UNIFORMITY OF MULTIUNIT TABLETS UNDER PILOT PLANT CONDITIONS AS A FUNCTION OF UNIT SIZE AND FILLER COMPOSITION

GLEICHFÖRMIGKEIT VON MULTIPARTIKULÄREN TABLETTEN UNTER PRODUKTIONSBEDINGUNGEN IN ABHÄNGIGKEIT DER GRÖßE DER UNTEREINHEITEN UND DER ZUSAMMENSETZUNG DES FÜLLSTOFFES

DISSERTATION

der Fakultät für Chemie und Pharmazie
der Eberhard-Karls-Universität Tübingen
zur Erlangung des Grades eines Doktors
der Naturwissenschaften

2003

vorgelegt von

HELENE REY

Tag der mündlichen Prüfung	24. Januar 2003
Dekan	Prof. Dr. H. Probst
1. Berichterstatter	Prof. Dr. P. C. Schmidt
2. Berichterstatter	Prof. Dr. S. Laufer

Die vorliegende Arbeit entstand auf Anregung und unter der Leitung von

Herrn Prof. Dr. P. C. Schmidt

am Lehrstuhl für Pharmazeutische Technologie der Eberhard-Karls-Universität in Tübingen.

Meinem verehrten Doktorvater, Herrn Prof. Dr. P. C. Schmidt, danke ich für die Möglichkeit, diese Arbeit in seiner Gruppe anzufertigen, für seine ständige Bereitschaft zur Hilfe und zur Diskussion und die Schaffung optimaler Arbeitsbedingungen. Außerdem möchte ich mich bei ihm für die Möglichkeit zur Teilnahme an Exkursionen, an Weiterbildungsveranstaltungen zur Fachapothekerin für Pharmazeutische Technologie und an Kongressen bedanken.

Ebenso danke ich Herrn Dr. Karl Wagner für die Förderung dieser Arbeit durch zahlreiche Diskussionen. Seine fachliche Betreuung und Unterstützung waren mir stets eine große Hilfe und haben zum Gelingen dieser Arbeit beigetragen.

Den Firmen FMC Corp. und BASF AG danke ich für die Bereitstellung von Materialen. Der Firma Abbott GmbH & Co. KG danke ich für die Ermöglichung der Tablettierung von Theophyllin-Mikrotabletten. Der Firma Ritter Pharma-Technik GmbH gilt mein Dank für die Überlassung der Stempelwerkzeuge.

Herrn Geiger und den Mitarbeitern der Werkstatt des Pharmazeutischen Institutes danke ich für die Reparaturen und die Anfertigung des Förderbands.

Bei Frau Renate Beer, Herrn Roland Walker und Herrn Klaus Weyhing bedanke ich mich für die Unterstützung am Lehrstuhl, sowie insbesondere bei Frau Martina Brenn für ihre ständige Hilfe bei „deutschen Korrekturen“.

Mein besonderer Dank gilt Herrn Abebe Endale und Frau Kelly Chow für das sehr sorgfältige und schnelle Korrekturlesen des Manuskripts.

Bei meinen Kollegen, den ehemaligen aber auch den derzeitigen, so wie den ausländischen Gästen am Lehrstuhl, bedanke ich mich für die gute Zusammenarbeit, die zahlreichen Diskussionen und das sehr angenehme Arbeitsklima. Sie haben mit

ihrer hilfsbereiten und freundschaftlichen Art dazu beigetragen, dass ich mich während meiner Zeit in Tübingen sehr wohl fühlte.

Enfin, ma dernière pensée revient à mes parents sans qui ce travail n'aurait jamais abouti. Merci pour la confiance qu'ils m'ont accordée et leur soutien dans mes choix et décisions, même si ceux-là n'ont pas toujours été les plus simples ni les plus faciles.

A ma famille

CONTENTS

ABBREVIATIONS

DIN	Deutsche Industrie Norm
e.g.	exempli gratia
et al.	et alii
h	hour
min	minute
No	number
p	page
rpm	revolutions per minute
s	second
S.D.	standard deviation
USP	The United States Pharmacopeia
UV	ultraviolet
x_{10}, x_{50}, x_{90}	particle volume diameter
v/v	volume in volume
w/w	weight in weight

Notes:

Error bars in figures represent the 95 % confidence interval of the mean.

Registered trademark will be used without particular designation.

Parts of this thesis have been presented in:

- H. Rey, K. G. Wagner, P. Wehrlé and P. C. Schmidt
  „Development of matrix-based theophylline sustained-release microtablets"
  Drug Dev. Ind. Pharm. **26**, 21-26 (2000)

- H. Rey, K. G. Wagner and P. C. Schmidt
  „Tabletten aus Mikrotabletten - im Grenzbereich der Mischungsstabilität"
  Oral presentation, GVC VDI- Gesellschaft Verfahrenstechnik und Chemieingenieurwesen, Erfurt (2000)

- H. Rey, K. G. Wagner and P. C. Schmidt
  „Tabletten aus Mikrotabletten – Versuch unter Produktionsbedingungen"
  Oral presentation, GVC VDI- Gesellschaft Verfahrenstechnik und Chemieingenieurwesen, Freiburg (2001)

- H. Rey and K. G. Wagner
  „Bimodal verteilte Tablettiermischungen – im Grenzbereich von Segregation und Fließfähigkeit"
  Oral presentation, GVC VDI- Gesellschaft Verfahrenstechnik und Chemieingenieurwesen, Stade (2002)

- H. Rey, P. C. Schmidt and K. G. Wagner
  „Tableting of pellets and micro tablets into disintegrating tablets: the problem of weight uniformity"
  Poster, 4th World Meeting ADRITELF/APGI/APV, Florence, 103-104 (2002)

CHAPTER 1

INTRODUCTION

Peroral controlled-release multiunit dosage forms (e.g., pellets, granules or microparticles) are becoming more and more important on the pharmaceutical market, as they provide several advantages compared to single-unit dosage forms (e.g., tablets or capsules) (Ghebre-Sellassie 1994). Risks such as spontaneous drug release from a single-unit tablet due to damaged coating or its attachment in the stomach or intestine causing an irritation of the gastric or intestinal mucosa, are reduced by the use of multiunit forms (Adriaens *et al*. 2002). After disintegration of the tablets in the stomach, single units equal to or below 2 mm in diameter and having a density lower than 2.5 g/cm^3 behave like a liquid and have a short transit time through the stomach avoiding drug accumulation (Clarke *et al.* 1993, 1995). Moreover, such small single units enable a more reproducible dispersion throughout the gastrointestinal tract leading to a reduction of drug release variations and an improved bioavailability. Thus, it results in a decrease in drug dose and side effects (Sandberg *et al.* 1988, Sivenius *et al.* 1988, Stefan *et al*. 1988, May and Rambeck 1989, Follonier and Doelker 1992, Abrahamsson *et al.* 1996, Amighi *et al.* 1998, Peh and Yuen 1997, Hosny *et al.* 1998).

With regard to the final dosage form, the multiparticulates can be filled into hard gelatin capsules (Stegemann 1999, Chopra *et al.* 2002) or be compressed into disintegrating tablets (Flament *et al.* 1994, Maganti and Çelik 1994). The advantages of tableting multiparticulates include less difficulty in oesophageal transport, and thus a better patient compliance. Tablets can be prepared at a lower cost because of the higher production rate of tablets presses. The expensive control of capsule integrity after filling is also eliminated. In addition, tablets containing multiparticulates could be scored without losing the controlled release properties, which allows a more flexible dosing regimen (Bodmeier 1997).

Sustained-release multiunit dosage forms can be achieved by compressing of coated or matrix-type multiparticulates such as pellets or micro tablets. Several studies have already reported that during the compression process, coated pellets may be damaged by interactions between the feeder, punches and die of the tablet press or between the components of the mixture leading to some increase in drug release (López-Rodríguez *et al.* 1993, Beckert 1995, Wagner 1999). Matrix systems present the advantage that the release of the drug is not dependent on the properties and the state of the film coating. Moreover, micro tablets, which are tablets having a diameter of 2 mm or less, represent an interesting alternative to pellets. Since micro tablets are produced by compression, many steps of pellet production, like moisturizing, extruding, spheronizing, and drying can be avoided (Flemming and Mielck 1996). Furthermore, micro tablets are uniform in form and size and show a regular surface.

Pellets or micro tablets are mixed with excipients before being compressed into multiunit tablets. The difference in form, size and density of the different mixing components are critical factors, which can influence the stability and demixing tendency of such mixtures. Some authors have recommended filler-binders that are almost equal in size to the pellets used (Aulton *et al.* 1994, Çelik and Maganti 1994, Flament *et al.* 1994, Lundqvist *et al.* 1997, Pinto *et al.* 1997), whereas others have demonstrated a reduction of segregation while using a fine microcrystalline cellulose like Avicel PH 101 (Haubitz *et al.* 1996, Wagner *et al.* 1999). Non-segregating mixtures of pellets or micro tablets and filler-binders are necessary to obtain tablets of uniform weight and drug content, and thus to ensure a high quality in production.

The objective of this work was to investigate the influence of the size of single units (pellets or micro tablets) on the uniformity of the tablet weight and content of the active ingredient of the resulting tablets under pilot plant conditions. In order to achieve this goal, four different sizes of pellets in a range from 355 µm to 1700 µm and micro tablets of 2 mm in diameter were compressed into 13-mm tablets on a rotary tablet press (Korsch PH 230) within 1 hour. Weight and content variations were investigated and the percentage of rejected tablets was defined. The flow properties of

the different mixtures were determined according to DIN 53916 and using a self-constructed conveyor belt. The influence of the filler composition on the flow properties was also studied. Finally, properties of the multiple unit dosage forms such as crushing strength, friability and disintegration time were reported as well as the effect of the compression process on the release of theophylline from multiunit tablets.

CHAPTER 2

LITERATURE REVIEW OF THE PRODUCTION OF MULTIUNIT TABLETS AND DESCRIPTION OF THE STUDY MODEL

2.1 Literature review of the production of multiunit tablets

2.1.1 Description of the single units used for the production of multiunit tablets

Multiunit tablets are produced by compressing single units that are in general granules, pellets or micro tablets. According to Follonier and Doelker (1992), the granules are divided into microspheres and microcapsules. The methods for preparing granules are based either on physical methods such as fluidized bed granulation, spray-drying, spray-congealing and solvent evaporation, on physicochemical methods such as coacervation, or on chemical methods such as interfacial polymerisation (Por Li *et al.* 1988). The production of pellets is a quite complex process, as it includes many steps such as moisturising, extruding, spheronising and drying (Kleinebudde 1998). Moreover, pellets present the major disadvantage of being irregular shaped particles (Munday 1994). Hence, micro tablets that are tablets having a diameter equal to or smaller than 2 mm could represent an interesting alternative to pellets since they are produced by compression (Flemming and Mielck 1995, 1996, Butler *et al.* 1998, Rey *et al.* 2000). Thus, many steps of pellets production can be avoided, defined sizes and strengths can be easily achieved and the variability within a batch can be minimised. Because of their uniform size, smooth surface, low porosity and high strength, micro tablets could be coated more reproducibly than usual pellets. They are more robust and they need less coating material (Munday 1994, Vecchio *et al*. 2000). Moreover, it is possible to produce micro tablets with higher drug contents than normal-sized tablets (Lennartz and Mielck 1998).

One way to achieve sustained-release multiunit tablets is to compress coated single units. The polymers used in the film-coating of solid dosage forms usually fall into two broad groups based on either cellulose or acrylic polymers (Bodmeier and Paeratakul 1994). Ethylcellulose is used frequently as coating material for the preparation of pellets. However, it forms quite brittle films that are not suitable for further tableting (Béchard and Leroux 1992, Tirkkonen and Paronen 1993, Maganti and Çelik 1994). Polyacrylates are more qualified for these purposes, as they are more flexible (Lehmann 1984, Lehmann *et al.* 1994, Lehmann and Süfke 1995, Beckert *et al*. 1996).

In order to control the drug release of multiunit tablets, the film coating has to withstand the applied compaction pressure. The film can deform, but should not rupture. Damages to the coating would result in a loss of the sustained release properties and cause dose dumping. Several studies have reported on the formulation and the process parameters necessary to obtain pellet-containing tablets that have the same properties as the individual coated units (Beckert 1995, Bodmeier 1997, Wagner 1999).

Besides the well-known principle of film-tablets, most concepts of controlled release tablets are based on more or less compact porous or slowly eroding matrix structures. Sustained release matrix tablets are obtained by direct compression of drugs with spray dried polymer powders. Lehmann (1984) and Cameron *et al.* (1987) have described such systems using acrylic resins. A matrix is a uniform mixture of drug, excipients and polymer that is homogeneously fixed in a solid dosage form (Carstensen 2001). The drug substance, which has a solubility in the dissolution medium is dispersed in the matrix, which is insoluble in the dissolution medium. The matrix is more or less porous so that the liquid will intrude the matrix and will dissolve the drug substance.

The production of matrix micro tablets has been already described (Rey *et al*. 1998, Sujja-areevath *et al.* 1998, Cox *et al.* 1999, De Brabander *et al.* 2000a+b) but until now, no studies have reported about the tableting of multiunit tablets consisting of matrix micro tablets.

2.1.2 Excipients for the tableting of multiunit tablets

Compaction of multiparticulates into tablets could either result in disintegrating tablets providing a multiparticulate system during gastrointestinal transit or in intact tablets due to adhesion or partial fusion of the multiparticulates in a larger compact (Johansson *et al.* 1995). Ideally, the compacted single units should disintegrate rapidly into the individual units in gastrointestinal fluids; they should not stick together forming a non-disintegrating matrix during compaction (Chemtob *et al.* 1986, Sveinsson *et al*. 1993). Thus, various external excipients have to be added to single units to assist the compaction process (López-Rodríguez *et al*. 1993, Maganti and Çelik 1993). The ideal filler material used for the tableting of single units should prevent the direct contact of the units and act as cushioning agent during compression. Compaction forces have to be absorbed preferentially and mainly by the excipients in order to let the single units intact. The protective effect of different tableting excipients on the compression of granules is studied indirectly through dissolution studies (Torrado and Augsburger 1994). The amount of excipient used should be sufficient to separate and protect the units. Lehmann *et al*. (1990 and 1994) reported that an amount of filler and disintegrant between 30-50 % was necessary to reduce damages of coated pellets. When approximately 30 % of tableting excipients including disintegrants were compressed with the coated particles, the interspaces were filled and the pellets were separated. Hence, the tablets disintegrated rapidly and the damages of particles and changes of release profiles could be reduced to an insignificant level.

Moreover, the addition of excipients should result in hard and rapidly disintegrating tablets at low compression forces. Flamment *et al.* 1994 have shown that tablets containing active pellets alone lacked the required hardness. Thus, inert granules were added to facilitate the cohesion of the tablet. According to the requirements of the European Pharmacopoeia, the multiunit tablets have to liberate the subunits within 15 min. Besides their compaction properties, the excipients have to result in a uniform blend with the single units, avoiding segregation and therefore weight variation and poor drug content uniformity of the resulting tablets (Bodmeier 1997).

2.1.3 Microcrystalline cellulose as filler/binder for multiunit tablets

Microcrystalline cellulose is certainly the most commonly used diluent for the compression of single units into tablets. Table 2.1 reviews studies dealing with the production of disintegrating sustained-released multiunit tablets containing microcrystalline cellulose as filler/binder. In certain studies, microcrystalline cellulose was used directly as supplied by the manufacturer whereas in other studies, it was first mixed with other additives and then granulated or extruded into pellets.

Torrado and Augsburger (1994) have studied the protective effect of different excipients on the tableting of theophylline granules coated with Eudragit RS. Two excipients namely polyethylene glycol 3350 and microcrystalline cellulose were found to cause the lowest damages of the granules during tableting. These results were explained with the yield pressure of the two excipients, which were lower than that of the pellets. Therefore, the energy of compaction was absorbed by the external excipients and these excipients were preferentially deformed. This protective effect of microcrystalline cellulose was confirmed in another study by Tunón and Alderborn (2001) in which the pellets after disintegration of the tablets were similar in size to the original pellets. A very few pellet fragments were obtained during disintegration. The compaction had only affected the shape of the individual pellets resulting in more irregular pellets. Moreover, Wagner *et al*. (2000a) observed that pellets compressed with the fine microcrystalline cellulose Avicel PH 101 (x_{50} = 50 µm) remained approximately spherical. The fine Avicel PH 101 was able to fill the pores of the pellets lattice much more tightly than coarse Avicel granules (x_{50} = 194 µm).

In regards to the physical properties of multiunit dosage forms, López-Rodríguez *et al.* (1993) and Maganti and Çelik (1993) showed that tablets of coated pellets containing microcrystalline cellulose presented a higher crushing strength than tablets of coated pellets without microcrystalline cellulose. External excipients, being small and irregular particles, when added to the pellets, introduce new bounding sites, which lead to an increase in the number of potential cohesive and adhesive bonds, thereby producing relatively strong compacts. Mixtures consisting of pellets and

microcrystalline cellulose as external additive were found to be more compressible and produced stronger compacts than the tableting of pellets with pregelatinized starch or soy polysaccharide. Moreover, the size of microcrystalline cellulose had shown an effect on the crushing strength of tablets. Tablets compressed with Avicel PH 101 had demonstrated a significantly higher crushing strength than tablets produced with Avicel granules (Wagner *et al.* 1999).

Concerning the disintegration time, the use of microcrystalline cellulose as external excipients has provided compacts that have disintegrated and regenerated the coated particles within less than 10 s as opposed to 7-10 min for other excipients such as spray dried lactose, spray dried sorbitol, compressible sucrose, polyethylene glycol 8000, pregelatinized starch (Béchard and Leroux 1992).

In addition to the physical properties, multiunit tablets containing microcrystalline cellulose showed low friability with values below 1 %. It was also observed that the friability depends on the microcapsules content. 50 % of microcapsules and Avicel showed a friability of 0.89 %, whereas at 75 % of microcapsules, the tablet could not be held together. In general, Avicel allowed the incorporation of a greater percentage (w/w) of single units without serious degradation of tablet performance than other excipients (Prapaitrakul and Whitworth 1990, Flament *et al.* 1994). An increase in the amount of single units had logically an effect on the other physical properties of the multi unit tablets. Increasing the single unit content decreases the tablet breaking load and the disintegration time. Pellets that are large and spherical in shape as compared to small, irregular powder particles, have a low surface to volume ratio, and this might result in a decreased area of contact between the particles as they consolidate (Lundqvist *et al.* 1997). According to the studies from López-Rodríguez *et al.* (1993), Prapaitrakul and Whitworth (1990) and Aulton *et al.* (1994), the optimal amount of microcrystalline cellulose used to compress single units without serious degradation of tablet performance varied between 25 % and 40 % (w/w), corresponding to an amount of single units from 60 % to 75 % (w/w). Moreover, Beckert *et al.* (1998) have observed that a pellet content in the range of 50-70 % (w/w) resulted in multiunit tablets that complied with the requirements for weight and content uniformity of European Pharmacopoeia. The explication was based on the percolation theory.

Stauffer (1985) used the term percolation to describe continuous structures (clusters) formed throughout the length, width and height of a system. When a binary system is considered, it depends on the concentration of each component, whether only one or both components percolate. The minimum concentration of a component at which a percolating cluster may be found is called the percolation threshold. Below this concentration only isolated clusters of one component can exist. Infinite clusters form above the percolation threshold. A bicoherent structure builds up if both components percolate. Beckert (1995) found that up to 50 % (w/w) of pellets, a percolating cluster of pellets that prevent segregation was ensured.

On one hand, a lot of authors agree that the particle size of external additives is a parameter of major importance in order to obtain a uniform mixture. Segregation is influenced by factors such as markedly differing particle size, density or shape. The difference in size distribution between powders and pellets is expected to lead to segregation, resulting in tableting problems, such as weight variation and poor content uniformity. Therefore, the excipients should have a mean diameter close to that of the active single units to produce a stable mixture. Consequently, it seems necessary to choose a large particle size of excipients or to prepare placebo pellets or granules (Aulton *et al.* 1994, Çelik and Maganti 1994, Flament *et al.* 1994, Beckert *et al*. 1996, Pinto *et al*. 1997, Lundqvist *et al.* 1997). On the other hand, Haubitz *et al*. (1996) compressed mixtures consisting of 70 % (w/w) theophylline pellets (800-1250 µm) and the fine microcrystalline cellulose Avicel PH 101 (x_{50} = 50 µm) and observed that in spite of the greater differences of particle sizes no distinct segregation occurred. In addition, Wagner *et al.* (1999, 2000b) investigated the pellet-distribution in single tablets via image analysis. The most homogeneous distribution of the pellets, particularly at intermediate and high machine speed was achieved with the fine Avicel PH 101. On the contrary to Avicel PH 101, coarser filler-binders led to segregation within the tablets at high machine speed. Avicel PH 101 has a large surface area and a fibrous surface texture, thus building a close percolating infinite cluster stabilising the pellets at their location in the mixture. A homogeneous distribution of the single units within the tablet presents also the advantage of divisible tablets.

Table 2.1 Review of studies on the tableting of disintegrating multiunit tablets using microcrystalline cellulose as filler/binder

Authors	Single unit	Size of single unit [µm]	Drug	Coating	Content of single units [% (w/w)]	Type of microcrystalline cellulose
Prapaitrakul *et al.* (1989, 1990)	microcapsules	125-250	phenylpropanol-amine resin complexes	cellulose acetate butyrate	15-75	not defined
Béchard and Leroux (1992)	pellets	250-420 420-590 590-840	chlor-pheniramine maleate	ethylcellulose	60	Avicel PH 101 or Avicel PH 200
López-Rodríguez *et al.* (1993)	pellets	600-850	acetylsalicylic acid	Eudragit RS	75-95	Avicel PH 102
Maganti and Çelik (1993)	pellets	500-1000	propranolol HCl	-	80-90	Emocel 50M
Tirkkonen and Paronen (1993)	microcapsules	147-297	indomethacin	ethylcellulose	33	Avicel PH 101
Aulton *et al.* (1994)	pellets	10000	ibuprofen	Eudragit RS /RL	60	Avicel PH 200

Authors	Single unit	Size of single unit [µm]	Drug	Coating	Content of single units [% (w/w)]	Type of microcrystalline cellulose
Flament *et al*. (1994)	pellets	355-1000	theophylline	Eudragit NE	50	granules of microcrystalline cellulose (250-1000 µm)
Torrado and Augsburger (1994)	pellets	410-590	theophylline	Eudragit RS	25	granules of Avicel PH 101 (710-850 µm)
Heinämäki *et al.* (1995)	pellets	700-1600 1000-2000	theophylline	Eudragit RS/RL	50	Avicel PH 102
Beckert *et al.* (1996)	pellets	500-1250	bisacodyl	Eudragit L 30D-55	10-90	Avicel PH 200
Haubitz *et al*. (1996)	pellets	800-1250	theophylline	Eudragit NE	70	Avicel PH 101
Mount *et al*. (1996)	pellets	840-1190	theophylline	Eudragit L 30D-55	10-50	Avicel PH 101 or pellets of Avicel PH 101 (840-1190 µm)

Authors	Single unit	Size of single unit [µm]	Drug	Coating	Content of single units [% (w/w)]	Type of microcrystalline cellulose
Li *et al.* (1997)	pellets	840-1000	pseudo-ephedrine HCl pseudo-ephedrine base	Eudragit S-100 Eudragit RS	50	Avicel PH 101
Lundqvist *et al.* (1997)	pellets	1000-1400	riboflavin	-	20-60	pellets of Avicel PH 101 (1000-1400 µm)
Pinto *et al.* (1997)	pellets	1000-1400	indomethacin	-	15-50	pellets of Avicel PH 101 (1000-1400 µm)
Beckert *et al.* (1998)	pellets	800-1250	bisacodyl	Eudragit L 30D-55	10-70	Avicel PH 101 or Avicel PH 200 or Avicel granules (500-1000 µm)
Kühl and Mielck. (1998)	pellets	1000-1190	placebo (sugar)	-	30-60	Avicel PH 200
Lundqvist *et al.* (1998)	pellets	1000-1400	theophylline	ethylcellulose methylcellulose	20-60	pellets of Avicel PH 101 (1000-1400 µm)

Authors	Single unit	Size of single unit [µm]	Drug	Coating	Content of single units [% (w/w)]	Type of microcrystalline cellulose
Wagner *et al.* (1999)	pellets	850-1000	coloured placebos	Eudragit FS 30D	70	Avicel PH 101 or Avicel granules (194, 621 and 1055 µm)
Wagner *et al.* (2000 a+b)	pellets	1000	bisacodyl	Eudragit FS 30D	60-70	Avicel PH 101 or Avicel granules (194 µm)
Tunón and Alderborn (2001)	pellets	1000-1250	coloured placebos	-	12.5	pellets of Avicel PH 101 (710-1000 µm)
Tunón and Alderborn (2002)	pellets	1000-1250	salicylic acid	ethylcellulose	12.5	pellets of Avicel PH 101 (180-300 or 710-900 µm)

2.2 Description of the study model

30 kg-batches consisting of 60 % (w/w) single units and excipients were compressed on a rotary tablet press (Korsch PH 230/17) for 1 hour in order to investigate the influence of the size of the single units and the composition of fillers on the weight variation and content uniformity of the multiunit tablets.

2.2.1 Types of pellets and micro tablets as single units

Four categories of pellet sizes and two types of micro tablets with a diameter of 2 mm were used as single units to be compressed into multiunit tablets (Table 2.2 and Table 2.3). Placebo micro tablets consisting of 99 % (w/w) StarLac and 1 % magnesium stearate were compressed on an instrumented Korsch Pharma 230/17 (see Chapter 6) and they were used for the study of uniformity of weight. Theophylline micro tablets were used to study the uniformity of micro tablets per tablet and the dissolution behaviour of a sustained release formulation. The sustained-release micro tablets were based on a polymer matrix, which delivers the drug within 8 hours (see Chapter 5). Rey *et al.* (2000) have already described such micro tablets. The production of theophylline micro tablets was divided into two steps: production of theophylline granules and tableting of the granules with 2 % magnesium stearate. Theophylline granules were prepared in a fluidised bed granulator (WSG 5, Glatt GmbH) by top spraying a 6 % aqueous dispersion of Eudragit RS 30 D plus 10 % triethyl citrate onto a powder mixture of 70 % theophylline, 12 % Eudragit RS PO and 12 % magnesium stearate. The theophylline micro tablets were compressed on an instrumented rotary tablet press Kilian TX 40 at a compaction pressure of 200 MPa (see Chapter 6).

Table 2.2 Description of the different pellets used for the tableting of multiunit tablets

Single unit	x_{10}	x_{50}	x_{90}	Composition
Suglets 355-425 (batch No. 104 F)	288	390	532	Sugar spheres
Suglets 850-1000 (batch No. 106 E)	660	950	1374	Sugar spheres
Suglets 1180-1400 (batch No. 909 T)	799	1118	1521	Sugar spheres
Pellets, neutral 1400-1700*	1411	1466	1596	Saccharose, corn starch

* data from the supplier

Table 2.3 Properties of the different micro tablets used for the tableting of multiunit tablets

Type of micro tablets	Diameter [mm]	Composition [w/w]	Tablet weight [mg] ± S.D.	Crushing strength [N] ± S.D.
Placebo	2	StarLac 99 % magnesium stearate 1 %	7.02 ± 0.11	7.6 ± 1.5
Theophylline	2	theophylline granules 98 % magnesium stearate 2 %	7.24 ± 0.08	10.8 ± 0.4

2.2.2 Filler/binders for multiunit tablets

The filler used for the tableting of multiunit tablets was either a fine microcrystalline cellulose Avicel PH 101 (x_{50} = 50 µm) or a binary mixture of 30 % (w/w) Avicel PH 101 and 70 % (w/w) of a coarser microcrystalline cellulose Avicel PH 200 (x_{50} = 180 µm). The other excipients were 4 % (w/w) Kollidon CL as disintegrant, 0.1 to 0.4 % (w/w) Aerosil 200 as glidant and 0.5 % (w/w) magnesium stearate as lubricant. The amount of filler was varied in a range of 35.1-35.4 % depending of the amount of

Aerosil 200. The composition of the different mixtures is described in Chapter 6, Table 6.7.

2.2.3 Tablet press parameters for the production of multiunit tablets

Mixtures were compressed on an instrumented rotary tablet press Korsch PH 230/17, equipped with 8 pairs of round flat-faced B-tooling punches and a diameter of 13 mm at a compaction force of 150 MPa. An intermediate machine speed of 50 rpm was used to compress the multiunit tablets with an average output of 24000 tablets per hour. The tablet weight was adjusted at the beginning between 0.95-1.00 g corresponding to a theophylline content of 390-410 mg per tablet. During the process, the parameters of the machine were not changed in order to correct the tablet mass. The time needed to compress 30 kg of a pilot plant batch was roughly 1 hour.

Due to the fact that large pellets or micro tablets are compressed into multiunit tablets using fine filler/binders, there is a demixing tendency in the feeding system of the rotary tablet press. In general a gravity or a force feeder could be used. A preliminary study has shown that the use of a force feeder was not suitable for tableting of micro tablets. The force feeder is composed of two wheels consisting of stirring blades, which can damage the micro tablets through friction. Moreover, it was observed that the tablet weight decreased significantly during the tableting process (Figure 2.1). This was the result of segregation of the micro tablets within the force feeder by the centrifugal forces of the stirring blades. Therefore for all tableting experiments a gravity feeder was used.

