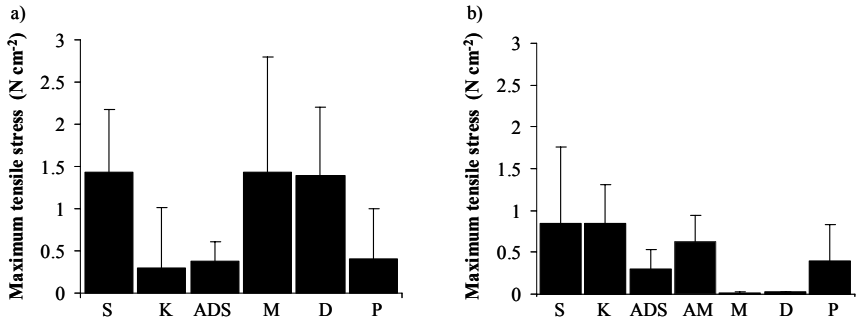

Figure 9. *Maximum tensile stress in detaching tablet specimens (a) and powder specimens (b) from mucus membrane from pig intestine. Mean values ± s.d., n=5. S, sodium alginate; K, Kollidon CL; ADS, Ac-Di-Sol; AM, Ac-Di-Sol milled; M, Mannitol; D, DCP; P, Probe.*

Evaluation of methods and formulation factors related to bioadhesive properties using tablets, powders and interactive mixtures

In paper III, the bioadhesive strength of tablets, powders and mixtures of sodium alginate, Kollidon CL, Ac-Di-Sol and DCP were tested by evaluating the force required to separate the formulation from the mucosa (Figs. 9a and 9b). Sodium alginate, a well-known bioadhesive component (e.g. Smart et al., 1984; Robert et al., 1988), was used in this study as a reference, representing the material with the greatest possible bioadhesive capabilities.

Tablets and powders

The results from studies of tablet formulations (Fig. 9a) gave an unexpected ranking of the materials. Sodium alginate, DCP and mannitol had high bioadhesive values, while Kollidon

CL and Ac-Di-Sol tablets and the metal probe (i.e. no sample) had lower bioadhesion values. Investigation of powders (Fig. 9b) resulted in a ranking of materials that was closer to that expected; the values for DCP and mannitol were significantly lower and those for Kollidon CL and Ac-Di-Sol were closer to those of the bioadhesive sodium alginate.

The unexpectedly high bioadhesive values for DCP and mannitol tablets was probably attributable to some kind of attraction between the smooth surface of the tablet and the mucosa. It has been suggested that dehydration of the mucosa, caused by water movement from the mucosa to the dry powder, may have resulted in adhesion between the two surfaces (Mortazavi and Smart, 1993). However, as Mortazavi and Smart (1993) also concluded, adhesion involves more than just dehydration. For example, dehydration is obviously not involved in the results obtained with the metal probe. Mikos and Peppas (1989) found, by measuring the surface tension of mucus solutions, that surface effects could explain the mucoadhesion, especially for weakly adhesive materials. This mechanism, sometimes called the wetting theory, is more applicable to fully hydrated systems and uses measurements of interfacial tensions to predict spreading, i.e. the intimate contact of the bioadhesive with the mucosa. A low interfacial tension value for the bioadhesive-tissue interface increases the possibility of obtaining adhesive bonds (Chickering and Mathiowitz, 1999).

The porosity of tablets made of DCP, Kollidon CL and Ac-Di-Sol was relatively high (33-49%). Although there have been indications in the literature that tablet porosity does not affect bioadhesion (Ponchel et al., 1987; Tobyn et al., 1995), the possibility that a high tablet porosity could facilitate transport of water into the tablet and cause adhesion cannot be excluded. This seems especially relevant for the test conditions used in this study, i.e. no preswelling of the tablets and a short contact duration.

Unexpectedly, instead of fracturing between the tablet and the mucus layer or through the mucus layer, Kollidon CL and Ac-Di-Sol tablets fractured through the tablet itself. These materials, which quickly absorb large amounts of liquid, are usually used as disintegrants (Gissinger and Stamm, 1980). It is assumed that the fast absorption of liquid made the tablet weak, so that a fracture occurred at the interface of the wet and dry portions within the tablet. These results indicate that it would be feasible to characterise the adhesive properties of materials using uncompacted powder specimens instead of a compressed tablet form.

Interactive mixtures

The coating of microparticles with a bioadhesive material has been used both to compare the bioadhesive properties of materials (Ranga Rao and Buri, 1989) and to enhance the bioadhesive properties of a material (Gåserød et al., 1998). Alternatively, bigger carrier particles can be covered by smaller dry particles by dry mixing, i.e. by forming interactive mixtures. When drug particles are then added to the carrier particles using this technique, in

contrast to the coated particle system (e.g. Gåserød et al., 1998), the drug is released quickly as it is held at the absorption site.

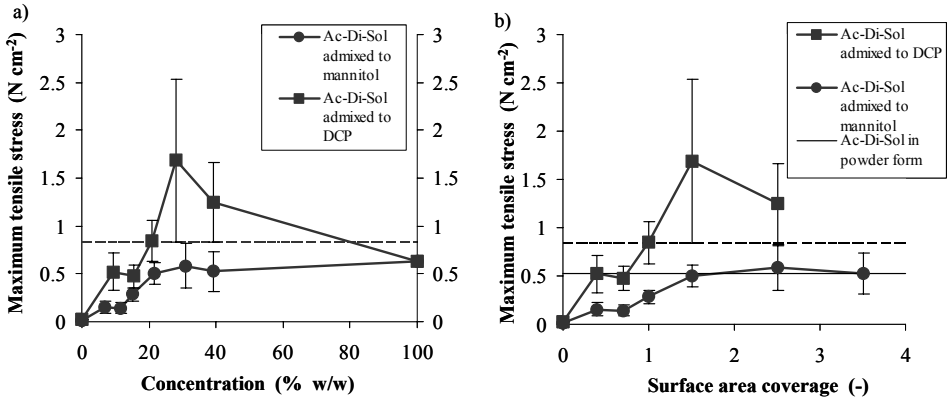

Figure 10. *Maximum tensile stress in detaching powder specimens from pig intestinal mucus membrane as a function of a) concentration of milled Ac-Di-Sol (Medium) mixed with mannitol or DCP and b) surface area coverage of mannitol and DCP particles by milled Ac-Di-Sol (Medium) particles. Data for pure Ac-Di-Sol (Medium), sodium alginate and Kollidon CL in powder form are shown as reference lines (solid line for Ac-Di-Sol and dashed line for both sodium alginate and Kollidon CL. Mean values ± s.d., n=5.*

The effect of bioadhesive component proportions

The interactive mixtures consisted of Ac-Di-Sol (medium fine particle size) as the bioadhesive material, with DCP or mannitol as carrier materials. Tensile stress between the mucosa and the nonbioadhesive carrier particles was improved when the coarse DCP or mannitol was mixed with the medium fine particle size of Ac-Di-Sol (Fig. 10a). The bioadhesive properties improved initially with increases in the concentration of Ac-Di-Sol, as shown earlier with tablets containing bioadhesive materials (Ponchel et al., 1987). Tobyn et al. (1997), who also investigated tablets made from mixtures of formulation excipients and bioadhesive materials, suggested that the excipients decreased the work of adhesion.

