Optimization of the Liquisolid Technology –

Identification of Highly Effective Tableting Excipients for Liquid Adsorption

Dissertation

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Christina M. Hentzschel

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Manchmal hat man eine sehr lange Straße vor sich.
Man denkt, die ist so schrecklich lang;
das kann man niemals schaffen, denkt man.

Und dann fängt man an, sich zu beeilen.
Und man eilt sich immer mehr.
Jedes Mal, wenn man aufblickt, sieht man,
dass es gar nicht weniger wird, was noch vor einem liegt.
Und man strengt sich noch mehr an, man kriegt es mit der Angst,
und zum Schluss ist man ganz außer Puste und kann nicht mehr.
Und die Straße liegt immer noch vor einem.
So darf man es nicht machen.

Man darf nie an die ganze Straße auf einmal denken, verstehst du?
Man muss nur an den nächsten Schritt denken,
an den nächsten Atemzug, an den nächsten Besenstrich.
Und immer wieder nur an den nächsten.

Dann macht es Freude; das ist wichtig, dann macht man seine Sache gut.
Und so soll es sein.

Auf einmal merkt man, dass man Schritt für Schritt die ganze Straße gemacht hat.
Man hat gar nicht gemerkt wie, und man ist nicht außer Puste.

Das ist wichtig.

Michael Ende

Reviewer of the dissertation:	Professor Dr. Claudia S. Leopold
	Professor Dr. Detlef Geffken
Reviewer of the disputation:	Professor Dr. Claudia S. Leopold
	Professor Dr. Sascha Rohn
	Dr. Werner Pauer
Date of the disputation:	February 25th, 2011

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Summary

Poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent a technological challenge because their poor bioavailability is only caused by poor water solubility resulting in low drug absorption. Numerous methods have been applied to improve water solubility and drug release, respectively, among which the liquisolid technology is one of the most promising approaches. With this technique liquid formulations such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material. Usually, microcrystalline cellulose and colloidal silica are used as the carrier and the coating material, respectively. Hence, the liquisolid technology allows the transformation of liquid systems into solid drug delivery systems such as tablets. The liquisolid approach has been successfully applied in release enhancement of low dose poorly soluble drugs. However, the formulation of high dose poorly soluble drugs is one of the limitations of this technique because of the high amount of liquid vehicle needed. Consequently, high amounts of carrier and coating material are required ultimately leading to an unacceptably high tablet weight.

In the present work various conventional and novel tableting excipients were investigated with regard to their physical, flow, and tableting properties as well as their liquid adsorption capacity. The objective was to identify the most effective excipient for liquid adsorption while maintaining acceptable flow and tableting properties and thus, to optimize the liquisolid approach.

First, two traditional and two novel tableting excipients were physically characterized and investigated for their tableting properties. Avicel® PH102 (microcrystalline cellulose) was compared to the novel co-processed excipient Prosolv® SMCC90 (silicified microcrystalline cellulose), whereas Anhydrous Emcompress® (anhydrous dicalcium phosphate) was compared to the novel spherically granulated excipient Fujicalin® (anhydrous dicalcium phosphate). It could be shown that because of the silification process in the case of Prosolv® and the unique manufacturing process in the case of Fujicalin® the novel excipients have a significantly larger specific surface

area than the well-known excipients Avicel® and Emcompress®. Moreover, the investigated novel tableting excipients showed better tableting properties than their traditional counterparts. Because of their large specific surface area and good tabletability the novel tableting excipients were expected to be ideal carrier materials for liquisolid systems.

In a second study, the physical and tableting properties of various silicates, namely Silica Aerogel (a special type of silica with an extremely large specific surface area), Neusilin® US2 (magnesium aluminometasilicate), Florite® (calcium silicate) and Aerosil® 200 (colloidal silica), were investigated. In contrast to Aerosil®, compaction of Silica Aerogel, Neusilin®, and Florite®, respectively, led to tablets with acceptable hardness proving their suitability as tableting excipients. Due to their extremely large specific surface area silicates were shown to adsorb high amounts of liquid and are therefore ideal carrier materials for liquisolid formulations in contrast to commonly used tableting excipients. Because of its poor tabletability Aerosil® was unsuitable as carrier material.

Furthermore, the liquid adsorption capacity of liquisolid formulations was found to be strongly dependent on the selection of the carrier and coating materials. Replacement of the commonly used carrier and coating materials by excipients with large specific surface areas and good flow and tableting properties (such as Fujicalin® and Neusilin®) led to considerably higher liquid adsorption capacities. By selection of Neusilin® as carrier as well as coating material instead of the commonly used materials Avicel® (carrier) and Aerosil® (coating) the liquid adsorption capacity was increased by a factor of seven.

Finally, it was found that highest drug release rates are measured with liquisolid compacts containing a drug solution as liquid portion. Therefore, a formulation with fast drug release requires a high amount of liquid vehicle, if the desired drug dose is high and/or drug solubility in the liquid vehicle is low. Hence, high amounts of carrier and coating materials are needed with the consequence of an increased tablet weight and an unacceptably large tablet size. Replacement of the commonly used carrier and coating materials by the highly adsorptive silicate Neusilin® results in a reduction of the tablet weight and thus an optimization of the liquisolid approach.

Zusammenfassung

Schwer lösliche, gut permeable Arzneistoffe stellen eine technologische Herausforderung dar, da ihre geringe Bioverfügbarkeit lediglich durch die geringe Löslichkeit hervorgerufen wird. Es gibt zahlreiche Verfahren, welche die Löslichkeit bzw. die Freisetzung eines Arzneistoffes verbessern, wobei die Liquisolid-Technologie eine der vielversprechendsten Methoden darstellt. Mit Hilfe dieser Technik werden flüssige Formulierungen, wie z.B. Lösungen oder Suspensionen von schwer löslichen Arzneistoffen in einem nicht-flüchtigen flüssigen Vehikel durch einfaches Mischen mit ausgewählten Hilfsstoffen, welche als Carrier- und Coating-Material bezeichnet werden, in fließfähige und komprimierbare Pulver überführt. Üblicherweise werden mikrokristalline Cellulose und hochdisperses Siliziumdioxid als Carrier- und Coating-Material eingesetzt. Die Liquisolid-Technologie ermöglicht somit die Überführung eines flüssigen Systems in eine feste Arzneiform, wie z. B. eine Tablette. Sie wird erfolgreich angewandt, um eine beschleunigte Freisetzung von niedrig dosierten, schwer löslichen Arzneistoffen zu erzielen. Die Formulierung von hoch dosierten Arzneiformen stellt jedoch eine der Grenzen dieser Technologie dar, da in diesem Fall große Mengen an flüssigem Vehikel benötigt werden. Um diese großen Flüssigkeitsmengen aufzunehmen, sind auch größere Mengen an Carrier- und Coating-Material erforderlich, was letztendlich zu inakzeptabel hohen Tablettenmassen führt.

Im Rahmen dieser Arbeit wurden mehrere traditionelle wie auch neue Tablettierhilfsstoffe sowohl in Bezug auf ihre physikalischen Eigenschaften, ihr Fließverhalten, ihr Tablettierverhalten und auch auf ihre Flüssigkeitsaufnahmefähigkeit hin untersucht. Ziel der Untersuchungen war die Identifizierung des effektivsten Hilfsstoffes, welcher auch bei hoher Flüssigkeitsaufnahme ausreichend gute Fließ- und Tablettiereigenschaften aufweist.
Zunächst wurden zwei traditionelle und zwei neue Tablettierhilfsstoffe physikalisch charakterisiert und bezüglich ihrer Tablettiereigenschaften miteinander verglichen. Avicel® PH102 (mikrokristalline Cellulose) wurde mit dem neuen co-prozessierten Hilfsstoff Prosolv® SMCC90 (silifizierte mikrokristalline Cellulose) und Anhydrous Emcompress® (Calciumphosphat-Anhydrat) mit dem neuen sphärisch granulierten Hilfsstoff Fujicalin® (Calciumphosphat-Anhydrat) verglichen. Der Silifizierungsprozess von Prosolv® bzw. der spezielle Herstellungsprozess von Fujicalin® führen dazu, dass

diese beiden Hilfsstoffe eine wesentlich größere spezifische Oberfläche aufweisen als die beiden traditionellen Hilfsstoffe. Weiterhin konnte gezeigt werden, dass Prosolv® und Fujicalin® auch in ihren Tablettiereigenschaften den traditionell eingesetzten Hilfsstoffen weit überlegen sind. Diese Erkenntnisse führten zu der Vermutung, dass sich die beiden neuen Hilfsstoffe gut als Trägermaterialien für die Liquisolid-Technologie eignen.

In einer weiteren Studie wurden die folgenden vier Silikate untersucht: Silica-Aerogel (eine spezielle Silikat-Art mit sehr großer spezifischer Oberfläche), Neusilin® US2 (Magnesium-Aluminium-Metasilikat), Florite® (Calciumsilikat) und Aerosil® 200 (hochdisperses Siliziumdioxid). Die Kompaktierung von Silica-Aerogel, Neusilin® wie auch Florite® ergab im Gegensatz zu Aerosil® ausreichend harte Tabletten. Die sehr große spezifische Oberfläche der Silikate ließ vermuten, dass diese eine große Menge Flüssigkeit aufnehmen können und daher ebenfalls den üblicherweise für die Liquisolid-Technologie verwendeten Trägermaterialien weit überlegen sind. Das gewöhnlich als Coating-Material eingesetzte Aerosil® wurde allerdings auf Grund seiner schlechten Tablettiereigenschaften als Trägermaterial ausgeschlossen.

Es konnte gezeigt werden, dass die Auswahl des Carrier- und des Coating-Materials einen großen Einfluss auf die Flüssigkeitsaufnahmekapazität der Liquisolid-Formulierungen hat. Der Austausch der gewöhnlich verwendeten Carrier- und Coating-Materialien durch Hilfsstoffe mit einer großen spezifischen Oberfläche und guten Fließ- und Kompaktiereigenschaften wie Fujicalin® und Neusilin® führte zu einer beträchtlichen Erhöhung der Flüssigkeitsaufnahme. Bei Verwendung von Neusilin® sowohl als Carrier- als auch Coating-Material anstelle der gewöhnlich verwendeten Materialien Avicel® (Carrier) und Aerosil® (Coating) konnte die Flüssigkeitsaufnahmekapazität sogar um das siebenfache gesteigert werden.

Schließlich wurde festgestellt, dass die schnellste Wirkstofffreisetzung mit Liquisolid-Tabletten beobachtet wird, die eine Arzneistofflösung als flüssigen Anteil enthalten. Dies bedeutet für eine schnell freisetzende Arzneiform große Mengen an flüssigem Vehikel falls der Arzneistoff hoch dosiert bzw. die Wirkstofflöslichkeit in dem Vehikel gering ist. Folglich werden in diesem Fall hohe Mengen an Carrier- und Coating-Material benötigt, was wiederum zu einer Zunahme der Tablettenmasse führt. Der Ersatz der üblicherweise verwendeten Carrier- und Coating-Materialien durch das hochadsorptive Neusilin® ermöglicht die Reduktion der Tablettenmasse.

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1. Liquisolid technology – a method to enhance and prolong drug release

Liquisolid technology – a method to enhance and prolong drug release

1.1 Introduction

With the liquisolid technology as described by Spireas [1] a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles is incorporated into the porous carrier material (Fig. 1). Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine are best suitable as liquid vehicles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles [2]. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material.