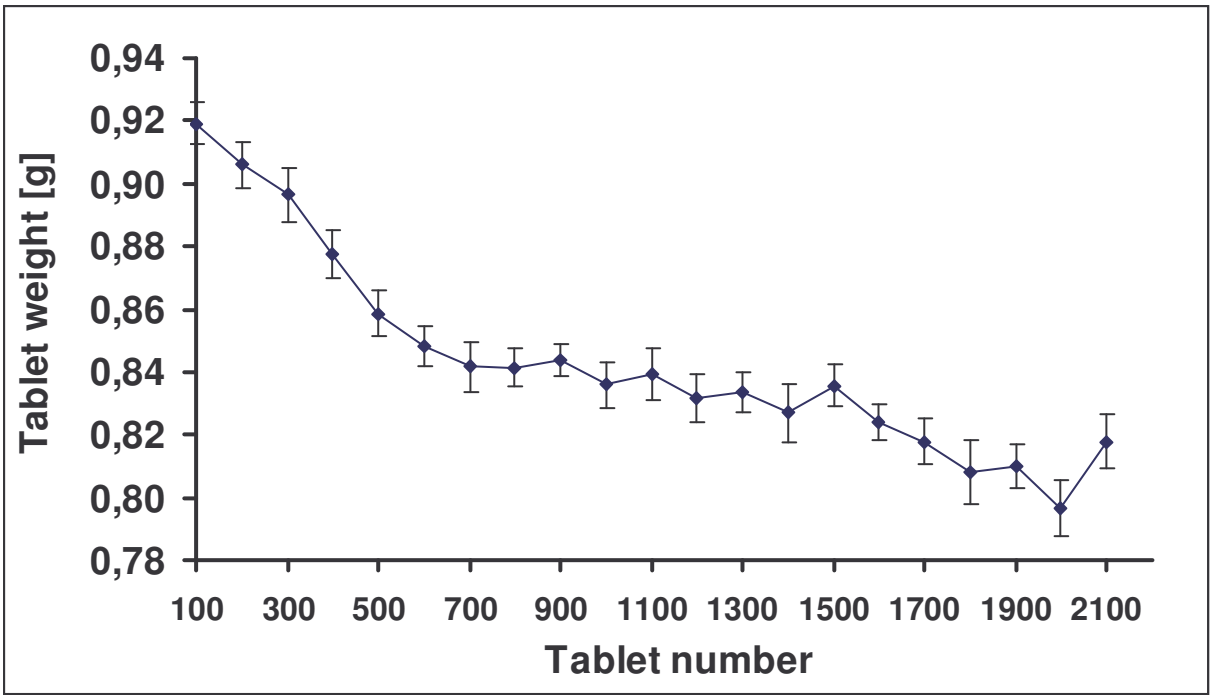

Figure 2.1 *Variation of tablet weight during the tableting of 60 % (w/w) placebo micro tablets, 35.2 % Avicel PH 101, 4 % Kollidon CL, 0.3 % Aerosil 200 and 0.5 % magnesium stearate on a Korsch Pharma 230/17 rotary tablet press at 50 rpm and using a force feeder. Each point represents n=20 tablets. Error bars represent the 95 % confidence interval*

CHAPTER 3

INFLUENCE OF SINGLE UNIT SIZE ON THE TABLET WEIGHT AND UNIFORMITY OF SINGLE UNITS PER TABLET

3.1 Introduction

Multiunit tablets consisting of single units of varying sizes and excipients were compressed on an instrumented rotary tablet press Korsch Pharma 230/17. The aim of the study was to adjust the system tablet formulation/tablet press in order to produce multiunit tablets that guarantee weight uniformity and uniformity of single units within one tablet under pilot plant conditions. As a reference experiment Ludipress, known as a free-flowing material for direct compression was firstly compressed with 0.5 % magnesium stearate. The tableting of Ludipress was then compared to the tableting of the different batches of single units.

3.2 Tableting of Ludipress

3.2.1 Characterisation of Ludipress

Ludipress is an alpha-lactose monohydrate based granule that was introduced into the pharmaceutical market in 1988. Besides α-lactose monohydrate, it contains Kollidon 30 and Kollidon CL. Concentrations and attributes of these three constituents are described in Table 3.1. Lang (1986) and Bolhuis and Chowan (1996) have reported applications of Ludipress as an excipient for the manufacture of tablets by direct compression.

Table 3.1 Attributes and concentration of the constituents of Ludipress

Constituent	Concentration [%]	Attribute
α-Lactose monohydrate	93.0 ± 2.0	Filler, binder
Kollidon 30 (polyvinylpyrrolidone)	3.5 ± 0.5	Binder
Kollidon CL (crospovidone)	3.5 ± 0.5	Disintegrant

Ludipress is a coprocessed product obtained by a special granulation process of α-lactose monohydrate particles with polyvinylpyrrolidone and crospovidone. It has been demonstrated that the use of specially designed coprocessed materials could improve the advantages of the starting materials while overcoming their respective disadvantages (York 1992). Most important are the binding and blending properties of these excipients, which must be better than those of a physical mixture of the starting materials.

The granule characteristics of Ludipress have been investigated in several studies (Baykara *et al.* 1991, Muñoz-Ruiz *et al.* 1992, Rubensdörfer 1993, Heinz *et al.* 2000). Flowability of powders is an important characteristic during tableting as it can critically affect the uniformity of tablet weight and thus the coefficient of weight variation. Flow properties are generally determined using angle of repose, flow rate and/or bulk density measurements. Surface properties and particle shape are also parameters that influence the powder flow directly.

The morphology of Ludipress has been investigated by scanning electron microscopy (Schmidt and Rubensdörfer 1994). It was shown that Ludipress is made up of a large number of small crystals leading to granules with smooth surfaces and spherical shapes. Rheological characteristics of Ludipress have been compared to the physical blend of the base materials of Ludipress and other filler/binders such as Avicel PH 101, Avicel PH 200, Cellactose, Tablettose, Fast-Flo Lactose, anhydrous α-lactose and it was found that Ludipress had smaller angle of repose, better flow rate and smaller Hausner ratio (Muñoz-Ruiz *et al.* 1993, Schmidt and Rubensdörfer 1994, Goto *et al.*

1999). Table 3.2 shows the powder characteristics of Ludipress that was used in this work. With an angle of repose of 30.0° and a Hausner-ratio of 1.13 (values below 1.25 indicate good flow property, Hausner 1967), it was confirmed that Ludipress is a suitable excipient for direct compression.

Table 3.2 Characteristics of Ludipress (Lot No. 62_1227)

Component	Angle of repose [°]	Flow rate [ml/s]	Bulk density [g/ml]	Tapped density [g/ml]	Hausner-ratio	Particle size distribution [µm]
Ludipress Lot No. 62_1227	30.0	17.26	0.581	0.658	1.13	x_{10} = 52.44 x_{50} = 179.30 x_{90} = 385.15

3.2.2 Tableting

Powder characteristics of Ludipress confirmed that it is a suitable excipient for direct compression. However, the compression of pure Ludipress encounters high frictions in the dies, so that the addition of a lubricant, such as magnesium stearate, is necessary. Magnesium stearate has been mixed with Ludipress in concentrations varying from 0.5 to 2 % to reduce frictional forces (Plaizier-Vercammen and Van den Bossche 1992, Schuchmann 1999).

A 30 kg-batch of Ludipress and 0.5 % of magnesium stearate was compressed at 150 MPa on a rotary press (Korsch Pharma 230/17). The filling depth and the band height were adjusted at the beginning of the tableting process and the adjustments were kept constant during the next 60 min. Samples of 20 tablets were taken randomly every 3 minutes within 60 min and the weight variations were analysed. Figure 3.1 depicts the weight variation of tablets during compression and the limits of tolerance according to the European Pharmacopoeia 4th edition.

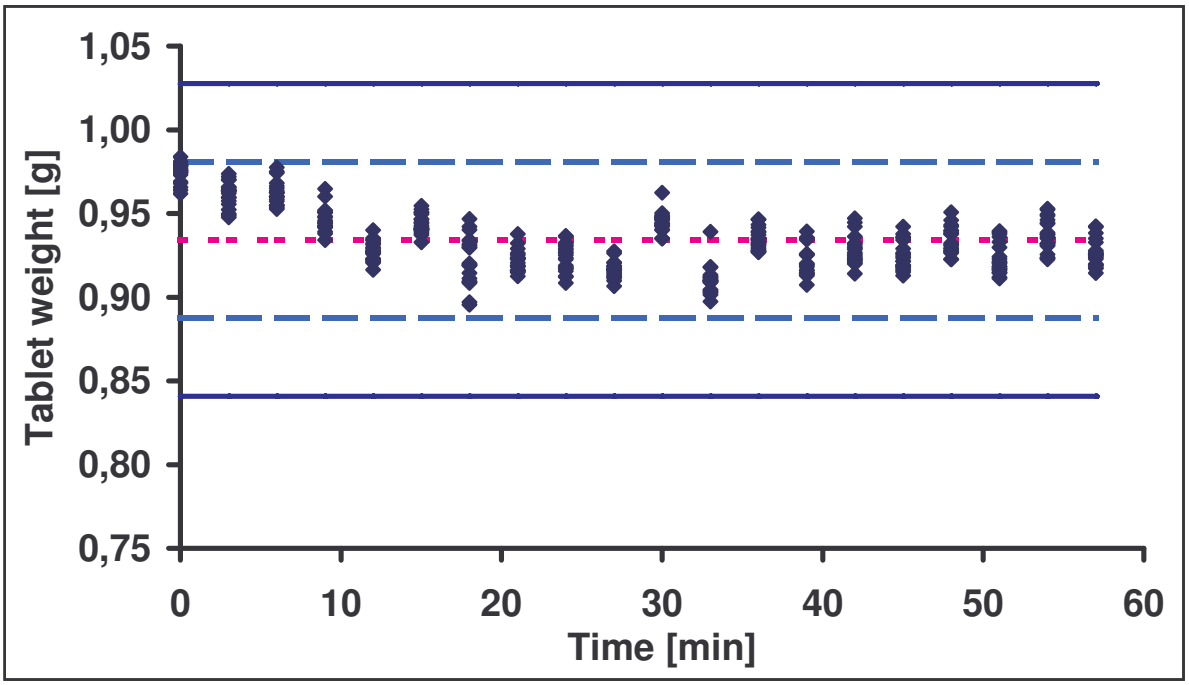

Figure 3.1 *Weight variation of tablets consisting of 99.5 % (w/w) Ludipress and 0.5 % magnesium stearate during the compression. (--) Average weight, (– –) ± 5 % limit of tolerance, (—) ± 10 % limit of tolerance.*

As shown in Figure 3.1, it was observed that the weight of two tablets in the first sample (time 0 min) exceeded the 5 % limit but not the 10 % limit of tolerance.

Although Ludipress is known as a free-flowing powder, it took up to 9 minutes until the machine delivered tablets with a constant weight. The coefficient of weight variation for the total number of 400 tablets was 1.9 %. Omitting the first 60 sampled tablets, corresponding to 9 minutes of production, the coefficient of variation decreased to 1.3 %. Several authors have reported a coefficient of variation of less than 1 % for the weight uniformity of tablets consisting of Ludipress and magnesium stearate but the tests were performed on only 20 tablets (Plaizier-Vercammen and Van den Bossche 1992, Muñoz-Ruiz *et al.* 1993). The results indicate, that after an initial phase where the powder settled within the feeder, a constant tablet weight was observed. Due to its good flow properties, Ludipress could act as a reference material for trials with pellets and micro tablets.

3.3 Tableting of pellets and micro tablets under pilot plant conditions

The influence of the single unit size (pellets in a range of 355 to 1700 µm or micro tablets of 2 mm) on the various properties of the multiunit tablets prepared thereof was studied. The aim was to investigate to which extent multiunit tablets containing single units of varying diameter comply with the requirements of the European Pharmacopoeia 4th edition.

Firstly, the optimum single unit content of tablets containing pellets or micro tablets was determined. 3 kg-batches containing 60 %, 70 % and 80 % (w/w) of micro tablets were compressed at 150 MPa on a rotary tablet press (Korsch Pharma 230/17). The tablet press was fitted with eight 13 mm-flat-faced punches and the speed of the machine was set at 50 rpm. Table 3.3 shows the composition and physical properties of the resulting tablets such as crushing strength and friability.

Table 3.3 Composition and properties of the multiunit tablets

Micro tablets (Ø = 2 mm) [%]	60	70	80
Avicel PH 101 [%]	35.2	25.2	15.2
Kollidon CL [%]	4	4	4
Aerosil [%]	0.3	0.3	0.3
Magnesium stearate [%]	0.5	0.5	0.5
Crushing strength [N]	77	41	29
Friability [%]	0.37	>> 10 %	>> 10 %

It was demonstrated that the crushing strength of the tablets decreased significantly from 77 to 29 N by increasing the content of micro tablets from 60 % to 80 %. Tablets with a hardness of 29 N were extremely weak. Moreover, the friability test of tablets containing more than 60 % micro tablets failed, as most of the tablets were broken

after 100 revolutions of the drum. Thus, a maximum single unit content of 60 % (w/w) was established for the pilot plant experiments.

Five different batches of 30 kg, consisting of pellets or micro tablets and excipients, were compressed to investigate the influence of the single unit size on the tablet weight and content uniformity under pilot plant conditions.

60 % (w/w) pellets in a range of 355 µm to 1700 µm or micro tablets of 2 mm were mixed with Avicel PH 101 as a filler, Kollidon CL as a binder, Aerosil 200 as a glidant and magnesium stearate as a lubricant. The amount of Kollidon CL and magnesium stearate was fixed at a level of 4 % and 0.5 %, respectively. The amount of the microcrystalline cellulose, Avicel PH 101, was varied in a range of 35.1 % to 35.4 % according to the amount of Aerosil 200 needed to allow the mixture to flow properly out of the funnel. The composition of the five mixtures is described in Chapter 6 (mixtures 2, 3, 4, 5 and 6, Table 6.7). Tablets were compressed using an instrumented rotary tablet press (Korsch Pharma 230/17) equipped with a gravity feeder. 8 of the 17 punch stations were equipped with 13 mm flat-faced B-tooling. The machine speed and the compression force were set at 50 rpm and 150 MPa, respectively. The weight of the tablets was adjusted between 0.9 g and 1 g at the beginning of the compression process. During the 60 min of tableting, the tablet press parameters were kept constant.

3.3.1 Weight uniformity

The European Pharmacopoeia 4th edition gives specifications to assure the quality of tablets by testing the weight uniformity. The uniformity of weight is performed on 20 tablets taken randomly. For tablets greater than 250 mg, not more than 2 of the individual weights deviate from the average weight by more than 5 % and no tablet deviates by more than 10 %.

During the production of 30 kg-batches, approximately 24 000 tablets were produced within 60 min. In order to characterise the tablet weight variations and the tablet weight distribution during the tableting process, samples of 20 tablets were withdrawn

every 3 min during the 60 min production time and analysed. The average weight of all tablets and the 5 % and 10 % limits of tolerance were calculated.

Tablets consisting of pellets in a range of 355-425 µm (mixture 2, Table 6.7) have shown excellent weight uniformity during the production time. The production time began after the initial phase; as the tablet press has delivered tablets with constant weight (see *Tableting of Ludipress,* section 3.2). Figure 3.2 depicts the weights of 20 tablets sampled every 3 min during 60 min, the average weight and the 5 % and 10 % limits of tolerance. As shown in the figure, the weights of individual tablets were tightly distributed over the average weight. None of the tablets has exceeded the 5 % tolerance limits. The relative standard deviation of the weight of all investigated tablets was found to be low at 1.08 %.

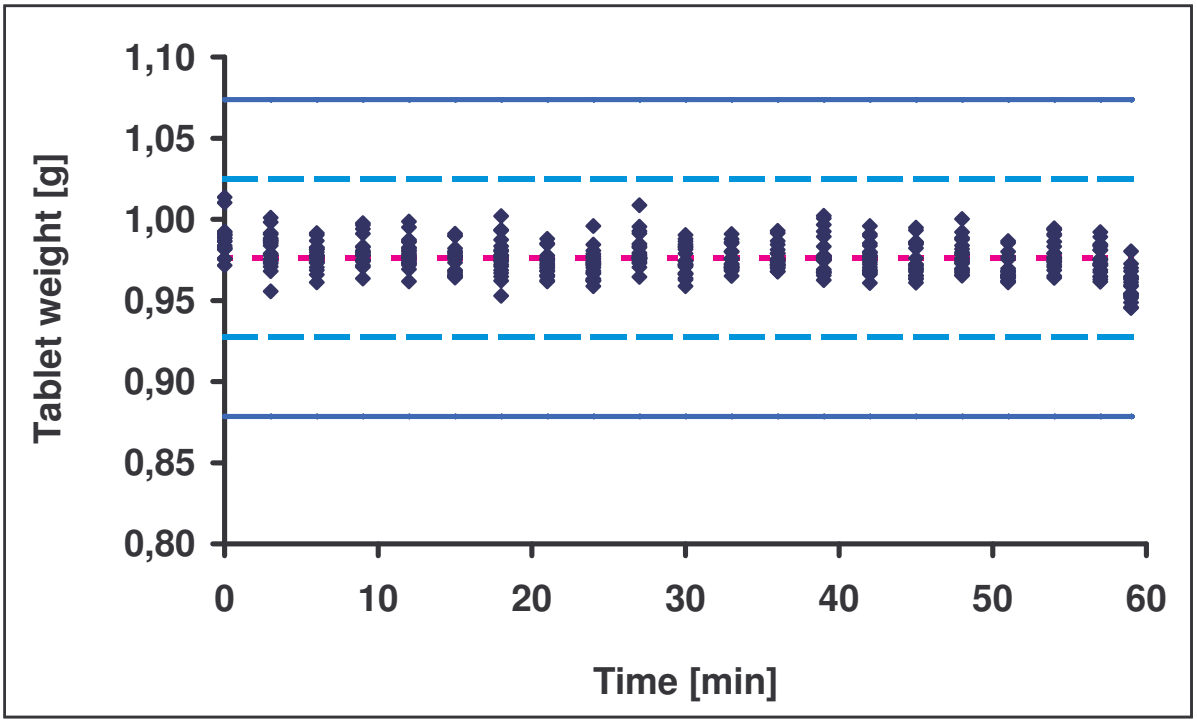

Figure 3.2 Weight variation of tablets during the compression of pellets Ø=355-425 µm and Avicel PH 101 as a filler. (--) Average weight, (– –) ± 5 % limit of tolerance, (—) ± 10 % limit of tolerance.

Figures 3.3, 3.4, 3.5 and 3.6 depict the weight variation of tablets during the compression of pellets in a range of 850 to 1700 µm (mixtures 3, 4 and 5, Table 6.7) and micro tablets with 2 mm in diameter (mixture 6, Table 6.7). The results of the weight variation analysis of Ludipress and the multiunit tablets are summarised in Table 3.4. Though the amount of Aerosil was optimised for each batch, increasing the single unit size in a range of 355 µm to 1700 µm led to a significant increase of the weight variation of the multiunit tablets from 1.08 % to 2.90 %. Above a pellet size of 850 µm, the weights of the multiunit tablets showed a higher deviation from the average weight than pellets in a range of 355-425 µm. Tablets consisting of pellets in a range of 1400-1700 µm have demonstrated the highest weight variation (2.90 %) (Figure 3.5). However, tablets consisting of micro tablets have shown a coefficient of variation of 2.56 %, which was not more than the coefficient of variation of pellets in a range of 1180-1400 µm. Moreover, tablets containing single units in a range of 850 µm to 2 mm were above the 5 % limit of tolerance. However, none of the tablets exceeded the 10 % limit of tolerance during the tableting of all batches.

During tableting of multiunit tablets, the filling hopper was refilled several times in order to maintain a constant powder level. The arrows on Figures 3.3, 3.4, 3.5 and 3.6 indicate the refilling of the hopper. It was observed that the refilling of the hopper was not correlated with the tablet weight variations.

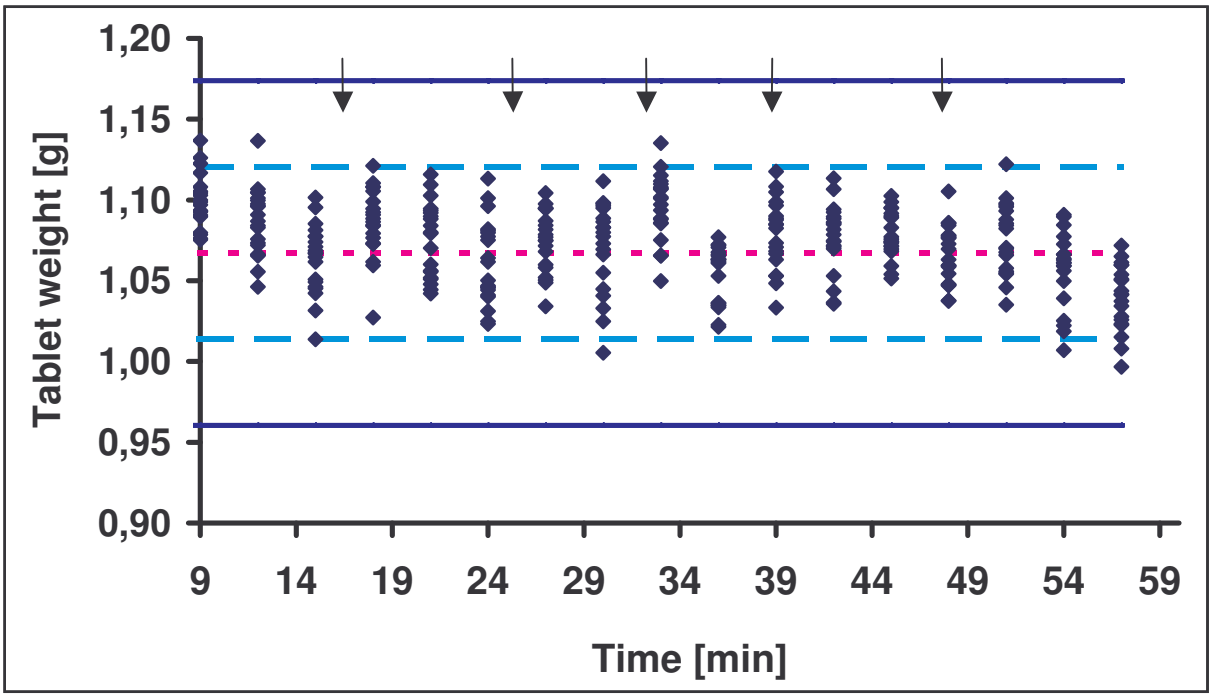

Figure 3.3 *Weight variation of tablets during the compression of pellets Ø=850-1000 µm and Avicel PH 101 as a filler. (--) Average weight, (– –) ± 5 % limit of tolerance, (—) ± 10 % limit of tolerance, ↓ refilling of the hopper*

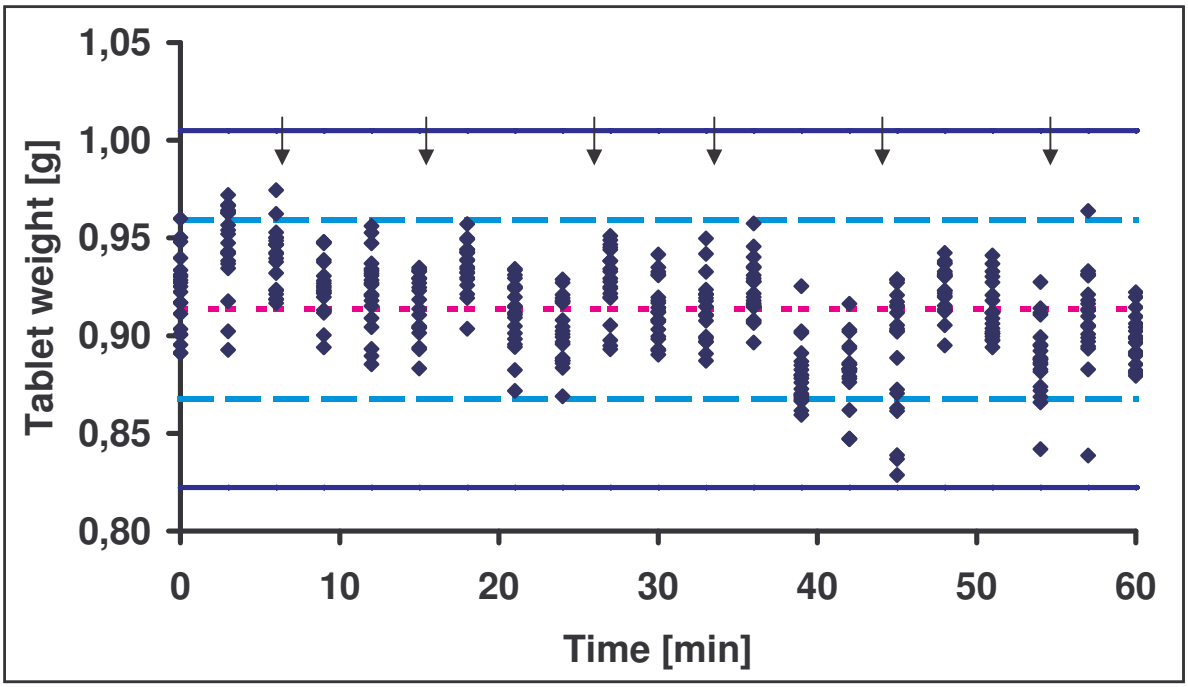

Figure 3.4 *Weight variation of tablets during the compression of pellets Ø=1180-1400 µm and Avicel PH 101 as a filler. (--) Average weight, (– –) ± 5 % limit of tolerance, (—) ± 10 % limit of tolerance, ↓ refilling of the hopper*

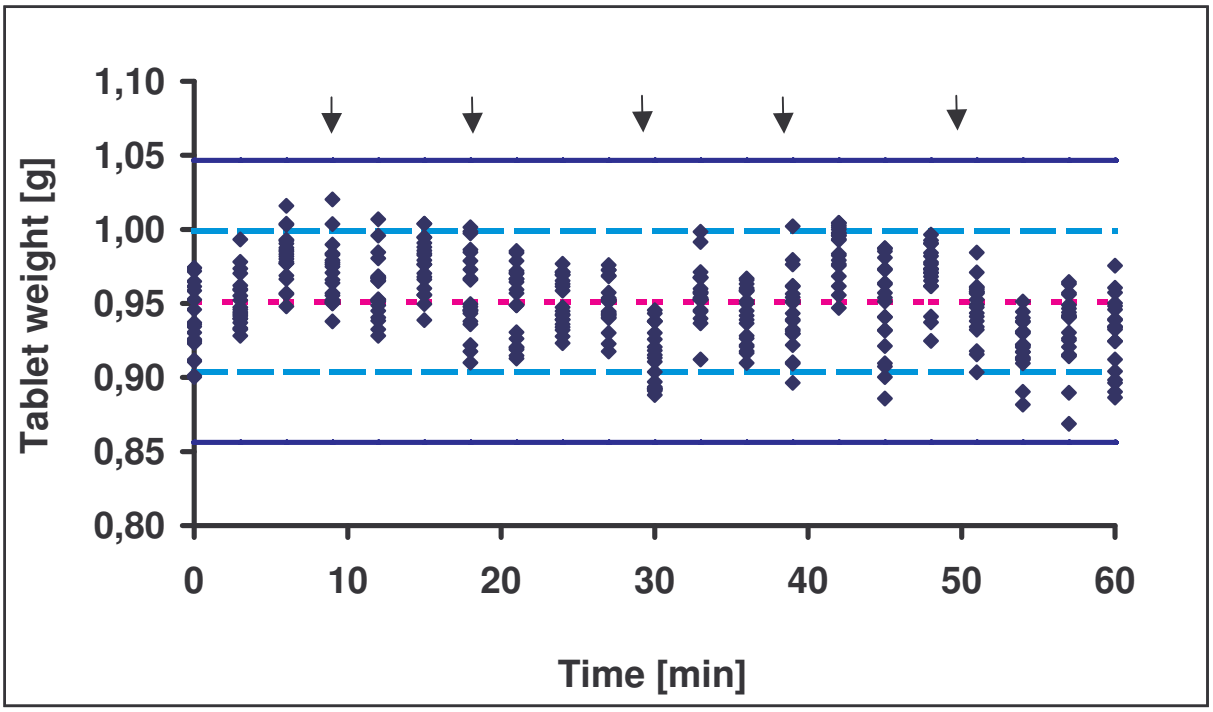

Figure 3.5 *Weight variation of tablets during the compression of pellets Ø=1400-1700 µm and Avicel PH 101 as a filler. (--) Average weight, (– –) ± 5 % limit of tolerance, (—) ± 10 % limit of tolerance, ↓ refilling of the hopper*

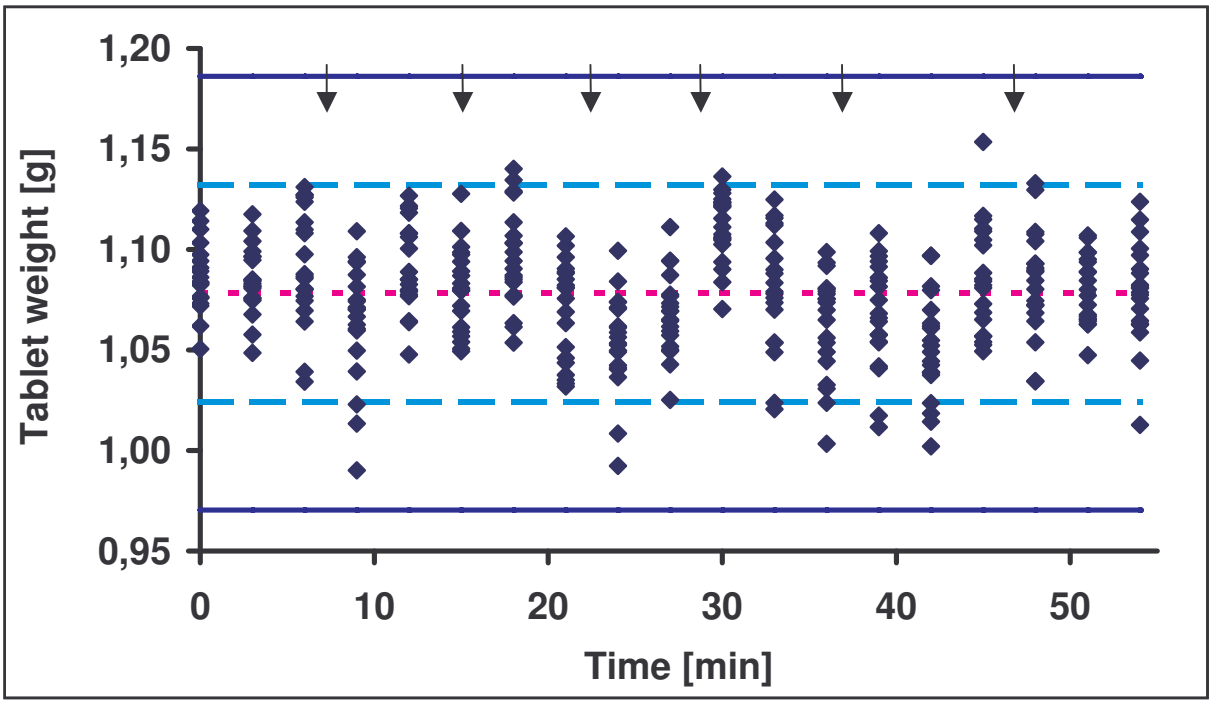

Figure 3.6 *Weight variation of tablets during the compression of micro tablets of 2 mm in diameter and Avicel PH 101 as a filler. (--) Average weight, (– –) ± 5 % limit of tolerance, (—) ± 10 % limit of tolerance, ↓ refilling of the hopper*

*Table 3.4 Analysis of weight variations of Ludipress and multiunit tablets**

	Ludipress	Pellets 355-425 µm	Pellets 850-1000 µm	Pellets 1180-1400 µm	Pellets 1400-1700 µm	Micro tablets 2000 µm
Tablet weight average [g] ± S.D.	0.9286 ± 0.0127	0.9761 ± 0.0105	1.0729 ± 0.0254	0.9136 ± 0.0251	0.9514 ± 0.0276	1.0783 ± 0.0276
Coefficient of variation [%]	1.37	1.08	2.37	2.75	2.90	2.56
Total number of tablets produced	19200	22800	19200	24000	24000	22400
Total number of sampled tablets	340	400	340	420	420	380
Number of tablets above the 5 % limits of tolerance	0	0	10	27	37	21
Number of tablets above the 10 % limits of tolerance	0	0	0	0	0	0
Real percentage of rejected tablets** [%]	0-0.8	0-0.7	1.3-5.6	3.9-10.6	5.8-11.8	2.9-7.9

**The initial phase was not taken into account*
***according to Schaafsma and Willemze (1973)*

The Pharmacopoeias give the specifications required for a sample of 20 tablets to present the quality characteristic “uniformity of weight”. According to the European Pharmacopoeia, there are two possibilities, either the sample of 20 tablets meets the specifications or it does not. However, pharmacopoeias do not have specifications on how production can perform a quality with a high degree of acceptance probability. The acceptance probability describes the probability with which a sample taken randomly during the production process will satisfy the quality requirements. From the

production point of view, a high acceptance probability of 99 % or more is logically expected.