Interactive mixtures of DCP containing the two highest concentrations of Ac-Di-Sol (28.2 and 39.3% w/w) resulted in significantly higher tensile stress values than those for powders of pure Ac-Di-Sol (Fig. 10a). A synergistic effect on the mechanical strength of tablets composed of mixtures has also been reported (Mattsson and Nyström, 2000); tablets formulated from mixtures were stronger than predicted from the individual materials. This was explained by an increase in fracture surface area in tablets containing the mixture of coarse and fine particles, compared to those containing the fine component alone.

Similarly, when the fine bioadhesive particles are mixed with larger carrier particles, the surface area of the adhesive component in contact with the mucosa is greater than if only a flat, monoparticulate layer of bioadhesive component is exposed to the mucosa. This effect was, however, not seen with mixtures containing mannitol, probably because of the higher water solubility of mannitol, as discussed below.

As seen in Fig. 10a, the increase in bioadhesive strength is significant up to a certain proportion of Ac-Di-Sol. When the surface area ratio exceeded unity (corresponding to concentrations >20% w/w), the bioadhesive strength began to level off, i.e. an increase in the amount of Ac-Di Sol did not increase tensile stress values significantly. The plateau in bioadhesion was possibly attributable to the surface area coverage of the bioadhesive component of the carrier (Fig.10b). For surface area ratios exceeding unity, an excess of fine powder coated on the coarse carriers probably at least partly increased the tendency for the fracture to go through a multiparticulate layer of adhering powder, and thus a transition of the fracture path from mucus to powder specimen was anticipated for both mixture types at high concentrations of Ac-Di-Sol.

The effect of carrier solubility

DCP mixtures were significantly more bioadhesive (had higher tensile stress) than mannitol mixtures. This may be a result of the higher water solubility of mannitol. Thus, the fracture for the mannitol mixtures might have gone through partly dissolved peripheral regions of the interactive mixtures and not entirely through the mucus layer. Additionally, Tobyn et al. (1997) suggested that addition of a highly water-soluble additive reduces the water content when the material dissolves, and thus makes the water unavailable for the bioadhesive material, with decreased bioadhesion as a result. According to this theory, the mannitol particles dissolve in the water, which reduces the amount of water available for the Ac-Di-Sol particles and subsequently reduces their availability for the adhesive process. However, such an explanation is not totally in agreement with the dehydration theory by Mortazavi and Smart (1993) described earlier.

The effect of size of the bioadhesive component particles

Table 5 summarises the results when varying particle size fractions of Ac-Di-Sol were mixed with DCP and when DCP was mixed with micronised Kollidon CL. The surface area coverage ratio is the same (1.0) for all samples of Ac-Di-Sol and the concentration varies as a result of the different particle sizes. If surface coverage of the carrier material is a dominating factor, a surface area ratio of unity would be expected to give the same bioadhesive results for all samples, since the same area of bioadhesive material and mucosa would be in contact. However, the intermediate size fraction had by far the strongest bioadhesive effect. This may have been a factor of the absolute amount of added bioadhesive component. Since water absorption by Ac-Di-Sol is so fast, the dehydration of

the mucosa (Mortazavi and Smart, 1993) may have contributed to the mechanism of bioadhesion. It is possible, in that case, that the weight or volume concentration of added bioadhesive component is of greater import than the surface area ratio of the material. However, the coarsest size fraction of Ac-Di-Sol would then be expected to cause the strongest dehydration and thus the highest tensile stress and, as reported above, this was not the case. The tensile stress associated with the coarser particle size of Ac-Di-Sol was not significantly different from that of the finer size, despite a much higher concentration. This may have been due to weaker adhesive interactive forces between carrier and powder particles so that the fracture, at least in parts, went between the carrier and powder particles. Thus, the medium sized particles of Ac-Di-Sol gave the optimum mixture for a bioadhesive system composed of Ac-Di-Sol and DCP. Because of its small particle size, Kollidon CLM would also be expected to give a high tensile stress value if surface coverage was the limiting factor, but that did not occur. Despite the high surface area coverage of the carrier particles (1.5), the concentration of Kollidon CLM was too low to induce any pronounced bioadhesive capability with DCP. It is suggested that the low concentration of Kollidon CLM meant that the system absorbed little liquid, resulting in low tensile stress.

Table 5. *Bioadhesive properties of mixtures containing DCP and a bioadhesive material of varying particle size (data from paper III). Mean values (± s.d.), n=5.*

Bioadhesive material mixed with DCP	Concentration of bioadhesive material (% w/w)	Surface area ratio (-)	Maximum tensile stress (N/cm^2)
Ac-Di-Sol			
Coarse (>5 μm)	35.9	1.0	0.469 (±0.142)
Medium	20.8	1.0	0.845 (±0.220)
Fine (<5 μm)	12.3	1.0	0.460 (±0.141)
Kollidon CL M[a]	7.5	1.5	0.022 (±0.002)

[a] Micronised Kollidon CL.

The fracture path and the limiting maximum bioadhesive strength

Evaluation of the bioadhesive mechanisms of a material is generally a rather complex process, and it could be of interest to qualitatively indicate the dominant fracture path for each test specimen. To do this, the weakest plane of the system should be established, as discussed by others (e.g. Smart, 1999; Hägerström and Edsman, 2001).

Possible fracture paths for the specimens used in this study are presented in Fig. 11 (11a for tablets, 11b for powder particles and 11c for interactive mixtures). If bioadhesive forces, i.e. mechanical interpenetration, have been created between the mucosa and the specimen, the fracture should occur at position A (through the mucus layer) or, possibly, when water movement is a dominant adhesion mechanism, at position B (at the interface between specimen and mucus layer). As discussed above, the fracture went through the tablet (position C in Fig 11a) for tablets made of Kollidon CL and Ac-Di-Sol rather than

occurring at position A or B. For powder specimens, a monolayer of particles must be applied to the metal probe to reduce the risk that multiparticulate layers will cause the fracture to follow a path between the particles (position C in Fig. 11b). The adhesive interactive forces between the carrier (in this study, mannitol or DCP) and the bioadhesive material in interactive mixtures must be stronger than the forces between the mucosa and the mixture. The latter is dependent both on the ability of the materials to create these adhesive forces and on the particle size, as discussed above.

In this study, taking into account all data generated for tablets, powders and mixtures, there seemed to be a maximum tensile stress of approximately 1.5 N/cm^2. This value of 1.5 N/cm^2 is thought to reflect the intrinsic strength of the mucus layer (path A in Fig 11), for these specific materials and test conditions. Lower tensile stress values would then reflect a weakening of the bioadhesive joint. This could occur if the material has a low ability to create bioadhesive interactions (fracture path at position B in Fig. 11) or if there is a problem with the specimen (fracture path at C or F in Fig. 11). Further, if strongly bioadhesive materials with no specimen problems are tested, there should be no differences in the relative values between the tested materials.