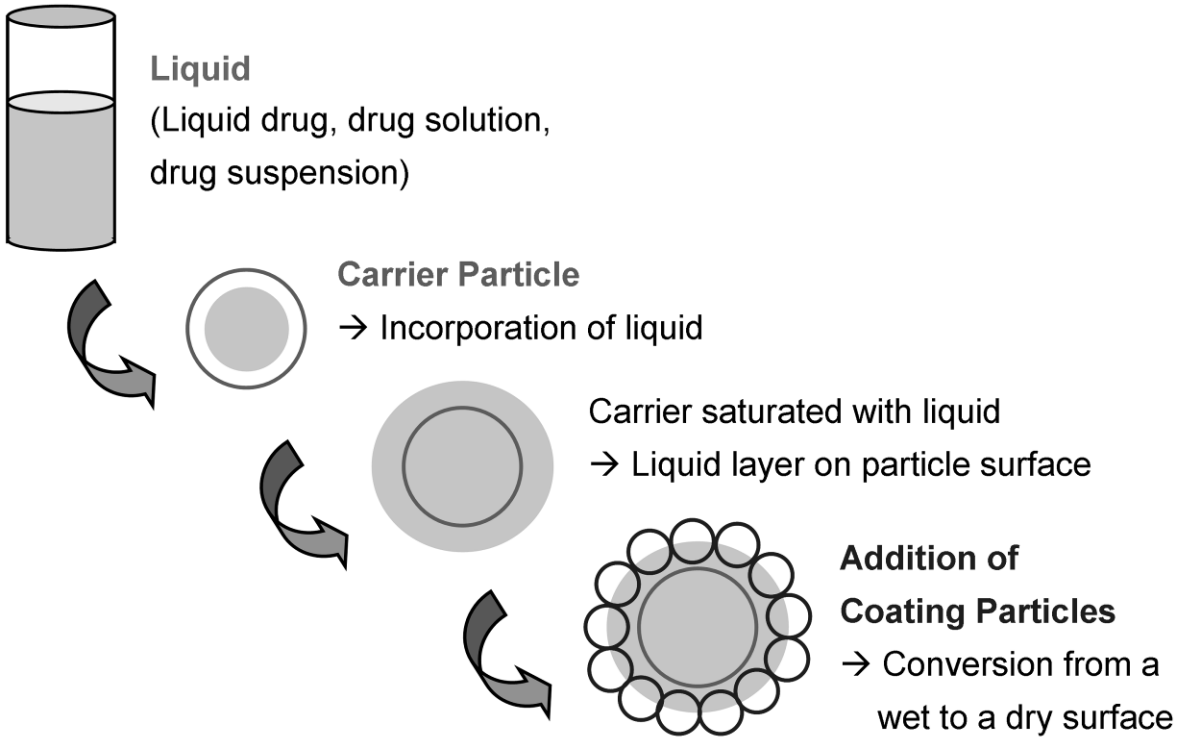

Fig. 1: Schematic representation of liquisolid systems [2]

Various excipients such as lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce liquisolid compacts (Fig. 2).

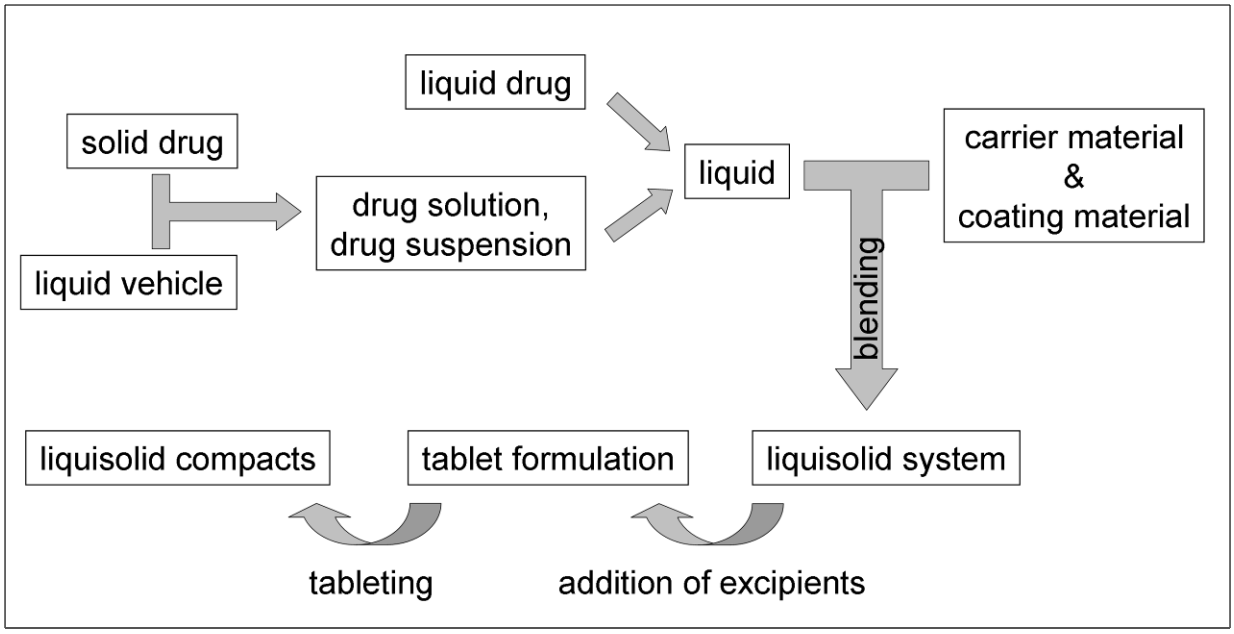

Fig. 2: Schematic outline of the steps involved in the preparation of liquisolid compacts [1]

Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release due to an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles [3-8]. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability [9, 10].

As shown in Fig. 3, drug release from liquisolid compacts is significantly faster than that from their directly compressed counterparts. Here, liquisolid compacts with hydrocortisone containing a 5 % [w/w] drug solution in polyethylene glycol 400 were investigated using microcrystalline cellulose and colloidal silica as carrier and coating materials, respectively [11].

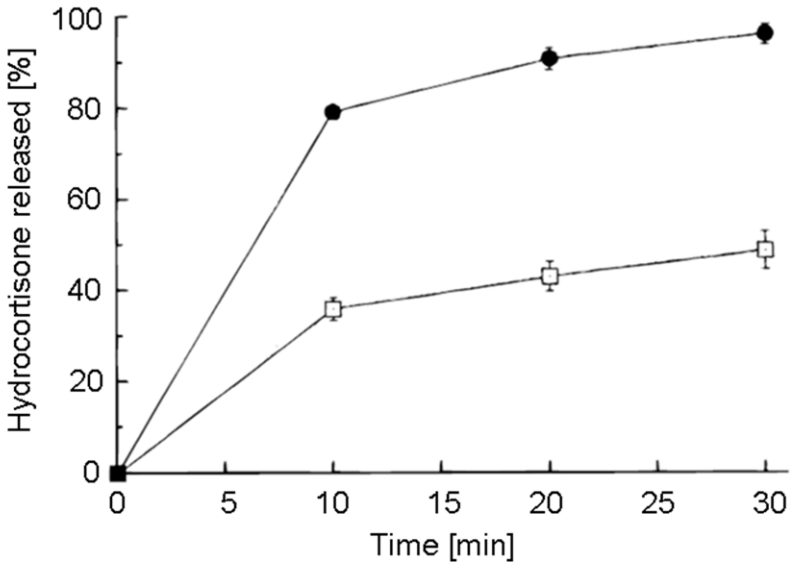

Fig. 3: Hydrocortisone release profiles from liquisolid compacts containing a 5 % [w/w] drug solution in polyethylene glycol 400 (●) and from directly compressed tablets (□) with the same drug dose of 10 mg [11]

Moreover, the liquisolid technology may also be used to prolong dissolution rate [1, 8, 12, 13]. Sustained release oral dosage forms are beneficial with regard to patient compliance because of the reduced dosing frequency. Ideally, a sustained release dosage form leads to therapeutic plasma levels, which are maintained throughout the dosing interval. It has been shown that with hydrophobic carriers such as Eudragit® RL and RS instead of hydrophilic carriers, sustained release systems may be obtained [13]. Sustained release from liquisolid compacts with the conventional carrier and coating materials may also be observed after addition of a matrix forming material such as hydroxypropyl methylcellulose [1].

With the liquisolid technology it is possible to prepare sustained release tablets with a zero order drug release pattern (Fig. 4). Here, liquisolid compacts with nifedipine containing a 30 % [w/w] drug suspension in polyethylene glycol 400 were prepared using microcrystalline cellulose and colloidal silica as carrier and coating materials, respectively [1]. In addition, 22 % [w/w] of the matrix former hydroxypropyl methylcellulose with a viscosity grade of 15 mPa·s was added to obtain sustained drug release.

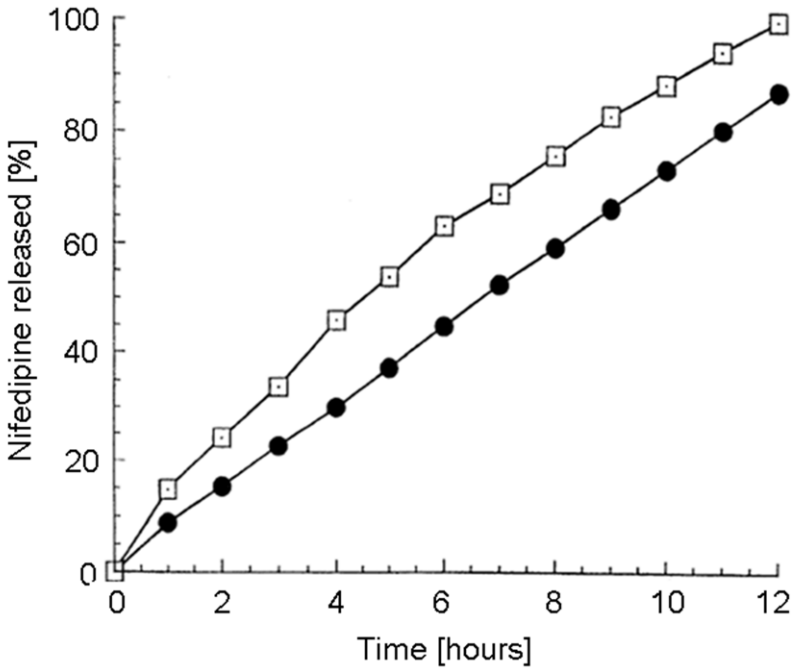

Fig. 4: Nifedipine release profiles from sustained release liquisolid compacts containing a 30 % [w/w] drug suspension in polyethylene glycol 400 (●) and from commercial tablets (□) (Procardia XL) with the same drug dose of 30 mg [1]

1.2 Theory of Liquisolid systems

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquisolid systems has been developed by Spireas [1, 14]. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination.

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose.

The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression [15]. The compactability may be determined by the so-called “pactisity” [1, 15] which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces.

The terms “acceptable flow and compression properties” imply the desired and thus preselected flow and compaction properties which must be met by the final liquisolid formulation.
Depending on the excipient ratio (*R*) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed “liquid load factor L_f“ [w/w] and is defined as the weight ratio of the liquid formulation (*W*) and the carrier material (*Q*) in the system:

$$L_f = W / Q \qquad \text{Eq. (1)}$$

R represents the ratio between the weights of the carrier (*Q*) and the coating (*q*) material present in the formulation:

$$R = Q / q \qquad \text{Eq. (2)}$$

The liquid load factor that ensures acceptable flowability ($^{\Phi}L_f$) can be determined by:

$$^{\Phi}L_f = \Phi + \phi \cdot (1/R) \qquad \text{Eq. (3)}$$

where Φ and ϕ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability ($^{\Psi}L_f$) can be determined by:

$$^{\Psi}L_f = \Psi + \psi \cdot (1/R) \qquad \text{Eq. (4)}$$

where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively. In Table 1 examples of liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles are listed.