Altenschmidt and Häusler (1998) have presented a statistical interpretation of the European Pharmacopoeia specifications. They have derived process limits to guarantee a production with a high degree of acceptance probability. Figure 3.7 depicts the acceptance probability as a function of the coefficient of variation in the case of ideal production; meaning that the average of the production corresponds to the desired average. It was observed that the degree of the acceptance probability is correlated with the coefficient of variation. An increasing coefficient of variation leads to a decreasing acceptance probability. In order to produce tablets, which satisfy the quality requirements with 99 % of acceptance probability, the coefficient of variation is limited. The limit of the coefficient of variation depends on the weight of the tablet; tablets weighing 250 mg or more have a limit of 2.2 %, tablets in a range of 80-250 mg have a limit of 3.3 %, and tablets of 80 mg or less have a limit of 4.4 %. Furthermore, in case the actual average drifts from the desired average, the limit of the coefficient of variation decreases. Figure 3.8 illustrates the allowed deviation of the average as a function of the coefficient of variation with 99 % of acceptance probability. As long as the process parameters are below the curve, the production process will perform a quality with a degree of 99 % of acceptance probability.

As regards the analysis of weight variations of multiunit tablets (Table 3.4), the coefficients of variation, determined after the initial phase where the powder settled within the feeder, varied between 1.08 and 2.90 %. Considering that the tablet weight was more than 250 mg and that the production was performed in the ideal case where the actual weight average corresponds to the desired average, only the tableting of pellets in a range of 355-425 µm have demonstrated 99 % of acceptance probability (Figure 3.7). Moreover, it means also that a deviation of the weight average up to 2.9 % is allowed in order to assure an acceptance probability of 99 % (Figure 3.8). The acceptance probabilities of the batches consisting of pellets in a range of 850-1700 µm and micro tablets were decreased in a range of 75-95 %.

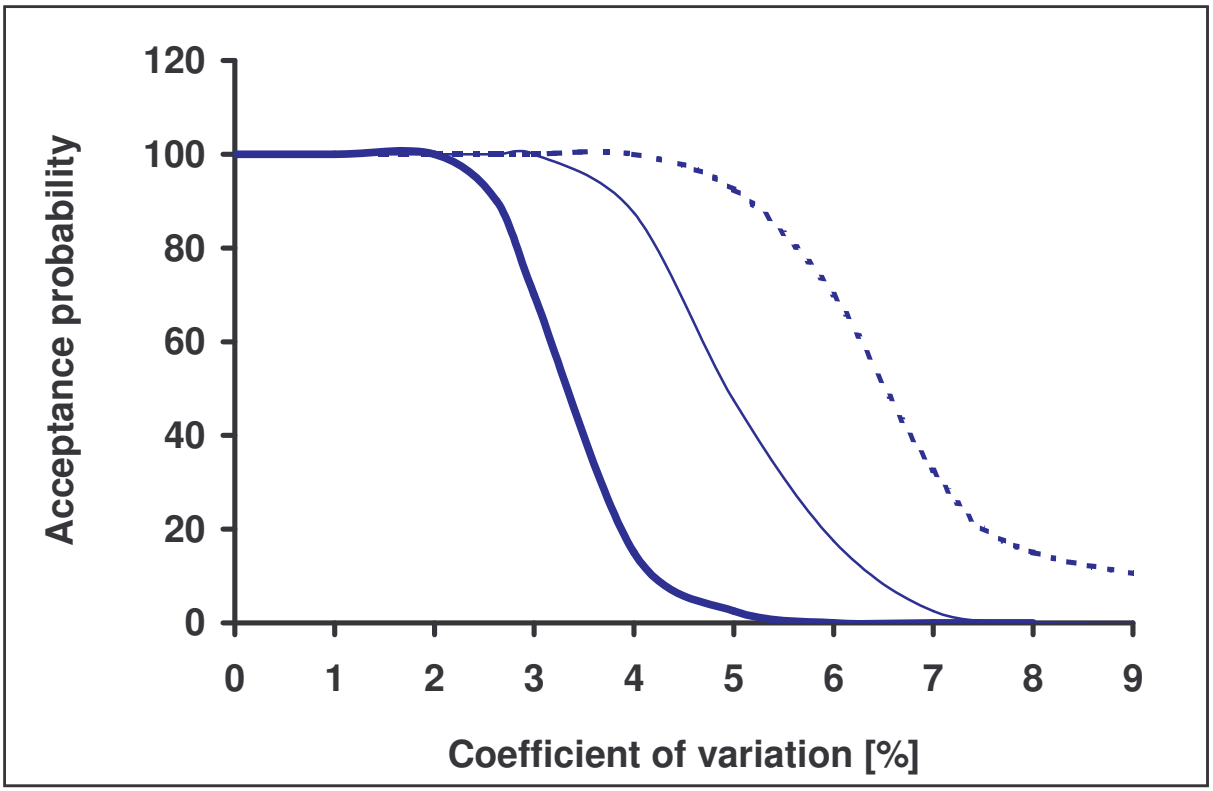

Figure 3.7 Acceptance probability in ideal production case for tablets weighing (-) 250 mg and more, (-) from 80 to 250 mg, (--) 80 mg and less

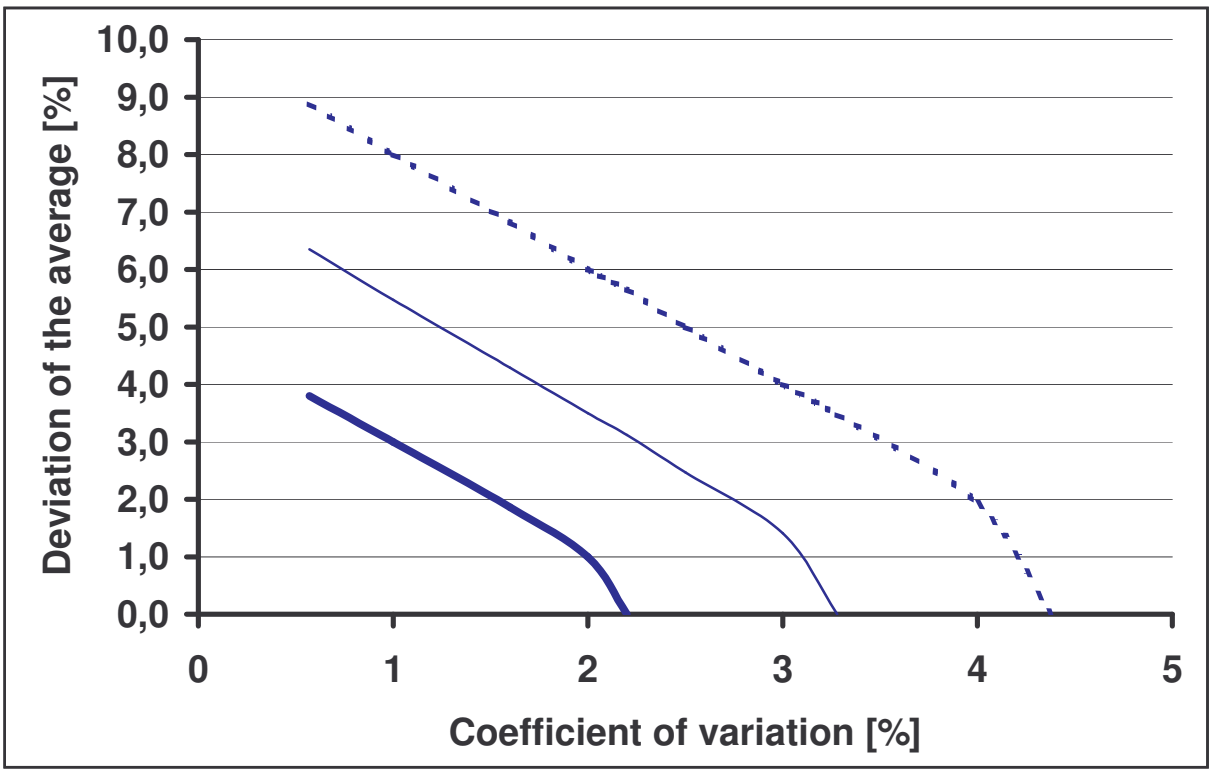

Figure 3.8 Allowed deviation of the average as a function of the coefficient of variation with 99 % acceptance probability for tablets weighing (-) 250 mg and more, (-) from 80 to 250 mg, (--) 80 mg and less

From the point of view of the manufacturer, it is important to determine the real percentage of rejected tablets during the production. According to Schaafsma and Willemze (1973), it is possible to estimate statistically the real percentage of rejected tablets with 99 % of probability from the percentage of rejected tablets obtained during a process by using tables of confidence interval. The percentage of rejected tablets was defined as the percentage of tablets, which weights were above the 5 % and/or the 10 % limits of tolerance of the European Pharmacopoeia. Thus, the real percentage of rejected tablets was determined by reporting the total number of sampled tablets and the number of tablets, which weight exceeded the 5 % and/or the 10 % limits of tolerance (Table 3.4) into the table of 99 % confidence limits (Schaafsma and Willemze 1973, Table H, p 466-467). The real percentages of rejected tablets from the tableting of Ludipress and multiunit tablets are depicted in Table 3.4. The real percentage of rejected tablets is greater than the first value, or smaller than the second value with 99 % of probability. It means also that the real percentage of rejected tablets is within the written interval with 98 % probability. As shown in Table 3.4, increasing the pellet size led to a higher real percentage of rejected tablets. It is interesting to note that tablets consisting of pellets in a range of 355-425 µm provided similar percentage of rejected tablets as the free-flowing excipient Ludipress with less than 0.7 % rejects with a 99 % probability.

3.3.2 Uniformity of micro tablets per multiunit tablet

The uniformity of micro tablets per tablet was investigated for multiunit tablets consisting of theophylline micro tablets. The theophylline content of micro tablet was constant and was determined to be 68.5 % (± 0.4) by UV-spectrophotometry at 271.2 nm (see Chapter 6).

A method consisting of counting the micro tablets was developed to determine the content of micro tablets per multiunit tablet. Firstly, it was checked if the counting method was reliable by evaluating a correlation between the counting method and the UV-method.

For the counting method, a multiunit tablet was placed on a sieve No. 5 (mesh size 0.315 mm) and the tablet was disintegrated by pouring water. The isolated micro tablets were counted. Micro tablets present the advantage that they remain nearly intact after compression into multiunit tablets. Nevertheless, the broken micro tablets were reconstituted optically. The theophylline content of tablets was determined using UV-spectrophotometry and compared to the number of micro tablets per tablet. The linear regression and the coefficient of determination were calculated. A good correlation (R^2 = 0.9807) was found between theophylline content and the number of micro tablets per tablets (Figure 3.9). As a result, it was demonstrated that the counting method was adequate in order to determine the content of micro tablets per tablet.

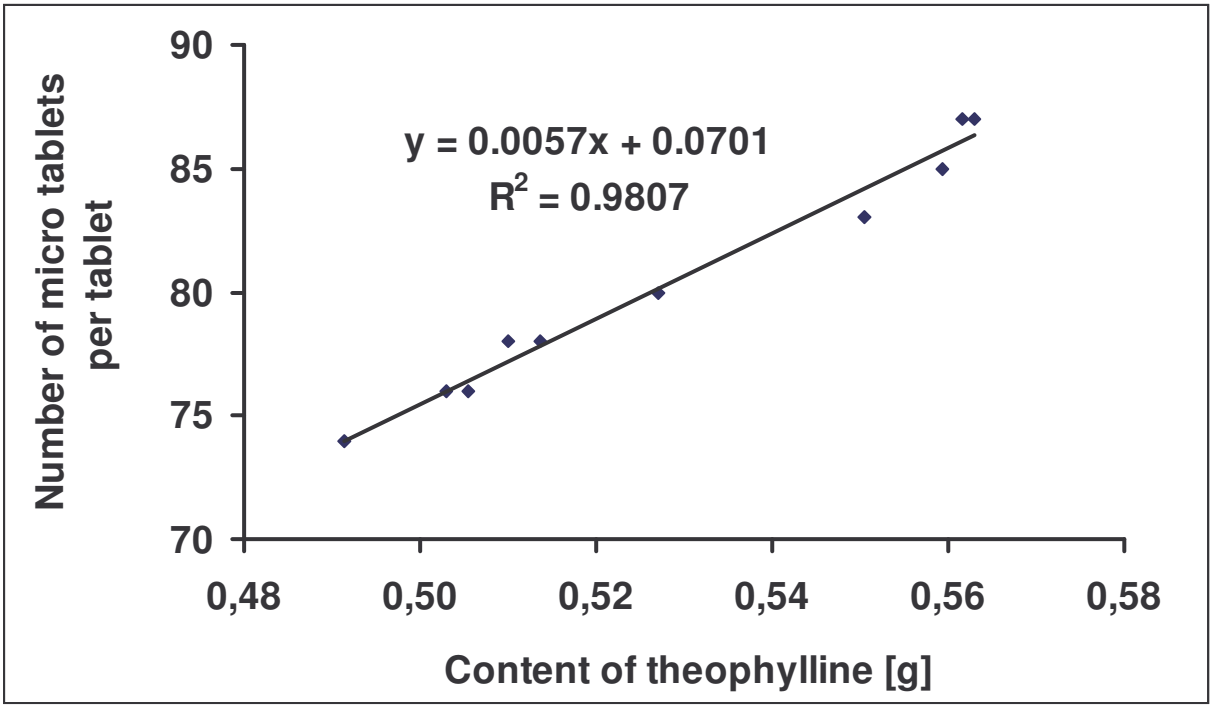

Figure 3.9 Correlation between theophylline content determined by UV-spectrophotometry and the number of micro tablets per tablet.

A 30 kg-batch containing 60 % (w/w) micro tablets (mixture 6, Table 6.7) was compressed for 60 min on a rotary press (Korsch Pharma 230/17). The total number of tablets produced was 24000, 55 multiunit tablets were taken at random within 60 min and weighed on an analytical balance. The tablets were then disintegrated in water and

the liberated micro tablets were counted. The content of micro tablets in % based on the weight of the multiunit tablet was calculated. The results of the 55 tablets are represented in Table 3.5.

Table 3.5 Content of micro tablets per multiunit tablet

Total number of tablets produced	22400
Total number of analysed tablets	55
Average weight of theophylline micro tablets [mg]	7.24
Content of micro tablets per multiunit tablets [% (w/w)]	61.29
± S.D.	± 2.05
Coefficient of variation [%]	3.35

The average content of micro tablets from 55 multiunit tablets was found at a level of 61.29 % (w/w), which is slightly higher than the initial content of the tableting mixture (60 %). This difference can be attributed to the tableting process. Air movements produced by the rotor of the machine set at 50 rpm and by the lower punch going down just before the filling of the die can lead to a loss of fine powder and consequently to an increase of the content of micro tablets per tablet (Egermann 1991).

3.3.3 Correlation between number of micro tablets per tablet and tablet weight

In order to determine to which factor the weight variations were attributed, the composition of multiunit tablets was investigated. The number of micro tablets per tablet as a function of the tablet weight is depicted in Figure 3.10.

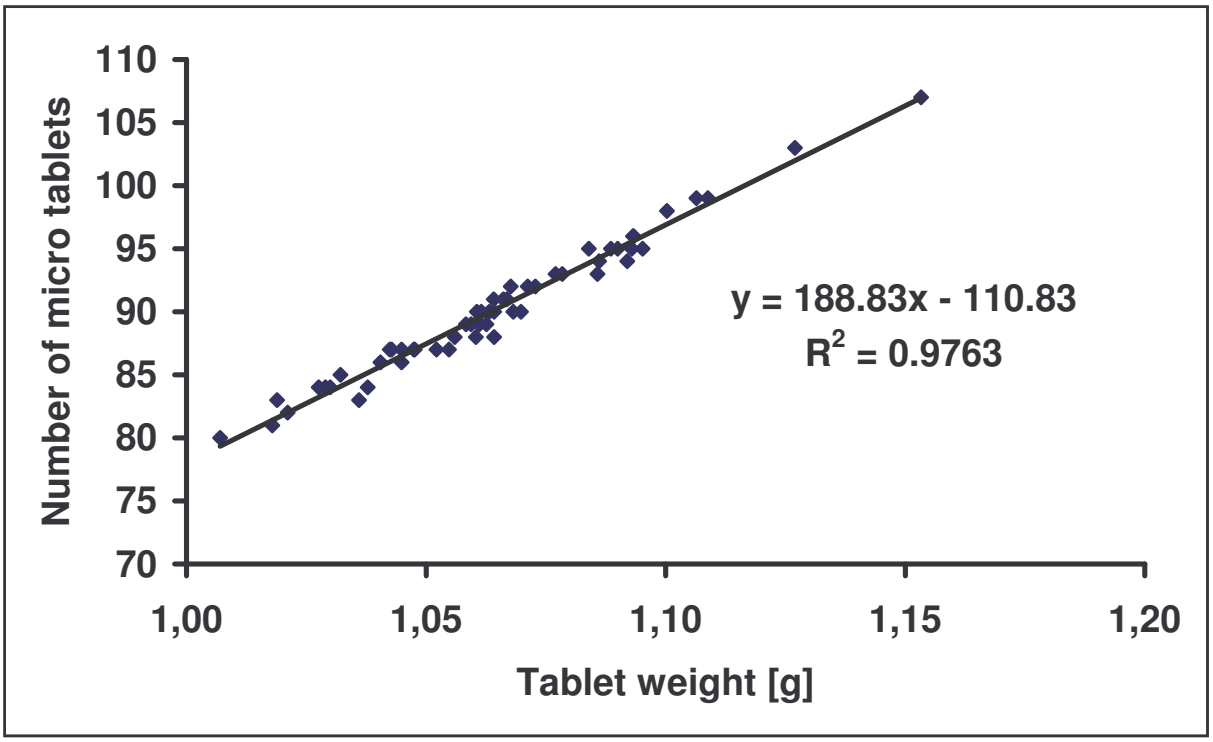

Figure 3.10 Correlation between the number of micro tablets and the weight of the multiunit tablet.

A good correlation (R^2 = 0.9763) was found between the number of micro tablets contained in a tablet and the tablet weight. An increase in tablet weight led to an increase in the number of micro tablets. From this linear correlation important conclusions can be drawn:

- The percentage of micro tablet (w/w) based on the tablet weight remained constant. Thus, the content of micro tablets subsequently the content of theophylline per multiunit tablet was constant during the pilot plant scale.
- Consequently, any segregation of the mixture occurred during the tableting process.
- Therefore, the weight variations were due to variations in the filling of the die, leading to think that the mixtures had poor flow properties.

3.3.4 Discussion of the results

In this section, the influence of the size of single units on the weight variation of multiunit tablet was investigated. Ludipress was taken as a reference material due to its free-flowing properties. The tableting of Ludipress was then compared to the tableting of pellets and micro tablets. The coefficient of variation of the tablet weight and the percentage of rejected tablets were used to investigate the production of multiunit tablets. The tableting of Ludipress has shown that after an initial phase where the powder settled within the feeder, a constant tablet weight was observed. In order to produce multiunit tablets, which satisfy the requirements of the European Pharmacopoeia with 99 % probability, Altenschmidt and Häusler (1998) have demonstrated that the coefficient of variation has to be 2.2 % for tablets having a weight of ≥ 250 mg in case where the desired weight average corresponds to the actual average. In case where the actual weight average deviates from the desired average, the limit of the coefficient of variation decreases (Figure 3.8). Considering the tableting of pellets in range of 355-425 µm, which has demonstrated a coefficient of variation of 1.08 %, a deviation up to 2.9 % of the desired weight average would be allowed in order to produce tablets, which meet the European requirements with 99 % of probability. Multiunit tablets consisting of pellets in the range of 850 µm to 1700 µm and micro tablets have showed greater coefficient of variations than 2.2 % and the percentage of rejected tablets reached a level of 11.8 % with the coarser pellets. After observing that the content of micro tablets per tablet remained constant, it was demonstrated that the weight variations were due to variations in the filling of the die, leading to think that the mixtures had poor flow properties.

CHAPTER 4

FLOWABILITY STUDIES AND TABLETING OF FLOW-OPTIMISED FORMULATIONS

In the previous chapter, it has been observed that the production of multiunit tablets consisting of pellets or micro tablets could lead to weight variations outside the specifications of the European Pharmacopoeia when the pellet size was above about 850 µm or when micro tablets of a diameter of 2 mm were used. These weight variations were not due to segregation or demixing within the mixture, as the content of micro tablets per tablet remained constant and a linear correlation between tablet weight and the number of micro tablets per tablet was found. The weight variations resulted from the poor flowability of the tableting mass, which led to irregular filling of the dies of the tablet press.

Augsburger and Shangraw (1966) may have been the first to highlight the need to determine powder flow for pharmaceutical applications. The flow of solids is involved in many pharmaceutical operations such as tableting, encapsulation, blending, tumbling, or fluidised bed drying. The critical factor in the tableting of powders is often the flow properties of the tableting mass. Uniform tablet weights and uniform doses of active ingredients, as well as production rates, are dependent on the ability of the solid blend to feed rapidly and in a reproducible manner into the dies. Consequently, it appears essential that an accurate assessment of flow properties should be done as early as possible in the development process to ensure quality and to meet specifications of Pharmacopoeias.

Many studies are related to the assessment of powder flow. Angle of repose and mass flow rate are certainly the more simple and the more widely tests used to determine flow characteristics. Some methods are determining flow properties by evaluation of packing properties through bulk density determination such as Carr's compressibility index (Carr 1965) or Hausner's ratio (Hausner 1967). Tan *et al.* (1990) and Podczeck

and Newton (1999) have reported the use of Carr's compressibility index in predicting capsule filling performance. Other methods of predicting powder flow include shear cell measurements according to Jenike (Schulze 1995) and the determination of the critical orifice diameter. The critical orifice diameter determination has been successful to select excipients in the manufacture of micro tablets (Flemming and Mielck 1995). More recent sophisticated flow characterisation approaches relate to vibrating spatula (Hickey and Concessio 1994) and avalanching methods (Kaye *et al.* 1995, Lee *et al.* 2000).

In this work, the flow properties of the mixtures were studied with the two following methods: the funnel method according to DIN 53916 and a belt conveyor method.

4.1 Determination of flowability according to DIN 53916

4.1.1 Angle of repose and flow rate

The angle of repose and the flow rate of the different tableting blends (mixtures 1-6, Table 6.7) were investigated using the Pfrengle funnel according to DIN 53 916. The time for 150 ml of blend to completely discharge from the funnel was recorded and the flow rate was calculated. Table 4.1 depicts the values for the angle of repose and the flow rate of the different mixtures.

Table 4.1 Flow properties of the tableting mixtures containing pellets of different sizes and micro tablets in comparison to Ludipress

	Ludipress	Pellets [µm]				Micro tablet 2 mm
		355-425	850-1000	1180-1400	1400-1700	
Angle of repose [°] ± S.D	30.0 ± 0.69	36.1 ± 0.50	37.6 ± 0.92	39.1 ± 0.90	38.9 ± 0.67	37.1 ± 0.41
Flow rate [ml/s] ± S.D	17.26 ± 2.20	13.36 ± 1.22	13.97 ± 0.85	8.94 ± 1.86	8.40 ± 1.77	7.77 ± 1.17

As shown in Table 4.1, increasing the single unit size decreases the flowability of the mixtures. Ludipress has demonstrated the smallest angle of repose and the highest flow rate; that confirms its free-flowing property. For the other blends, the flow was designed as difficult according to Devise *et al.* (1975), as the angle of repose values were in a range of 36.1° to 39.1°.

4.1.2 Statistical analysis of the flow rates

Analysis of variance, also known as ANOVA, is a general method of analysing data from experiments, whose objective is to compare two or more means. If only two groups are to be compared, a F-test in combination with a t-test can be used to compare the means statistically. If more than two groups are to be compared, the correct statistical procedure to compare the means is the one-way analysis of variance ANOVA (Bolton 1990).

In order to compare the flow rate means of the different mixtures, a one-way ANOVA was carried out. The null hypothesis of equal flow rate means was tested at the 5 % level of significance. It was observed that flow rate means of Ludipress, pellets and micro tablets mixtures were significantly different ($p<0.05$); indicating that at least two of the flow rate means can be different.

However, a significant ANOVA test does not immediately reveal which of the multiple mixtures tested differ. The question that automatically follows is: Are all mixtures different from one another, or are some mixtures not significantly different ? In order to solve this question, multiple comparison procedures were undertaken.

The Newman-Keuls test is a multiple comparison test using the multiple range factor Q in a sequential fashion. For routine purposes, the Newman-Keuls method is satisfactory (Snedecor and Cochran 1967). In this test, the means to be compared were first arranged in order of magnitude. The differences needed for significance for the comparison of 2, 3, 4, 5 and 6 means were calculated as:

$$Q*(S^2/N)^{1/2}$$

where Q multiple range factor based on the tables of studentised range at 5 % level. It depends on the number of means being tested and the degrees of freedom of S^2

S^2 within mean square in the one-way ANOVA

N sample size

Considering the flow rate means of the six tableting mixtures (Table 4.1), the differences needed for 2, 3, 4, 5 and 6 means to be considered significantly different were calculated and are represented as follows:

Number of mixtures	2	3	4	5	6
Critical difference	3.48	4.21	4.65	4.98	5.21

The results of the Newman-Keuls test for the 6 ordered flow rate means are depicted in Table 4.2. Any two means connected by the same underscored line are not significantly different. Whereas two means not connected by the underscored line are significantly different.

Table 4.2 Results of the Newman-Keuls test performed on the flow rate means of the mixtures consisting of 60 % (w/w) single units and 40 % (w/w) Avicel PH 101.

Micro	Pellets [µm]				Ludipress
tablet 2 mm	1400-1700	1180-1400	355-425	850-1000	
7.77	8.40	8.94	13.36	13.97	17.26

Newman-Keuls test has revealed that the six mixtures (Table 4.1) were divided into two groups significantly different from each other according to flow rate values. In a first group were found the coarse single units such as micro tablets, pellets in a range of 1400-1700 µm and in a range of 1180-1400 µm. And in the other group were included the free-flowing excipient Ludipress and the small pellets (Ø = 850-1000 µm and Ø = 355-425 µm).

4.2 Determination of flowability using a conveyor belt

Taylor *et al.* (2000) have demonstrated that individual tests failed at some point to measure and rank flow properties of powders and that some of the methods could not detect small differences in flow between similar materials. This can be partially explained by variations in the mechanics of performing the flow tests or the interpretation of results. Even though Amidon *et al.* (1999) have recommended procedures for the measurement of flow properties, powder flow cannot be fully characterised by one single test methodology. Thus the combination of various tests is a better approach to achieve reliable data.

A conveyor belt was designed to characterise the flow properties of mixtures (see Figure 6.7). In the previous section, it was demonstrated that mixtures consisting of single units of various sizes were divided into two significantly different groups according to flow rates. The conveyor belt recorded the amount of powder blends flowing out of the funnel onto a circular belt and carrying the powder to a balance (type PM 6100, Mettler Toledo GmbH). The accumulated mass of powder versus time was plotted in 0.5-second intervals.

The speed of the conveyor belt was set at 2.15 cm/s and the gap between the funnel tip and the belt was set at exactly 3 mm using a micrometer screw. The gap is a major parameter of the conveyor belt that controls the flow of the mixture. When the gap is larger than 3 mm, the single units roll out of the belt and when the gap is smaller than 3 mm, the single units cannot flow freely out of the funnel. Hence, a setup with a gap size greater or smaller than 3 mm leads to inaccurate results (see Figure 4.1).