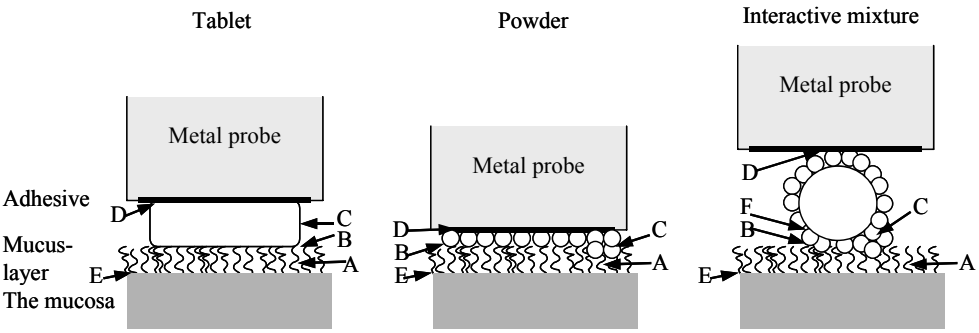

Figure 11. *Schematic model of possible regions of failure during measurements of bioadhesion between the mucosa and tablets, powders and interactive mixtures. The possible regions are: A, through the mucus layer; B, at the interface between the specimen and the mucus layer; C, within the specimen; D, at the interface between the bioadhesive component and the specimen; E, between the mucosa and the mucus layer; and F, between particles within the interactive mixtures.*

A new sublingual tablet concept for rapid oromucosal absorption

In papers IV and V, a new sublingual tablet system using low doses of fentanyl citrate (Rapinyl®) was presented and evaluated. This tablet was formulated using the results of papers I-III.

Breakthrough pain and the use of fentanyl

Fentanyl is a potent synthetic opioid which is given in low doses (100-1000 μg) (Zhang et al., 2001). As the citrate salt, fentanyl is sparingly soluble in water; since the molecule is small and highly lipophilic, it is expected to easily permeate mucous membranes after complete dissolution (Dollery, 1991). Further, since fentanyl lacks the bitter taste associated with some opioids, it is suitable for sublingual administration (Gardner-Nix, 2001). Fentanyl is used in the treatment of breakthrough pain, which frequently appears in patients with cancer despite analgesic therapy, and which requires the use of supplemental opioid doses (Portenoy and Hagen, 1990; Portenoy and Lesage, 1999). Parenteral therapy would provide instant relief from this pain, but this route is not particularly convenient for the patient. Further, the onset of action of morphine is often delayed by up to 60 minutes after oral administration (Hanks et al., 1998). As described in the introduction, the sublingual mucosa offers many advantages, and sublingual administration of fentanyl would appear to have some potential, since the onset of action of fentanyl citrate is 10 to 15 minutes after sublingual administration of a solution (Zepetella, 2001).

An existing product in the form of a lollipop containing fentanyl citrate (Actiq™) was designed to allow rapid absorption of the drug from the oral cavity (Mock et al., 1986; Ashburn et al., 1989). In this formulation, fentanyl citrate was incorporated into a dissolvable candy matrix and placed on a stick. The patient holds the lollipop against the buccal mucosa and licks it. However, this dosage form stimulates saliva production and swallowing, and some drug is lost into the gastrointestinal tract (Zhang et al., 2002), with subsequent inter- and intra-individual variations in absorption and bioavailability as part of the dose is not adequately exposed to mucosal surfaces (Streisand et al., 1991; Zhang et al., 2002). In addition, a large part of the swallowed dose will be ineffective, since fentanyl undergoes extensive cytochrome P450 (CYP)-3A4-mediated metabolism in both the intestine and the liver (Labroo et al., 1997). In this context, a specially designed tablet formulation for increased contact time at the administration site would have the potential to be both therapeutically effective and easy for the patient to use.

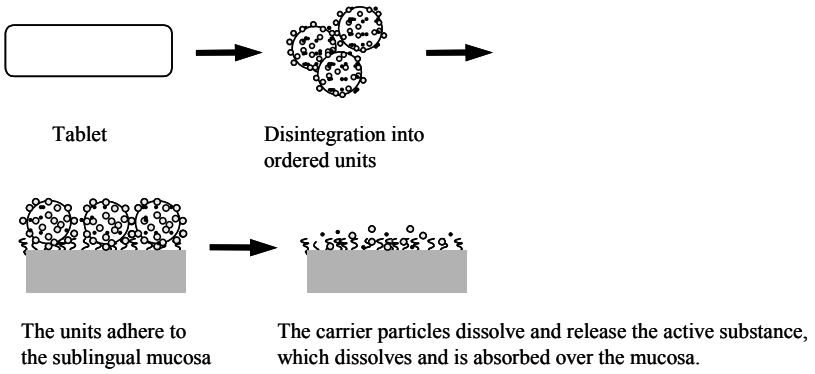

Figure 12. *Schematic model of the disintegration, bioadhesion and drug dissolution of the new sublingual tablet system.*

The new sublingual tablet concept

In this system, water-soluble carrier particles are covered with fentanyl citrate and a bioadhesive material during dry mixing. In principle, the tablet quickly disintegrates into the ordered units consisting of carrier, fentanyl citrate and bioadhesive component (Fig. 12). These units initially adhere to the mucosa. The water-soluble carrier particles gradually dissolve and fentanyl citrate dissolves along with them. With this approach, optimal exposure of active substance to the dissolving fluids is combined with bioadhesive retention of the drug in the oral cavity.

Figure 13 describes the formulation of the sublingual tablet (Rapinyl®) and Table 6 presents the composition of the tablet. Since fentanyl is a potent drug, an interactive mixture formulation was used to increase the homogeneity of the mixture and the drug content uniformity of the tablets. The content of fentanyl citrate in the formulated test tablets was 0.22% w/w (corresponding to 100 μg fentanyl base), 0.45% w/w (200 μg) and 0.90% w/w (400 μg). Since a small amount of drug is mixed with a large amount of a coarse excipient, it is important to have an adequate number of drug particles present (Paper I). This was achieved by using a small particle size (≤5 μm in diameter) (Nyström and Malmqvist, 1980; Paper I). In this study, the particle size of fentanyl citrate was not determined directly; however, the specific surface area was used as a surrogate measure. The surface area, at 2.3 m^2/g, was considered to indicate sufficiently small particles.

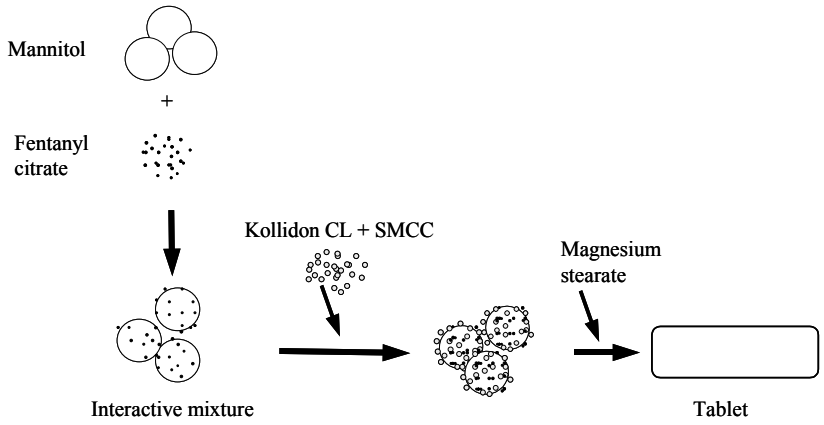

Figure 13.*Schematic model of the mixing and tableting procedures for the sublingual fentanyl tablets and the tablet components.*

Table 6. *Composition of the sublingual tablets and the microtablets (data from papers IV-VI).*

Material	100 µg (mg)	200 µg (mg)	400 µg (mg)	Placebo (mg)	Micro-tablets (mg)	Placebo (mg)
Fentanyl citrate	0.157[a]	0.314[b]	0.628[c]	-	-	-
Mannitol	59.4	59.3	59.0	59.6	-	-
SMCC	7.00	7.00	7.00	7.00	-	-
Kollidon CL	3.00	3.00	3.00	3.00		-
Levodopa	-	-	-	-	5.00	-
Carbidopa	-	-	-	-	1.25	-
MCC	-	-	-	-	5.69	9.54
Lactose	-	-	-	-	-	2.40
Magnesium stearate	0.400	0.400	0.400	0.400	0.06	0.06
Tablet weight[d]	70.0	70.0	70.0	70.0	12.0	12.0

[a] Corresponding to 100 µg fentanyl base.