Therefore, the optimum liquid load factor (L_o) required to obtain acceptably flowing and compressible liquisolid systems is equal to either $^{\Phi}L_f$ or $^{\Psi}L_f$, whichever represents the lower value.

Table 1: Liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles [1]

Powder excipient or system	Φ-values		Ψ-numbers	
	Propylene glycol	PEG 400	Propylene glycol	PEG 400
Avicel PH 102	0.16	0.005	0.224	0.242
Avicel PH 200	0.26	0.02	0.209	0.232
Cab-O-Sil M5 (silica)* with Avicel PH 102	3.31	3.26	0.560	0.653
Cab-O-Sil M5 (silica)* with Avicel PH 200	2.57	2.44	0.712	0.717

*included as coating material in carrier/coating powder systems

As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Q_o) and coating (q_o) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

$$Q_o = W / L_o \qquad \text{Eq. (5)}$$

and

$$q_o = Q_o / R \qquad \text{Eq. (6)}$$

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow [2] and compaction properties [1].

1.3 Liquisolid formulations for enhanced drug release

Many poorly soluble drugs have been formulated as liquisolid systems showing enhanced drug release. Different liquid vehicles, carrier and coating materials were used to formulate these drug delivery systems (Table 2).

Table 2: Formulations of liquisolid systems with enhanced drug release (abbreviations are listed at the end of the table)

Drug	Liquid vehicle	Carrier & coating material	Ref.
Aceclofenac	PEG 400	MCC & HPMC	[16]
Bromhexine HCl	PG	MCC & Colloidal Silica	[17]
Carbamazepine	PEG 200	MCC & Colloidal Silica	[18]
Clofibrate (liquid)	–	MCC & Colloidal Silica	[1]
Famotidine	PG	MCC & Colloidal Silica	[19]
Fenofibrate	PEG 400	MCC & Colloidal Silica	[20]
Fenofibrate	PG	MCC & Colloidal Silica	[21, 22]
Furosemide	Synperonic® PE/L 81	MCC & Colloidal Silica	[23]
Glibenclamide	PEG 400	Colloidal Silica & MCC	[24]
Griseofulvin	PEG 400	MCC & Colloidal Silica	[20]
Hydrochlorothiazide	PEG 200	MCC + Magnesium carbonate & Colloidal Silica	[25]
Hydrocortisone	PG	MCC & Colloidal Silica	[1, 11]
Hydrocortisone	N,N-dimethylacetamide/PEG 400 (7:3 v/v)	Various Silicas*	[26]
Ibuprofen	PEG 300	MCC & Colloidal Silica	[27]
Indomethacin	PG	MCC & Colloidal Silica	[5, 28]

Indomethacin	PEG 400	MCC & HPMC	[6]
Lamotrigin	PEG 400	MCC & Colloidal Silica	[20]
Methyclothiazide	PEG 400	MCC & Colloidal Silica	[1, 29]
Naproxen	Cremophor® EL	MCC & Colloidal Silica	[30]
Piroxicam	Polysorbate 80	MCC & Colloidal Silica	[3, 4]
Piroxicam	PG	MCC & Colloidal Silica	[31]
Polythiazide	PEG 400	MCC & Colloidal Silica	[32]
Prednisolone	N,N-dimethylacetamide/PEG 400 (7:3 v/v)	Various Silicas*	[26]
Prednisolone	PG	MCC & Colloidal Silica	[14]
Prednisone	PG	MCC & Colloidal Silica	[1]
Prednisone	N,N-dimethylacetamide/PEG 400 (7:3 v/v)	Various Silicas*	[26]
Repaglinide	Polysorbate 80	MCC & Calcium silicate	[9]

*: drug solution dispersed on various silicas (no compacts)

PEG: polyethylene glycol

PG: propylene glycol

Synperonic® PE/L 81: polyoxyethylene-polyoxypropylene block copolymer

Cremophor® EL: polyoxyl 35 castor oil

MCC: microcrystalline cellulose

HPMC: hydroxypropyl methylcellulose

1.3.1 Mechanisms of enhanced drug release from liquisolid systems

In the literature several mechanisms of enhanced drug release have been postulated for liquisolid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements [4, 18, 28].

a. Increased drug surface area

If the drug within the liquisolid system is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets [3-5, 11, 14].

Accordingly, with increasing drug content exceeding the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. With various drugs it could be shown that the release rates are directly proportional to the fraction of the molecularly dispersed drug (F_M) in the liquid formulation [3, 5, 11, 14]. F_M is defined by Spireas as the ratio between the drug's solubility (S_d) in the liquid vehicle and the actual drug concentration (C_d) in this vehicle carried by each system [11].

Therefore:

$$F_M = S_d / C_d \qquad \text{Eq. (7)}$$

where $F_M = 1$ if $S_d \geq C_d$.

In Fig. 5 the effect of the fraction of the molecularly dispersed drug (F_M) on the release rate of hydrocortisone formulated as liquisolid compacts containing various drug concentrations in varying amounts of propylene glycol as liquid vehicle is shown. It is obvious that the drug release rate increases linearly with increasing F_M. Interestingly, this linear increase may be observed only above a certain F_M-limit.

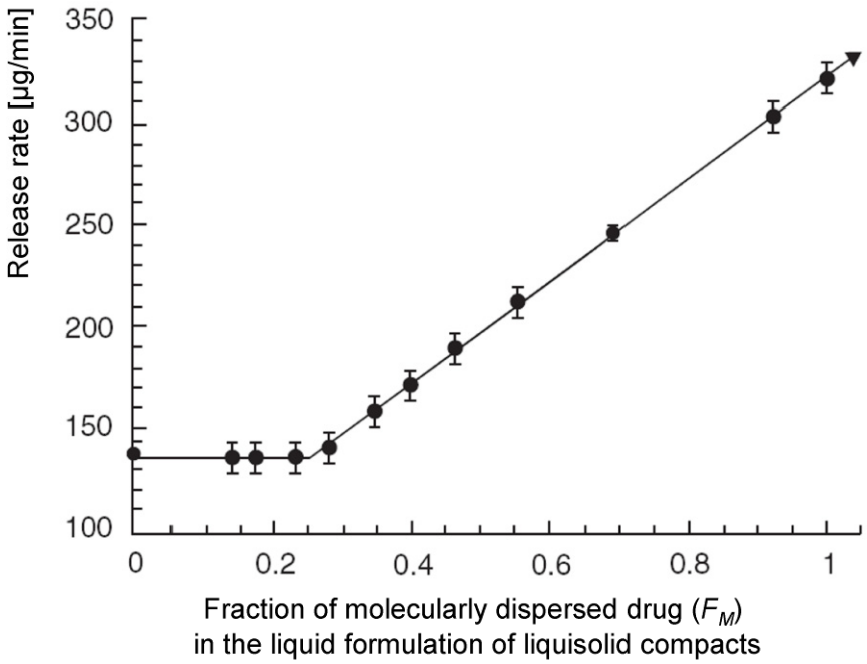

Fig. 5: Effect of the fraction of molecularly dispersed drug (F_M) on the hydrocortisone release rate at 30 min of liquisolid compacts (means ± SD , n = 3) [11]

Accordingly, lower F_M-values and higher fraction of undissolved drug in the liquid vehicle, respectively, are not sufficient to increase percentage of drug released at 30 min. However, this may not be transferred to other time points of drug release.

b. Increased aqueous solubility of the drug

In addition to the first mechanism of drug release enhancement it is expected that C_s, the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a cosolvent [3-5, 11, 14]. The overall increase in the solubility of drugs caused by liquisolid systems was confirmed by Yadav et al. [6, 16, 20, 33].

c. Improved wetting properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles [4] and water rising times [6, 16, 20].

1.3.2 Optimization of liquisolid formulations with enhanced drug release

The liquisolid technology has been successfully applied to low dose, poorly water soluble drugs. The formulation of a high dose, poorly soluble drug is one of the limitations of the liquisolid technology. As the release rates are directly proportional to the fraction of molecularly dispersed drug (F_M) in the liquid formulation a higher drug dose requires higher liquid amounts for a desired release profile. Moreover, to obtain liquisolid systems with acceptable flowability and compactability high levels of carrier and coating materials are needed. However, this results in an increase in tablet weight ultimately leading to tablet sizes which are difficult to swallow. Therefore, to overcome this and various other problems of the liquisolid technology several formulation parameters may be optimized (Table 3).

Table 3: Optimization of formulation parameters for liquisolid systems with immediate drug release

Formulation parameter	Optimization	Effect
liquid vehicle	high drug solubility in the vehicle	increased fraction of the molecularly dispersed drug (F_M)
carrier and coating materials	high specific surface area	increased liquid load factor (L_f)
addition of excipients	polyvinylpyrrolidone (PVP)	increased liquid load factor (L_f), increased viscosity of liquid vehicle, inhibition of precipitation
	superdisintegrant	fast disintegration
excipient ratio (*R)*	high *R*-value	fast disintegration, inhibition of precipitation

In various studies the effect of different types of non-volatile liquid vehicles has been investigated. The results suggest that the selection of a liquid vehicle with a high solubilizing capacity for the drug and thus, an increased F_M, leads to enhanced release profiles [5, 14, 17, 23, 28]. That means that by selection of a liquid vehicle with optimum solubilizing properties the amount of liquid and thus, the weight and size of the liquisolid compacts can be reduced. However, in addition to the drug solubility in the liquid vehicle other physicochemical characteristics of the liquid vehicles such as polarity, viscosity, molecular weight, chemical structure, and lipophilicity may also have an effect on drug release [14].

A further approach to minimize tablet weight is to increase the liquid load factor by using carrier and coating materials with a high specific surface area or by adding PVP to the liquid formulation. It was found that the higher the specific surface area of an excipient the higher the liquid load factor [2]. For instance, the liquid adsorption capacity of microcrystalline cellulose (1.18 m²/g) is higher than that of lactose (0.35 m²/g), starch (0.6 m²/g), and sorbitol (0.37 m²/g) [4]. Fujicalin® (30 m²/g), a spherically granulated dicalcium phosphate anhydrous, and Neusilin® US2 (300 m²/g), a magnesium aluminometasilicate, turned out to be very effective excipients for liquid adsorption while maintaining acceptable flow and compaction properties [34, 35].

Khaled [25] noticed precipitation and consequently retention of the drug in the cavities of porous excipients upon contact of the liquid formulation with the release medium. This retention could be minimized by using either a diluted drug solution or PVP as crystallization inhibitor [18, 25]. Moreover, PVP may also act as binder during compaction leading to an increase of the liquid load factor [18].

The release rate of a drug from a dosage form is dependent on its disintegration and the dissolution rate of the drug. Therefore, it is very important for liquisolid systems with enhanced drug release to ensure that disintegration is not the rate-limiting step and drug dissolution is not hindered by a slow disintegration of the dosage form. It was found that the release rate increases by addition of superdisintegrants such as sodium starch glycolate or croscarmellose sodium to the liquisolid formulation [6, 16, 20].

Another formulation parameter that may be optimized is the ratio of carrier to coating material (*R*). An increase in the *R*-value results in an enhanced release rate if microcrystalline cellulose and colloidal silica are used as carrier and coating materials, respectively. Liquisolid compacts with high *R*-values contain high amounts of microcrystalline cellulose, low quantities of colloidal silica, and low liquid/powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced drug release. In contrast, if high amounts of colloidal silica are used, which means that the *R*-value is low, the liquisolid compact is overloaded with liquid formulation due to a high liquid load factor. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/ recrystallization of the drug and thus decreased release rates [18, 29]. Moreover, as colloidal silica is a hydrophobic material high amounts of it can cause retardation of drug release. Therefore, Spireas et al. recommend a minimum *R*-value of 20 [29]. In the case of liquisolid sustained release compacts lower *R*-values may be used [34, 35] (see below).