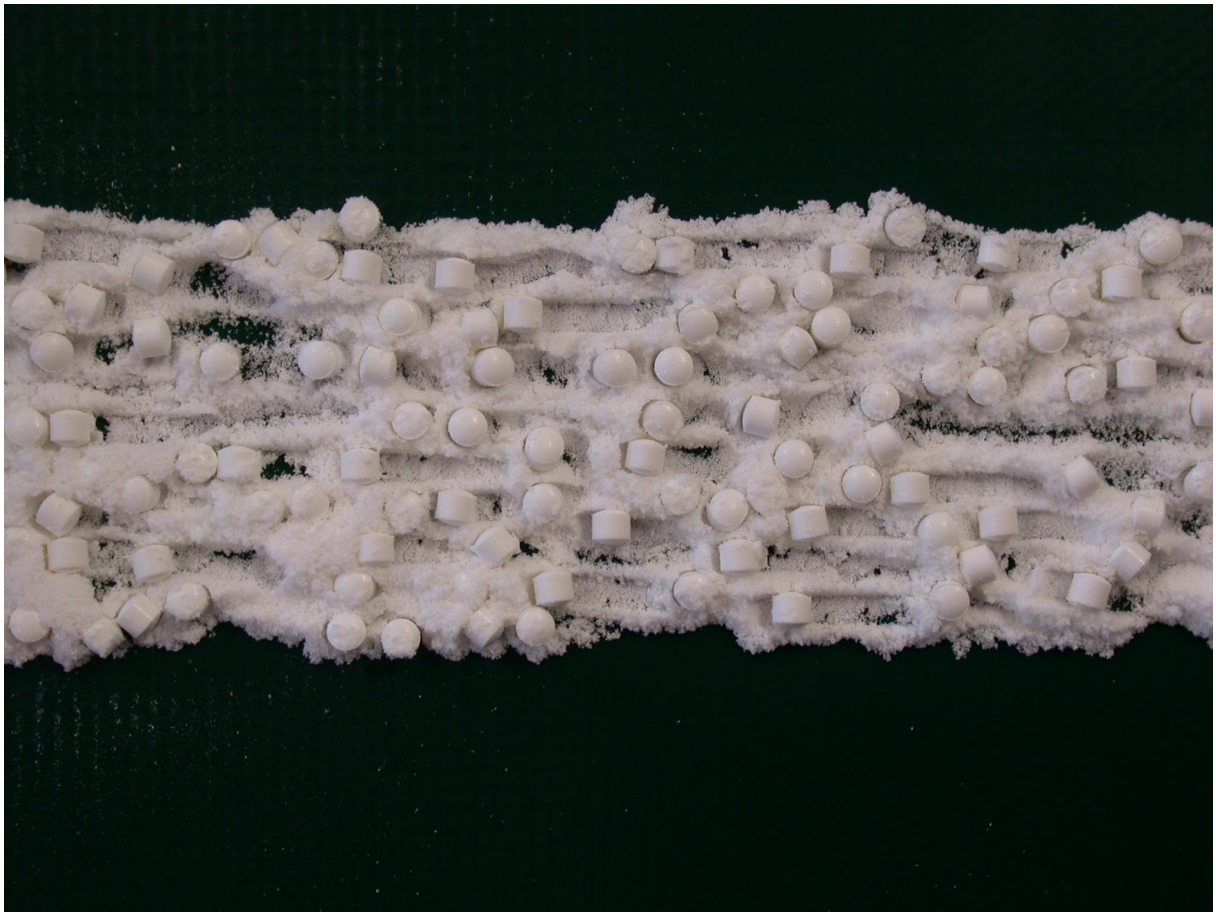

Figure 4.1 View of the powder mass accumulated on the moving belt by setting up a 2.5 mm-gap between the funnel tip and the belt.

Flow properties of Ludipress and the tableting mixtures consisting of 60 % (w/w) pellets (mixtures 2,3,4 and 5, Table 6.7) were studied with the conveyor belt for 1 min. The mass of powder accumulated on the balance was plotted versus time (Figure 4.2). Flow profiles of Ludipress and the tableting mixtures were almost linear within 1 min and no plateau was detected. This indicates that the sample was flowing continuously out of the funnel. A straight line would have been the representation of an ideal flow of material, meaning a constant flow.

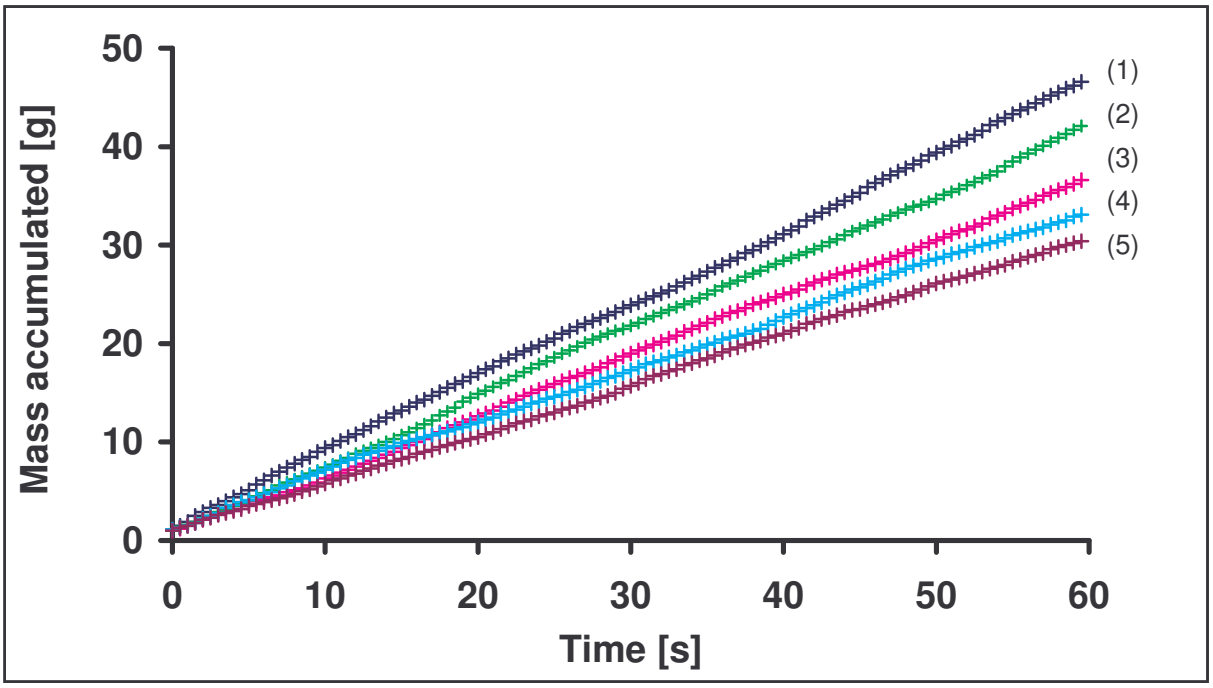

Figure 4.2 *Mass accumulated versus time of Ludipress and tableting mixtures consisting of pellets, Avicel PH 101, Kollidon CL, Aerosil 200 and magnesium stearate (mixtures 1-5, Table 6.7). (1) Ludipress, (2) pellets Ø=850-1000 µm, (3) pellets Ø=355-425 µm, (4) pellets Ø=1180-1400 µm, (5) pellets Ø=1400-1700 µm*

In order to compare the flow behaviour of the mixtures, the slopes of the linear regressions of mass accumulated versus time curves were calculated. Mean of three measurements, standard deviation and coefficient of determination of the linear regressions are summarised in Table 4.3. Steeper slopes of mass accumulated represent better flow. Ludipress has exhibited the best flow rate and then, in a decreasing order, mixtures consisting of pellets 850-1000 µm, pellets 355-425 µm, pellets 1180-1400 µm and finally the mixture consisting of the coarser pellets 1400-1700 µm. A one-way analysis of variance (ANOVA) has revealed that at least two means were significantly different ($P<0.05$). A Newman-Keuls test was performed and has demonstrated that Ludipress and every mixture were significantly different from one another. The conveyor belt has pointed out more significant differences between the mixtures compared to the flow rates measured with Pfrengle's funnel.

Table 4.3 Analysis of mass accumulated curves

	Ludipress	Pellets 355-425	Pellets 850-1000	Pellets 1180-1400	Pellets 1400-1700
Slope	0.7372	0.6009	0.6811	0.5232	0.5024
± S.D	± 0.0140	± 0.0063	± 0.0065	± 0.0108	± 0.0052
Coefficient of determination (R^2)	0.9991	0.9992	0.9994	0.9989	0.9994

In chapter 3, it has been shown that the compression within 60 min of tablets consisting of single units (pellets or micro tablets), Avicel PH 101, Kollidon CL, Aerosil and magnesium stearate led to weight variations. The coarser the pellets, the greater were the weight variations. The flow properties of two mixtures consisting in pellets in a range of 355-425 µm and 1400-1700 µm (mixtures 2 and 5, Table 6.7) were investigated for 1 hour with the conveyor belt. The experiment was performed three times with each mixture. The mass accumulated of material versus time was recorded in 0.5 s-intervals and the slopes were calculated by linear regression. The residual plots were computed as the difference between the experimental values and the regression values of the mass accumulated. The residual plots are illustrated in Figure 4.3.

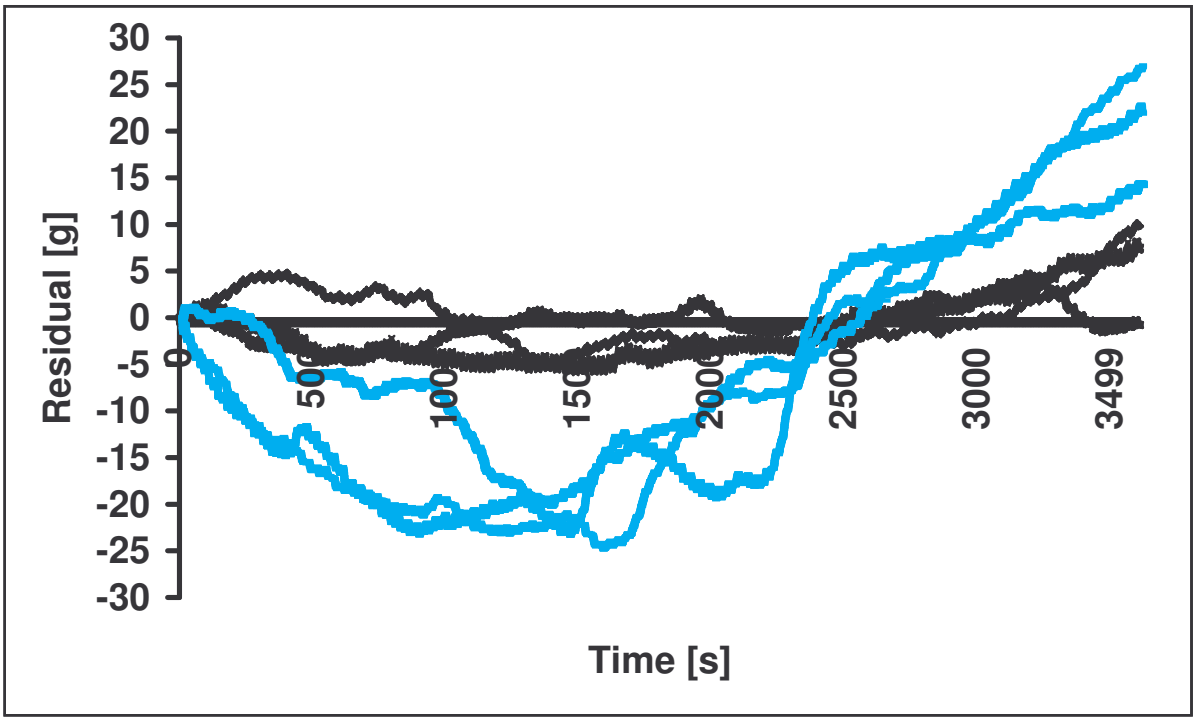

Figure 4.3 Residual plots from mass accumulated of tableting mixture consisting of pellets in a range of 355-425 µm (-) and pellets in a range of 1400-1700 µm (-)(n=3)

A striking difference between the deviations of mass accumulated of mixtures containing the small and the coarse pellets was observed. The deviations have reached 25 g for the pellets in a range of 1400-1700 µm, whereas they have only reached 5 g for the pellets in a range of 355-425 µm.

The conveyor belt method was adequate to differentiate flow properties of the tableting mixtures. The flow profile represented as the mass of accumulated powder versus time was affected by the size of the single units. The bigger the pellets, the higher were the variations of flow. The same observation was done regarding the weight variations during tableting, leading to confirm that the variations of tablet weight during compression are due to flow property of the mixtures.

4.3 Characterisation of the mixtures

A detailed analysis of the composition of the mixtures can explain the negative effect of coarse single units (pellets or micro tablets) on the flow properties. For this purpose, 50.0 g of mixtures consisting of 60 % (w/w) single units (corresponding to 30.0 g) and 40 % (w/w) Avicel PH 101 (corresponding to 20.0 g) were considered. The number of pellets contained in 30 g of pellets and respectively the number of micro tablets contained in 30 g of micro tablets were computed. By dividing the bulk volume of the mixture by the number of single units contained in it, the volume of one unit: pellet/Avicel PH 101, respectively micro tablet/Avicel PH 101, was calculated. A schematic representation of one unit pellet/excipient is depicted in Figure 4.4. Finally, by subtracting the volume of one pellet (or micro tablet) from the volume of one unit, the volume of Avicel PH 101 in one unit can be determined. Table 4.4 shows the results of the analysis of the different mixtures in detail.

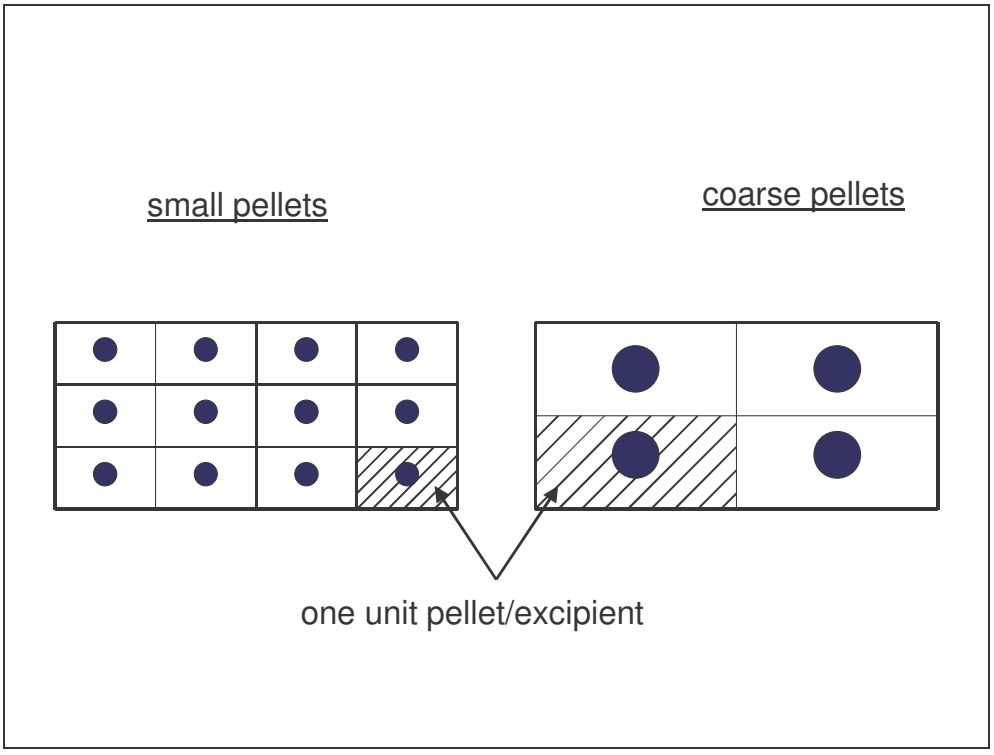

Figure 4.4 Schematic representation of one unit pellet/Avicel PH 101 as a function of the pellet size

Table 4.4 Volumetric analysis of mixtures consisting of pellets or micro tablets and Avicel PH 101 [60:40 % (w/w)]

Pellet or micro tablet sizes [µm]	355-425	850-1000	1180-1400	1400-1700	2000
Mean diameter [µm]	390	925	1290	1550	2000
Volume of one single unit [mm^3]	$3.11*10^{-2}$	0.41	1.12	1.95	4.19
Number of single units in 30 g	631800	47340	17460	10050	4680
Bulk volume of 50.0 g mixture [mm^3]	85667	77667	75667	74333	73333
Volume of a unit: pellet/Avicel PH 101 (or micro tablet/Avicel PH 101) [mm^3]	0.14	1.64	4.33	7.40	15.67
Volume of Avicel PH 101 in a unit [mm^3]	0.11	1.23	3.21	5.45	11.48

The analysis depicted in Table 4.4 has shown that the number of single units contained in 1 g of pellets, or micro tablets, was decreased drastically with increasing the single unit size. In a mixture consisting of 60 % (w/w) single units, there were 135 times more pellets of 390 µm than micro tablets of 2 mm in diameter. Consequently, the volume of one unit: pellet/Avicel PH 101 (or micro tablet/Avicel PH 101) has increased in a range of 0.14 to 15.67 mm^3 with increasing the single unit size in a range of 355 µm to 2 mm. Furthermore, the volume of Avicel PH 101 contained in one unit has increased from 0.11 mm^3 (pellets Ø=390 µm) to 11.48 mm^3 (2 mm-micro tablets). The bigger the volume of excipient, the bigger is its influence on the flow properties of the mixture. Marshall and Sixsmith (1976) have reported in their study that Avicel PH 101 has bad flow properties. In addition, Khan and Rhodes (1976) have observed that the long-drawn, rod-like shape of Avicel PH 101 particles present a low

bulk density, which is certainly responsible for its poor flowability. Thus, the bad flow properties of Avicel PH 101 have become more important on the flow properties of mixtures containing coarse single units. Moreover, due to the fibrous structure of Avicel PH 101 particles, the mixtures form bridges in the filling hopper, which lead to a high weight variation of tablets.

4.4 Improvement of the flowability

In the last two sections (4.1 and 4.2), according to the angle of repose, flow rate and conveyor belt results, it was demonstrated that mixtures consisting of single units of different sizes and Avicel PH 101 as major excipient present significantly different flow properties. The coarser the single units, the worst were the flow properties. Moreover, it was observed that the volume of Avicel PH 101 contained in one unit: single unit/Avicel PH 101was increased with increasing single unit size. Thus, the bad flow properties of the excipient became dominant on the flowability of the mixture. In order to reduce the volume of Avicel PH 101 and consequently improve the flowability of the mixture consisting of single units of critical size, namely pellets in a range of 1400-1700 µm and micro tablets, a coarser microcrystalline cellulose type Avicel PH 200 was employed. Avicel PH 200 particles are round aggregates of approximately 207 µm in diameter. Flow properties of Avicel PH 200 are better compared to fine microcrystalline cellulose powders, due to bigger particle size and the round shape of the particles (Muñoz-Ruiz *et al.* 1994, Doelker *et al.* 1995, Kibbe 2000). The properties of Avicel PH 101 and Avicel PH 200 are described in Table 4.5.

Table 4.5 Properties of different types of microcrystalline cellulose

	Particle size [µm]			True density [g/cm^3]
	x_{10}	x_{50}	x_{90}	
Avicel PH 101 (Lot 6113C)	19.22	50.09	113.09	1.579
Avicel PH 200 (Lot M019C)	54.39	206.83	489.34	1.552

4.4.1 Flowability of Avicel PH 101/Avicel PH 200-mixtures

Avicel PH 200 and Avicel PH 101 were mixed in various ratios and the flow properties of the tableting mixtures consisting either of pellets in a range of 1400-1700 µm or of micro tablets were measured (Table 4.6 and Table 4.7, respectively).

Table 4.6 Flow properties of tableting mixtures consisting of 60 % pellets (Ø=1400-1700 µm), 35.2 % Avicel PH 101/PH 200 in different ratios, 4 % Kollidon CL, 0.3 % Aerosil and 0.5 % magnesium stearate.

Avicel PH 101/PH 200	100/0	70/30	50/50	30/70	0/100
Angle of repose [°]	38.88	37.86	35.19	34.32	32.09
± S.D	± 0.67	± 0.64	± 0.60	± 0.78	± 0.75
Flow rate [ml/s]	8.40	8.71	8.97	11.19	13.30
± S.D	± 1.77	± 0.26	± 0.37	± 2.57	± 1.06

Table 4.7 Flow properties of tableting mixtures consisting of 60 % micro tablets (Ø=2 mm), 35.2 % Avicel PH 101/PH 200 in different ratios, 4 % Kollidon CL, 0.3 % Aerosil and 0.5 % magnesium stearate.

Avicel PH 101/PH 200	100/0	70/30	50/50	30/70	0/100
Angle of repose [°]	37.08	37.09	35.52	34.12	32.54
± S.D	± 0.41	± 0.37	± 0.35	± 0.47	± 0.64
Flow rate [ml/s]	7.77	7.96	9.03	9.18	10.89
± S.D	± 1.17	± 0.07	± 0.36	± 0.35	± 0.19

Tableting mixtures containing pellets in a range of 1400-1700 µm have shown a decreasing angle of repose from 38.88° to 32.09° with increasing amount of Avicel PH 200. In addition, the flow rate has increased from 8.40 ml/s to 13.30 ml/s with increasing amount of Avicel PH 200. Similar observations were made regarding the tableting mixture containing micro tablets; the higher the amount of Avicel PH 200, the better was the flow property. Thus, it was concluded that the addition of Avicel PH 200 could significantly improve the flow properties of tableting mixtures consisting of Avicel PH 101 and coarse single units ($P<0.05$). In a related study, Lahdenpää *et al*. (1996) have investigated the physical characteristics of three Avicel PH grades using a mixture design. They found that the flowability of Avicel PH 101 was the poorest, but when mixed with the more granular Avicel PH 200, better flow properties were achieved. Nevertheless, using only Avicel PH 200 will ensure the best flowing properties, but it will also result in poorer bond formation (tablet strength), especially with 0.5 % magnesium stearate, as reported by Doelker *et al*. (1995). Consequently, a proportion of the fine Avicel PH 101 has to be retained. Moreover, Avicel PH 101 is necessary to ensure a homogeneous single unit distribution within the tablets due to its large surface area and a fibrous texture (Wagner 1999).

4.4.2 Influence of the filler type on the tableting of pellets (Ø=1400-1700 µm)

Multiunit tablets containing pellets in a range of 1400-1700 µm, a mixture of Avicel PH 101/PH 200 [30:70 (w/w)], Kollidon CL, Aerosil and magnesium stearate (mixture 7, Table 6.7) were produced for 60 min on a rotary tablet press (Korsch Pharma 230/17). A sample of 20 tablets was withdrawn every 3 min during the 60 min production time and the tablet weight uniformity was analysed. The average weight of all tablets and the 5 % and 10 % limits of tolerance were calculated and the results are depicted in Figure 4.5.

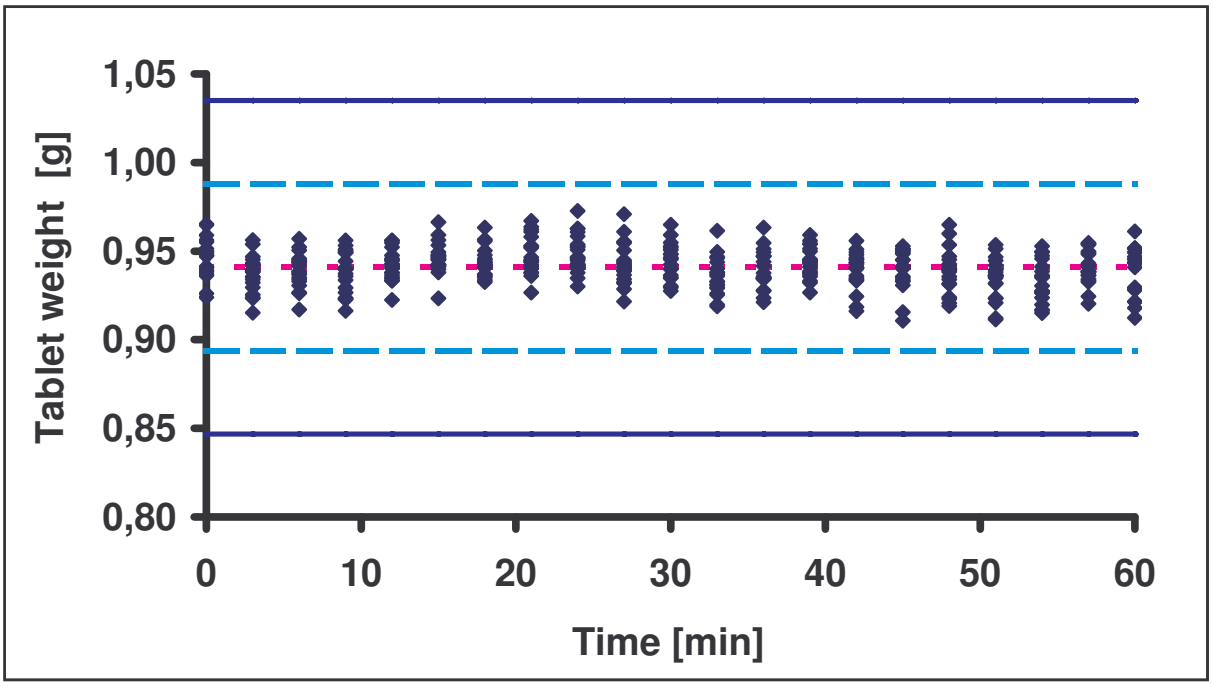

Figure 4.5 *Weight variation of tablets during the compression of 60 % pellets Ø=1400-1700 µm, 35.2 % Avicel PH 101/Avicel PH 200 [30:70 (w/w)], 4 % Kollidon CL, 0.3 % Aerosil, and 0.5 % magnesium stearate (mixture 7, Table 6.7). (--) Average weight, (– –) ± 5 % limit of tolerance, (—) ± 10 % limit of tolerance.*

Tablets containing the two types of microcrystalline cellulose, i.e. Avicel PH 101 and Avicel PH 200, and pellets in a range of 1400-1700 µm have shown excellent weight uniformity within the 60 min tablet production time. Comparing to the same experiment performed using the fine Avicel PH 101 as filler alone (Figure 3.5, Chapter 3), it was observed that the weight variations were reduced from 2.90 % to 1.19 % (Table 4.8). Moreover, by using both microcrystalline celluloses, no tablet has exceeded the 5 % or the 10 % tolerance limits of the average weight. According to Schaafsma and Willemze (1973), the percentage of rejects was less than 0.7 with a 99 % probability. Lahdenpää *et al.* (1997) have reported that the weight variations of tablets consisting of Avicel PH 101 could be reduced when larger and granular particles of Avicel PH 200 are admixed, independently of the compression force in a range of 4 to 30 kN. The results of this work support strongly their observations.

Table 4.8 Analysis of weight variations of multiunit tablets consisting of pellets in a range of 1400-1700 µm and different fillers from a pilot plant experiment running over 60 minutes

	Pellets Ø=1400-1700 µm	
Filler	Avicel PH 101	Avicel PH 101 /Avicel PH 200 [30:70]
Tablet weight average [g] ± S.D.	0.9514 ± 0.0276	0.9409 ± 0.0112
Coefficient of variation [%]	2.90	1.19
Total number of tablets produced	24000	24000
Total number of sampled tablets	420	420
Number of tablets above the 5 % limits of tolerance	37	0
Real percentage of rejected tablets*	5.8-11.8	0-0.7

**According to Schaafsma and Willemze (1973)*

4.4.3 Influence of the filler type on the tableting of micro tablets

Two 30-kg batches of multiunit tablets consisting of micro tablets were compressed on a rotary tablet press (Korsch 230/17) for 60 min. The first batch contained Avicel PH 101 as a filler, while the second batch contained a mixture of Avicel PH 101 and Avicel PH 200 in a proportion of 30:70 (w/w) (see mixtures 6 and 8, Table 6.7). In order to follow the weight variations during the production time, tablets were withdrawn every 3 s using a self-constructed tablet discharge unit (see Figure 6.6). The tablets were sampled and stored in the same sequence as they were produced.

Exactly 1200 tablets were analysed and the tablet weight variation results during the compression are depicted in Figure 4.6 and Figure 4.8 depending on the filler

employed. Multiunit tablets consisting of micro tablets and Avicel PH 101 as a filler have shown great weight variations during 60 min tableting (Figure 4.6). The coefficient of variation of the tablet weight was 3.54 % (Table 4.9). From 1200 tablets analysed, 155 have exceeded the 5 % limits of tolerance and 10 have exceeded the 10 % limits of tolerance. Compared to multiunit tablets consisting of micro tablets and a mixture of Avicel PH 101/PH 200 [30:70] (w/w) as filler, the coefficient of variation was significantly reduced to 1.72 % and only two tablets have exceeded the 5 % limits of tolerance (Figure 4.8). According to Altenschmidt and Häusler (1998), the tableting of micro tablets and the two types of microcrystalline cellulose will satisfy the requirements of the European Pharmacopoeia with 99 % of acceptance probability. Furthermore, during the tableting, a deviation of the tablet weight average up to 1.6 % of the desired value can occur without failing the requirements (Figure 3.8).

Table 4.9 Analysis of weight variations of 1200 multiunit tablets consisting of micro tablets (Ø=2 mm) and different fillers.

Filler	Avicel PH 101	Avicel PH 101 /Avicel PH 200 [30:70]
Tablet weight average [g] ± S.D.	0.9768 ± 0.0345	1.0079 ± 0.0174
Coefficient of variation [%]	3.54	1.72
Number of tablets above the limits of tolerance		
5 %	155	2
10 %	10	0

Fourier (1822) has shown that it is possible to describe a variable function as a sum of infinite sinus functions, which are characterised by amplitude and frequency.

Thus, the tablet weight variations occurred during the tableting process as a function of the time can be characterised by a sum of sinus functions that are defined by an

amplitude and a frequency. The weight variation curve and the frequency spectrum are two different representations of the same function. A fast Fourier transformation was performed on the weight variation curves (Figure 4.6 and Figure 4.8) using the program Microcal ™ Origin® (Version 6.0). The results of the fast Fourier transformation are listed in Table 4.10, and the frequency spectra are depicted in Figure 4.7 and Figure 4.9.

Table 4.10 Results of the Fast Fourier Transformation of the weight variation curves of tablets consisting of micro tablets and different fillers.