[b] Corresponding to 200 µg fentanyl base.

[c] Corresponding to 400 µg fentanyl base.

[d] Nominal value

Further, using interactive mixtures consisting of close to identical ordered units, the drug dissolution rate is improved (Westerberg, 1992). However, the dissolution rate is affected by the particle size of both the drug and the carrier as well as by the physicochemical properties of the carrier (Westerberg, 1992). Westerberg et al. (1986) found that the carrier particle is required to be highly soluble for rapid drug dissolution. In this sublingual tablet, the carrier material was mannitol, which has been shown previously to have good carrier properties such as high water solubility (Wade and Weller, 1994). High dissolution rates were also maintained after tableting mixtures containing mannitol (Westerberg and Nyström, 1991). Drug dissolution is also affected by the surface area coverage of the carrier. Low surface area coverage (<20%) normally results in complete deagglomeration of drug particles and rapid dissolution; an intermediate degree of surface area coverage (20-100%) can also result in rapid drug dissolution even though some of the drug particles will be released in the form of small agglomerates rather than as discrete particles (Westerberg, 1992). However, as mentioned in the introduction, these values are also dependent on the characteristics of the drug (e.g. agglomeration tendency and particle size). In this study, the surface area coverage of mannitol with fentanyl citrate particles was 7% (100 μg), 14% (200 μg) and 27% (400 μg).

A bioadhesive component was included in the formulation in order to increase contact time at the absorption site and thereby reduce the potential intra- and inter-individual variability resulting from swallowing the drug. Based on the results in paper III, interactive mixtures could be an alternative in this context. However, in that study it was shown that highly water soluble carrier materials are less bioadhesive than insoluble carriers, probably because the tensile fracture goes through the partly dissolved particles rather than through the mucosa or between the mucosa and the bioadhesive material. However, it is not always desirable to concentrate only on optimal bioadhesion and the choice of carrier for these fentanyl tablets involved consideration of both a high dissolution rate to optimise absorption of fentanyl over the sublingual mucosa and at the same time adequate bioadhesive properties to minimise swallowing of the substance. Since mannitol fulfils both these criteria, (Westerberg, 1992; paper III) it was chosen as the carrier material. In paper III, Kollidon CL was shown to have bioadhesive properties and was therefore expected to prolong the residence time of the ordered units at the sublingual mucosa. Kollidon CL also has the advantage of being a very effective disintegrant (e.g. Kornblum and Stoopak, 1973; Shangraw et al., 1980). SMCC was used as the binder in the formulation and since SMCC is moderately deformable (Mattson and Nyström, 2001) it was not expected to significantly impair the disintegration process (paper II).

Primary characteristics of the fentanyl tablets in vitro

The tablets were characterised regarding weight, tablet strength and friability (Table 7). The weight and friability results were within the limits specified in the European Pharmacopoeia (1997) and the tablet porosity was approximately 25% for all three batches.

Table 7. *Technical properties and drug content of sublingual tablets (data from paper IV).*

Tablet strength (μg fentanyl)	Weight[a] (mg)	Friability[b] (%)	Crushing strength[c] (N)	Average fentanyl content[d] (% of expected)	Uniformity of content (min-max) (%)	Disintegration time	
						With discs[e] (s)	With out discs[f] (s)
100	70.2 (±0.78)	0.44	12.1 (±1.38)	95	91.0-101.4	50	<10
200	70.0 (±0.59)	0.74	11.3 (±1.69)	95	87.7-105	33	<10
400	69.3 (±0.73)	0.64	11.7 (±2.27)	96	88.2-94.4	45	<10

[a] Mean values (±s.d.), n=20.

[b] n=1.

[c] Mean values (±s.d.), n=35.

[d] Ten tablets were analysed. The mean content of fentanyl was calculated and related to the nominal content for the tablets (i.e. 100, 200 and 400 μg).

[e] Maximum value from 12 tablets (2x6). The measurements were performed with discs.

[f] The measurements were performed without discs. Maximum value from 6 tablets.

The tests of mean drug content and uniformity of content showed that only minor segregation had occurred during tablet processing (i.e. mixing and tableting) (Table 7).

In principle, the tablets should disintegrate rapidly, to instantly generate many ordered units of mannitol, fentanyl citrate and Kollidon CL (Fig. 12). The disintegration time of the three batches of tablets containing fentanyl citrate corresponding to 100, 200 and 400 μg fentanyl base was in the range of 33-50 seconds using discs and less than 10 seconds without discs (Table 7). The higher value with discs was probably caused by adhesion of the tablets to the discs (because of the addition of bioadhesive), which fudged the endpoint. It seems reasonable from these results to predict that the tablet will adhere to the mucosa in the mouth. The *in vitro* data obtained with discs probably better reflects the disintegration time *in vivo* into ordered units. However, the peristaltic movements that occur in the mouth may contribute to a more rapid disintegration of the tablets.

The dissolution tests revealed that fentanyl citrate was dissolved almost instantly from the tablets. Data for the amount of dissolved fentanyl as a function of time are presented in Fig. 14. For tablets of 100 and 200 μg fentanyl, roughly 75% of the substance was dissolved from the tablet within one minute, and more than 95% within 3 minutes. Drug dissolution from tablets containing 400 μg was slightly slower: 75% within 2 minutes and 95% within 5 minutes. The dissolution profiles for all tablets are comparable with those obtained for ordered mixtures by Westerberg and Nyström (1991), i.e. compaction of the ordered units did not negatively influence the dissolution rate. After initially rapid disintegration, ordered

units are quickly exposed to the solvent and drug dissolution starts more or less instantly. The somewhat lower dissolution rate for tablets containing 400 µg fentanyl was thus not due to retardation by the disintegration process, but was probably due to the higher surface area coverage of the hydrophobic drug (Westerberg and Nyström 1993).

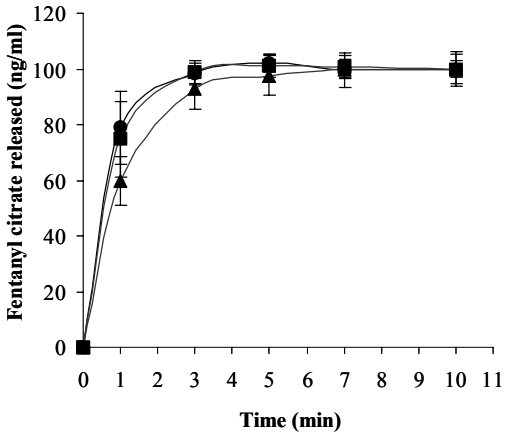

Figure 14. *Amount of fentanyl (%) dissolved from the tablets containing fentanyl citrate corresponding to 100 µg, 200 µg and 400 µg fentanyl base, as a function of time (minutes). Mean values ± S.D., n=6.*

Table 8. *Non-compartmental pharmacokinetic parameters of fentanyl following sublingual administration. Mean values (± s.d.), n=8. (Data from paper V).*