1.3.3 Stability of liquisolid systems with enhanced drug release

To obtain information on the stability of liquisolid systems, the effects of storage on the release profile and the crushing strength of liquisolid compacts were investigated. Stability studies of liquisolid systems containing polythiazide (40 °C/ 42 and 75 % R.H., 12 weeks) [32], hydrocortisone (ambient conditions, 10 months) [1], carbamazepine (25 °C/ 75 % R.H., 6 months) [18], indomethacin (25 °C/ 75 % R.H., 12 months) [28], piroxicam (25 °C/ 75 % R.H., 6 and 9 months, respectively) [4, 31], or naproxen (20 °C/ 76 % R.H., 4 weeks) [30] showed that storage at different conditions neither had an effect on the hardness nor on the release profiles of liquisolid compacts. This indicates that the technology is a promising technique to enhance the release rate without having any physical stability issues.

1.4 Liquisolid formulations for sustained drug release

Numerous methods have been described to produce sustained release formulations, among which the liquisolid technology is a quite new and promising technology resulting in a sustained release pattern with zero order kinetics [8, 12]. So far, only few drugs have been formulated as liquisolid systems with prolonged drug release. In Table 4 the fomulations of these drugs with the respective liquid vehicle, carrier and coating material as well as the additional retarding agent (matrix forming material) are listed.

Table 4: Formulations of liquisolid systems with sustained drug release (abbreviations are listed at the end of the table)

Drug	Liquid vehicle	Carrier & coating material	Additional retardant agent	Ref.
Nifedipine	PEG 400	MCC & Colloidal Silica	HPMC (15 mPa·s)	[1, 13]
Propranolol HCl	Polysorbate 80	Eudragit® RS or RL & Colloidal Silica	HPMC* (4000 mPa·s)	[36, 37]
Theophylline	Polysorbate 80	Eudragit® RS or RL & Colloidal Silica	HPMC* (4000 mPa·s)	[38]
Tramadol HCl	PG	MCC & Colloidal Silica	HPMC (4000 mPa·s)	[39]

PEG: polyethylene glycol
PG: propylene glycol
MCC: microcrystalline cellulose
HCl: hydrochloride
HPMC: hydroxypropyl methylcellulose
*: only some batches

1.4.1 Mechanisms of sustained drug release from liquisolid systems

With X-ray crystallography and DSC measurements it could be confirmed, that sustained drug release from these liquisolid compacts is not caused by a change in crystallinity or by complex formation of the drug during the manufacturing process of the sustained release liquisolid formulations [36, 37]. Liquisolid formulations with sustained drug release may contain hydrophobic carriers such as Eudragit® RL or RS instead of hydrophilic carriers, the latter being used for fast release liquisolid formulations [37, 38]. Hydrophobic carriers may lead to poor wetting properties of the compacts resulting in slow disintegration and thus, prolonged drug release.

Furthermore, the liquid vehicle may affect drug release. A comparison of drug release from conventional matrix tablets (direct compression) and liquisolid compacts, both containing Eudragit® RS or RL as matrix forming material, showed that the retardation effect of liquisolid compacts with polysorbate 80 as liquid vehicle is much more pronounced than that of conventional matrix tablets [37, 38]. This confirms the important role of the liquid vehicle in sustaining drug release from liquisolid matrix systems. It was shown that the liquid vehicle polysorbate 80 may act as a plasticizer [40] and thus, decreases the glass transition temperature of the polymer Eudragit® RS. Accordingly, with liquisolid compacts the coalescence of the polymer particles occurs at lower temperatures than with conventional matrix tablets. This more pronounced coalescence of polymer particles of liquisolid compacts leads to a matrix with lower porosity and higher tortuosity. Consequently, the drug is surrounded by a fine network of the hydrophobic polymer resulting in a sustained release of the drug [41, 42].

Moreover, it has been shown that the addition of hydroxypropyl methylcellulose (HPMC) increases the retardation effect of liquisolid compacts [1, 13]. HPMC is commonly used for the preparation of hydrophilic matrix systems. Depending on its molecular weight the polymer either swells in contact with water and forms a hydrated matrix layer through which the drug has to diffuse or erodes resulting in a zero order drug release kinetic [43]. In the case of HPMC it was also found that a stronger retardation effect was observed with liquisolid compacts as compared to directly compressed tablets (conventional formulation) [38].

1.4.2 Optimization of liquisolid formulations with sustained drug release

In contrast to liquisolid compacts with immediate drug release liquisolid sustained release formulations may be optimized by selection of low *R*-values, suspensions with a high percentage of undissolved drug and by avoidance of disintegrants.

If the *R*-value is low, which means that the applied amount of silica is high, the liquisolid compacts are overloaded with liquid formulation due to a high liquid load factor. In such cases oversaturation might occur resulting in local precipitation of the drug and thus, decreased release rates [18, 29]. Moreover, the higher the percentages of undissolved drug in the liquid formulation the slower the release rate. This is especially important for poorly soluble drugs, as the dissolution rate of these drugs is low. In addition, as drug release from a tablet is dependent on the disintegration of the tablet and the subsequent dissolution of the drug, the absence of disintegrants, which prevents disintegration, will slow down drug release.

Furthermore, it was shown with liquisolid compacts that the higher the HPMC concentration and the higher the amount of Eudragit® RS / RL, respectively, the more pronounced the decrease in drug release [37, 38].

1.5 In vivo evaluation of immediate release liquisolid systems

The liquisolid technology is a promising approach for the enhancement of drug release of poorly soluble drugs as described in subchapter 1.3. However, the improved bioavailability to be expected from liquisolid systems has not been investigated in detail.

Khaled et al. studied the absorption characteristics of hydrochlorothiazide liquisolid compacts in comparison with commercial tablets in beagle dogs [10]. Significant differences in the area under the plasma concentration-time curve, the peak plasma concentration, and the absolute bioavailability of the liquisolid and the commercial tablets were observed. However, for the mean residence time, the mean absorption time, and the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15 % higher than that from the commercial formulation.

Fahmy et al. investigated the in vitro and in vivo performance of famotidine liquisolid compacts in comparison with directly compressed tablets and commercial famotidine tablets, respectively [19]. The dissolution rate of famotidine in 0.1 N HCl was shown to be enhanced with the liquisolid compacts compared to directly compressed tablets. The in vivo evaluation of famotidine liquisolid compacts was compared to that of commercial famotidine tablets using six healthy male volunteers aged between 20 and 40. It was found that there were no significant differences between the mean peak plasma concentrations (c_{max}), the mean times of peak plasma concentrations (t_{max}), or the mean area under the plasma concentration-time curve (AUC). Unfortunately, the in vivo evaluation of the directly compressed tablets was not determined in this study and thus, an improved bioavailability of liquisolid compacts compared to directly compressed tablets could not be shown.

Tayel et al. measured drug release of the poorly soluble antiepileptic drug carbamazepine from liquisolid compacts and commercial tablets [44]. It was observed that drug release from liquisolid compacts and that from commercial tablets is comparable. Furthermore, an oral dose of carbamazepine administered to mice led to

less protection against an electroshock-induced convulsion with liquisolid compacts compared to the commercial product. This lower pharmacological activity of liquisolid compacts is probably due to the high drug concentration in the liquid vehicle and thus a precipitation of carbamazepine in the silica pores.

El-Houssieny et al. investigated the bioavailability and biological activity (glucose tolerance in rabbits) of repaglinide formulated as liquisolid compacts and commercial tablets, respectively [9]. It was found that the relative bioavailability of repaglinide from the liquisolid compacts was significantly higher than that from the commercial tablets. The increase in insulin blood level was more pronounced with the liquisolid compacts than with the commercial tablets indicating a higher bioavailability from the liquisolid compacts. Moreover, liquisolid compacts of repaglinide decreased blood glucose levels significantly more than the commercial tablets.

These partially contrary results of bioavailability of liquisolid formulations show that still more in vivo data is needed to confirm the superiority of liquisolid compacts. The varying bioavailability of the above mentioned liquisolid formulations may be explained by a different percentage of dissolved drug in the liquid vehicle. However, in most of the studies an improved bioavailability from liquisolid formulations was observed compared to the commercial tablets.

1.6 Comparison between liquisolid systems and alternative technologies

The liquisolid technology can be used both for the enhancement and the retardation of drug release. It is a promising technique because of the simple manufacturing process, low production costs, and the possibility of industrial production due to good flow and compaction properties of the liquisolid formulations.
Within the next two subchapters the liquisolid technology is compared to alternative technologies and their advantages and disadvantages are pointed out.

1.6.1 Technologies for the enhancement of drug release

Release enhancement of poorly soluble drugs may be achieved by an increase of the drug surface area, the drug solubility, or by formulating the drug in its dissolved state. Several methodologies such as micronization, adsorption onto high surface area carriers, co-grinding, formulation of inclusion complexes, solid dispersions, and lipid based formulations (e.g. SEDDS) are used for enhancement of drug release [45-47].

A simple method for increasing the surface area of the drug is micronization [48]. However, in practice the effect of micronization is often disappointing, especially if the drugs are encapsulated or tableted. Micronized drugs have the tendency to aggregate as a result of their hydrophobicity and electrostatic charge, thus, reducing their available surface area [49, 50].

Adsorption of poorly soluble drugs on hydrophilic silica aerogels was found to enhance drug dissolution [51, 52]. This can be explained by both an increase in the specific surface area of the drug adsorbed to the aerogel and an at least partial amorphisation of the drug. However, drug adsorption is dependent on the selected drug and sometimes only low drug loads are achieved. Another disadvantage of this technique is the complex manufacturing process: Silica aerogels are loaded with drugs by adsorption from their solutions in supercritical carbon dioxide [52, 53].

Co-grinding of poorly soluble drugs with different excipients may also result in an amorphisation of the drug and thus improved dissolution characteristics [54]. Crospovidone [55, 56], polyvinylpyrrolidone [56], and different types of silica [57, 58] are suitable for that purpose. Co-grinding is another straight forward procedure to achieve drug release enhancement.

Complexes of a lipophilic drug with cyclodextrin, commonly known as inclusion complexes, can be easily formulated by mixing the drug with the carrier [59]. The most commonly used carrier β-cyclodextrin acts as a solubilizer and stabilizer consisting of a truncated cone type structure with an outer hydrophilic and an inner hydrophobic surface [60-63]. However, the maximum possible drug load of these systems is relatively low and the inclusion complexation only works with drugs that fit into the cavities of the cyclodextrin molecule.

Solid dispersions consist of one or more active ingredients dispersed in a readily soluble solid hydrophilic matrix prepared by a melting (fusion) or solvent method [64]. With the melting method the drug is added to the molten carrier and the mixture is stirred until a homogenous melt is obtained. With the solvent method drug and carrier are dissolved in small amounts of solvent with final solvent evaporation. The higher release rates of solid dispersions may be ascribed to a number of factors which include formation of the amorphous form of the drug, reduction of particle size to nearly the molecular level, improved wetting properties, and solubilisation of the drug by the carrier [61, 65-70]. The advantages of this methodology are the molecular dispersion of the drug within the hydrophilic carrier and the comparably high drug stability. However, for the preparation of solid dispersions usually special equipment is needed such as a spray dryer or a fluid bed apparatus.