	Frequency [Hz]	Amplitude	Power	Interval period [min]
Avicel PH 101	0.00163	117.18	33.77	10:14
Avicel PH 101 /Avicel PH 200 [30:70]	0.00846 0.00944	64.01 65.58	10.07 10.57	1:58 1:46

If the weight variation curves contain periodic parts, i.e. if the weight variations occurred at a constant interval, the amplitudes on the frequency spectrum (Figure 4.7 and Figure 4.9) will be high. A peak having a high amplitude describes an event that is characteristic for the tablet weight variations.

Considering the frequency spectrum Figure 4.7, a striking peak having an amplitude of 117 was observed at a frequency of 0.00163 Hz. Thus, the weight variations of multiunit tablets consisting of micro tablets and Avicel PH 101 were recurred in an interval period of 614 s. The Fourier transform from the weight variations of tablets consisting of micro tablets and the two microcrystalline celluloses has revealed two peaks at the frequencies of 0.00846 Hz and 0.00944 Hz (Figure 4.9). The amplitude of these two peaks is not high enough to say that the variations of tablet weight are recurring at intervals of 1:58 min or 1:46 min, respectively.

In conclusion, by performing a Fourier transformation, it was observed that the compression of tablets consisting of micro tablets and Avicel PH 101 as a filler led to weight variations, which recurred periodically, whereas the addition of Avicel PH 200 to the tableting mixture led to significantly less tablet weight variations, which occurred randomly. As it was not possible to correlate these periodical variations with any parameters of the machine such as the speed of the rotor or the motor revolutions, it can be concluded that the variations were attributed to the tableting mixture.

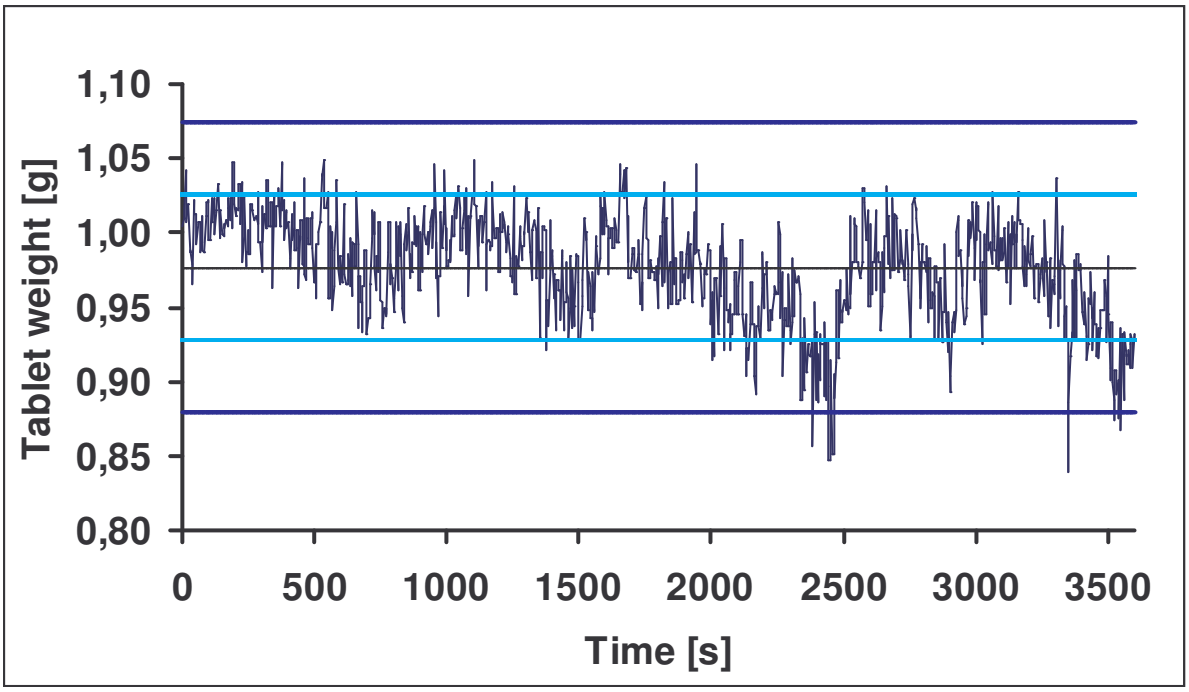

Figure 4.6 *Weight variation of tablets during the compression of 60 % micro tablets, 35.2 % **Avicel PH 101**, 4 % Kollidon CL, 0.3 % Aerosil, and 0.5 % magnesium stearate (mixture 6, Table 6.7). (–) Average weight, (—) ± 5 % limit of tolerance, (▬) ± 10 % limit of tolerance.*

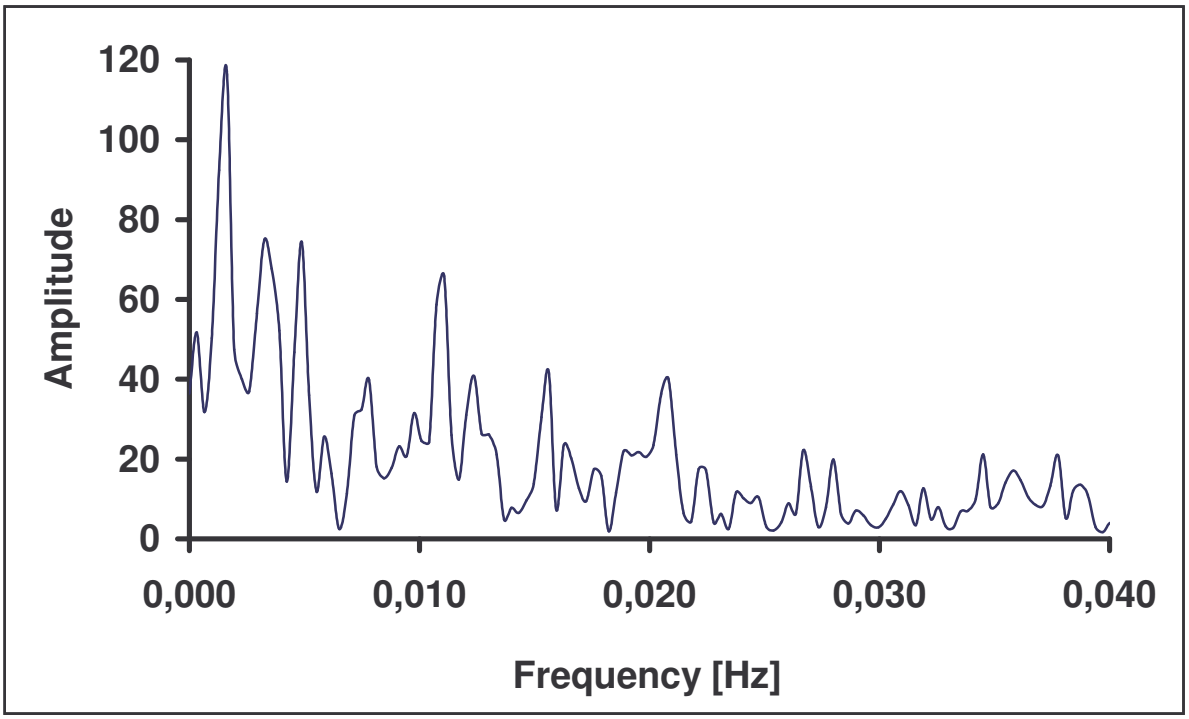

Figure 4.7 *Fourier transform of weight variation data from Figure 4.6*

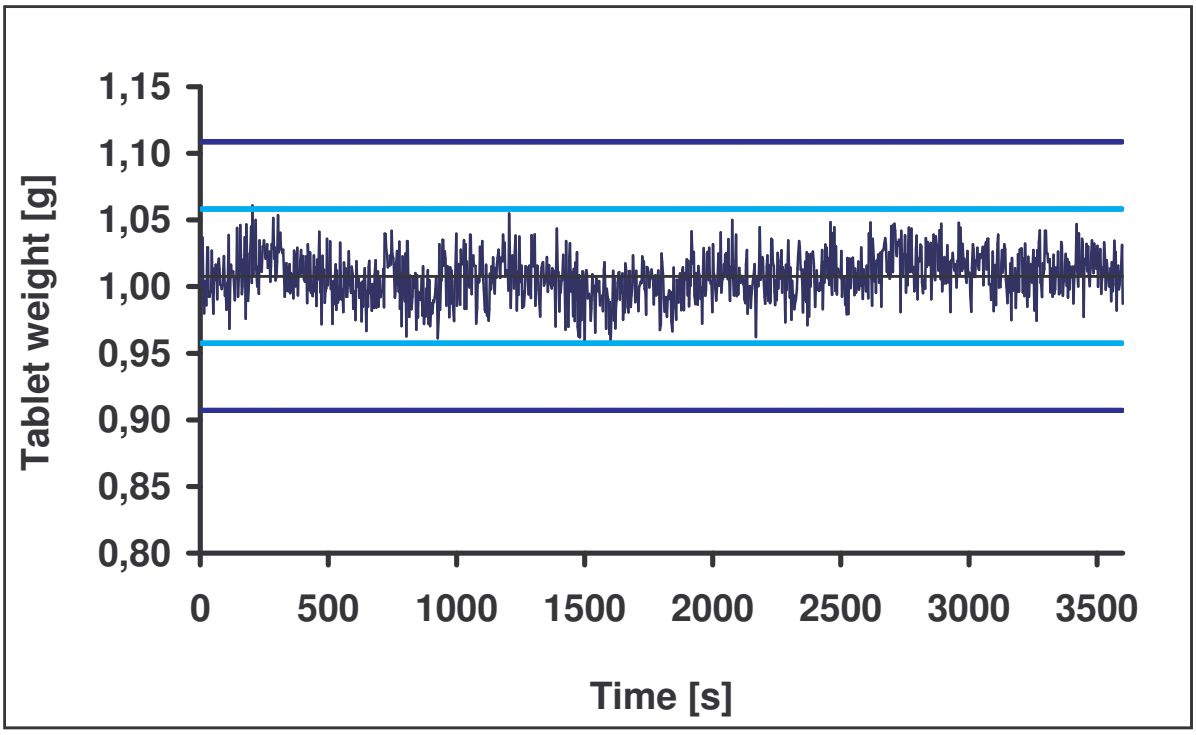

Figure 4.8 *Weight variation of tablets during the compression of 60 % micro tablets, 35.2 % **Avicel PH 101/Avicel PH 200 [30:70]**, 4 % Kollidon CL, 0.3 % Aerosil, and 0.5 % magnesium stearate (mixture 8, Table 6.7). (–) Average weight, (—) ± 5 % limit of tolerance and (▬) ± 10 % limit of tolerance.*

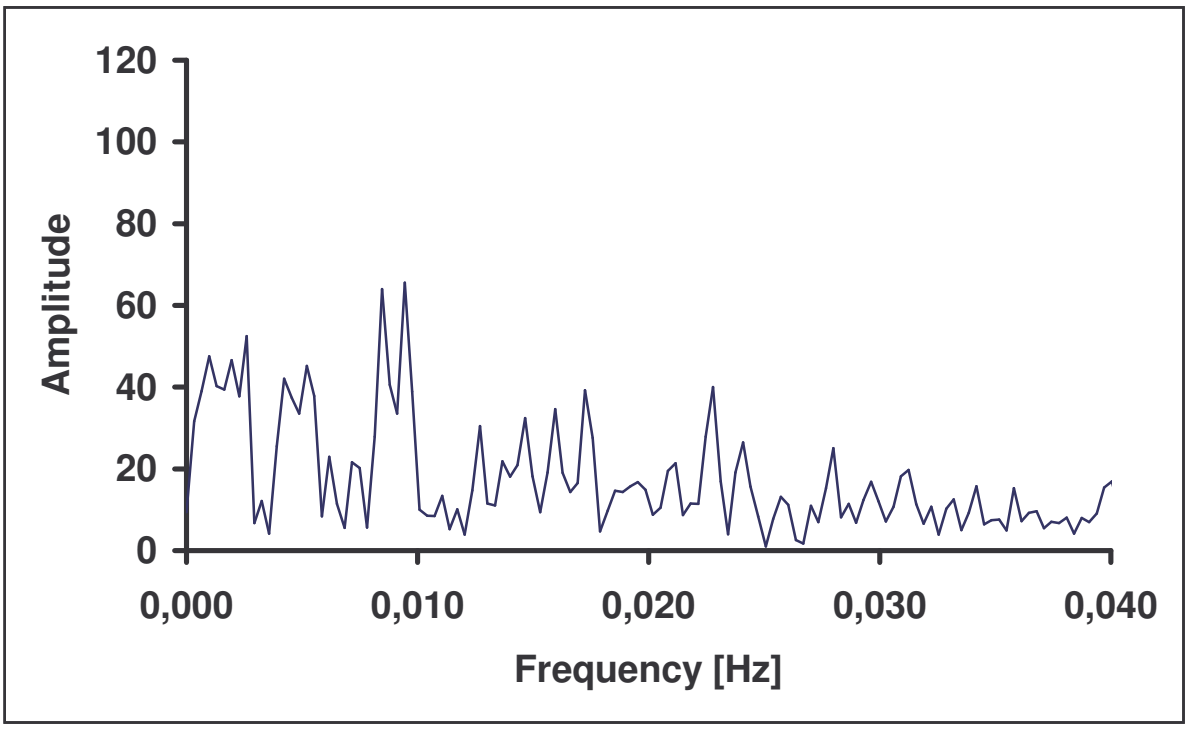

Figure 4.9 *Fourier transform of weight variation data from Figure 4.8*

CHAPTER 5

PROPERTIES OF TABLETS PREPARED FROM PELLETS AND MICRO TABLETS

During the production of multiple unit dosage forms, the tablets have to meet the requirements of Pharmacopoeias and additional specifications in order to ensure a high quality. In addition to the uniformity of mass and of content, characteristics of tablets such as crushing strength, friability, disintegration time and dissolution have to be evaluated.

5.1 Crushing strength and friability

A tablet requires a certain hardness to withstand mechanical shocks of handling during manufacture, packaging and shipping. In addition, by divisible tablets a high crushing strength will ensure that the tablets will not break into small pieces. A minimal crushing strength of 50 N and a friability value below 1 % will lead to acceptable hardness of tablets.

5.1.1 Influence of the percentage of single units on crushing strength and friability of the multiunit tablets

The crushing strength and friability of multiunit tablets consisting of 60 %, 70 % or 80 % (w/w) micro tablets and compressed at 150 MPa on a rotary press (Korsch PH 230/17) were already reported in Table 3.3 (Chapter 3). It was observed that the percentage of single units was a major factor influencing the crushing strength. The higher the content of micro tablets, the lower the crushing strength was. The crushing strength was decreased drastically from 77 N for 60 % micro tablets to 29 N for 80 % micro tablets. With a friability of 0.37 %, multiunit tablets consisting of 60 % micro tablets met the European Pharmacopoeia requirements. The friability of multiunit

tablets composed of 70 % and 80 % micro tablets could not be measured, as the tablets were broken after performing the friability test. Beckert (1995) has related the decrease of crushing strength to the decrease of excipient quantity, therefore to a decrease of contact points between the particles.

5.1.2 Influence of the single unit size on crushing strength and friability of the multiunit tablets

Multiunit tablets consisting of 60 % (w/w) micro tablets or pellets of 4 different sizes were compressed at 150 MPa on the rotary Korsch PH 230/17. The other excipients of the tablets were Avicel PH 101 ranging from 35.1 to 35.4 %, 4 % Kollidon CL, Aerosil ranging from 0.1 % to 0.4 % and 0.5 % magnesium stearate (mixtures 2-6, Table 6.7). Crushing strength and friability of the multiple unit tablets, which were described in Table 3.4, are reported in Table 5.1. The bigger the single unit, the lower was the crushing strength of the resulting tablets. Pellets in a range of 355-425 µm have given very hard tablets with a crushing strength of 200 N, whereas tablets consisting of micro tablets had a crushing strength of 77 N. In a mixture consisting of 60 % (w/w) single units, the number of small pellets is much higher than the number of micro tablets (see Table 4.4). Considering the number of particles, it means that there are much more points of contact between the different components in a tablet formed with small single units than coarse one, hence resulting in higher crushing strength values.

Regarding the friability of the tablets, it was logically observed that a decrease in crushing strength has led to an increase in friability. But, according to European Pharmacopoeia, the hardness of the multiunit tablets was satisfying.

Table 5.1 Influence of single unit size on crushing strength and friability of multiunit tablets (formulations 2 to 6, Table 6.7) compressed at 150 MPa

Single unit	Pellets 355-425 µm	Pellets 850-1000 µm	Pellets 1180-1400 µm	Pellets 1400-1700 µm	Micro tablets 2 mm
Crushing strength [N]	200	164	110	103	77
Maximal value [N]	267	206	156	151	105
Minimal value [N]	138	94	60	55	60
Friability [%]	0.18	0.20	0.20	0.26	0.37

5.1.3 Influence of the type of excipient on crushing strength and friability of the multiunit tablets

In order to study the influence of the type of excipient on crushing strength and friability of multiunit tablets, two types of microcrystalline cellulose were used, namely Avicel PH 101 and a mixture of Avicel PH 101 and Avicel PH 200 in a proportion of 30:70 % (w/w). The composition of the tablets was 60 % single units, 35.2 filler, 4 % Kollidon CL, 0.3 % Aerosil and 0.5 % magnesium stearate (see mixtures 5-8, Table 6.7). The single units were either pellets in a range of 1400-1700 µm or micro tablets of 2 mm in diameter. The crushing strength and friability of these multiunit tablets are presented in Table 5.2.

Table 5.2 Influence of excipient type on crushing strength and friability of multiunit tablets (formulations 5 to 8, Table 6.7) compressed at 150 MPa

Single unit	Pellets 1400-1700 µm	Pellets 1400-1700 µm	Micro tablets 2 mm	Micro tablets 2 mm
Filler type	Avicel PH 101	Avicel PH 101/PH 200 [30:70 % (w/w)]	Avicel PH 101	Avicel PH 101/PH 200 [30:70 % (w/w)]
Crushing strength [N]	103	49	77	74
Maximal value [N]	151	80	105	102
Minimal value [N]	55	28	60	47
Friability [%]	0.26	0.71	0.37	0.40

According to the results of Table 5.2, the excipient type had a striking influence on the crushing strength and the friability of multiunit tablets consisting of pellets in a range of 1400-1700 µm. Tablets containing Avicel PH 101 alone were strong, whereas the addition of Avicel PH 200 has led to weaker tablets. Tablets obtained with the mixture of the fine and the coarse Avicel were too weak according to the minimal value of the crushing strength. Ladhenpää *et al*. (1997) have reported that the particle size and density parameters were the most important factors influencing the crushing strength of tablets prepared from Avicel of different grades.

Unlike tablets made of pellets in a range of 1400-1700 µm, the crushing strength and the friability of tablets consisting of micro tablets did not seem to be influenced by the type of excipient. This observation can be explained by the hardness of the micro tablets, which is greater compared to the hardness of pellets. It seems in case of the micro tablets that the crushing strength is conferred by the micro tablets themselves and less by the number of particles, which is the case for the multiunit tablets consisting of pellets.

5.2 Disintegration time

According to the European Pharmacopoeia 4th edition, uncoated tablets have to disintegrate in water within 15 min to comply with the test. Consequently, transposed to multiunit tablets, it means that single units have to be separated from the excipients within 15 min.

5.2.1 Influence of the single unit size on the disintegration time of the multiunit tablets

Multiunit tablets consisting of 60 % (w/w) single units were compressed at 150 MPa on a rotary press. The other components of the tablets were Avicel PH 101 in a range of 35.1 to 35.4 %, 4% Kollidon CL, Aerosil in range of 0.1 % to 0.4 % and 0.5 % magnesium stearate (mixtures 2-6, Table 6.7). Kollidon CL, a cross-linked povidone, acts as tablet disintegrant. It is generally used at a 2 to 5 % concentration (Gordon *et al.* 1987, Gordon *et al.* 1993). Table 5.3 reports the disintegration time of tablets consisting of 4 sizes of pellets (355-425 µm, 850-100 µm, 1180-1400 µm and 1400-1700 µm) and micro tablets (2 mm). All multiunit tablets have shown a disintegration time within 15 min. But the disintegration time was highly influenced by the size of the single units. Tablets consisting of pellets in a range of 355–425 µm had a disintegration time of 14 min, whereas tablets from micro tablets compressed at the same compression force have disintegrated within 13 s. Nevertheless, by tableting pellets in a range of 355-425 µm at a lower compression force, it is possible to reduce the disintegration time. Regarding the crushing strength and disintegration time, it was not surprising to find a correlation; the higher the crushing strength, the higher was the disintegration time.

Table 5.3 Influence of the single unit size on the disintegration time of multiunit tablets

Single unit	Pellets 355-425 µm	Pellets 850-1000 µm	Pellets 1180-1400 µm	Pellets 1400-1700 µm	Micro tablets 2 mm
Disintegration time	14 min	3 min 11 s	35 s	31 s	13 s

5.2.2 Influence of the type of excipient on the disintegration time of the multiunit tablets

The influence of the type of excipient on the disintegration time of multiunit tablets was investigated. The mixtures consisting of 60 % single units, 35.2 % filler, 4 % Kollidon CL, 0.3 % Aerosil and 0.5 magnesium stearate were compressed at 150 MPa on a rotary tablet press (mixtures 5-8, Table 6.7). The filler was either Avicel PH 101 or a mixture of Avicel PH 101/PH 200 in a proportion 30:70 % (w/w). Tablet disintegration time has shown a similar dependence on the type of excipient as the tablet crushing strength. The disintegration time of tablets made of pellets in a range of 1400-1700 µm was really affected by the type of excipient. Ladhenpää *et al.* (1997) have reported that the disintegration of microcrystalline cellulose tablets was attributed to the penetration of hydrophilic liquid into the tablet matrix by means of capillary pores and the subsequent breaking of the hydrogen bonding between cellulose microcrystals. Small, fibrous particles of Avicel PH 101 pack densely and have a large bonding area with relatively small interparticular pores. The addition of large and granular Avicel PH 200 results in large interparticular pores. Water can easily reach the hydrogen bonds between cellulose microcrystals and can cause their breaking and thus rapid disintegration of tablets.

Unlike tablets made of pellets in a range of 1400-1700 µm, the type of excipient did not affect the disintegration time of tablets made of micro tablets. The disintegration time values were not significantly different. These tablets have disintegrated rapidly in

water in about 13 s, which is again in good agreement with the hardness values of these tablets.

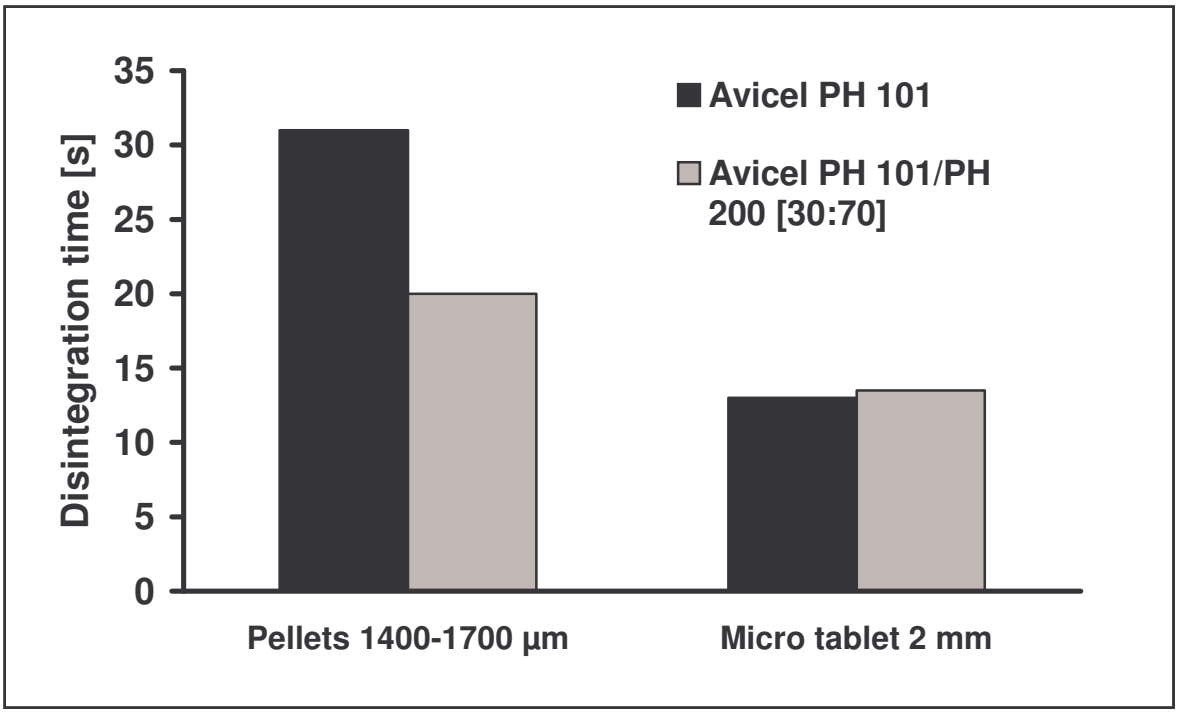

Figure 5.1 Influence of the type of excipient on the disintegration time of multiunit tablets

5.3 Dissolution

Theophylline micro tablets based on an Eudragit RS PO matrix, which delivered the drug within 8 hours, were compressed on a rotary tablet press (Kilian TX 40) at a compaction pressure of 200 MPa. Rey *et al.* (2000) have described in detail the production of such micro tablets. The micro tablets were composed of 98 % theophylline granules and 2 % magnesium stearate whereas theophylline granules consisted of 70 % theophylline, 12 % Eudragit RS PO, 12 % magnesium stearate and 6 % Eudragit RS 30 D (with 10 % TEC as plasticizer) (see section 6.4). Drug release profiles were carried out using a paddle apparatus Sotax AT7 at a rotational speed of 50 rpm. The dissolution medium was 900 ml maintained at 37 °C. The different mediums tested were purified water, 0.1 N HCl, phosphate buffer with Triton X100

adjusted to pH 4.5 and phosphate buffer at a pH 3.0 during 3.5 h followed by pH 7.4. The two phosphate buffers are described in USP 25 under "theophylline extended-release capsules" tests 4 and 7 respectively. The influence of the dissolution medium on the theophylline release from micro tablets within an 8-h period was investigated (Figure 5.2).

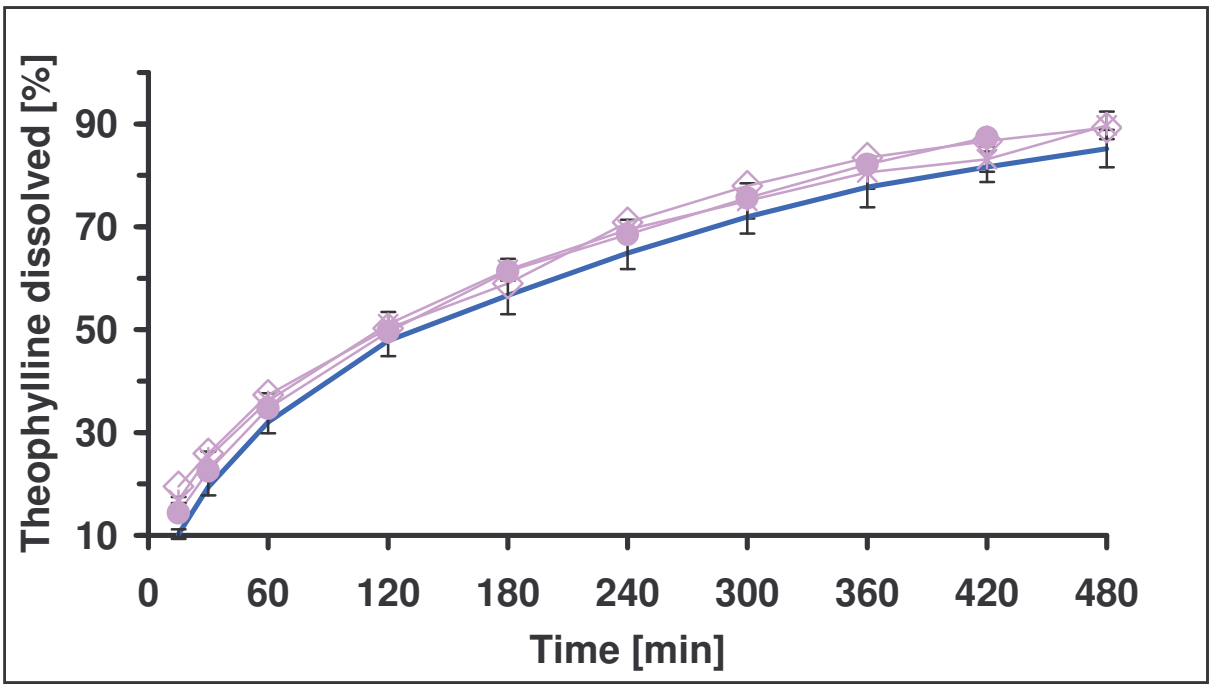

Figure 5.2 *Influence of the dissolution medium on theophylline release from micro tablets based on a Eudragit RS PO-matrix (n=3). (-) purified water, (●) pH 4.5 phosphate buffer, (◇) pH 3.0 phosphate buffer during 3.5 h and pH 7.4, (×) 0.1N HCl. Error bars represent the 95 % confidence interval.*

After 8 hours, the micro tablets were still present in the dissolution vessels. The dissolution medium has shown no significant effect on the drug release from micro tablets based on an Eudragit RS PO matrix as dissolution rates were quite similar. Consequently, further dissolution tests were performed in purified water.

After the compression of multiunit tablets, it is important that the single units held their release characteristics. Several studies have already reported that damages of

coated units during the compression into multiunit tablets were responsible for a significant increase of the drug release (Béchard et Leroux 1992, Lehmann *et al.* 1993, Beckert *et al.* 1996). Matrix tablets present the advantage over coated forms that the release of drug is not dependent on the change of the film coating after the compaction process.