	100 µg	200 µg	400 µg
$AUC_{0\rightarrow\infty}$ (ng/ml*min)	74.26 (±30.98)	159.08 (±39.21)	290.84 (±92.52)
C_{first} (ng/ml)	0.051 (±0.027)	0.084 (±0.076)	0.169 (±0.141)
t_{first} (min)	10.7 (±3.20)	8.0 (±2.67)	9.0 (±4.07)
C_{max} (ng/ml)	0.243 (±0.14)	0.471 (±0.160)	0.908 (±0.334)
t_{max} (min)	39.7 (±17.4)	48.7 (±26.3)	56.7 (±24.6)
$t_{1/2}$ (hrs)	6.08 (±2.04)	6.28 (±1.59)	5.37 (±1.71)

Pharmacokinetic study

Eight patients with cancer received the sublingual tablet in three single doses (100, 200 and 400 μg), separated by wash-out periods of at least 3 days. The areas under the plasma concentration-time curves (AUC) were calculated; the values increased approximately four-fold when the given dose increased from 100 μg to the 400 μg dose (Table 8). This indicates that the biopharmaceutical and pharmacokinetic processes were linear. The average plasma concentration-time profiles revealed that the absorption rate, i.e. time to peak plasma exposure (t_{max}) of fentanyl, was dose dependent (Fig. 15). When the patients received the higher dose of fentanyl, the absorption rate was slower, as seen in the higher t_{max} values (Fig.15 and Table 8). However, the time to reach the first quantified plasma concentration (t_{first}) of fentanyl was short (11, 8 and 9 minutes for 100, 200 and 400 μg respectively) and was the same for the three doses (Table 8). This indicates that the initial absorption rate of fentanyl was unaffected by the dose size.

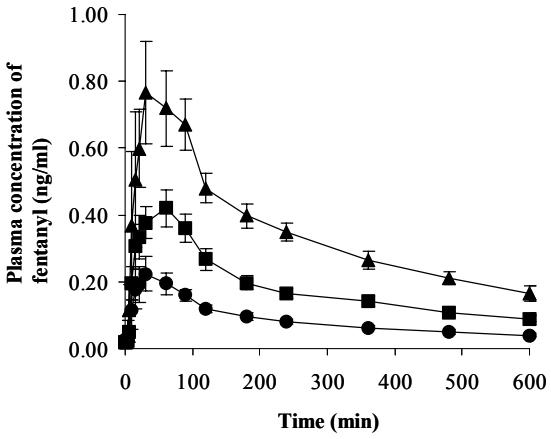

Figure 15. *Plasma concentration-time profiles of fentanyl following a single sublingual dose corrsponding to 100, 200 and 400 μg fentanyl base. Mean values ± S.E.M., n=8.*

In the *in vitro* dissolution studies, a large volume of dissolution medium was used (300 ml, pH 7.3). However, the volume of fluid used *in vivo* is obviously much smaller. Since the solubility of fentanyl citrate is 25 mg/ml in water (Dollery et al., 1991), approximately 0.025 ml fluid would theoretically be required to dissolve a dose of fentanyl citrate corresponding to 400 μg fentanyl base. The somewhat lower absorption rate for the higher dose (400 μg) could perhaps be explained by the requirement for a larger volume of fluid for rapid and complete dissolution compared to the lower doses. Since the volume of saliva

was not measured, it cannot be excluded that this volume was insufficient to obtain equal absorption rates for the three doses. Further, as described above, the dissolution rate was lower for the higher dose, indicating that the higher surface area coverage of the hydrophobic drug may also have impaired the initial dissolution. However, since the initial absorption rates were the same for the three doses, the dissolution process seems to have been sufficient initially. Thus, the influence of saliva volume and surface area coverage of the carrier on the dissolution rate and its in vivo relevance requires further investigation for better understanding of the somewhat lower sublingual absorption rate for the higher dose.

No second peak corresponding to possible gastrointestinal absorption was seen in the plasma concentration profiles of the three doses. It therefore appears that the bioadhesive component (Kollidon CL) promoted the retention of the ordered units under the tongue without hindering the release and local absorption of fentanyl. It appears that the fraction of the fentanyl dose that was swallowed was smaller than with the lollipop described earlier (Actiq™) (Streisand et al., 1998). This was further supported by comparing the AUC values with pharmacokinetic data from intravenous administration (data from the literature: Mather et al., 1998). Based on this comparison, at least 70% of the doses administered reached the systemic circulation (Table 8). In addition, the linear increase in the AUC values indicated that swallowing of fentanyl was not more pronounced at the higher dose, despite the lower dissolution and absorption rate.

Table 9. *Pharmacokinetic parameters and their interindividual variability for the sublingual fentanyl tablet (Rapinyl®) and the fentanyl lollipop (Actiq™). Mean values (±coefficient of variation (%)).*

	Rapinyl® 200 µg[a]	Actiq™ 200 µg[b]	Rapinyl® 400 µg[a]	Actiq™ 400 µg[b]
$AUC_{0\rightarrow\infty}$ (ng/ml*min)	159 (±25)	172 (±56)	291 (±32)	400 (±91)
C_{max} (ng/ml)	0.47 (±34)	0.4 (±25)	0.91 (±37)	0.8 (±25)
$t_{1/2}$ (min)	377 (±25)	193 (±48)	322 (±32)	386 (±115)

[a] Data obtained from the study presented in paper V, in 8 patients with cancer.

[b] Data obtained from a study in 12 healthy volunteers by Streisand et al. (1998).

There were differences in interindividual variability (coefficient of variations) in the pharmacokinetic parameters (AUC, C_{max} and $t_{1/2}$) between this study in cancer patients using the new sublingual tablet (Rapinyl®) and the study in healthy volunteers using the lollipop (Actiq™) (Streisand et al., 1998). Table 9 summarises the pharmacokinetic parameters for the two dose levels 200 and 400 µg of Rapinyl® and Actiq™ respectively. The interindividual variability of AUC and $t_{1/2}$ values was lower with Rapinyl® than with

Actiq™, while that of C_{max} was slightly higher with Rapinyl®. Based on the lower interindividual variability in systemic exposure seen with Rapinyl® it is suggested that the in vivo performance of the sublingual tablet is more likely to be reproducible, since it seems to have better pharmaceutical and biopharmaceutical properties than the lollipop (Actiq™).

Clinical usefulness of the sublingual tablet

The fast-acting sublingual tablet described in this paper has potential to be a valuable addition to the arsenal of drugs for breakthrough pain. The technique could also be useful for substances other than fentanyl where a rapid onset of effect is desirable. However, the new sublingual tablet system would probably be less useful for hydrophilic drug molecules, since this group of drugs will not undergo sufficiently rapid absorption across the sublingual mucosa to effectively utilise the advantages of rapid disintegration and drug dissolution that are built into this system.

A new approach for individualised dosage

Paper VI presents a new approach for individualised dosage and reports results of its evaluation in patients with Parkinson's disease. Although the classical tablet form has many advantages, it is not always suitable for the fine-tuning of doses to individual patients. Normally, there are only a limited number of standard tablet strengths and combining tablets containing different amounts of the active substance or dividing tablets have been the usual methods of achieving a more individualised dose. However, the drug therapy of some diseases could be improved by using a more finely-tuned dose. Levodopa for treatment of Parkinson's disease (Granérus, 1999), morphine for pain relief (Hasselström and Olsson, 1999), levothyroxin for hypothyroidism (Hallengren, 1999) and warfarin for anticoagulation (Bergqvist and Johnsson, 1999) all require individualised dosages, and administration of these drugs involves the dispensing of tablets with different strengths or the use of divided tablets.