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant, cosolvent and drug, which emulsify spontaneously to produce oil in water emulsions when introduced into an aqueous phase under gentle agitation [71]. Generally, SEDDS are either administered as liquid dosage forms or as soft gelatin capsules. Basically, solid dosage forms are preferred over liquid preparations for many reasons including ease of manufacture, patient compliance, dosage uniformity, and stability. Liquid SEDDS may be transformed to solid self-emulsifying systems

(SSEDDS) by addition of powder carriers [72-75]. The liquisolid technology may be used to transform liquid SEDDS into acceptably flowing and compressible powders. One of the drawbacks of this technique is the high surfactant concentration [45].

1.6.2 Technologies for the retardation of drug release

There are several retardation principles for oral sustained release dosage forms including inert insoluble matrices, hydrophilic colloid matrices, membrane-controlled drug delivery systems, ion exchange resins, and osmotic systems [76, 77].

In a matrix tablet the drug is dispersed in either an insoluble or a soluble carrier which forms the matrix [78, 79]. Carrier materials for insoluble matrices are water insoluble polymers, fats, and waxes. From insoluble matrices the drug is released as soon as a solvent enters the matrix and dissolves the particles. The addition of channelling agents increases drug release by leaving tortuous capillaries after leaching [80, 81]. The empty matrix (ghost matrix) is excreted with the feces. Carrier materials for hydrophilic colloid matrices are water swellable or erodible polymers such as hydroxypropyl methylcellulose of different molecular weight [43, 82]. In contact with water the polymer either swells and forms a hydrated matrix layer through which the drug has to diffuse or erodes resulting in a zero order drug release kinetic [83]. Matrix formulations are widely used due to their simple manufacturing process, a high maximum possible drug load, low production costs, and low risk of dose dumping.

Oral dosage forms coated with water insoluble film forming polymers show a membrane-controlled drug diffusion. Hydration of the coating film increases the permeability of the film and facilitates diffusion of the drug. Typical polymers used include ethylcellulose and polymethacrylates, e.g. Eudragit® RS, RL and NE grades [84-88]. To modify the release characteristics of the film water soluble substances may be added as pore forming agents increasing the release rate [89]. However, manufacture of coated dosage forms requires special equipment, the process is time-consuming, and dose dumping may occur with single-unit systems as a result of film failure or damage.

Cationic or anionic drugs may be bound to an ion exchange resin due to its ionic structure [90, 91]. Drug release from these complexes depends on the pH and electrolyte concentration in the gastrointestinal tract. Release is faster in the acidic environment of the stomach than in the luminal contents of the small intestine [92]. Of course, this mechanism of sustained drug release can only be adopted to ionic drugs.

An osmotic pump system is composed of a core tablet surrounded by a semi-permeable membrane with a hole generated by a laser beam. The core tablet consists of the drug, a water soluble polymeric osmotic agent and/or a salt [93, 94]. The semi-permeable membrane allows water to diffuse into the core tablet and to dissolve the drug and osmotic agent. As the osmotic pressure inside the dosage form increases, the drug solution or suspension is pumped out of the hole following a zero order kinetic. However, attention has to be paid to the integrity and consistency of the coating film and the accurate size of the hole [95].

1.7 Conclusion

Nowadays, new chemical entities often possess a high molecular weight and a high lipophilicity. Especially poorly soluble and highly permeable active pharmaceutical ingredients represent a technological challenge, as their poor bioavailability is solely caused by poor water solubility, which may result in low drug absorption. Numerous methods have been described to improve water solubility and drug release, respectively, among which the liquisolid technology is one of the most promising approaches. With this technology liquids such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material. As highest drug release rates are observed with liquisolid compacts containing a drug solution as liquid portion, liquisolid compacts may be optimized by selection of the liquid vehicle and the carrier and coating materials. Moreover, the addition of disintegrants may further accelerate drug release from liquisolid compacts.

The liquisolid technology may also be used for the preparation of sustained release formulations with zero order release pattern. Thus, a constant plasma level will be reached, which is maintained throughout the dosing interval. For sustained release liquisolid compacts, the selection and the concentration of the excipients such as liquid vehicle, retarding agent (matrix forming material) as well as carrier and coating material play an important role.

The liquisolid approach is a promising technology because of the simple manufacturing process, low production costs and the possibility of industrial manufacture due to the good flow and compaction properties of liquisolid formulations.

2. Comparison of traditional and novel tableting excipients – physical and compaction properties

Comparison of traditional and novel tableting excipients – physical and compaction properties

Abstract

Novel tableting excipients are continuously developed and advertised with superior flow and compaction characteristics.

The objective of this study was to compare two traditionally used and two novel tableting excipients with regard to their physical and tableting properties as well as their magnesium stearate sensitivity. Avicel® PH102 (microcrystalline cellulose) was compared to the novel co-processed excipient Prosolv® SMCC90 (silicified microcrystalline cellulose), whereas Anhydrous Emcompress® (anhydrous dicalcium phosphate) was compared to the novel spherically granulated excipient Fujicalin® (anhydrous dicalcium phosphate).

True density was determined with a helium pycnometer, particle size via laser diffraction and specific surface area by gas adsorption. Flowability was characterized by the Hausner ratio and the powder flow rate. Tableting properties were characterized by tabletability (tensile strength vs. compaction force) and mean yield pressure derived from the Heckel Plot. The magnesium stearate sensitivity of the excipients was investigated by determination of the tensile strength of tablets containing different magnesium stearate concentrations.

Due to the silification process in the case of Prosolv® and the unique manufacturing process in the case of Fujicalin®, the novel excipients showed a comparably larger specific surface area. Hardest tablets by far could be obtained with Prosolv®, followed by Avicel® and Fujicalin®. Emcompress® tablets showed the lowest hardness values. Avicel® and Prosolv® were sensitive to magnesium stearate, whereas Fujicalin® and Emcompress® did not show lubricant sensitivity. This confirms the plastic deformation behavior of microcrystalline cellulose and the brittle fracture of anhydrous dicalcium phosphate.

In conclusion, compared to the traditional excipients the investigated novel tableting excipients were advantageous with regard to their specific surface area with the option of liquid adsorption and their tableting properties.

2.1 Introduction

Direct compaction of powder blends is usually preferred over compaction of granules due to the comparably simple and more economical manufacturing process: less equipment is needed, processing times are reduced, and energy costs are lower. Furthermore, during direct compaction no solvents or heat are needed, which could affect product stability. However, various problems may occur during direct compaction, e.g. poor flowability and/or binding properties and a lack of content uniformity. Therefore, improved excipients with better functionality are needed.

One approach in the development of new excipients with improved properties is co-processing of two or more materials [96]. Co-processing usually results in a material, which shows better flow and compaction properties than the physical blend of its components.

The co-processed silicified microcrystalline cellulose Prosolv® SMCC, a high functionality excipient, was developed to reduce some of the known disadvantages of conventional microcrystalline cellulose such as low bulk density, poor flowability, and high lubricant sensitivity. Prosolv® is a combination of a filler/binder and a glidant consisting of 98 % microcrystalline cellulose and 2 % colloidal silica. It exhibits better flowability and tabletability than plain microcrystalline cellulose [97-99]. Moreover, Prosolv® shows less lubricant sensitivity [100, 101] and higher prevention of sticking [102]. With FT-IR, ^{13}C-NMR, powder X-ray diffraction, mercury porosimetry, helium pycnometry, scanning electron microscopy, and particle size analysis it has been shown that silification affects neither the chemical structure nor the polymorphic properties of microcrystalline cellulose [103, 104]. Thus, in the case of the application of silicified microcrystalline cellulose in solid oral dosage forms the regulatory approval process may be sped up because microcrystalline cellulose and colloidal silica are commonly used excipients that are known to be safe.

Another novel excipient with interesting properties is Fujicalin®, an innovative anhydrous dicalcium phosphate with improved tabletability and flowability compared to conventional anhydrous dicalcium phosphate. The unique synthesis process of

Fujicalin® consists of a restricted crystal growth of anhydrous dicalcium phosphate followed by spray drying of an aqueous dispersion of these microcrystals. Thereby, porous spherical particles cotaining microcrystals of anhydrous dicalcium phosphate are obtained [105, 106]. Due to its high porosity and large specific surface area, Fujicalin® has a high liquid adsorption capacity [107].

As novel tableting excipients are continuously developed and advertised with superior properties, the objective of this study was to compare two traditionally used and two novel tableting excipients with regard to their physical and tableting properties as well as their potential advantages during tablet manufacture. Avicel® PH102 was compared to the novel co-processed excipient Prosolv® SMCC90, whereas Anhydrous Emcompress® was compared to the novel spherically granulated excipient Fujicalin®. Moreover, the magnesium stearate sensitivity of the excipients was investigated and compared to the different deformation characteristics of the excipients.

2.2 Materials and methods

Materials

Avicel® PH102 (microcrystalline cellulose, MCC), FMC BioPolymer, Cork, Ireland; Prosolv® SMCC90 (silicified microcrystalline cellulose, SMCC), JRS Pharma, Rosenberg, Germany; Anhydrous Emcompress® (anhydrous dicalcium phosphate, ADCP), JRS Pharma, Rosenberg, Germany; Fujicalin® (spherically granulated anhydrous dicalcium phosphate, SGADCP), Fuji Chemical Industry, Toyama, Japan; Magnesium stearate (MgSt), Baerlocher, Unterschleissheim, Germany.

Methods

Determination of the specific surface area of the excipients

The specific surface area (SSA) of the excipients was determined by gas adsorption using a Sorptomatic 1990 (Carlo Erba Instruments, Rodano, Italy). The samples were degassed under vacuum for 24 h and exposed to nitrogen at 77.4 K. According to the Brunauer-Emmet-Teller (BET) equation [108] the specific surface area of the excipients was evaluated within a relative pressure range p/p_0 between 0.05 and 0.3.

Determination of the particle size of the excipients

The particle size distribution of the samples was determined via laser diffraction using a dry dispersing system with a feeding air pressure of 1 bar (HELOS equipped with RODOS, Sympatec, Clausthal-Zellerfeld, Germany).

Determination of the true density of the excipients

The true density of the excipients was determined by helium pycnometry using a 10 cm^3 sample cup equipped with a fritted filter cap (Accupyc 1330, Micromeritics, Aachen, Germany). Prior to testing the excipients were dried for 5 days over phosphorus pentoxide. Each measurement included 10 purge cycles followed by 10 measuring cycles.

Flowability of the excipients

Prior to the flowability tests the excipients were mixed with magnesium stearate (0.5 % [w/w]: MCC, SMCC, SGADCP; 1 % [w/w]: ADCP) for 5 min in a Turbula blender (T2F, Willy A. Bachofen, Muttenz, Switzerland) at 72 rpm.
Flow properties of the excipients were determined by measurement of the Hausner ratio and the powder flow rate. The Hausner ratio was calculated as the quotient of tap and bulk density. Bulk and tap densities were determined with a jolting volumeter (STAV 2003, J. Engelsmann, Ludwigshafen, Germany) according to the Pharmacopoeia Europaea. The mass-related powder flow rate in [g/s] was measured with a funnel (orifice diameter 7 mm) by recording the weight change over time with a precision balance (BL 1500 S, Sartorius, Göttingen, Germany). The volume-related powder flow rate in [cm³/s] was calculated as the quotient of the mass-related powder flow rate and the bulk density.

Tableting of the excipients

Tablets were prepared with an eccentric press (EXI instrumented with strain gauges and displacement transducer, Fette, Schwarzenbek, Germany) equipped with flat faced punches of 10 mm diameter. Tablet weight was adjusted to approximately 350 mg for the microcrystalline celluloses and 450 mg for the dicalcium phosphates. Compaction speed was set to 16 rpm. All experiments were performed at 21 °C / 45 % R.H..