Multiunit tablets composed of matrix micro tablets in a range of 60 % to 70 % (w/w), Avicel PH 101 in a range of 25.2-35.2 %, 4 % Kollidon CL, 0.3 % Aerosil and 0.5 % magnesium stearate were then compressed at 150 MPa on a Korsch PH 230/17. The dissolution test was carried out in 900 ml purified water at a rotational speed of 50 rpm. Theophylline profiles of micro tablets and multiunit tablets consisting of the same micro tablets were compared (Figure 5.3). Multiunit tablets were also tested for compliance with the specifications of USP 25 Drug release test 7. The limits of tolerance of the dissolution rates are listed in Table 5.4. According to the dissolution profiles, it was observed that the release of theophylline from multiunit tablets and micro tablets was similar. Thus, the compression from micro tablets into multiunit tablets did not influence the subsequent drug release. Moreover, the content of micro tablets in a range of 60-70 % did not affect the release. In addition, it was observed that multiunit dosage forms have fulfilled the requirements of USP 25 for theophylline-release preparations as the dissolution rates were found within the tolerance limits.

Table 5.4 Tolerance limits for dissolution rates according to USP 25 drug release test 7

Time (h)	Amount dissolved
1	between 10 % and 40 %
2	between 35 % and 70 %
4	between 60 % and 90 %
8	not less than 85 %

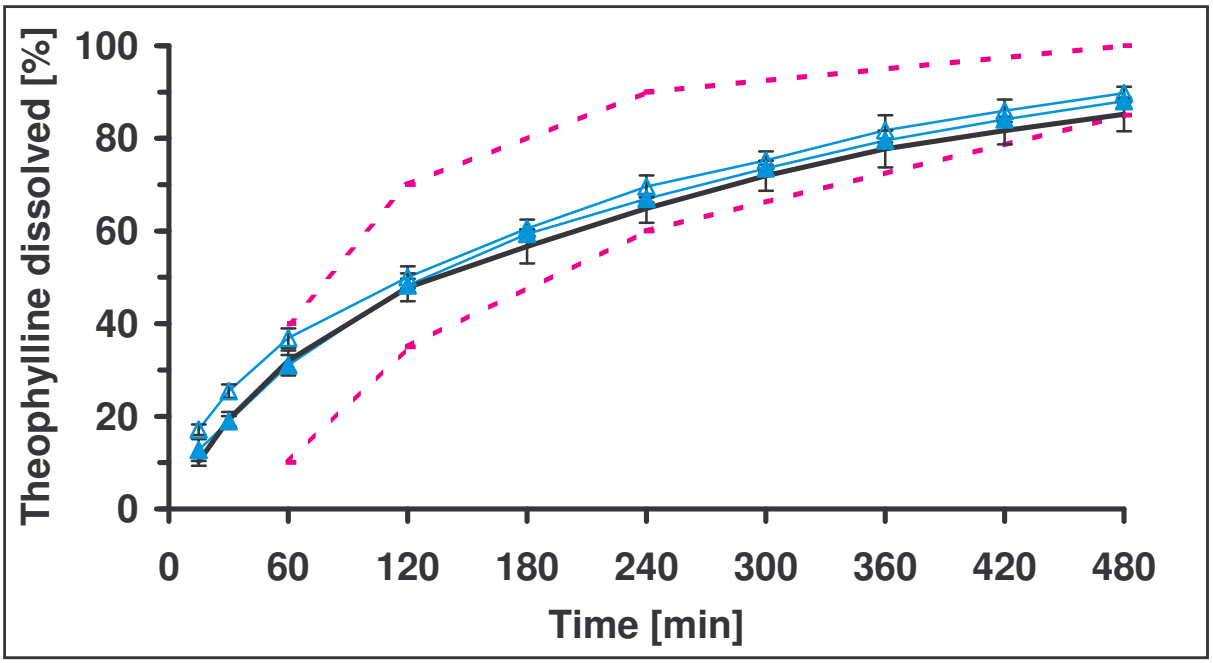

Figure 5.3 *Theophylline release from micro tablets (-) and from multiunit tablets containing 60 % (w/w) micro tablets (Δ) and 70 % micro tablets (▲) in purified water. (- -) Tolerance limits of USP 25 Test 7. Error bars represent the 95 % confidence interval.*

CHAPTER 6

MATERIALS AND METHODS

6.1 Materials

Table 6.1 Excipients and chemicals

Name	*Batch*	*Manufacturer / supplier*
Aerosil 200	S326030	Degussa AG
Avicel PH 101	6629C /6050C / 6113C	FMC Corp./ Lehmann & Voss & Co.
Avicel PH 200	M019C	FMC Corp./ Lehmann & Voss & Co.
Eudragit RS PO	0460738073	Röhm GmbH & Co. KG
Eudragit RS 30 D	0480318065	Röhm GmbH & Co. KG
Hydrochloric acid 37 %	113386	Merck KGaA
Kollidon CL	87_0817 / 36_0185	BASF AG
Ludipress	62_1227	BASF AG
Magnesium stearate	190151	Bärlocher GmbH
Monobasic potassium phosphate	A127771918	Merck KGaA
Pellets, neutral 1400-1700	B 08650842	Hanns G. Werner GmbH
Phosphoric acid 85 %	K3673775	Merck KGaA
Sodium hydroxide	B118598	Merck KGaA
StarLac	L0126	Meggle GmbH
Suglets 355-425	104F	NP Pharm S.A
Suglets 850-1000	106E	NP Pharm S.A
Suglets 1180-1400	909T	NP Pharm S.A
Theophylline, anhydrous, powder 200	346954	Abbott GmbH & Co. KG
Triethyl citrate	N7Y190-H813066M	Röhm GmbH & Co. KG
Triton X100	45274	Fluka

6.2 General equipment

Table 6.2 List of general equipment

Equipment	*Manufacturer / supplier*
Balance Mettler AE 200	Mettler Toledo GmbH
Balance Mettler PC 1616	Mettler Toledo GmbH
Balance Mettler PM 6100	Mettler Toledo GmbH
Gyro-wheel mixer	Self-constructed
Stirrer, IKA Combimag RCH	Janke & Kunkel
Turbula-mixer T2C	Bachofen
Ultra-Turrax T25	Janke & Kunkel
UV-Vis spectrophotometer 550S	Perkin-Elmer GmbH

6.3 Data processing

Computer: Pentium III 733 MHz, 512 MB RAM, 20 GB hard disk.

Table 6.3 List of softwares

Software	*Manufacturer / supplier*
Compression Research System	Korsch Pressen GmbH
Mastersizer 2000 version 4.0	Malvern
Microcal ™ Origin version 6.0	Microcal Software
Microsoft DOS 2.2 and 6.22	Microsoft
Microsoft Excel 2000	Microsoft
Microsoft Power Point 2000	Microsoft
Microsoft Word 2000	Microsoft
VCH Biblio for Windows	VCH publishing society

6.4 Preparation of the micro tablets

6.4.1 Granulation

2800 g of theophylline powder, 480 g of Eudragit RS PO and 480 g of magnesium stearate were mixed in a fluidised bed granulator (WSG 5, Glatt GmbH) for 10 min. Afterwards the mixture was granulated by top spraying 4000 g of an aqueous dispersion consisting of Eudragit RS 30 D as a binder and triethyl citrate as a plasticizer. The aqueous granulating dispersion was prepared by dissolving 24 g of triethyl citrate in 3176 g of water under agitation using an Ultra-Turrax homogeniser for 10 min (Ultra-Turrax T25, Janke & Kunkel). The solution was then added into 800 g of the polymer dispersion with continuous stirring (Stirrer IKA Combimag RCH, Janke & Kunkel). The spray dispersion was supplied by a peristaltic pump (Watson Marlow 505S) and was stirred throughout the spraying process. The composition of the granules and the granulating parameters are listed in Table 6.4.

Table 6.4 Description and preparation of theophylline granules

Products	Amount [g]	Dry substance [g]
Theophylline, anhydrous, powder 200	2800.0	2800.0
Eudragit RS PO	480.0	480.0
Magnesium stearate	480.0	480.0
Eudragit RS 30 D	800.0	240.0
Triethyl citrate	24.0	24.0
Water	3176.0	
Total	7760.0	4024.0
Solids content of the spray dispersion [w/w]		6.6 %
Equipment	WSG 5	

Spray nozzle diameter [mm]	1.8
Batch [g]	3760.0
Spray suspension [g]	4000.0
Preheating time [min]	7
Spraying time [min]	33
Inlet air temperature [°C]	65
Outlet air temperature [°C]	30
Atomizing air pressure [bar]	2.5
Suspension flow rate [g/min]	121.2
Drying time [min]	25

The dried granules were sieved by hand and fractions below 500 µm were taken for compression of micro tablets (Flemming and Mielck 1995).

6.4.2 Composition of the micro tablets

Micro tablets containing theophylline and StarLac respectively were prepared. The composition of theophylline micro tablets and the StarLac containing micro tablets is given in Table 6.5. Theophylline micro tablets were produced from theophylline granules as described under section 6.4.1.

Table 6.5 Composition of the micro tablets in % (w/w)

	Theophylline micro tablets	Placebo micro tablets
Theophylline granules	98	-
StarLac	-	99
Magnesium stearate	2	1
Batch size	20 kg	36 kg

6.4.3 Blending

Theophylline granules were blended with 2 % magnesium stearate in a laboratory blender (type 951922, Servolift GmbH) for 20 min. Magnesium stearate was passed through sieve No. 5 (mesh size 0.315 mm) before mixing.

3 batches of 12 kg from StarLac and 1 % magnesium stearate were blended for 20 min at 40 rpm in a self-constructed gyro-wheel mixer using a steel drum (∅ = 40 cm, h = 45 cm). Magnesium stearate was passed through sieve No. 5 (mesh size 0.315 mm) before mixing. The three batches were combined for tableting.

6.4.4 Tableting of the micro tablets

Rotary tablet press Korsch Pharma 230/17

The rotary tablet press Korsch Pharma 230/17 (Korsch Pressen GmbH) is a modern medium-range machine with 17 pairs of punches and production rates between 25 000 and 125 000 tablets per hour. The tablet machine was fitted with 2*4 strain gauges (type HBM 6/120 LY 11, Hottinger Baldwin Messtechnik GmbH) that were placed in a full-bridge configuration on the upper and lower holders of the main rollers. The construction principle and the instrumentation of the tablet machine have been described by Vogel (1992).

Calibration

The calibration of the compression force at the upper and lower roller holders was performed according to Leitriz *et al.* (1995) with a piezo-electric transducer (type 9021A, Kistler Instruments GmbH) and a charge amplifier (Type 5007, Kistler Instruments GmbH). The acquisition of the data was performed using a MGC Plus system as described by Dressler (2002). The sensitivity of the carrier frequency bridge amplifier was set at 1 mV/V. The calibration chain is depicted in Figure 6.1.

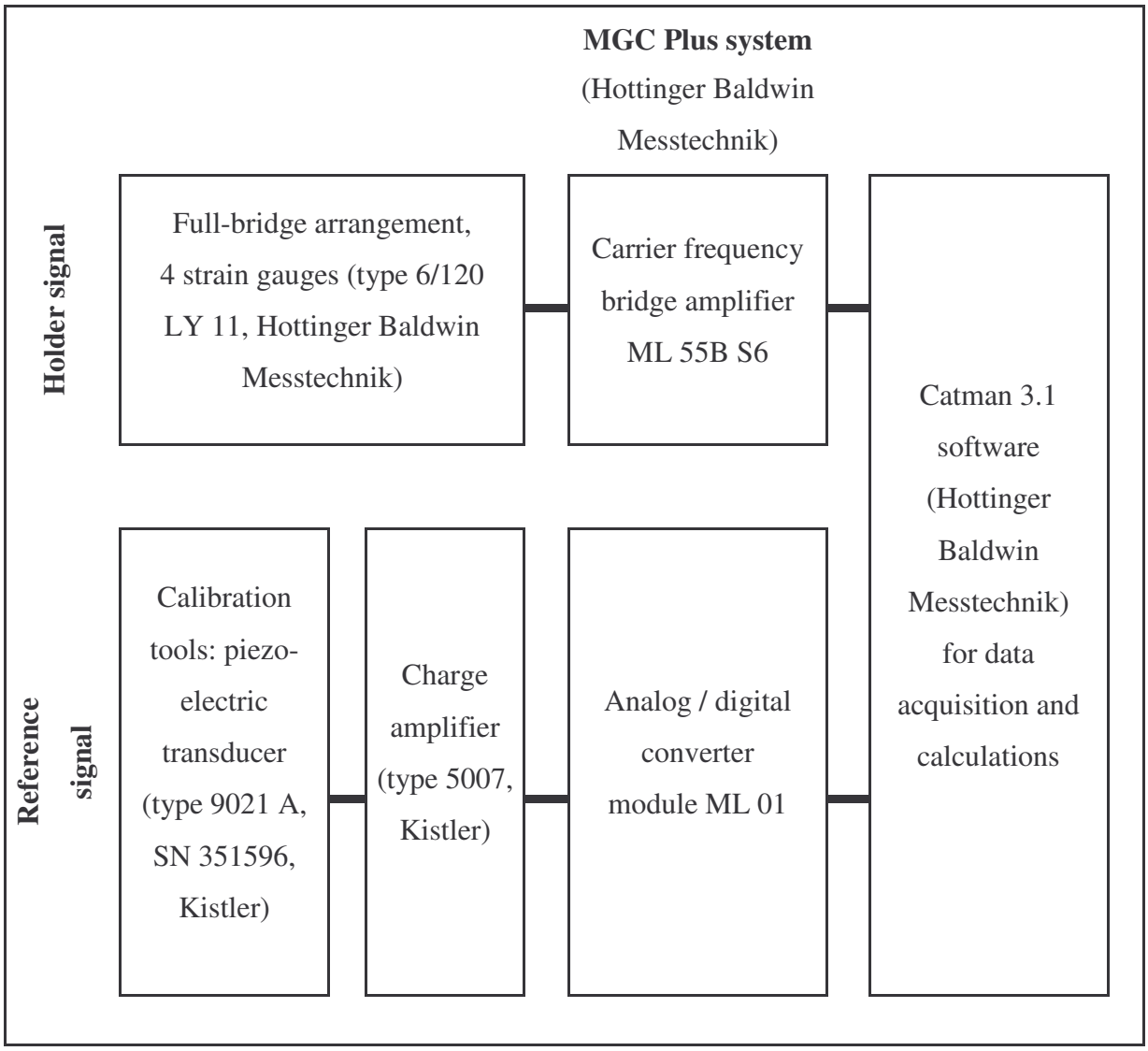

Figure 6.1 Static calibration of compression force

Six different compression levels (2, 5, 10, 15, 20 and 25 kN) were employed for the calibration of the compression force. The levels were adjusted by varying the band

height from 2.2 mm to 1.5 mm). The measurements were repeated 6 times for each compression level. Linear regression (Sachs 1997, Schmidt 1997) and analysis function (Leitritz *et al.* 1995) were calculated. Calibration factors resulting from the analysis function were stored in the CRS software (Korsch Pressen GmbH). The results of the calibration are illustrated in Table 6.6.

Table 6.6 Results of the static calibration of compression force

Parameter	Upper punch	Lower punch
Number of calibration points	36	36
Degrees of freedom	34	34
Significance level	95 %	95 %
Slope	0.1377	0.2442
Intercept	-0.1778	-0.0408
Variance in y	0.0007	0.0007
Variance of slope	$3.00*10^{-7}$	$2.87*10^{-7}$
Variance of intercept	$7.18*10^{-5}$	$6.94*10^{-5}$
Correlation coefficient	0.9997	0.9999
Coefficient of determination	0.9994	0.9998
Regression function	y = 0.1377*x-0.1778	y = 0.2442*x-0.0408
Regression function through the origin	y = 0.128*x	y = 0.242*x
Analysis function through the origin	x = 7.8125*y	x = 4.1322*y

Figure 6.2 and Figure 6.3 illustrate the calibration curves of the upper and lower punches with 95 % confidence interval. The confidence interval was magnified ten times for a better visualisation. The residual plots of the calibration are depicted in Figure 6.4 and Figure 6.5.

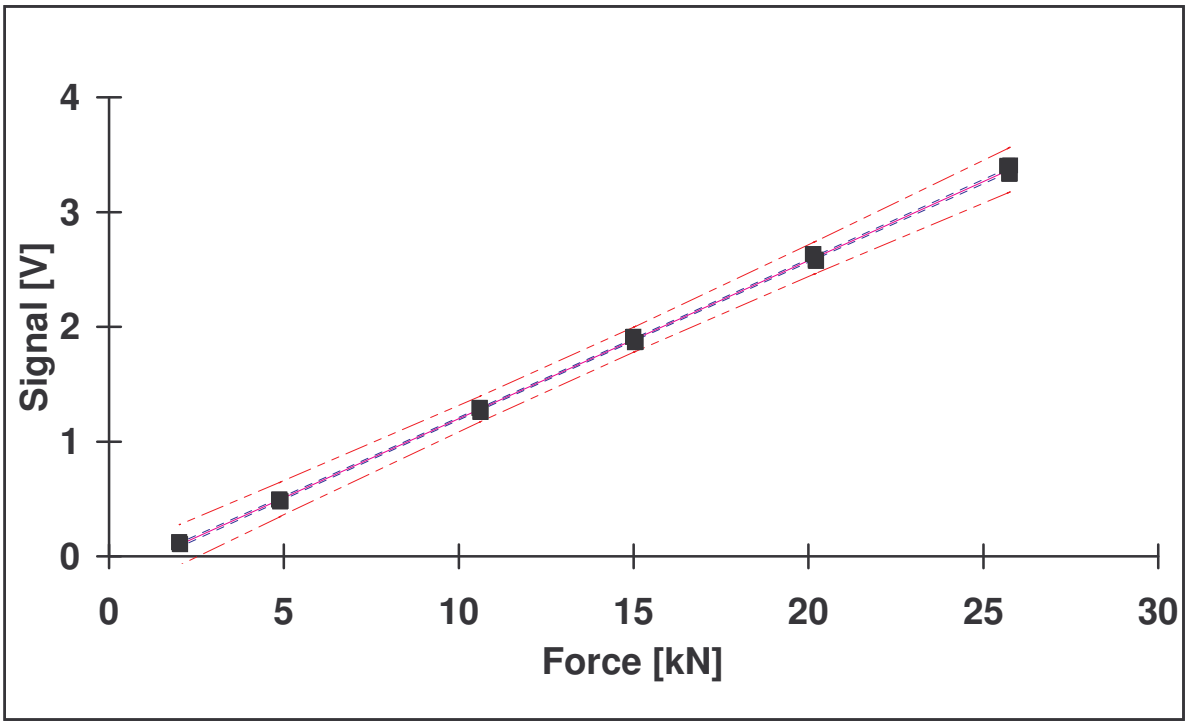

Figure 6.2 Calibration curve of the upper punch and its 95 % confidence interval

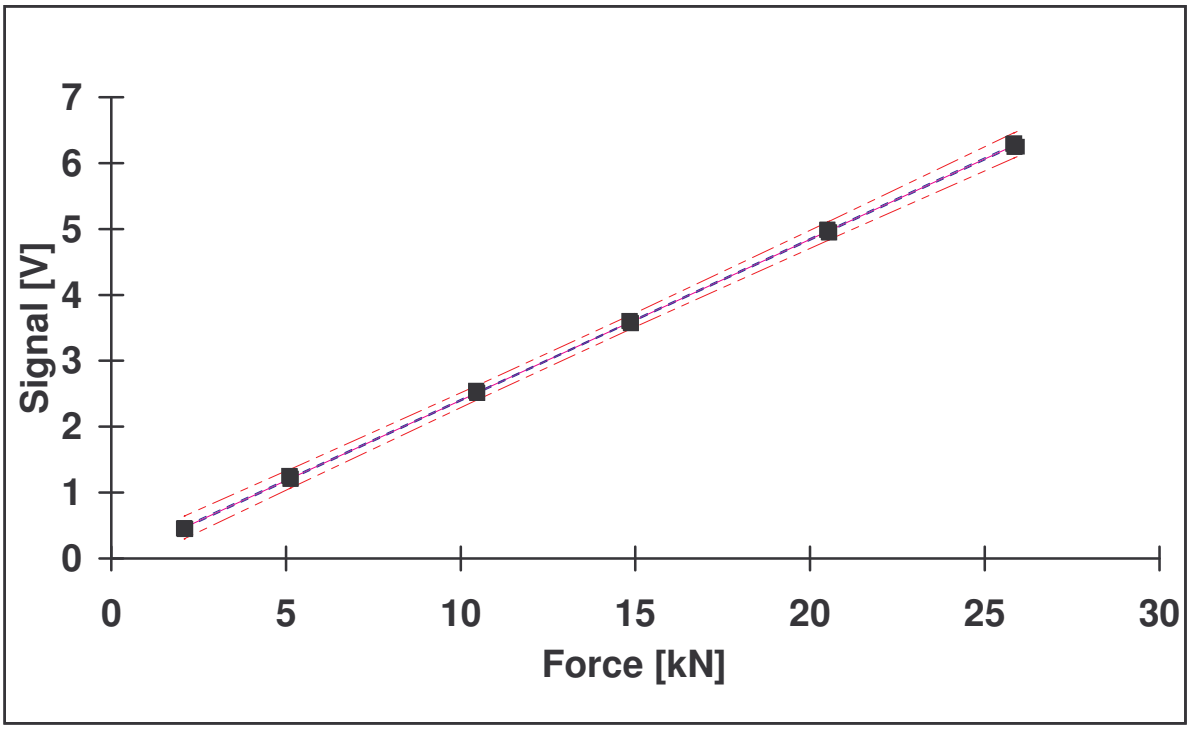

Figure 6.3 Calibration curve of the lower punch and its 95 % confidence interval

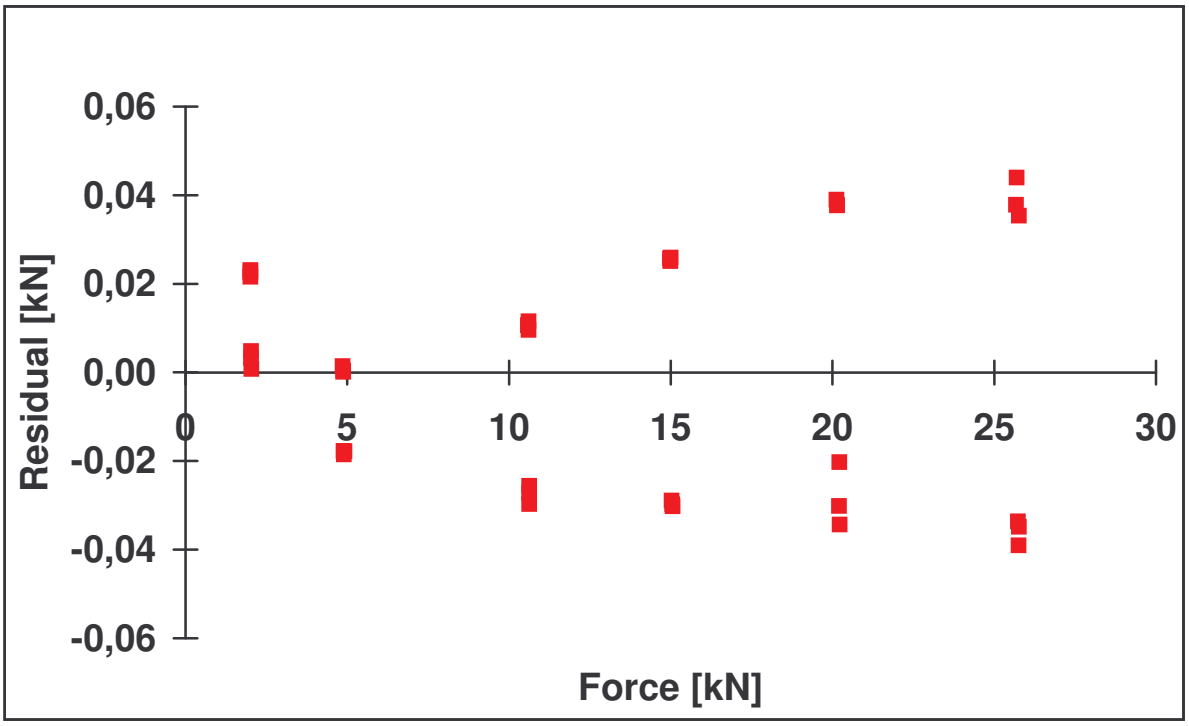

Figure 6.4 Residual plots of the upper punch calibration

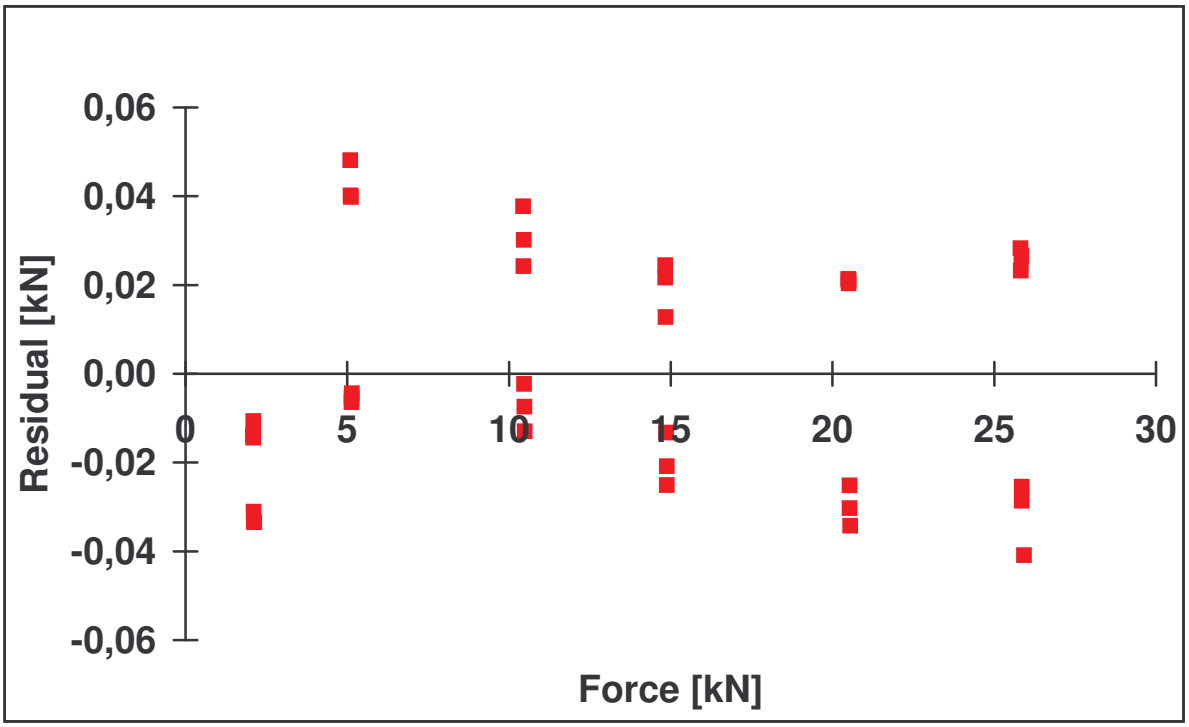

Figure 6.5 Residual plots of the lower punch calibration

Tableting of micro tablets

Theophylline micro tablets were compressed on an instrumented rotary tablet press (Kilian TX 40, Kilian & Co. GmbH)[1] and StarLac containing micro tablets were compressed on an instrumented Korsch Pharma 230/17 (Korsch Pressen GmbH) fitted with a force feeder. The Korsch Pharma Press was equipped with one pair of punches each containing 19 small concave punches of a diameter of 2 mm (Ritter Pharma-Technik GmbH). The speed of the tablet machine was kept constant at 50 rpm. A band height of the micro tablets of 0.8 mm and a compaction pressure of 200 MPa were employed.

Data acquisition and processing were performed by the Compression Research System CRS (Korsch Pressen GmbH). The system was switched on 30 min before the beginning of the compression, the amplifiers were controlled and the strain gauges were adjusted. The compression forces at the lower and upper punches were checked on an oscilloscope and the values were saved every 15 min.

[1] We gratefully acknowledge Abbott GmbH & Co. KG, Germany, for compressing the theophylline micro tablets.

6.5 Tableting of pellets and micro tablets into multiunit tablets under pilot plant conditions

6.5.1 Composition of pilot plant tableting mixtures

The compositions of the various 30 kg-batches are described in Table 6.7.

Table 6.7 Composition of 30 kg- tableting mixtures in % (w/w)

Ingredients	Mixtures							
	1	2	3	4	5	6	7	8
Ludipress	99.5							
Pellets [µm] 355-425		60						
850-1000			60					
1180-1400				60				
1400-1700					60		60	
Micro tablets						60		60
Avicel PH 101		35.1	35.4	35.2	35.2	35.2	10.56	10.56
Avicel PH 200							24.64	24.64
Kollidon CL		4	4	4	4	4	4	4
Aerosil		0.4	0.1	0.3	0.3	0.3	0.3	0.3
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

6.5.2 Blending of pilot plant tableting mixtures

The ingredients of each mixture (Table 6.7) consisting of 3*10 kg-batches were blended without magnesium stearate in a gyro-wheel mixer using a stainless steel

drum for 20 min. The mixing speed was set at 40 rpm. The lubricant was passed through sieve No. 5 (mesh size 0.315 mm) and mixed with the mixtures for additional 10 min. The three batches were combined for tableting.

6.5.3 Tableting of pilot plant batches

Multiunit tablets were compressed on an instrumented rotary tablet press (Korsch Pharma 230/17, Korsch Pressen GmbH) using a gravity feeder (Art. No 8590052, Korsch Pressen GmbH). The description and the calibration of the tablet press were described under section 6.4.4. Eight of the 17 punch stations were equipped with 13 mm round flat-faced punches of type B (Ritter Pharma-Technik GmbH). The speed level and the compression force were set at 50 rpm and 150 MPa, respectively, thus a tableting time of 1 hour resulted. The filling depth and the band height were adjusted at the beginning and were kept constant during tableting. During tablet compression, a minimum material level in the filling hopper was maintained by hand in order to avoid weight variations due to fluctuation of the material level.

A tablet discharge (Figure 6.6) was used in order to collect tablets every 3 s. The tablet discharge was equipped with a rotary magnet type D52-LOR-N (Kuhnke GmbH) and a self-constructed metal shunting device that were fastened via two guide rails with snap mechanism. The rejected tablets were guided to the corresponding rail by means of the rotary magnet and the shunting device. The magnet was supplied with current and the activation of the magnet was performed using a MS-DOS 6.22 programme (Microsoft GmbH).