Parkinson's disease and the use of levodopa

Parkinson's disease (PD) is a progressive, disabling neurological disorder, which is mainly caused by loss of dopamine-producing neurons in the substantia nigra pars compacta with resultant lack of dopamine in the brain (e.g. Agid, 1991). Since the late 1960s, levodopa has been the most effective pharmacological treatment of the disease (e.g. Lees, 2002). A method of intraduodenal infusion of levodopa was developed to obtain more stable plasma levodopa concentrations (thus potentially minimising side effects); this resulted in less dependence on gastric emptying which, if irregular, can cause marked fluctuations in

plasma levodopa levels after administration of tablets (e.g. Bredberg et al., 1993; Nilsson et al., 2001, Nyholm et al., 2002). Another method is to use controlled-release levodopa tablets, which provide more stable plasma concentrations than conventional oral tablets (e.g. Grahnén et al., 1992). However, for patients in the early stages of PD, the adverse effects of levodopa can often be managed by minimising or titrating the dose on an individual basis (Durif, 1999). Dissolving the drug in water and adding ascorbic acid to make a levodopa/carbidopa/ascorbic acid solution (LCAS) has sometimes been utilised (Kurth et al., 1993; Kurth, 1997). However, using LCAS for individual dosage adjustment still involves division of tablets or swallowing an accurate volume of liquid. At present, available levodopa tablets contain 50, 100, 200 and 250 mg of the drug. Dividing the 50 mg tablets allows dosage adjustments in 25 mg steps, but individual oral doses with a sensitivity of 5 mg would be desirable.

The new concept

The principle

In order to fine-tune the dose, a solid dosage form consisting of individual solid units, each containing a sub-therapeutic amount of the required dose, was prepared. To be useful, each unit should contain as close as possible to identical amounts of the active ingredient, in the range of 2 to 20 % of the required dose. Units such as these are preferably produced using conventional tableting procedures. The dispensing of varying numbers of these units allows adjustment of the dose for each individual patient. While powders could also be used to this end, it is more difficult to achieve a precise volume or dose when using a measuring spoon than when using the standardised volume based filling of a die during automatic tableting procedures. Alternatively, the required precision could theoretically be obtained by using monosized pellets or granules instead of tablets. However, current techniques such as extrusion/spheronization, wet granulation, spraying onto excipient beads etc., do not allow the production of close-to-identical granular units. This can only be achieved by traditional tableting compression methodology. Thus, in this thesis, tableting was used to obtain units of relatively small dimensions, each containing a precise, subtherapeutic amount of the active ingredient. Because of the relatively small dimensions (diameter: 3 mm, thickness: 1.3 mm) of these tablets, they are hereafter referred to as microtablets.

The counting device

Because of the limited dimensions of the microtablets, some kind of counting device is required for patient assistance. In this study, an automatic dose dispenser is described and evaluated (Fig. 16). This is an improved and upgraded version of a prototype presented previously (Aquilonius et al., 1998). The dispenser comprises a cassette filled with microtablets (approximately 2300 tablets), buttons operated by the patient (with an associated digital display) for dose adjustment, a battery-driven electronic motor, a photocell monitoring the number of microtablets dispensed from the cassette to a receiving compartment, and an actuator, by which the microtablets are emptied from the receiving

compartment into a collector or a glass of water (Fig. 16). The usefulness of the automatic dose dispenser and patient acceptance of the device were evaluated in patients with PD.

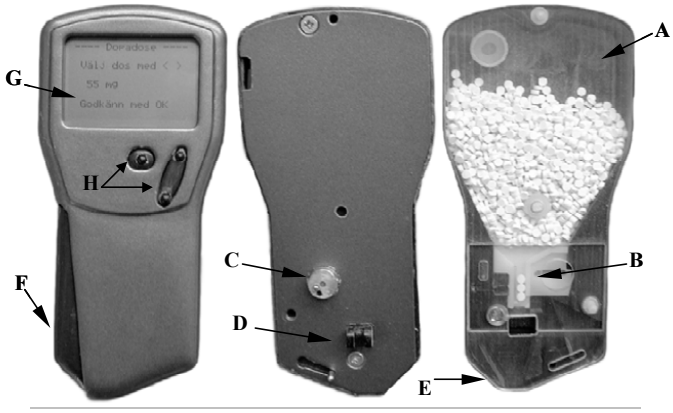

Figure 16. *The dose dispensing device, consisting of a cassette filled with microtablets (A), plastic components (B), electronic motor (C), and a photocell (D) which monitors the number of microtablets transported from the cassette to the receiving compartment (E). An actuator (F) releases the microtablets into a collecting vessel or a glass of water. The digital display (G) and buttons (H) are used to adjust the dose. The weight of the device, without microtablets, is 232 grams and the dimensions are 132 mm (height), 63 mm (width) and 32 mm (thickness).*

Table 10. *Technical properties and drug content of microtablets (data from paper VI).*

Weight[a] (mg)	Height[a] (mm)	Porosity[a] (%)	Friability[b] (%)	Radial tensile strength[a] (MPa)	Average content of levodopa and carbidopa[a] (mg)	Uniformity of content of levodopa and carbidopa[c] (min-max) (%)
12.3 (±0.29)	1.32 (±0.02)	11.2 (±2.3)	0.44 (±0.01)	3.89 (±0.37)	5.12 (±0.097)[d] 1.22 (±0.022)[e]	96.3-102.5[d] 96.6-104.0[e]

[a] Mean values (± s.d.),n=20

[b] Mean values (± s.d.),n=3

[c] n=20

[d] Levodopa

[e] Carbidopa

Properties of the microtablets

The composition and the properties of the microtablets are presented in Table 6 and Table 10. The mean weight of the tablets, the average content and the uniformity of levodopa and carbidopa content were all within the limits specified by the European Pharmacopeia (2002) (Table 10). This implies that only minor segregation had occurred during processing (i.e. mixing, granulation and tableting).

As described above, the tablets are stored in the cassette and transported within the dispensing device by mechanical movement of the plastic components. Therefore, it is important that the microtablets are sufficiently strong to withstand this treatment, i.e. both storage within the cassette and transportation through the device. The results showed that the microtablets containing levodopa and carbidopa were relatively dense (porosity 11.2%) with both high radial tensile strength and low friability (Table 10). A common industrial specification limit for friability is a maximum weight loss of 1.0%. The obtained value (0.44%) is well within this limit and should be sufficient in this context. During the handling study, placebo tablets were run through the dispensing device several times with only small amounts of weight loss estimated. However, it will be important to study tablet strength and friability in detail in the development of the final version of the device, to ascertain that the tablets can withstand this handling.

Clinical usefulness of the automatic dose dispenser

All patients were generally satisfied with their own management of the automat. The investigators reported that seven patients were able to start the device properly, while 13 either pressed the button too long or more than once, due to tremor (Table 11). It was apparent that the buttons were too sensitive. Entering the dose was also difficult for some patients because of this high sensitivity. All patients could release the microtablets into the glass. Since the microtablets were very small, it was anticipated that patients with tremor and/or dyskinesia might find it troublesome to handle them. However, since all patients managed to pick up five tablets from a flat surface (a table), the size seems adequate for manual handling if needed. One patient also claimed that she would like to use the microtablets for her medication, but felt no absolute need for using the dispensing device.