Characterization of the tablets

Tablets were characterized after a relaxation time of at least 24 h. Crushing force, tablet diameter, and tablet thickness were determined using a hardness tester (TBH30, Erweka, Heusenstamm, Germany). The tensile strength was calculated according to Fell et al. [109-111]. Tabletability of the excipients was evaluated by plotting the tensile strength versus the compaction force. From the Heckel plot [112, 113], i.e. the relationship between the logarithm of the reciprocal porosity and the compaction pressure, the mean yield pressure, which represents the reciprocal slope of the linear portion of the compression curve, was determined [114]. For determination of the mean yield pressure a pressure range from 50 to 120 MPa was

selected for the microcrystalline celluloses and from 70 to 120 MPa for the dicalcium phosphates, respectively. The quantification of the mean yield pressure of each excipient included 10 measurements.

Investigation of the magnesium stearate sensitivity of the excipients

For the investigation of lubricant sensitivity magnesium stearate at concentrations of 0.5, 1, 2 % [w/w] for MCC, SMCC, SGADCP and 1, 1.5, 2 % [w/w] for ADCP was added to the excipients by mixing in a Turbula blender for 5 min at 72 rpm. In this case compaction was performed with a rotary press (XL100, Korsch, Berlin, Germany) instrumented with strain gauges and equipped with flat faced punches of 10 mm diameter. Compaction speed was set to 20 rpm. Tabletability of the excipients was evaluated as described in the above mentioned subchapter.

2.3 Results and discussion

Physical properties of the excipients

The physical properties of the investigated excipients are shown in Table 5. It is obvious that the true densities of the microcrystalline celluloses are significantly lower than those of the dicalcium phosphates. The particle size of MCC was comparable to that of SMCC, whereas ADCP exhibited a 1.5 fold larger particle size than SGADCP. The SSAs of the traditional and the novel excipients differed significantly from each other. Due to the silification process (SMCC) and the unique manufacturing process (SGADCP) [106] these novel excipients showed a much larger SSA: the SSA of SGADCP was more than 1.5 fold larger than that of ADCP with 20.7 m²/g, whereas the SSA of SMCC was more than 4 fold larger than that of MCC with 1.2 m²/g. This increased SSA of the novel excipients offers the possibility of special applications such as adsorption and uptake of liquids [107].

Table 5: Physical properties of the investigated excipients (means ± SD, n = 3)

	MCC	SMCC	ADCP	SGADCP
Particle size d_{50} [µm]	114.6 ± 0.1	93.8 ± 1.0	198.1 ± 1.3	125.4 ± 0.8
True density [g/cm³]	1.558 ± 0.002	1.567 ± 0.002	2.789 ± 0.001	2.823 ± 0.003
SSA [m²/g]	1.2 ± 0.1	5.3 ± 0.1	20.7 ± 0.2	32.4 ± 0.8

Flowability of the excipients

The flowability of the excipients is shown in Table 6. Except for ADCP all bulk and tap densities of the excipients were similar. In contrast to the true densities of the dicalcium phosphates (Table 5), the bulk as well as tap densities of ADCP and SGADCP differed significantly from each other. The lower bulk and tap densities of

SGADCP, which are comparable to those of MCC and SMCC, may be explained by its porous structure. SMCC showed no improvement in flow compared to MCC: neither a lower Hausner ratio, nor a higher powder flow rate was observed. Because of its spherical shape SGADCP exhibited better flowability compared to ADCP manifesting itself in a lower Hausner ratio and a higher volume-related powder flow rate. Due to its porous structure the mass-related powder flow rate of SGADCP is lower than that of ADCP.

Table 6: Flow properties of the investigated excipients (means ± SD, n = 3; powder flow rate: n = 5)

	MCC	SMCC	ADCP	SGADCP
Bulk density [g/cm³]	0.406 ± 0.001	0.379 ± 0.001	0.767 ± 0.003	0.460 ± 0.001
Tap density [g/cm³]	0.496 ± 0.002	0.472 ± 0.003	0.923 ± 0.005	0.517 ± 0.002
Hausner ratio	1.22 ± 0.00	1.25 ± 0.01	1.20 ± 0.00	1.12 ± 0.00
Powder flow rate, mass-related [g/s]	1.69 ± 0.09	1.52 ± 0.02	4.35 ± 0.05	3.00 ± 0.05
Powder flow rate, volume-related [cm³/s]	4.17 ± 0.22	4.01 ± 0.06	5.67 ± 0.06	6.53 ± 0.10

Tableting properties of the excipients

In Fig. 6 the tabletability of the investigated excipients is shown. As expected, all excipients show an increase in tensile strength with increasing compaction force. However, the tensile strength of the excipient compacts differed significantly from each other. For instance, at a compaction force of 10 kN, SMCC tablets showed a tensile strength of about 7 MPa, MCC tablets about 5 MPa, SGADCP tablets about 3 MPa, and ADCP tablets about 0.5 MPa. This means, that both novel excipients (SMCC and SGADCP) led to improved tabletability resulting in harder tablets in comparison to their

traditional counterparts. The low tensile strength of ADCP tablets results from the poor binding properties of this dicalcium phosphate.

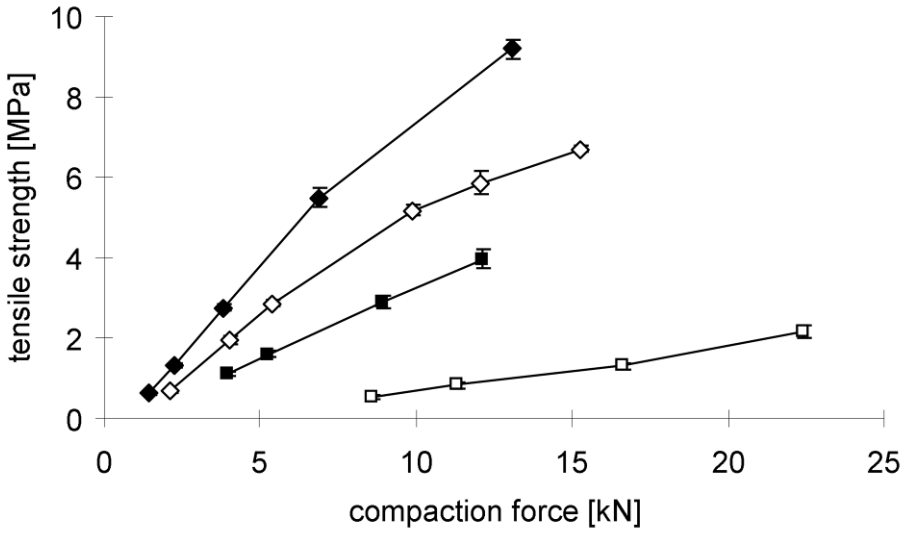

Fig. 6: Tabletability of the investigated excipients (means ± SD, n = 10)
◇ MCC, ◆ SMCC, □ ADCP, ■ SGADCP

To characterize the deformation process of the excipients, Heckel plots were recorded. The Heckel plot is used to determine the plastic deformation properties of a powder to be compacted [115, 116]. A high slope of the linear portion of the compression curve and thus a low mean yield pressure represent a high degree of plastic deformation [114, 117]. The Heckel plots of the investigated excipients are shown in Fig. 7. It is obvious that the Heckel plot of MCC is similar to that of SMCC and the Heckel plot of ADCP is similar to that of SGADCP.

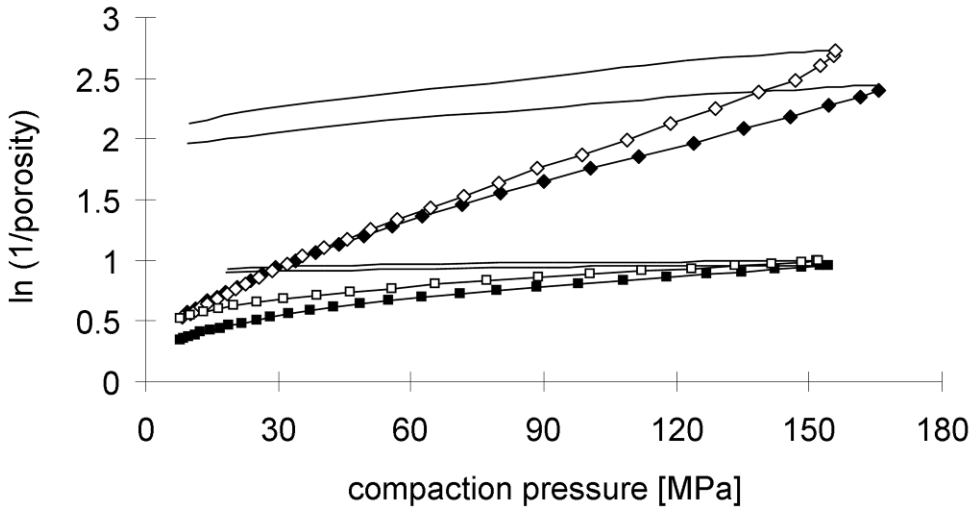

Fig. 7: Heckel plots of the investigated excipients (n = 1)
compression curve: ◇ MCC, ◆ SMCC, □ ADCP, ■ SGADCP
decompression curve: no symbols

The determination of the mean yield pressure resulted in a coefficient of determination R^2 of at least 0.998 in all cases. MCC exhibited a mean yield pressure of 79 ± 3 MPa, SMCC of 97 ± 1 MPa, ADCP of 440 ± 9 MPa, and SGADCP of 342 ± 5 MPa. It is apparant that the mean yield pressure of MCC and SMCC is much lower than that of ADCP and SGADCP. This confirms the plastic deformation properties of microcrystalline cellulose and the brittle fracture of anhydrous dicalcium phosphate [118-121].

Moreover, with the Heckel plot the degree of elastic deformation characteristics of a powder may be determined [122, 123]. High elastic energy causes a breaking of bonds and an increase of tablet porosity, which results in a reduced tensile strength of the tablets ultimately leading to capping [124]. Thus, a low elastic energy is favorable. In contrast to the decompression curves of ADCP and SGADCP, those of MCC and SMCC were highly bent indicating a high degree of elastic recovery of the tablets [125]. As the decompression curves of ADCP and SGADCP were almost parallel to the x-axis, tablets of dicalcium phosphate did not show elastic recovery.

Magnesium stearate sensitivity of the excipients

The negative effect of magnesium stearate on the tabletability of powders is well known [126]. Film formation of the lubricant occurs during mixing, which causes a reduction of the interparticle bonding [127].

The influence of the magnesium stearate concentration on the tabletability of the respective excipients is shown in Fig. 8. The tensile strength of MCC and SMCC compacts decreased with increasing lubricant concentration (Figs. 8a, 8b). However, this lubricant sensitivity was less pronounced with SMCC than with MCC. The tableting properties of ADCP and SGADCP remained almost unaffected by addition of magnesium stearate (Figs. 8c, 8d). This may be explained by the different deformation properties of these excipients as described in the above mentioned subchapter: MCC and SMCC as microcrystalline celluloses show plastic deformation [128] whereas fragmentation is the main deformation mechanism of the dicalcium phosphates ADCP and SGADCP [105, 119]. Magnesium stearate as film forming lubricant causes a reduction of the interparticle bonding and thus the tensile strength of tablets consisting of plastically deforming compounds decreases with increasing magnesium stearate concentration. In contrast, with brittle excipients new contact areas free from magnesium stearate are formed during compaction and thus, the lubricant does not influence the tensile strength of these materials.