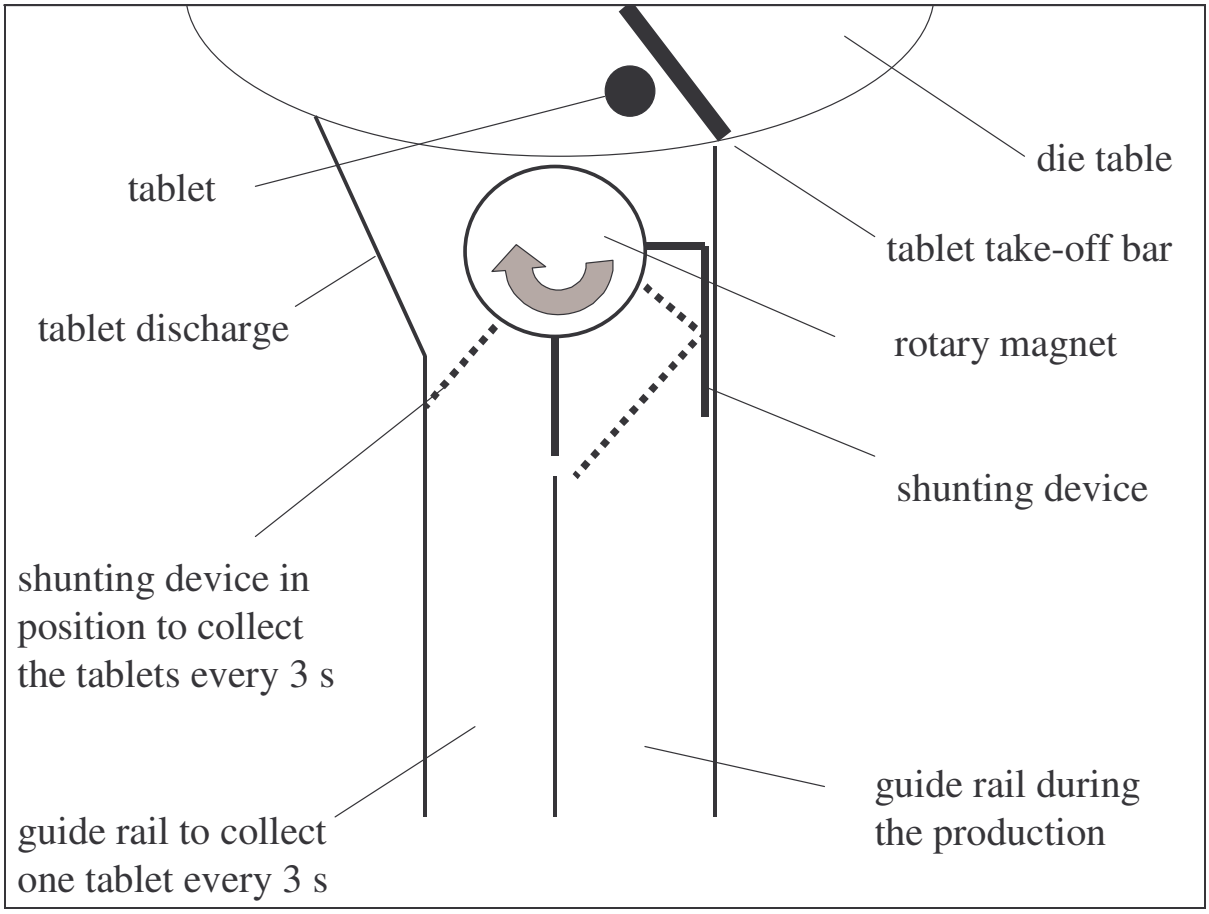

Figure 6.6 Schematic diagram of the tablet discharge and the shunting device

Data acquisition and processing were performed by the Compression Research System CRS (Korsch Pressen GmbH). The system was switched on 30 min before the beginning of the compression, the amplifiers were controlled and the strain gauges were adjusted. The compression forces at the lower and upper punches were checked on an oscilloscope and the values were saved every 15 min.

6.6 Analytical methods

6.6.1 Powder analysis

Bulk and tapped density

50.0 g of each substance (m) to be examined were introduced without compacting into a 250 ml graduated cylinder using a powder funnel. The unsettled volume (V_0) was read and the bulk density [g/ml] was calculated as the quotient m/V_0 according to the "Deutsche Industrie Standard" DIN 53912. Measurements were performed in triplicate and the mean value was calculated.

An Engelsmann tap meter (JET ST 2, Engelsmann AG) was used to measure the tapped density according to DIN 53194. 1250 taps were carried out and the corresponding volume (V_{1250}) was recorded. Measurements were performed for each substance in triplicate and the mean value was calculated. The tapped density [g/ml] is expressed as the quotient m/V_{1250}.

The Hausner factor was calculated as the ratio of tapped and bulk density of the powders. Hausner factor values < 1.25 indicate good flow properties whereas values > 1.25 exhibit poor flow properties (Hausner 1967).

True density

The true density was determined using a Beckman air comparison pycnometer (Model 930, Beckman Instruments Inc.) at room temperature. Micro tablets and pellets were first ground with a mortar and pestle for ten minutes and an amount of material representing 80 % (v/v) of the sample cup was exactly weighed (Mettler AE 200, Mettler Toledo GmbH). The zero measurement and the starting number (108.05) were checked before measurements according to the machine's operating procedure.

True density was calculated as the quotient of weighed substance to true volume. The mean value of three measurements was determined.

Particle size

The particle size distribution of 20 g of theophylline granules was measured by a Sympatec-HELOS laser diffraction spectrometer KA Compact (Sympatec GmbH). The gravity-dispersing system GRADIS, a focal length of 500 mm and a measuring time of 10 s were employed. A reference measurement without powder was performed before each sample. Data acquisition and analysis were performed using the software HELOS (version 4.6.58, Sympatec GmbH) on a HP Vectra M2 4/66 computer. The mean value of three measurements was taken.

The particle size distributions of Avicel PH 101, Avicel PH 200, Ludipress and the pellets (Ø=355-425 µm, Ø=850-1000 µm, Ø=1180-1400 µm) were measured by laser diffraction spectrometer Mastersizer 2000 (Malvern Instruments GmbH) using the dry-dispersing system Scirocco 2000 (Malvern Instruments GmbH). The dispersing air pressure was set at 1 bar for Ludipress and the pellets and at 3 bar for Avicel PH 101 and Avicel PH 200. Data were directly supplied by means of software (Malvern Instruments GmbH). A reference measurement without powder was performed during 10 s before each sample. The mean value of three measurements of 10 s was calculated.

Angle of repose and flow rate

The angle of repose was measured using a Pfrengle funnel according to DIN 53916. 150 ml of material were flowing through a 10 mm-orifice funnel on a disc of a radius (r) of 50 mm. The distance between the aperture of the funnel and the disc was 75 mm. The height (h) of the powder cone was measured and the angle of repose (α) was calculated using the following equation: $\tan \alpha = h/r$. The mean value of five samples was taken.

The flow rate [ml/s] was defined as the time needed for a defined volume of material to flow out of the funnel. The mean value of five samples was calculated.

Flowability using a conveyor belt

A new method was designed to measure the flowability of the different mixtures using a conveyor belt. The setup of this method is shown in Figure 6.7 and Figure 6.8. The conveyor belt consists of a circular strip of plastic material of 77 cm in length and 10 cm in width (Reiff-Technische Produkte GmbH). The belt rotates at a speed of 2.15 cm/s (motor type 3557K024CR, Dr. F. Faulhaber GmbH). Mixtures are passed through the funnel to the belt and conveyed to a balance (type PM 6100, Mettler Toledo GmbH). The dimensions of the funnel are listed in Table 6.8. The gap between the funnel and the belt was set to 3 mm using a micrometer (0.01 mm, Mitutoyo Messgeräte GmbH). The weight of the powders conveyed was recorded every 0.5 s and cumulative as well as differential curves were plotted automatically (HP VEE Program, version 5.0). Mixtures 1, 3, 4 and 7 (Table 6.7) were investigated for 1 min and mixtures 2 and 5 (Table 6.7) were investigated for 1 min and 60 min. All measurements were repeated 3 times.

Table 6.8 Dimensions of the funnel [cm]

Diameter of the funnel	7.9
Diameter of the orifice	1.9
Total height of the funnel	14.5
Height of the upper vertical part	5.8
Height of the lower conical part	5.7
Height of the orifice	3

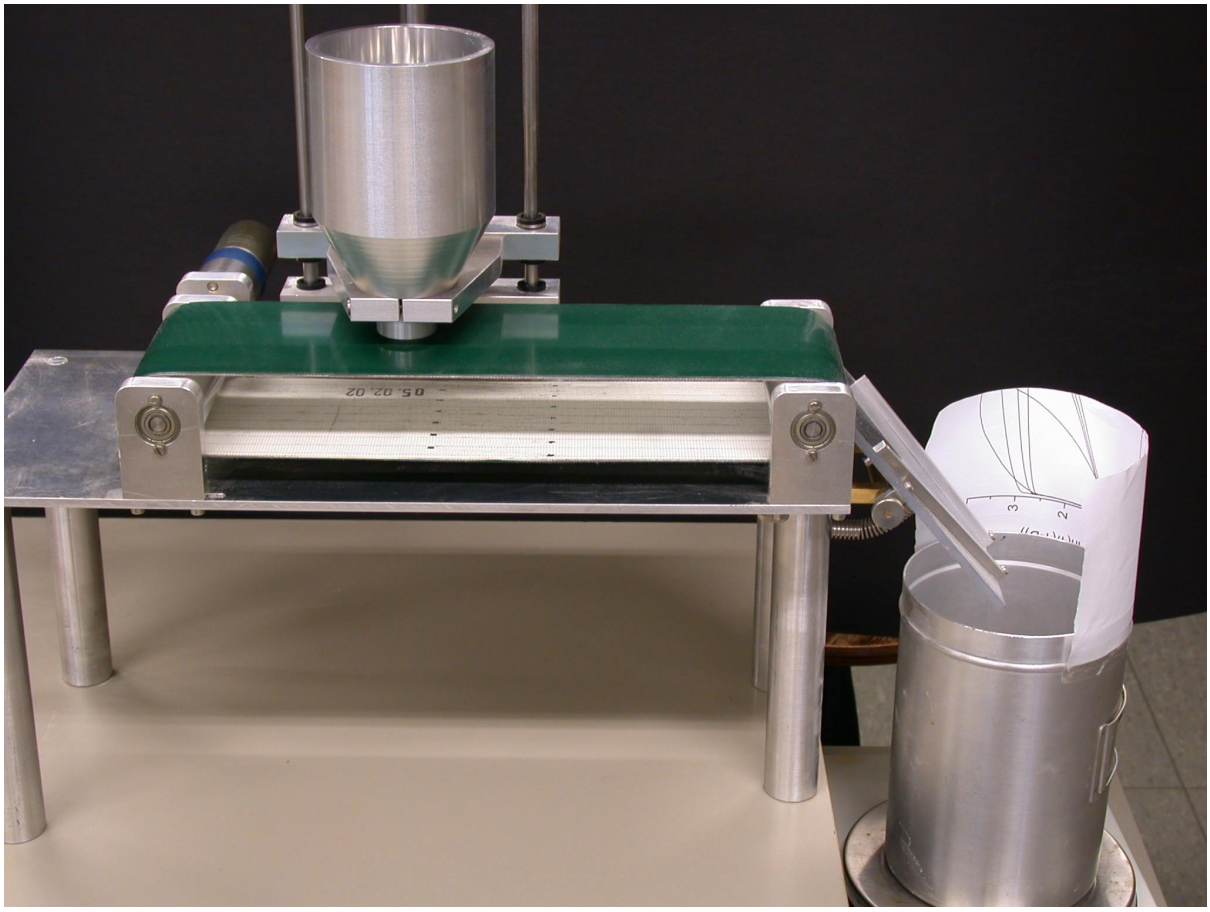

Figure 6. 7 Setup of the conveyor belt

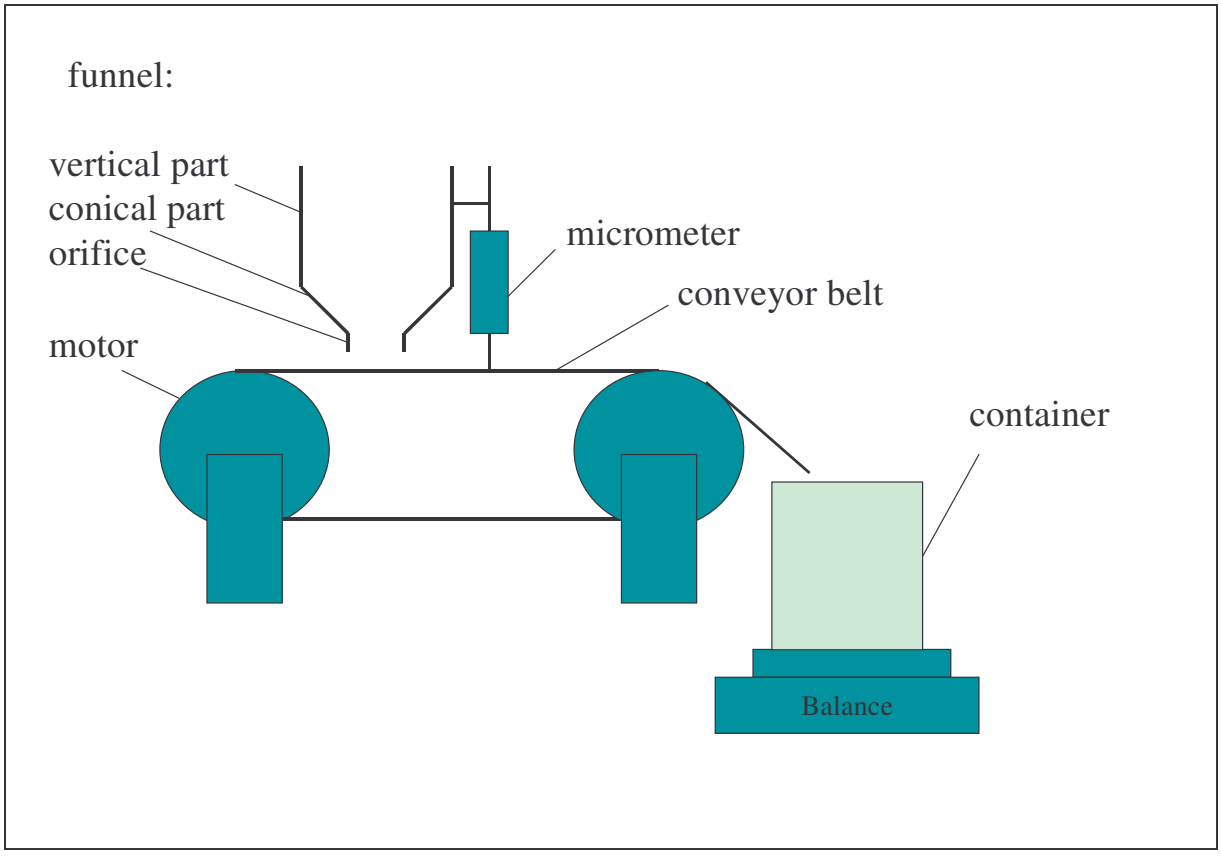

Figure 6.8 Schematic diagram of the conveyor belt

6.6.2 Physical characterisation of the tablets

The following characteristics of the tablets were determined 24 hours after tableting.

Tablet mass

The tablet mass was determined on an analytical balance (AE 200, Mettler Toledo GmbH). Mean, standard deviation and coefficient of variation were calculated.

Crushing strength

The crushing strength of the micro tablets was determined according to the European Pharmacopoeia 2002 (2.9.8 "Resistance to crushing of tablets") using a crushing strength tester Model 6D (Dr. Schleuniger Pharmatron AG). The crushing strength of the multiunit tablets was investigated using a crushing strength tester TBH 30 (Erweka GmbH). Tablet fragments were removed from the jaws before the next measurement. Mean, standard deviation and coefficient of variation were calculated.

Disintegration time

The disintegration test was performed according to the European Pharmacopoeia 2002 (2.9.1 "Disintegration of tablets and capsules") using a disintegration tester type PTZ 1 (Pharmatest Apparatebau). A 1-liter beaker was used and the temperature of the water was maintained at 36-38 °C. The disintegration time was defined as the time required for the pellets or the micro tablets of 6 multiunit tablets to be totally separated from the excipients. The mean value of three determinations was calculated.

Friability

The tablet friability was determined according to the European Pharmacopoeia 2002 (2.9.7 "Friability of uncoated tablets"). 10 tablets were tested using a friability tester type PTF1 (Pharmatest Apparatebau) for 4 min at 25 rpm. Loose dust particles were removed from the tablets with air pressure before and after the test. The tablet friability was calculated from the loss of mass and expressed as the percentage of the initial mass.

6.6.3 UV-spectrophotometry

Spectrophotometer

Ultraviolet (UV) spectrophotometer	550S (Perkin-Elmer GmbH)
Cuvette	1 cm quartz cuvette, volume 2.5 ml

All theophylline samples were measured in increasing order. The cuvette was rinsed with about 3 ml of the sample before each measurement. Dilutions were carried out by means of Eppendorf Research 1000 pipette (Eppendorf AG) if the measured absorption was more than 0.8.

Calibration

The UV-absorption spectrum of theophylline between 200 and 400 nm in purified water was measured in order to determine the maximum absorption wavelength (scanning speed 60 nm/min).

Linearity

19.9 mg of theophylline were dissolved in purified water in a 500 ml volumetric flask (stock solution). 5, 10, 15, 20, 25, 30 and 35 ml from the stock solution were diluted to 100 ml using purified water. The samples were measured 6 times at 271.2 nm and a linear regression was calculated. The results are summarized in Table 6.9.

Reproducibility

In order to test the reproducibility of the method, a sample was measured 6 times. The mean value and the coefficient of variation were calculated (Table 6.10).

Recovery

580 mg of micro tablets containing 68.5 % (w/w) theophylline were homogenised for 20 min using an Ultra-Turrax (Janke & Kunkel) in 500 ml purified water (corresponding to a nominal theophylline content of 79.46 mg/100 ml). 9.0 ml of the homogenised solution was diluted to 10.0 ml using purified water. And 99.0 ml of the

homogenised solution were diluted to 100.0 ml using a standard solution containing 800 mg theophylline in 100 ml purified water. The resulting solutions contained between 90.0 % and 109.1 % of theophylline, based on the nominal content. The mean value of three measurements was calculated and the results are presented in Table 6.10.

Table 6.9 Data of the calibration of theophylline

Parameter	Theophylline
Measuring range [mg/100 ml]	0.199-1.393
Number of measurements	42
Correlation coefficient	0.9999
Slope	0.5817
Standard deviation (slope)	$9.52 * 10^{-4}$
Intercept	- 0.0045
Linear regression	f(x) = 0.5817 * x - 0.0045

Table 6.10 Statistical data of the validation of the UV-method

Parameter	Concentration of theophylline [mg/100 ml]	Percent of the nominal content [%]	Recovery rate [%]	Coefficient of variation [%]
Reproducibility	0.597			0.16
Recovery	71.514	90.0	99.58	0.45
	79.460	100.0	100.56	0.42
	86.665	109.1	99.32	0.49

Theophylline content

Micro tablets

Ten micro tablets were ground using a mortar and pestle for ten minutes and dispersed with purified water in a 100-ml volumetric flask. After dilution and filtration (glass fibre filter, type 13400-25-S, Sartorius AG), the theophylline content was assayed using an UV-spectrophotometer (Perkin Elmer 550S, Perkin-Elmer GmbH) at 271.2 nm. Each sample was measured three times.

Multiunit tablets

One multiunit tablet was ground using a mortar and pestle for ten minutes and dispersed with purified water in 1000-ml volumetric flask. After dilution and filtration (glass fibre filter type, 13400-25-S, Sartorius AG), the theophylline content was assayed using an UV-spectrophotometer (Perkin Elmer 550S, Perkin-Elmer GmbH) at 271.2 nm. Each sample was measured three times.

Dissolution test

Drug release profiles of the tablets were determined using a paddle dissolution apparatus (dissolution-tester Sotax AT7, Sotax AG) with the following equipments:

Pump	piston pump CY 7-50
Collector	fraction collector C 613
Software	DOS-version 2.2
Hardware	IBM, type AT, 1 MB memory, 80 MB hard disk
Interface	Type PA 29A
Filter	glass fibre (type 13400-25-S, Sartorius AG)

Before the collection of each sample, 10 ml of the dissolution medium were pumped in order to compensate the dead volume of the flexible tube.

The dissolution tests were carried out with 300 mg of micro tablets or one multiunit tablet per dissolution vessel. 900 ml of dissolution medium were used and maintained at 37 °C ± 0.5. Purified water was used for the dissolution of multiunit tablets, whereas purified water, 0.1 N HCl and phosphate buffers according to test 4 and test 7 of the USP 25 “theophylline extended-release capsules” were the mediums for the dissolution of micro tablets. Aliquots of 5-ml were taken automatically at specified time intervals: 15, 30, 60, 120, 180, 240, 300, 360, 420 and 480 min. During sampling, the removed volume was not replaced. The rotational speed of the paddles was set at 50 rpm. At the end of the dissolution test, the content of the vessels was homogenised for 10 min using an Ultra-Turrax T25 (Janke & Kunkle) and the solutions were filtrated through a glass fibre filter (type 13400-25-S, Sartorius AG). The total theophylline content was assayed using an UV-spectrophotometer (Perkin Elmer 550S, Perkin-Elmer GmbH) at 271.2 nm. The sum of all samples analysed plus the content of theophylline remaining in the vessel was considered as the 100 %-value. Results are expressed as a percent of the 100 %-value.

CHAPTER 7

CONCLUSION

In the present work, the production of multiunit tablets containing pellets or micro tablets under pilot plant conditions was described. Nowadays, the development of multiparticulate systems has gained a lot of interest, as they have demonstrated several advantages over conventional single-unit formulations: less risk of dose-dumping, less inter and intra-subject variability, higher degree of dispersion in the gastro-intestinal tract thus minimizing irritation due to high local drug concentrations. Multiunit tablets combine the advantages of multiunit systems with those of tablets, i.e. cost effectiveness and divisibility. One possibility to achieve multiunit tablets is to compress pellets. Micro tablets offer an alternative to pellets as they lead to dosage forms with smooth regular surface of equal dimensions and uniform weight. Micro tablets are very suitable for coating in order to sustain the drug release but the coating film has to withstand the applied compaction pressure while tableting into multiunit tablets. The tableting of matrix-type micro tablets was proposed as alternative for the production of sustained-release multiunit dosage forms.

The aim of this work was to produce multiunit tablets containing a high percentage of single units and to ensure uniformity of weight and content of single units per tablet under pilot plant conditions. The influence of the size of the single unit and the influence of the composition of the filler on the tablet mass and content uniformity were investigated. For this purpose, four sizes of pellets ranging from 355 µm to 1700 µm and two types of 2 mm-micro tablets were compressed with Avicel PH 101 or a mixture of Avicel PH 101/Avicel PH 200 as a filler, Kollidon CL as a disintegrant, Aerosil 200 as a glidant and magnesium stearate as a lubricant. StarLac containing placebo micro tablets were used for the weight uniformity study, and theophylline micro tablets based on an Eudragit RS PO matrix were used for the content uniformity and release studies. A content of 60 % (w/w) single units was established for the pilot

plant experiments. Batches of 30 kg of single units and excipients were mixed in a gyro-wheel mixer for 20 min at 40 rpm. The mixtures were compressed on an instrumented rotary tablet press Korsch Pharma 230/17. The parameters of the tablet press were:

- speed: 50 rpm
- compaction force: 150 MPa
- tableting time: 1 hour
- feeder type: gravity feeder
- punches: 8 pairs of 13 mm round flat-faced punches of type B

Influence of single unit size on the tablet weight and uniformity of single units per tablet

The production of non-segregating mixtures of single units and excipients has to be guaranteed in order to obtain tablets conforming to the pharmacopoeial requirements with respect to weight uniformity and presenting uniformity of single units within one tablet. The tableting within 1 hour of single units varying between 355 µm and 2000 µm with Avicel PH 101 as a filler led to higher weight variations when using units above 355-425 µm. The coarser the pellets, the greater were the weight variations and the percentage of rejected tablets. However, the weight variations of the multiunit tablets consisting of micro tablets were similar to those of medium sized pellets. The percentage by weight of micro tablets per tablet remained constant during the tableting process indicating that the weight variations were attributed to irregularities during filling of the die.

Flowability studies and tableting of flow-optimised formulations

The flow properties of the different 30 kg- batches were investigated according to DIN 53916 using a Pfrengle's funnel and a self-constructed conveyor belt. The self-constructed conveyor belt has demonstrated to be more adequate and reproducible to study flow properties. Moreover, more significant differences between the different mixtures were pointed out with the conveyor belt than with the Pfrengle's funnel. A mixture consisting of Ludipress was found to have the fastest flow rate, followed by mixtures of pellets in a range of 850-1000 µm, pellets of 355-450 µm, pellets of 1180-1400 µm and finally pellets of 1400-1700 µm. In regards to the mixture, it was shown that a mixture of 60 % (w/w) small pellets contains much more pellets than a mixture containing 60 % (w/w) micro tablets. Thus, the volume of one unit: pellet (or micro tablet)/excipient is much bigger for mixtures consisting of micro tablets than for mixtures consisting of small pellets. Consequently, the poor flow properties of the excipient are becoming dominant in mixtures of coarse pellets or micro tablets.

In order to reduce the negative influence of Avicel PH 101 on the flow properties of the batches, a mixture of Avicel PH 101/Avicel PH 200 in a proportion of 30:70 % (w/w) was mixed with pellets in a range of 1400-1700 µm and with micro tablets. The flow rates were increased and the tablet weight variations as well as the percentage of rejected tablets were drastically reduced.

Properties of tablets prepared from pellets and micro tablets

Crushing strength and friability

The crushing strength and the friability of the multiunit tablets compressed with Avicel PH 101 as a filler were dependent on the size of the single units. The bigger the single unit, the lower was the crushing strength and the higher the friability. The addition of the coarse Avicel PH 200 to the mixture consisting of pellets in a range of 1400-1700 µm led to tablets with a lower crushing strength and a higher friability. However, the composition of the filler had no influence on the crushing strength and friability of tablets produced from micro tablets. In case of the micro tablets, the crushing strength

is conferred by the micro tablets themselves and less by the number of particles, which is the case for the multiunit tablets consisting of pellets.

Disintegration time

The disintegration time of the multiunit tablets compressed with Avicel PH 101 was dependent on the single units size. The coarser the pellets, the faster were the disintegration times. However, the disintegration time of all the mixtures was lower than 15 min. The disintegration time of tablets made of pellets in a range of 1400-1700 µm was reduced from 31 s to 20 s when using the mixture Avicel PH 101/Avicel PH 200 [30:70] as a filler. However, the composition of the filler had no influence on the disintegration time of tablets prepared from micro tablets.

Dissolution

The release of theophylline from micro tablets based on an Eudragit RS PO matrix within an 8 hr-period has shown to be independent on the dissolution medium. The major advantage of the matrix micro tablets resulted in the fact that the compression process did not influence the theophylline release of the micro tablets, as the theophylline release profiles were similar before and after compression.

In order to produce multiunit tablets containing 60 % (w/w) of single units (pellets or micro tablets) under pilot plant conditions and to ensure uniformity of weight and content as well as satisfying physical properties, two formulations were developed depending on the single unit size.

For pellets in a range of 355-425 µm, the tableting mixture was:

- 60 % pellets
- 35.2 % Avicel PH 101, as a filler
- 4 % Kollidon CL, as a disintegrant

- 0.3 % Aerosil, as a glidant and
- 0.5 % magnesium stearate, as a lubricant

For pellets in a range from 850 µm to 1700 µm and 2 mm-micro tablets, it was necessary to add a coarser microcrystalline cellulose Avicel PH 200 to Avicel PH 101 in order to compensate the negative effect of the fine filler on the flow properties of the tableting mixtures. The formulation was then:

- 60 % single units, coarse pellets or micro tablets
- 35.2 % Avicel PH 101/Avicel PH 200 in a proportion of 30:70 % (w/w)
- 4 % Kollidon CL
- 0.3 % Aerosil
- 0.5 % magnesium stearate

This work has demonstrated that the size of single units had a major effect on the uniformity of multiunit tablets under pilot plant conditions. Although mixtures showing a great difference between the size of the single units and the excipients are expected to be unstable and to segregate, it was observed that the content of micro tablets per tablet remained constant. Actually, the tablet weight variations were related to the flow properties of the tablet mass. The optimisation of the composition of the filler/binder in order to improve the flow properties of the mixtures led to multiunit tablets conforming to the pharmacopoeial requirements with respect to weight uniformity.