The patients were also asked their opinion of the concept and all but one were positive about the concept of dose administration in general and 17 patients were interested in using the device for their own medication, thus replacing the conventional levodopa tablets. A patient on levodopa infusion said that he would not exchange his infusion for microtablets, but he would prefer microtablets before standard tablets if he had to choose. One patient was newly diagnosed with PD and preferred ordinary tablets, but he stated he would possibly change his mind in the future. One patient claimed that conventional tablets were easier and another did not want to use the device since he already took a great number of other medications. Further, all patients but one felt comfortable with the automatic counting of the correct dose, but some claimed they would check the number of tablets for the first

few times of use. Even though most patients were positive about future use, many mentioned modifications of the current prototype. Most patients found the device too large (14 of 20) and some thought it too heavy (13 of 20). Many patients suggested changing the size to more closely resemble that of cellular telephones. The buttons were too small for seven patients and the text of the display was considered too small by eleven patients; however, all patients were able to read the text. The outcome of this handling test was not clearly correlated with age or PD severity. These results are consistent with the results from the study of a previous prototype of the device in 14 patients with PD (Aquilonius et al., 1998). The mean Hoehn & Yahr score was slightly lower in that group, 2.2 (range 1-4) versus 2.75 in our group. All patients but one in the previous study emphasized a need for the dose dispensing device concept.

Table 11. *Patient test (data from paper VI), n=20.*

Patient tasks	Investigators' assessments of the patients' performance				Patients' answers*	
	Without problems	Some difficulties	After repeated instructions	Cannot perform the task	Yes	No
Starting the automatic dose dispenser	7	1	12	0	20	0
Entering dose	14	5	1	0	20	0
Confirming dose	19	1	0	0	20	0
Releasing tablets	19	1	0	0	20	0
Pouring tablets into a glass	20	0	-	0	20	0
Picking up 5 tablets from table	20	0	-	0	20	0

* To questions on ability to perform each task, such as "Do you think that you were able to start the automatic dose dispenser?" etc.

Summary and conclusions

In this thesis, a new sublingual tablet system based on interactive mixtures and a new concept for individualising the dosage of drugs in solid form have been presented and some important associated formulation factors have been investigated.

Conclusions concerning the possibility of achieving homogeneous mixtures

The results of Paper I indicated that it may be possible to obtain interactive dry mixtures of micronised drugs containing drug proportions as low as 0.015% w/w. It was apparent that factors such as drug particle size and size distribution are important in this respect. It was also apparent that the adhesive interactions between drug and carrier should be acceptably strong, and that the drug should not have any pronounced tendency to create strong agglomerates that cannot be broken during mixing. Only the mixing system which used the finest drug fraction in the highest proportion showed any resemblance to an ideal ordered mixture. However, even for this mixing system (size fraction C100), the effect of sample size was not entirely negligible. This indicates that ideal ordered mixtures were not obtained, and that some randomising factor was involved in the mixing process (i.e. interactive mixtures were formed). Two approaches were used to predict the homogeneity of the mixtures: particle number ratios by weight for the mixture and absolute number of drug particles by weight for individual samples. Although the former approach is primarily related to the existence of an ideal ordered mixture, it seems to provide a fairly good reflection of the possibility of achieving a homogeneous mixture for a normal range of sample sizes. This investigation then found that the particle number ratio by weight for the studied mixing system should preferably exceed approximately 500. The other approach (number of drug particles by weight for a specific sample size) is in fact closely related to Egermann's eq. 4 (1985b). Although this approach seems to be less applicable for mixing systems where the drug component is relatively coarse in comparison with the carrier material, it could be useful for mixing systems where micronised drugs are utilised. In these mixtures, it seems that the number of drug particles by weight should in practice exceed about 10^6 particles per sample, in order to obtain robust high quality mixtures. Consequently, drug particle size is a decisive factor and the results of this study support earlier findings (Nyström and Malmqvist, 1980) that the drug particles should probably not exceed 5 μm in diameter, and should preferably have a narrow size distribution, taking into consideration the statistical probability of finding sufficient numbers of drug particles on each carrier particle.

Conclusions concerning rapidly disintegrating tablets

Different combinations of binder, compound and a superdisintegrant (with a swelling mechanism) were studied to ascertain which binder properties were important in obtaining

rapidly disintegrating tablets which also had high tensile strength. To obtain tablets with a short disintegration time in combination with high tensile strength, the addition of a superdisintegrant was generally necessary. However, the microstructure surrounding the disintegrant particles may influence the disintegrating effect. The microstructure can be varied by e.g. addition of a highly deformable binder or a binder with high aqueous solubility, or the use of soluble compounds. Addition of a superdisintegrant to a deformable microstructure generally resulted in absence of improvement of the disintegration time. When the superdisintegrant swells in a deformable environment, the force that normally causes the bonds to break is instead absorbed by the deformable structure and the disintegrating effect does not occur. Addition of soluble materials also reduced the effectiveness of a superdisintegrant, probably due to increased viscosity of the liquid penetrating into the tablet and/or a rapid widening of voids and pores, thereby reducing the mechanical effect of a strongly swelling disintegrating agent. Using a less deformable binder (microcrystalline cellulose) gave a high tablet tensile strength and the addition of a superdisintegrant significantly decreased disintegration time, especially when used in combination with a water insoluble compound. Further, the results indicated no general relationship between porosity and disintegration time of the tablets, since other properties of the binder and compound, e.g. solubility and bonding ability, also influenced the disintegration.

Conclusions concerning in-vitro evaluation of bioadhesion (Paper III)

The biadhesion of both powder and tablet specimen forms of some materials was evaluated and the results indicated that it is feasible to characterise the bioadhesive properties of materials using uncompacted, powder specimens instead of using a compressed tablet form. When the tablet specimen was used, some of the materials gave unexpectedly high bioadhesive values, while powder specimens gave a more expected ranking of the materials. These unexpected adhesive properties for the tablets may in part be explained by water movement from the mucosa to the dry powder and/or into the porous tablet structure, which would promote adhesion between the two surfaces. Further, when superdisintegrants such as Ac-Di-Sol and Kollidon CL were tested in the tablets, the fracture went through the tablet and erroneously low bioadhesive values were obtained. This was probably a result of their extensive water absorption ability, which weakened the tablet. When coarse mannitol or DCP powders were mixed with the fine particulate Ac-Di-Sol (i.e. forming interactive mixtures) the bioadhesivity was improved. This indicates that addition of materials with a higher adhesion tendency could increase the adhesion of another, less bioadhesive material. The bioadhesivity of the mixtures increased up to a certain level and thereafter started to level off. The plateau in bioadhesion was possibly attributable to the surface area coverage of the bioadhesive component of the carrier exceeding unity. This results in an excess of powder, forming mulitiparticulate layers or agglomerates rather than adherence to the carrier particles. Further, mixtures of the more water soluble mannitol had lower bioadhesive strength compared to mixtures of DCP, which is practically insoluble. The fracture probably went within partly dissolved mannitol particles rather than between Ac-

Di-Sol particles and the mucosa which is the stronger fracture path. In conclusion, interactive mixtures, containing a bioadhesive component, could be an interesting formulation tool in the development of bioadhesive formulations such as instant release formulations for sublingual administration.The use of interactive mixtures of bioadhesive powders with aqueous-insoluble carriers at a proportion close to monoparticulate surface coverage could thus represent a generally applicable means of standardising the testing of bioadhesive capacity.