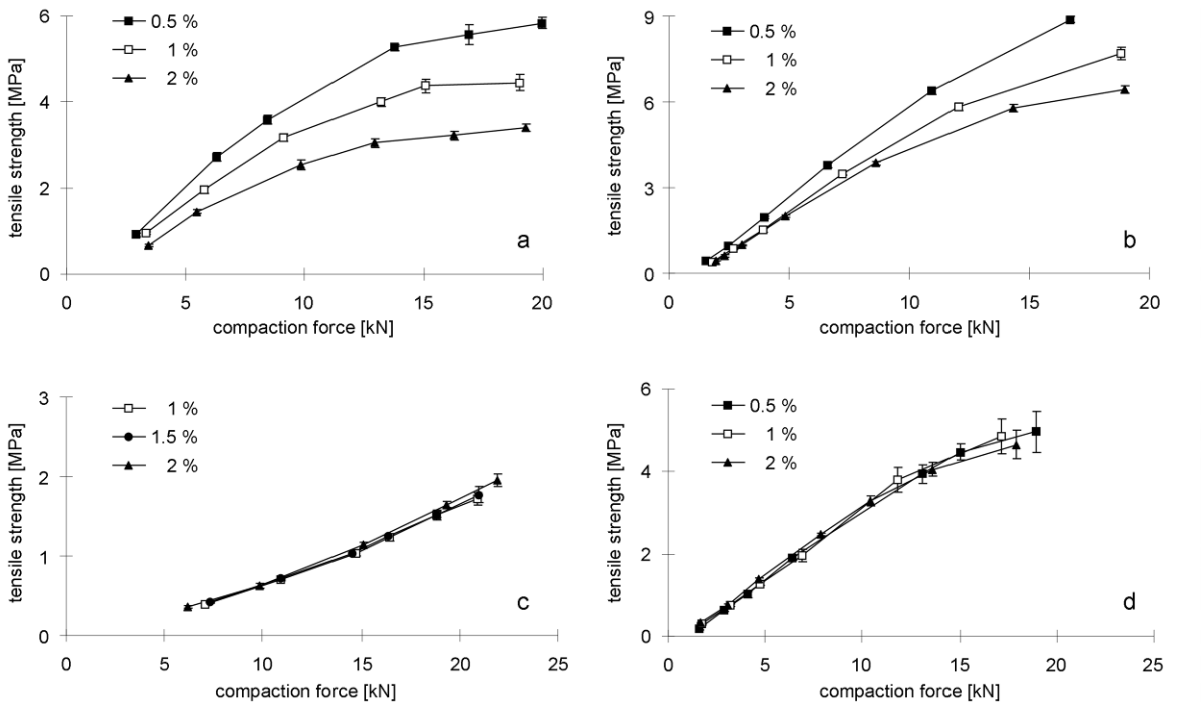

Fig. 8: Influence of magnesium stearate concentration on the tabletability of the investigated excipients (means ± SD, n = 10)
a) MCC, b) SMCC, c) ADCP, d) SGADCP

2.4 Conclusion

SMCC (Prosolv®) did not show improved flow properties in comparison to MCC (Avicel®), whereas the spherically shaped SGADCP (Fujicalin®) exhibited better flowability compared to ADCP (Anhydrous Emcompress®). The investigated novel tableting excipients showed better tableting properties than their traditional counterparts: harder tablets could be obtained at similar compaction forces. With the Heckel plot plastic deformation was confirmed as deformation property for the two types of microcrystalline cellulose and brittle fracture for the two types of dicalcium phosphate. Moreover, the two dicalcium phosphates did not show magnesium stearate sensitivity as observed with the two investigated microcrystalline celluloses. Furthermore, the increased specific surface area of these novel excipients offers the option of special applications such as uptake of liquids.

3. Tableting properties of silica aerogel and other silicates

Tableting properties of silica aerogel and other silicates

Abstract

In solid oral dosage forms silicates are commonly used as glidants in low concentration. However, due to their large specific surface area, silicates may also be used as carrier materials for drugs. Moreover, silicates allow amorphisation of drugs by co-grinding or processing with supercritical fluids.

The aim of this study was to investigate the physical and the tableting properties of Silica Aerogel (a special type of silica with an extremely large specific surface area), Neusilin® US2 (magnesium aluminometasilicate), Florite® (calcium silicate) and Aerosil® 200 (colloidal silica).

Powder blends of Avicel® PH102 (microcrystalline cellulose) and different amounts of the respective silicate were compacted and analyzed for their tabletability (tensile strength vs. compaction pressure) as well as their Heckel plot.

It was shown that with Neusilin® the tabletability appears to be independent of the silicate concentration, whereas with Florite® an increasing silicate concentration leads to a higher tensile strength. In contrast, the addition of Silica Aerogel and Aerosil® resulted in a decrease of the tensile strength. With Aerosil® a maximum tolerable concentration of 20 % [w/w] was determined. Plastic deformation of all powder blends decreased with increasing silicate concentration. This effect was most pronounced with Aerosil® and least with Florite®.

In conclusion, tablets with acceptable tensile strength were obtained with all plain silicates except for Aerosil®. Therefore, these silicates may be used in tablet formulations, e.g. as carrier materials for liquid or amorphous drugs.

3.1 Introduction

In solid oral dosage forms silicates are commonly used as glidants. Glidants are substances that improve the flowability of cohesive powders and granules. Their mechanism of action is mainly the reduction of the interparticle cohesion and adhesion forces [129]. The van der Waals forces between particles in dry powders can be reduced by addition of silicates which may act as spacers and increase the interparticle distance. Moreover, glidants are believed to act as pore fillers on the surface of the particles or granules which thereby are prevented from interlocking and thus are allowed to flow faster. A third option for improving the flowability is the reduction of adsorbed moisture accompanied by a decrease of interparticle cohesion and adhesion. Silicates are well suited for that purpose because of their small particle size and large specific surface area [130]. One of the most frequently used glidants is colloidal silica (e.g. Aerosil® 200) which exhibits a very small particle size in the colloidal range and a large specific surface area of about 200 m²/g. With the application of silicates as glidants, attention should be paid to the silicate concentration: optimum concentrations of glidants are 1 % or lower. Excess of glidant should be avoided as higher concentrations lead to a decrease of the flowability due to large cohesive forces caused by the large specific surface area of these fine particles [131].

A further important field of application of silicates in solid oral dosage forms is their use as carrier materials. Due to the large specific surface area, silicates are well suited for the adsorption of solid (e.g. amorphous) as well as liquid drugs.
One of the most promising carrier materials is Silica Aerogel which is prepared from silicon dioxide using supercritical extraction [132]. The extremely large specific surface area and the open pore structure of the material make Aerogels an ideal candidate as carrier material. Adsorption of drugs to hydrophilic Silica Aerogels has been shown to be a promising technique for drug release enhancement [51-53]. Upon contact with fluids, the structure of hydrophilic Aerogels collapses and a fast release of the loaded drug takes place. Furthermore, this methodology allows a long-time stabilization of amorphous drugs also leading to fast drug release.

Another silicate with exceptional properties is Neusilin® US2, a synthetic amorphous form of magnesium aluminometasilicate which is prepared by spray drying and thus provides an extremely large specific surface area and good flow and tableting properties. Co-grinding and preparation of solid dispersions with Neusilin® leads to a physical stabilization of amorphous drugs [57, 133] and thus enhanced drug release from formulations with these drugs [134-137]. The high porosity and large specific surface area of Neusilin® allow a high liquid adsorption capacity [107]. This may be of interest especially for the preparation of solid oral dosage forms such as liquisolid compacts [138] and solid self-emulsifying drug delivery systems which both show fast drug release [139-141].

Co-grinding of drugs with Florite®, a calcium silicate [142] with large micropores and excellent tabletability, also leads to a physical stabilization of amorphous drugs with enhanced drug release [134]. Moreover, it has been shown that this silicate is also suitable for adsorption of liquid [142] such as self-emulsifying drug delivery systems [139, 140] or liquid drugs.

However, in comparison to the application as glidant, the use of silicates as carrier materials requires higher amounts of silicate, ultimately leading to dosage forms containing just the drug adsorbed to the silicate. Therefore, as tablets represent widely used dosage forms, the objective of this study was to investigate the physical and tableting properties of the aforementioned silicates. As it was known from preliminary experiments that plain Aerosil® does not result in tablets of sufficient hardness, blends of microcrystalline cellulose and the respective silicate were prepared with varying silicate concentration.

3.2 Materials and methods

Materials

Hydrophilic Silica Aerogel monoliths [143]; Neusilin® US2 (magnesium aluminometasilicate), Fuji Chemical Industry, Toyama, Japan; Aerosil® 200 (colloidal silica), Evonik, Darmstadt, Germany; Florite® (calcium silicate), Tokuyama, Tokyo, Japan; Avicel® PH102 (microcrystalline cellulose), FMC BioPolymer, Cork, Ireland; Magnesium stearate, Baerlocher, Unterschleissheim, Germany. All other reagents used were of analytical grade.

Methods

Preparation of Silica Aerogel Microparticles

Hydrophilic Silica Aerogel monoliths prepared as described by Alnaief et al. [143] were milled with mortar and pestle and subsequently classified using a sieve shaker (AS 200, Retsch, Haan, Germany). A fraction of Aerogel particles between 63 µm and 160 µm mesh was selected for further investigation.

Determination of the specific surface area of the silicates

The specific surface area (SSA) of the silicates was quantified by gas adsorption using a Sorptomatic 1990 (Carlo Erba Instruments, Rodano, Italy). The samples were degassed under vacuum for 24 h and exposed to nitrogen at 77.4 K. According to the Brunauer-Emmet-Teller (BET) equation [108] the specific surface area of the silicates was determined within a relative pressure range p/p_0 between 0.05 and 0.3. Surface areas were measured in triplicate.

Determination of the particle size of the silicates

The particle size distribution of the samples was determined in triplicate by laser diffraction using a dry dispersing system with a feeding air pressure of 1 bar (HELOS equipped with RODOS, Sympatec, Clausthal-Zellerfeld, Germany).

Determination of the true density of the silicates

The true density of the silicates was determined in triplicate by helium pycnometry using a 10 cm³ sample cup equipped with a fritted filter cap (Accupyc 1330, Micromeritics, Aachen, Germany). Prior to testing the silicates were dried for 5 days over phosphorus pentoxide. Each measurement included 10 purge cycles followed by 10 measuring cycles.

Scanning electron microscopy of the silicates

The silicates were coated with a thin carbon layer and analyzed using a LEO 1525 scanning electron microscope (LEO Elektronenmikroskopie, Oberkochen, Germany) at an accelerating voltage of 5 kV.

Determination of the moisture sorption isotherms

The dynamic water sorption of the silicates was determined automatically by an adsorption test system (SPS 11, Projekt Messtechnik, Ulm, Germany) at 25 °C. Approximately 200 mg of the silicates were equilibrated at 60 °C and 0 % R.H. for 48 h in the test apparatus prior to testing. The relative humidity range was 0 – 90 % R.H. in steps of 10 % each. At each humidity step, the samples were allowed to equilibrate until a weight change of < 0.01 % / 30 min was reached.

Preparation of the tablets

Various powder blends with varying silicate concentration were prepared with Avicel® and the respective silicate. The ingredients were mixed for 5 min in a Turbula blender (T2F, Willy A. Bachofen, Muttenz, Switzerland) and compacted to tablets with an instrumented eccentric press (EXI, Fette, Schwarzenbek, Germany) equipped with flat faced punches of 10 mm diameter. External lubrication was performed by polishing the surface of the upper and lower punch as well as the die wall with magnesium stearate. 300 mg of the powder blends were filled manually into the die and compacted at a compaction speed of 16 strokes / min. For tablets consisting of 100 % silicate only 160 mg were compacted. All experiments were performed at 21 °C / 45 % R.H..