CHAPTER 8

REFERENCES

Abrahamsson, B.; Alpsten, M.; Jonsson, U. E.; Lundberg, P. J.; Sandberg, A.; Sundgren, M.; Svenheden, A. and Tölli, J.
"Gastrointestinal transit of a multiple-unit formulation (metroprolol CR/ZOK) and a non-disintegrating tablet with the emphasis on colon"
Int. J. Pharm. **140**, 229-235 (1996)

Adriaens, E.; Debunne, A. and Remon, J. P.
"Screening of the mucosal irritating potential of oral piroxicam formulations using an alternative method slugs"
Proc. 4th world meeting ADRITELF/APGI/APV, Florence (2002), 233-234

Altenschmidt, W. and Häusler, H.
"Produktionsparameter für die Gleichförmigkeit der Masse gemäß DAB 1997/Ph. Eur. 1997"
Pharm. Ind. **60**, 457-464 (1998)

Amighi, K.; Timmermans, J.; Puigdevall, J.; Baltes, E. and Moës, A. J.
"Peroral sustained-release film-coated pellets as a means to overcome physicochemical and biological drug-related problems. I. In vitro development and evaluation"
Drug Dev. Ind. Pharm. **24**, 509-515 (1998)

Amidon, G. E.; Augsburger, L. L.; Brittain, H. G.; Byrn, S. R.; Fox, C. D.; Peck, G. E.; Wurster, D. E.; Bergren, M. S.; Grant, D. J. W.; Marshall, K. and Itai, S.
"Physical test methods for powder flow characterization of pharmaceutical materials: a review of methods"
Pharmacopeial Forum **25**, 8298-8308 (1999)

Augsburger, L. L. and Shangraw, R. F.
"Effect of glidants in tableting"
J. Pharm. Sci. **55**, 418-423 (1966)

Aulton, M. E.; Dyer, A. M. and Khan, K. A.
"The strength and compaction of millispheres"
Drug Dev. Ind. Pharm. **20**, 3069-3104 (1994)

Baykara, T.; Duman, G.; Özsener, K.S.; Ordu, S. and Özates, B.
"Comparing the compressibility of Ludipress with the other direct tableting agents by using acetaminophen as an active ingredient"
Drug Dev. Ind. Pharm. **17**, 2359-2371 (1991)

Béchard, S. R. and Leroux, J.C.
"Coated pelletized dosage form: effect of compaction on drug release"
Drug Dev. Ind. Pharm. **18**, 1927-1944 (1992)

Beckert, T.
"Verpressen von magensaftresistent überzogenen Pellets zu zerfallenden Tabletten"
Ph.D. Thesis Tübingen, Germany 1995

Beckert, T. E.; Lehmann, K. and Schmidt, P. C.
"Compression of enteric-coated pellets to disintegrating tablets"
Int. J. Pharm. **143**, 13-23 (1996)

Beckert, T. E.; Lehmann, K. and Schmidt, P. C.
"Compression of enteric-coated pellets to disintegrating tablets: uniformity of dosage units"
Powder Technol. **96**, 248-254 (1998)

Bodmeier, R.
"Tableting of coated pellets"
Eur. J. Pharm. Biopharm. **43**, 1-8 (1997)

Bodmeier, R. and Paeratakul, O.
"Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage forms"
Pharm. Res. **11**, 882-888 (1994)

Bolhuis, G. K. and Chowhan, Z. T.
"Materials for direct compaction"
in: Alderborn, G. and Nyström, C. "Pharmaceutical powder compaction technology"
Marcel Dekker, New York (1996), 419-500

Bolton, S.
"Pharmaceutical statistics. Practical and clinical applications"
2nd edition, Marcel Dekker, New York (1990), 262-307

Butler, J.; Cumming, I.; Brown, J.; Wilding, I. and Devane, J. G.
"A novel multiunit controlled-release system"
Pharm. Technol. **22**(3), 122-138 (1998)

Cameron, C. G. and McGinity, J. W.
"Controlled-release theophylline tablet formulations containing acrylic resins. II. Combination resin formulations"
Drug Dev. Ind. Pharm. **13**, 1409-1427 (1987)

Carr, R. L.
"Evaluating flow properties of solids"
Chem. Eng. **72**, 163-168 (1965)

Carstensen, J. T.
"Advanced pharmaceutical solids"
Marcel Dekker, New York (2001), 473-475

Çelik, M. and Maganti, L.
"Formulation and compaction of microspheres"
Drug Dev. Ind. Pharm. **20**, 3151-3173 (1994)

Chemtob, C.; Chaumeil, J. C. and N'Dongo, M.
"Tablets of metronidazole microcapsules: release characteristics"
Int. J. Pharm. **29**, 83-92 (1986)

Chopra, R.; Podczeck, F.; Newton, J. M. and Alderborn, G.
"The influence of pellet shape and film coating on the filling of pellets into hard shell capsules"
Eur. J. Pharm. Biopharm. **53**, 327-333 (2002)

Clarke, G. M.; Newton, J. M. and Short, M. B.
"Gastrointestinal transit of pellets of differing size and density"
Int. J. Pharm. **100**, 81-92 (1993)

Clarke, G. M.; Newton, J. M. and Short, M. B.
"Comparative gastrointestinal transit of pellet systems of varying density"
Int. J. Pharm. **114**, 1-11 (1995)

Cox, P. J.; Khan, K. A.; Munday, D. L. and Sujja-areevath, J.
"Development and evaluation of a multiple-unit oral sustained release dosage form for S(+)-ibuprofen: preparation and release kinetics"
Int. J. Pharm. **193**, 73-84 (1999)

De Brabander, C.; Vervaet, C.; Fiermans, L. and Remon, J. P.
"Matrix mini-tablets based on starch/microcrystalline wax mixtures"
Int. J. Pharm. **199**, 195-203 (2000a)

De Brabander, C.; Vervaet, C.; Fiermans, L. and Remon, J. P.
"Bioavailability of ibuprofen from matrix mini-tablets based on a mixture of starch and microcrystalline wax"
Int. J. Pharm. **208**, 81-86 (2000b)

Devise, B.; Delacourte-Thibaut, A.; Guyot, J. C. and Traisnel, M.
"Mise au point d'une technique d'étude simplifiée de l'écoulement des poudres destinées à la compression"
Pharm. Acta Helv. **50**, 432-446 (1975)

DIN 53194
"Bestimmung des Stampfvolumens und der Stampfdichte"

DIN 53912
"Bestimmung der Schütt- und Rütteldichte von Pulvern und Granulaten"

DIN 53916
"Bestimmung der Rieselfähigkeit von Pulvern und Granulaten - Verfahren nach Pfrengle"

Doelker, E.; Massuelle, D.; Veuillez, F. and Humbert-Droz, P.
"Morphological, packing, flow and tableting properties of new Avicel types"
Drug Dev. Ind. Pharm. **21**, 643-661 (1995)

Dressler, J. A.
"Vergleichende Untersuchungen pharmazeutischer Hilfsstoffe unter Einsatz eines inkrementalen Weggebers zur präzisen Wegmessung an einer Exzenter-Tablettenpresse"
Ph.D. Thesis Tübingen, Germany 2002

Egermann, H.
"Gleichförmigkeit einzeldosierter Arzneizubereitungen"
in: Nürnberg, E. and Surmann, P. "Hagers Handbuch der pharmazeutischen Praxis"
5th edition, Springer, Berlin Heidelberg (1991), 1091-1096

European Pharmacopoeia 4th edition
"Resistance to crushing of tablets"
Council of Europe, Strasbourg (2002), 201

European Pharmacopoeia 4th edition
"Friability of uncoated tablets"
Council of Europe, Strasbourg (2002), 200-201

European Pharmacopoeia 4th edition
"Disintegration of tablets and capsules"
in: supplement 4.2 of European Pharmacopoeia 4th edition,
Council of Europe, Strasbourg (2002), 2637-2638

Flament, M.-P.; Leterme, P.; Gayot, A.; Gendrot, E.; Bruna, E. and Cousin, G.
"Development and industrial scale-up of tablets containing modified-release pellets"
Pharm. Tech. Eur. **6**(2), 19-25 (1994)

Flemming, J. and Mielck, J. B.
"Requirements for the production of micro tablets: suitability of direct-compression excipients estimated from powder characteristics and flow rates"
Drug Dev. Ind. Pharm. **21**, 2239-2251 (1995)

Flemming, J. and Mielck, J. B.
"Experimental micro tabletting: construction of an instrumented punch holder for an eccentric tabletting machine"
Eur. J. Pharm. Biopharm. **42**, 212-214 (1996)

Follonier, N. and Doelker, E.
"Biopharmaceutical comparison of oral multiple-unit and single-unit sustained-release dosage forms"
S.T.P. Pharm. Sci. **2**, 141-158 (1992)

Fourier, J. B. J.
"Théorie analytique de la chaleur"
Firmin Didot, Père et Fils, Paris (1822)

Ghebre-Sellassie
"I. Multiparticulate oral drug delivery"
Marcel Dekker, New York (1994)

Gordon, M. S. and Chowhan, Z. T.
"Effect of tablet solubility and hygroscopicity on disintegrant efficiency in direct compression tablets in terms of dissolution"
J. Pharm. Sci. **76**, 907-909 (1987)

Gordon, M. S.; Rudraraju, V. S.; Dani, K. and Chowhan, Z. T
"Effect of the mode of super disintegrant incorporation on dissolution in wet granulated tablets"
J. Pharm. Sci. **82**, 220-226 (1993)

Goto, K.; Sunada, H.; Danjo, K. and Yonezawa, Y.
"Pharmaceutical evaluation of multipurpose excipients for direct compressed tablet manufacture: comparisons of the capabilities of multipurpose excipients with those in general use"
Drug Dev. Ind. Pharm. **25**, 869-878 (1999)

Haubitz, H.; Mehnert., W. and Frömming, K.-H.
"Preparation of theophylline multiple units tablets"
Pharm. Ind. **58**, 83-86 (1996)

Hausner, H. H.
"Friction conditions in a mass of metal powder"
Int. J. Powd. Metall. **3**, 7-13 (1967)

Heinämäki, J. T.; Ojantakanen, S. S.; Hellén, L. M. and Yliruusi, J. K.
"Formulation and evaluation of multiple-unit compacts of sustained-release resin-coated pellets"
Pharm. Ind. **57**, 68-71 (1995)

Heinz, R.; Wolf, H.; Schuchmann, H.; End, L. and Kolter, K.
"Formulation and development of tablets based on Ludipress and scale-up from laboratory to production scale"
Drug Dev. Ind. Pharm. **26**, 513-521 (2000)

Hickey, A. J. and Concessio, N.
"Flow properties of selected pharmaceutical powders from a vibrating spatula"
Part. Part. Syst. Charact. **11**, 457-462 (1994)

Hosny, E. A.; El-Mahrouk, G. M. and Gouda, M. W.
"Formulation and in vitro and in vivo availability of diclofenac sodium enteric-coated beads"
Drug Dev. Ind. Pharm. **24**, 661-666 (1998)

Johansson, B.; Wirkberg, M.; Ek, R. and Alderborn, G.
"Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties"
Int. J. Pharm. **117**, 57-73 (1995)

Kaye, B. H.; Gratton-Liimatainen, J. and Faddis, N.
"Studying the avalanching behaviour of powder in a rotating disc"
Part. Part. Syst. Charact. **12**, 232-236 (1995)

Khan, K. A. and Rhodes, C. T.
"Comparative evaluation of some direct compression diluents"
Pharm. Acta Helv. **51**, 23-26 (1976)

Kibbe, A. H.
"Handbook of pharmaceutical excipients"
3rd edition, American Pharmaceutical Association and Pharmaceutical Press, Washington London (2000), 102-106

Kleinebudde, P.
"Herstellung von pellets"
Dtsch. Apoth. Ztg. **138**, 69-70 (1998)

Kühl, P. and Mielck, J. B.
"Tableting of pellets assisted by powder mixtures as matrices: compaction studies"
Proc. 2nd world meeting APGI/APV, Paris (1998), 229-230

Lahdenpää, E.; Niskanen, M. and Yliruusi, J.
"Study of some essential physical characteristics of three Avicel® PH grades using a mixture design"
Eur. J. Pharm. Biopharm. **42**, 177-182 (1996)

Lahdenpää, E.; Niskanen, M. and Yliruusi, J.
"Crushing strength, disintegration time and weight variation of tablets compressed from three Avicel® PH grades and their mixtures"
Eur. J. Pharm. Biopharm. **43**, 315-322 (1997)

Lang, S.
"Adjuvant for direct tabletting"
European Patent 0 192 173 (1986)

Lee, Y. S. L.; Poynter, R.; Podczeck, F. and Newton, J. M.
"Development of a dual approach to assess powder flow from avalanching behaviour"
AAPS PharmSciTech. **1**, article 21 (2000)

Lehmann, K.
"Formulation of controlled release tablets with acrylic resins"
Acta Pharm. Fenn. **93**, 55-74 (1984)

Lehmann, K.; Petereit, H.-U. and Dreher, D.
"Tablettieren überzogener Partikeln"
Acta Pharm. Technol. **36**, S7 (1990)

Lehmann, K.; Petereit, H.-U. and Dreher, D.
"Schnellzerfallende Tabletten mit gesteuerter Wirkstoffabgabe"
Pharm. Ind. **55**, 940-947 (1993)

Lehmann, K.; Petereit, H.-U. and Dreher, D.
"Fast disintegrating controlled release tablets from coated particles"
Drugs Made Ger. **37**, 53-60 (1994)

Lehmann, K. and Süfke, T.
"New methacrylic acid copolymers for improved coating technology"
Pharm. Res. **12**, S137 (1995)

Leitritz, M.; Krumme, M. und Schmidt, P. C.
"Vergleich von statischer und dynamischer Kraftkalibrierung bei einer Rundlauftablettenpresse"
Pharm. Ind. **57**, 1033-1038 (1995)

Lennartz, P. and Mielck, J. B.
"Minitabletting: improving the compactability of paracetamol powder mixtures"
Int. J. Pharm. **173**, 75-85 (1998)

Li, S. P.; Feld, K. M. and Kowarski, C. R.
"The effect of polymer coating systems on the preparation, tableting, and dissolution properties of sustained-release drug pellets"
Drug Dev. Ind. Pharm. **23**, 623-631 (1997)

López-Rodríguez, F. J.; Torrado, J. J.; Torrado, S.; Escamilla, C.; Cadórniga, R. and Augsburger, R. R.
"Compression behaviour of acetylsalicylic acid pellets"
Drug Dev. Ind. Pharm. **19**, 1369-1377 (1993)

Lundqvist, A. E. K.; Podczeck, F. and Newton, J. M.
"Influence of disintegrant type and proportion on the properties of tablets produced from mixtures of pellets"
Int. J. Pharm. **147**, 95-107 (1997)

Lundqvist, A. E. K.; Podczeck, F. and Newton, J. M.
"Compaction of, and drug release from, coated drug pellets mixed with other pellets"
Eur. J. Pharm. Biopharm. **46**, 369-379 (1998)

Maganti, L. and Çelik, M.
"Compaction studies on pellets: I. Uncoated pellets"
Int. J. Pharm. **95**, 29-42 (1993)

Maganti, L. and Çelik, M.
"Compaction studies on pellets: II. Coated pellets"
Int. J. Pharm. **103**, 55-67 (1994)

Marshall, K. and Sixsmith, D.
"The flow properties of microcrystalline cellulose powders"
J. Pharm. Pharmacol. **28**, 770-771 (1976)

May, T. and Rambeck, B.
"Fluctuations of Carbamazepine concentrations during the day for two slow-release preparations"
Ther. Drug Monit. **11**, 21-24 (1989)

Mount, D. L. and Schwartz, J. B.
"Formulation and compaction of nonfracturing deformable coated beads"
Drug Dev. Ind. Pharm. **22**, 609-621 (1996)

Munday, D. L.
"A comparison of the dissolution characteristics of theophylline from film coated granules and mini-tablets"
Drug Dev. Ind. Pharm. **20**, 2369-2379 (1994)

Muñoz-Ruiz, A.; Borrero-Rubio, J. M. and Jiménez-Castellanos, M. R.
"Rheology of a new excipient for direct compression: "Ludipress" "
Pharm. Acta Helv. **67**, 223-226 (1992)

Muñoz-Ruiz, A.; Monedero Perales, M. C.; Velasco Antequera, M. V.; Payán Villar, T.; Muñoz-Muñoz, N. and Jiménez-Castellanos, M. R.
"Rheology and compression characteristics of lactose based direct compression excipients"
Int. J. Pharm. **95**, 201-207 (1993)

Muñoz-Ruiz, A.; Velasco Antequera, M. V.; Monedero Perales, M. C. and Jiménez-Castellanos Ballesteros, M. R.
"Tableting properties of new granular microcrystalline celluloses"
Eur. J. Pharm. Biopharm. **40**, 36-40 (1994)

Peh, K.-K. and Yuen, K.-H.
"In vivo bioavailability of a multiparticulate matrix sustained-release theophylline preparation under fed and fasted conditions"
Drug Dev. Ind. Pharm. **23**, 15-18 (1997)

Pinto, J. F.; Podczeck, F. and Newton, J. M.
"Investigation of tablets prepared from pellets produced by extrusion spheronisation. Part I: the application of canonical analysis to correlate the properties of the tablets to the factors studied in combination with principal component analysis to select the most relevant factors"
Int. J. Pharm. **147**, 79-93 (1997)

Plaizier-Vercammen, J. A. and Van den Bossche, H.
"Evaluation of the tabletting properties of a new excipient for direct compression"
Pharm. Ind. **54**, 973-977 (1992)

Podczeck, F. and Newton, J. M.
"Powder filling in hard gelatine capsules on a tamp filling machine"
Int. J. Pharm. **185**, 237-254 (1999)

Por Li, S.; Kowarski, C. R.; Feld, K. M. and Grim, W. M.
"Recent advances in microencapsulation technology and equipment"
Drug Dev. Ind. Pharm. **14**, 353-376 (1988)

Prapaitrakul, W. and Whitworth, C. W.
"Compression of microcapsules I: effect of excipients and pressure on drug release"
Drug Dev. Ind. Pharm. **15**, 2049-2053 (1989)

Prapaitrakul, W. and Whitworth, C. W.
"Compression of microcapsules II: effect of excipients and pressure on physical properties"
Drug Dev. Ind. Pharm. **16**, 1427-1434 (1990)

Rey, H.; Wagner, K. G.; Wehrlé, P. and Schmidt, P. C.
"Development of theophylline sustained-release micro tablets"
Proc. 2nd world meeting APGI/APV, Paris (1998), 303-304

Rey, H.; Wagner, K. G.; Wehrlé, P. and Schmidt, P. C.
"Development of matrix-based theophylline sustained-release micro tablets"
Drug Dev. Ind. Pharm. **26**, 21-26 (2000)

Rubensdörfer, C.
"Einsatz und Charakterisierung von Ludipress® als Direkttablettierhilfsmittel"
Ph.D. Thesis Tübingen, Germany 1993

Sachs, L.
"Angewandte Statistik"
8th edition, Springer, Berlin Heidelberg (1997), 489-569

Sandberg, A.; Blomqvist, I.; Jonsson, U. E. and Lundborg, P.
"Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol: a comparison with conventional tablets"
Eur. J. Clin. Pharmacol. **33**, S9-14 (1988)

Schaafsma, A. H. and Willemze, F. G.
"Moderne Qualitätskontrolle. Statistische und organisatorische Grundlagen der Qualitätsgestaltung"
7th edition, Philips Fachbücher, Hamburg (1973), 210-213, 466-467

Schmidt, P. C.
"Einführung in der Erstellung einer Kalibriergeraden"
APV Kurs 293 "Praxis der Kalibrierung von Tablettenpressen und -prüfgeräten"
29.-30.09.1997, Tübingen, Germany

Schmidt, P. C. and Rubensdörfer, C. J. W.
"Evaluation of Ludipress as a "multipurpose excipient" for direct compression. Part I: powder characteristics and tableting properties"
Drug Dev. Ind. Pharm. **20**, 2899-2925 (1994)

Schuchmann, H.; Polke, R.; Heinz, R.; Kolter, K. and Wolf, H.
"Auslegung and scale up bei der Produktion von Tabletten auf der Basis von Direkttablettierhilfsmitteln"
Chem.-Ing.-Tech. **71**, 602-605 (1999)

Schulze, D.
"Zur Fließfähigkeit von Schüttgütern – Definition und Messverfahren"
Chem.-Ing.-Tech. **67**, 60-68 (1995)

Sivenius, J.; Heinonen, E.; Lehto, H.; Järvensivu, P.; Anttila, M.; Ylinen, A. and Riekkinen, P.
"Reduction of dosing frequency of carbamazepine with a slow-release preparation"
Epilepsy Res. **2**, 32-36 (1988)

Snedecor, G. W. and Cochran, W. G.
"Statistical methods"
6th edition, The Iowa State University Press Ames, Iowa (1967), 258-298

Stauffer, D.
"An introduction to percolation theory"
Taylor and Francis, London (1985)

Stefan, H.; Schneider, S. and Hennemann, U.
"Chronopharmakologische Serumkonzentrationsanalysen unter verschiedenen Carbamazepin (CSR)-Präparaten"
Akt. Neurol. **15**, 127-129 (1988)

Stegemann, S.
"Hard gelatin capsules today and tomorrow"
Capsugel Library BAS 192 E (1999)

Sujja-areevath, J.; Munday, D. L.; Cox, P. J. and Khan, K. A.
"Relationship between swelling, erosion and drug release in hydrophilic natural gum min-matrix"
Eur. J. Pharm. Sci. **6**, 207-217 (1998)

Sveinsson, S. J.; Kristmundsdóttir, T. and Ingvarsdóttir, K.
"The effect of tableting on the release characteristics of naproxen and ibuprofen microcapsules"
Int. J. Pharm. **92**, 29-34 (1993)

Tan, S. B. and Newton, J. M.
"Powder flowability as an indication of capsule filling performance"
Int. J. Pharm. **61**, 145-155 (1990)

Taylor, M. K.; Ginsburg, J.; Hickey, A. J. and Gheyas, F.
"Composite method to quantify powder flow as a screening method in early tablet or capsule formulation development"
AAPS PharmSciTech **1**, article 18 (2000)

Tirkkonen, S. and Paronen, P.
"Release of indomethacin from tabletted ethylcellulose microcapsules"
Int. J. Pharm. **92**, 55-62 (1993)

Torrado, J. J. and Augsburger, L. L.
"Effect of different excipients on the tableting of coated particles"
Int. J. Pharm. **106**, 149-155 (1994)

Tunón, A. and Alderborn, G.
"Granule deformation and densification during compression of binary mixtures of granules*"*
Int. J. Pharm. **222**, 65-76 (2001)

Tunón, A. and Alderborn, G.
"Influence of size of cushioning pellets on drug release from coated drug pellets"
Proc. 4th world meeting ADRITELF/APGI/APV, Florence (2002), 85-86

USP 25
"The United States Pharmacopeia"
25th edition, U.S. Pharmacopeial Convention Inc., Rockwille (2002), 1685-1686

Vecchio, C.; Spadoni, A. and Genovesi, A.
"Comparison between gastroresistant pellets and minitablets prepared by coating with an innovative pan equipment"
Proc. 3rd world meeting APV/APGI, Berlin (2000), 871-872

Vogel, P. J.
"Charakterisierung des Verformungsverhaltens von Tablettierhilfsstoffen mit einer Hochleistungsrundlauftablettenpresse unter praxisnahen Bedingungen"
Ph.D. Thesis, Tübingen, Germany 1992

Wagner, K. G.
"Tablettierung überzogener Pellets auf einer Hochleistungsrundlauftablettenpresse unter Einsatz von Eudragit FS 30 D"
Ph.D. Thesis Tübingen, Germany 1999

Wagner, K. G.; Krumme, M. and Schmidt, P. C.
"Investigation of the pellet-distribution in single tablets via image analysis"
Eur. J. Pharm. Biopharm. **47**, 79-85 (1999)

Wagner, K. G.; Krumme, M. and Schmidt, P. C.
"Pellet-containing tablets: examination of distribution and deformation behaviour"
S.T.P. Pharm. Sci. **10**, 327-334 (2000a)

Wagner, K. G.; Krumme, M. and Schmidt, P. C.
"Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press"
Eur. J. Pharm. Biopharm. **50**, 285-291 (2000b)

York, P.
"Crystal engineering and particle design for the powder compaction process"
Drug Dev. Ind. Pharm. **18**, 677-721 (1992)

CHAPTER 9

APPENDIX

9.1 Index of suppliers

Abbott GmbH & Co. KG (formerly Knoll AG), Knollstrasse, D-67061 Ludwigshafen
W. A. Bachofen Maschinenfabrik, Utengasse 15/17, CH-4002 Basel
BASF AG, Carl-Bosch-Str. 38, D-68056 Ludwigshafen
Bärlocher GmbH, Riesstr. 16, D-80992 München
Beckman Instruments Inc., Frankfurter Ring 115, D-80807 München
Degussa-Hüls AG, Postfach 11 05 33, D-60314 Frankfurt/Main
Engelsmann AG, Frankenthaler Str. 137-141, D-67059 Ludwigshafen
Eppendorf AG, Barkhausenweg 1, D-22331 Hamburg
Erweka GmbH, Ottostr. 20-22, D-63150 Heusenstamm
Dr. F. Faulhaber GmbH & Co., Postfach 1146, D-71094 Schönaich
Fluka Chemie AG, Industriestr. 25, CH-9470 Buchs
FMC Corp. / Lehmann & Voss & Co. (see Lehmann & Voss & Co.)
Glatt GmbH, Postfach 42, D-79589 Binzen
Hanns G. Werner GmbH & Co., Hafenstrasse 9, D-25436 Tornesch
Hottinger Baldwin Messtechnik GmbH, Im Tiefen See 45, D-64293 Darmstadt
Janke & Kunkel, Postfach 12 63, D-79217 Staufen
Kilian & Co. GmbH, Emdener Str. 10, D-50735 Köln
Kistler Instruments GmbH, Eulachstr. 22, CH-8408 Winterthur
Korsch Pressen GmbH, Breitenbachstr. 1, D-13509 Berlin
Kuhnke GmbH, Lütjenburger Straße 101, D-23714 Malente
Lehmann & Voss & Co., Postfach 30 34 24, D-20311 Hamburg
Malvern Instruments GmbH, Rigipsstr. 19, D-71083 Herrenberg
Meggle GmbH, Megglestr. 6-12, D-83512 Wasserburg
Mettler Toledo GmbH, Ockerweg 3, D-35396 Gießen
Microcal Software, Inc., Northampton, MA 01060 USA
Microsoft GmbH, Edisonstr. 1, D-85716 Unterschleißheim
Mitutoyo Messgeräte GmbH, Borsigstr. 8-10, D-41469 Neuss

NP Pharm S. A, 54 bis route de Paris, F-78550 Bazainville

Perkin-Elmer GmbH, Postfach 10 11, D-88662 Überlingen

Pharmatest Apparatebau, Postfach 11 50, D-63512 Hainburg

Reiff-Technische Produkte GmbH, Tübinger Str. 2-6, D-72762 Reutlingen

Röhm GmbH & Co. KG, Kirschenallee 1, D-64275 Darmstadt

Ritter Pharma-Technik GmbH, Neumann-Reichardt Str. 36-387, D-22041 Hamburg

Sartorius AG, Weender Landstr. 94-108, D-37075 Göttingen

Dr. K. Schleuniger, Schöngrünstr. 27, CH-4501 Solothurn

Servolift GmbH, Albert-Einstein-Str. 9, D-77656 Offenburg

Sotax AG, Binningerstr. 106, CH-4123 Allschwill

Sympatec GmbH, Burgstätter Str. 6, D-38678 Clausthal-Zellerfeld

VCH Verlagsgesellschaft, Boschstr. 12, D-69469 Weinheim

Watson-Marlow Ltd., Falmouth, TR 11 4RU, UK-Cornwall

9.2 Calibration data of the rotary tablet press Korsch Pharma 230/17

Table 9.1 Raw data of the static calibration of Korsch Pharma 230/17

Reference signal [kN]	*Upper punch signal [V]*	*Reference signal [kN]*	*Lower punch signal [V]*
25.7690	3.4063	25.9192	6.2487
25.7637	3.3353	25.8460	6.2982
25.6923	3.4043	25.8566	6.2488
25.7562	3.3302	25.8285	6.2906
25.6795	3.3965	25.8522	6.2446
25.7342	3.3325	25.8144	6.2923
20.2110	2.5853	20.4981	4.9866
20.1257	2.6328	20.5513	4.9443
20.2237	2.5729	20.5048	4.9875
20.1430	2.6339	20.5353	4.9494
20.2046	2.5745	20.4949	4.9861
20.1438	2.6339	20.5347	4.9442
14.9870	1.9112	14.8353	3.6041
15.0529	1.8654	14.8768	3.5675
14.9955	1.9132	14.8434	3.5972
15.0334	1.8635	14.8776	3.5720
14.9827	1.9112	14.8323	3.6062
15.0602	1.8659	14.8638	3.5762
10.6268	1.2559	10.4436	2.5476
10.5907	1.2913	10.4702	2.5141
10.6271	1.2585	10.4532	2.5364
10.6108	1.2949	10.4835	2.5066
10.6287	1.2603	10.4553	2.5429
10.6060	1.2923	10.4765	2.5105
4.8989	0.4783	5.1313	1.2060
4.8735	0.4935	5.0935	1.2513
4.8926	0.4783	5.1374	1.2085
4.8629	0.4933	5.1093	1.2472
4.9145	0.4812	5.1409	1.2103

4.8763	0.4941	5.1160	1.2485
2.0128	0.1210	2.0832	0.4541
2.0312	0.1052	2.1109	0.4436
2.0049	0.1214	2.0975	0.4570
2.0241	0.1057	2.1192	0.4434
2.0106	0.1216	2.1003	0.4614
2.0380	0.1036	2.1266	0.4451

My academic teachers were:

Anton, Beretz, Dirheimer, Ferard, Gairard, Gerard, Goeldner, Hasselmann, Heitz, Jung, Kieffer, Kilhoffer, Koffel, Lami, Landry, Laugel, Lugnier, Pesson, Poindron, Schmidt, Spiess, Stahl, Stamm, Stoclet, Vidon, Wachsmann, Wehrlé, Wermuth.

CURRICULUM VITAE

12 March 1974	Born in Strasbourg, France
1980-1985	Primary School, Vendenheim, France
1985-1992	Secondary School at the Collège de Mundolsheim, France and at the Lycée Fustel de Coulanges, Strasbourg, France
June 1992	Baccalauréat C in Mathematics, Physics and Chemistry
September 1992-September 1998	Study of Pharmacy at the University Louis Pasteur of Strasbourg
July 1993-August 1993	Practical Pharmacy Training Course, Strasbourg
1995-1998	Master of Biological and Medical Sciences
November 1996-April 1997	Clinical Training Course at the Hospital of Strasbourg
May 1997-February 1998	Research Training Course at the Institute of Pharmacy, Department of Technology, University of Tübingen, Germany
March 1998-August 1998	Industrial Training Course at Röhm GmbH, Darmstadt, Germany
December 1998	National Pharmacist's Diploma
Since February 1999	Research Assistant at the Institute of Pharmacy, Department of Technology, University of Tübingen. Began Ph.D. thesis under the supervision of Prof. Dr. P. C. Schmidt. Title: "Uniformity of multiunit tablets under pilot plant conditions as a function of unit size and filler composition"
April 2002	Fachapotheker für Pharmazeutische Technologie-diploma