Conclusions concerning the new sublingual tablet system

The sublingual tablet is based on tableted interactive mixtures consisting of a water-soluble carrier, a fine particulate drug (fentanyl citrate) and a bioadhesive component. The results from the in vitro test of content uniformity showed that the drug was homogeneously mixed and that only minor segregation had occurred during tablet processing (i.e. mixing and tableting). The disintegration and dissolution tests revealed that the tablets were rapidly disintegrated and that fentanyl citrate was dissolved almost instantly from the tablets. After single dose administration, plasma concentrations of fentanyl were obtained within 8-11 minutes, with no second peak corresponding to possible gastrointestinal absorption. The approximate absorption and bioavailability of fentanyl was 70%. This suggests that less than 30% of the dose was swallowed, which could at least in part be attributed to the addition of the bioadhesive component. The clinical implications for this new sublingual tablet principle appear promising. Fentanyl is often used for pain relief in a slow release form using the subcutaneous route. Although slow release opioids have been a major step for pain management, patients still experience acute episodes of breakthrough pain. Traditionally, this is managed with oral morphine, but the onset of action is often delayed up to 60 minutes with this route. The fast sublingual tablet described in this thesis appears to be a valuable addition to the arsenal of drugs for breakthrough pain. The technique could also be useful for substances other than fentanyl where a rapid onset of effect is desirable. However, the new sublingual tablet principle will probably be less useful for hydrophilic drug molecules since this group of drugs will not undergo sufficiently fast absorption over the sublingual mucosa to effectively utilise the advantages of rapid disintegration.

Conclusions concerning the new sublingual tablet system

The automatic dose dispenser contains microtablets, each containing a small amount of drug, which can be used to fine tune and individualise the drug dosage. In this thesis, patients with Parkinson’s disease tested the usability of the device, since these patients often suffer from tremor and/or dyskinesia, which could make the handling of the device difficult. Results from the handling study showed that all patients managed to manoeuvre the device, although some of them found the buttons too sensitive. Most of the patients (19 of 20) thought that the concept was a good idea for optimising drug therapy, and most (17 of 20) would like to use the device and the microtablets instead of regular levodopa tablets

in future. It is concluded that the dispensing device concept, once some technological adjustments have been made, offers potential for improvement of drug therapy and administration for patients with PD. This new concept, allowing fine-tuning of the dose, may also result in more optimal therapy for patients with other diseases requiring individualised dosage.

Acknowledgements

The work in this thesis has been carried out at the Department of Pharmacy, Faculty of Pharmacy, Uppsala University. Financial support from AstraZeneca (Sweden), Pharmacia Corporation (Sweden), Diabact AB, The Knut and Alice Wallenberg Foundation, Swedish Academy of Pharmceutical Sciences, IF Foundation, CR Leffman Scholarship Foundation and CD Carlsson Foundation are gratefully acknowledged. I am also sincerely grateful to all who in some way have helped me fulfil this thesis and especially:

Professor Christer Nyström, min handledare, för att du gett mig möjligheten att få arbeta med roliga och spännande projekt, för att du delat med dig av dina kunskaper, din entusiasm och ditt positiva tänkande. Jag har verkligen uppskattat att du stått ut med alla telefonsamtal och all e-post vilket har bidragit till du aldrig känts frånvarande trots att du inte alltid funnits på BMC.

Professor Göran Alderborn, för tillhandahållande av ändamålsenliga lokaler och vänlig atmosfär, samt för att du visat intresse för mitt arbete.

Dr Åsa Adolfson, inspirerande handledare under mitt examensarbete, för att du uppmuntrade mig till att börja doktorera.

Dr Sofia Mattsson, entusiastisk medförfattare, för att du är alltid har tid att dela med dig av kunskap samt allehanda hjälp, men framförallt för att du är en underbar vän.

Professor Sten-Magnus Aquilonius och Dag Nyholm, inspirerande och trevliga medförfattare, för gott samarbete och för att jag fått ta del av era medicinska kunskaper.

Mina vänner och medförfattare på Diabact AB; Margareta Duberg, Anders Sågström och Dr Marie Westerberg för att ni delat med er av era kunskaper och erfarenheter, Dr Thomas Lundqvist and Katarina Andersson för trevligt ressällskap och VD Björn Forsman för att du vill ge mig nya utmaningar. Jag ser fram emot juni!

Medförfattarna Professor Hans Lennernäs, Docent Bo Lennernäs och Docent Anders Pettersson, för att ni introducerat mig till "den kliniska världen" och hjälp med att förstå de kliniska slutsatserna.

Dr Christina Gustafsson, före detta pendlings- och labkompis, för att du är en fantastik vän och alltid kommer med uppmuntrande ord när de som bäst behövs.

Alla anställda på institutionen, speciellt före detta och nuvarande kollegor i pulvergruppen: Dr Åsa Adolfsson, Gunilla Andersson, Jonas Berggren, Elisabet Börjesson, Leif Dahlberg, Torsten Fjellström, Frauke Fichtner, Dr Christina Gustafsson, Mina Heidarian, Josefina Hellström, Dr Barbro Johansson, Dr Mitra Mosharraf, Dr Sofia Mattsson, Albert

Mihranyan, Dr Mitra Mosharraf, Dr Fredrik Nicklasson, Dr Helena Nicklasson, Martin Nilsson, Dr Tesfai Sebhatu och Åsa Tunón för praktisk hjälp, vetenskapliga och ovetenskapliga samtal samt trevligt sällskap både på lab och på konferensresor.

Eva Nises-Ahlgren och Ulla Wästberg-Galik för ni alltid vill hjälpa till och svara på mina frågor, speciellt i samband med färdigställandet av avhandlingen.

BMCs forskningsverkstad för kunnig hjälp och vänligt bemötande.

Dr Curt Nilsson för värdefulla diskussioner.

Åsa Tunón och Lena Strindelius, för att ni den senaste tiden haft full förståelse för mina funderingar kring font- och figurstorlekar, antal mellanslag och radmatningar m.m.!

Christina, Sofia, Helena och Lars för hjälp med korrekturläsning.

Mina rumskamrater under åren; Fredrik, Mitra, Gustaf, Linda, Eva och Frauke, för trevligt sällskap och all storts hjälp.

Camilla Carlesson and Antonella Penna for experimentally contribution to this thesis.

Antona Wagstaff for excellent and rapid linguistic revision of the papers and the thesis.

Mina före detta kollegor på Läkemedelsverket, speciellt Maud Bertze, Conny Eklund och Marianne Tjernström, för att ni hela tiden stöttat mig.

Mina vänner utanför institutionen för trevliga middagar och annat skoj.

Familjen Bredenberg för gästvänlighet och trevliga stunder.

Moster Barbro, morbror Börje och hans Christina för att ni alltid hejar på mig oavsett om jag tävlar på cykel, doktorerar, väntar barn eller köper hus.

Min bror Stefan och hans Sophia, för att ni alltid visat stort intresse för mitt arbete.

Pappa Sven-Olof och mamma Kerstin, för er uppmuntran, ert stöd och för att ni alltid finns när jag behöver er. Ett extra tack till mamma för markservice och barnpassning under den här våren, som varit otroligt intensiv både för Lars och mig.

Lars, för att du alltid stöttar mig och aldrig har tvivlat på att jag skulle klara av det här.

Ella, mitt hjärta ♥, för att du gör livet så roligt. Nu ska jag ägna mer tid åt njuta av dig och dina upptäckter!

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