Characterization of the tablets

Tablets were characterized after a relaxation time of at least 24 h. Crushing force, tablet diameter, and tablet thickness were determined using a hardness tester (TBH30, Erweka, Heusenstamm, Germany). The tensile strength was calculated according to Fell et al. [109]. Tabletability was characterized by plotting the tensile strength versus the compaction pressure. For generation of the Heckel plot the porosities of the tablets at maximum compaction pressure in the die were used [112, 113]. From the Heckel plot the mean yield pressure, which represents the reciprocal value of the slope, may be determined [114].

3.3 Results and discussion

Characterization of the silicates

The physical properties and the SEM pictures of the silicates are shown in Table 7 and Fig. 9, respectively. The specific surface area (SSA) and the structure of the investigated silicates differed significantly from each other. Florite® with its petaloid crystal structure and large micropores exhibited the smallest SSA which is slightly lower than that of Aerosil® with its loose particle aggregates. Neusilin® which is prepared by spray drying resulting in spherically shaped, porous, ultra light granules showed an almost 1.5 fold larger SSA than Aerosil®. The largest SSA by far was found with the Silica Aerogel. This extremely large SSA and the nano-sized open pore structure of Aerogels result from their unique manufacturing process [132].

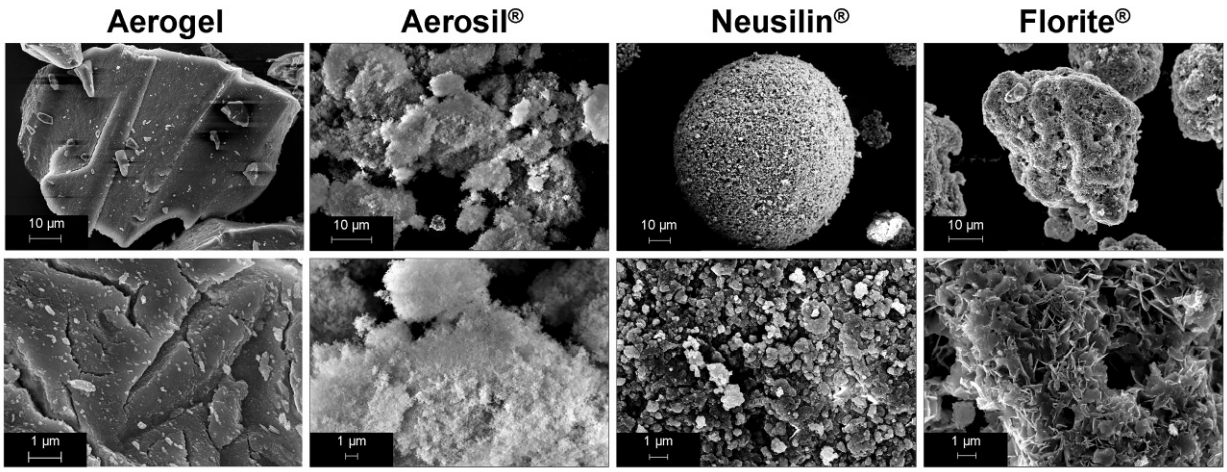

Fig. 9: SEM pictures of the silicates

The mean particle size of Neusilin® was found to be twice larger than that of Florite®. The particle size determined with Aerosil® represents the size of the loose aggregates formed by the nanometer-sized primary particles. The particle size of the Silica Aerogel microparticles was a result of the milling and sieving procedure of the Silica Aerogel monoliths. In contrast to Neusilin® and Silica Aerogel, Florite® and Aerosil® did not show free flowability due to their very small particle size and the resulting high cohesive forces [129]. Moreover, the spherical shape of Neusilin®, a result of its

manufacturing process, supports good flowability. Recently, Alnaief et al. [144] developed the in situ production of spherical Aerogel microparticles which show even better flowability than the milled Aerogel microparticles due to their spherical shape.
True densities of the silicates were similar, whereat Aerosil® exhibited the highest and Silica Aerogel the lowest value.

Table 7: Physical properties of the silicates (means ± SD; n = 3)

Silicate	Aerogel	Aerosil®	Neusilin®	Florite®
SSA [m²/g]	756 ± 13	201 ± 7	339 ± 1	142 ± 7
Particle size (d_{50}) [µm]	72.6 ± 1.6	17.0 ± 0.6	80.8 ± 0.7	33.1 ± 0.0
True density [g/cm³]	1.99 ± 0.02	2.83 ± 0.17	2.13 ± 0.01	2.47 ± 0.03

In Fig. 10 the moisture sorption isotherms of the silicates are shown. Aerosil® and Florite® showed a relatively low moisture sorption over the whole range of investigated R.H., whereas Neusilin® and Silica Aerogel showed a pronounced moisture uptake beyond 70 % R.H.. Whereas Aerosil® and Florite® adsorbed only 11 and 17 % water vapor, respectively, Neusilin® and Silica Aerogel adsorbed 74 and 101 %, respectively, at 90 % R.H.. From these results it may be concluded, that the use of Neusilin® and Silica Aerogel require specified processing conditions. This is especially important for the extremely humidity-sensitive hydrophilic Aerogel, because high moisture results in a collapse of its porous structure and thus a loss of its characteristic properties.

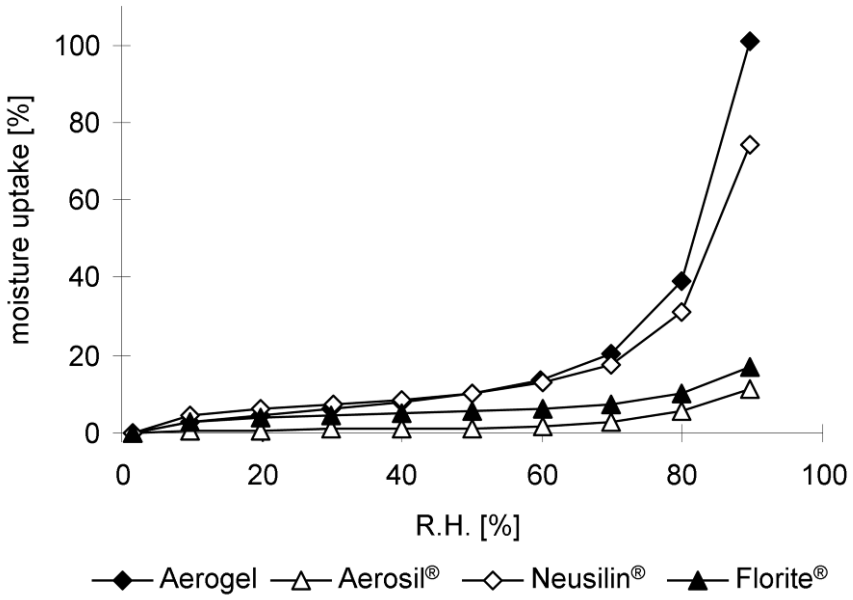

Fig. 10: Moisture sorption isotherms of the silicates

Tableting properties of the silicates

The influence of the silicate concentration on the tabletability of the investigated Avicel® / silicate powder blends is shown in Fig. 11. Obviously, the tableting properties of the powder blends were affected differently by the increase in silicate concentration. The tensile strength of the Aerogel and Aerosil® compacts continuously decreased with increasing silicate concentration (Figs. 11a, b), whereas this decrease was more pronounced with Aerosil® than with Aerogel tablets. The tableting properties of Neusilin® blends remained unaffected by the addition of silicate (Fig. 11c) even up to a silicate concentration of 100 % (= plain Neusilin®). In contrast, according to the data shown in Fig. 11d the tensile strength of Florite® tablets increased with rising silicate concentration resulting in extremely hard tablets: for the manufacture of a sufficiently hard tablet with a tensile strength of 1.5 MPa a compaction pressure of less than 15 MPa is required with plain Florite®.

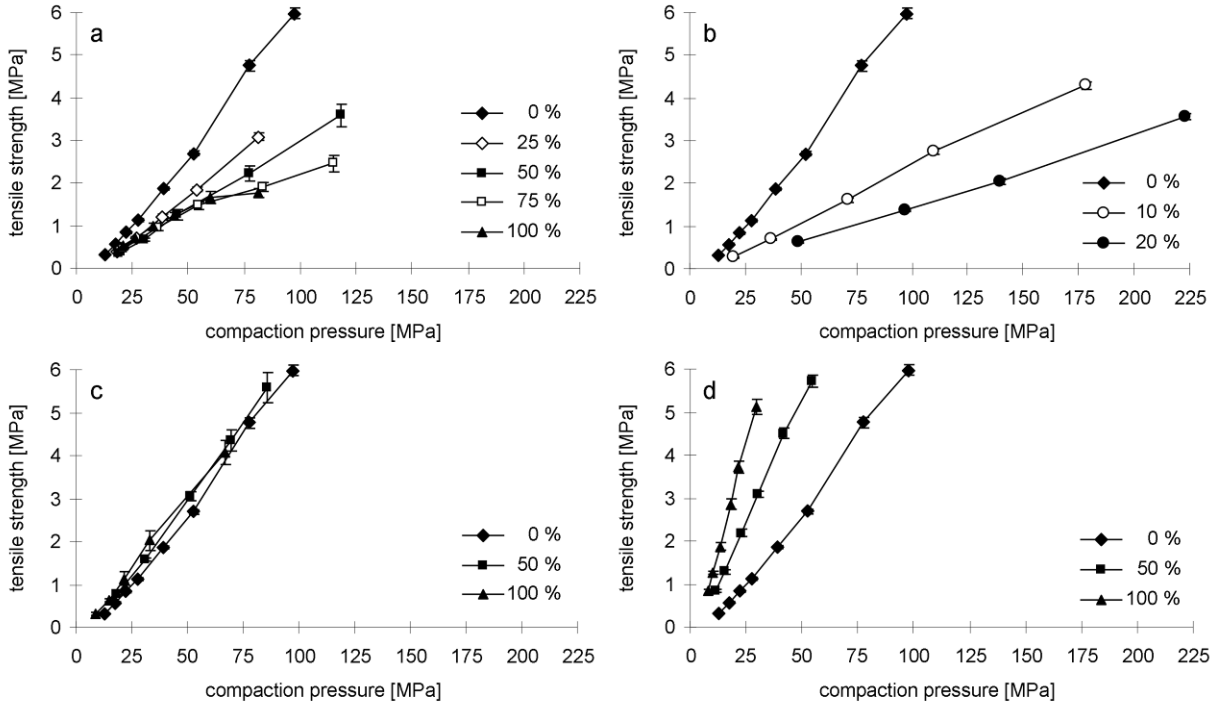

Fig. 11: Tabletability of the Avicel® / silicate powder blends with varying silicate concentrations (means ± SD; n = 6)
a) Aerogel, b) Aerosil®, c) Neusilin®, d) Florite®

These results show that even the plain silicates Neusilin®, Florite® and Aerogel can be compacted to tablets of acceptable tensile strength of 1.5 MPa. With Aerosil® blends a silicate concentration of up to 20 % resulted in a sufficient tensile strength at a compaction pressure of 100 MPa. Blends containing a silicate concentration of 30 % could not be compacted to tablets even at high pressures of 200 MPa.

To characterize the deformation process of the powder blends, the Heckel plot was recorded. The Heckel plot is used to determine the plastic deformation characteristics of a powder blend to be compacted [115, 116]. A high slope and thus a low mean yield pressure represent a high degree of plastic deformation [114]. The Heckel plots of the investigated blends are shown in Fig. 12.

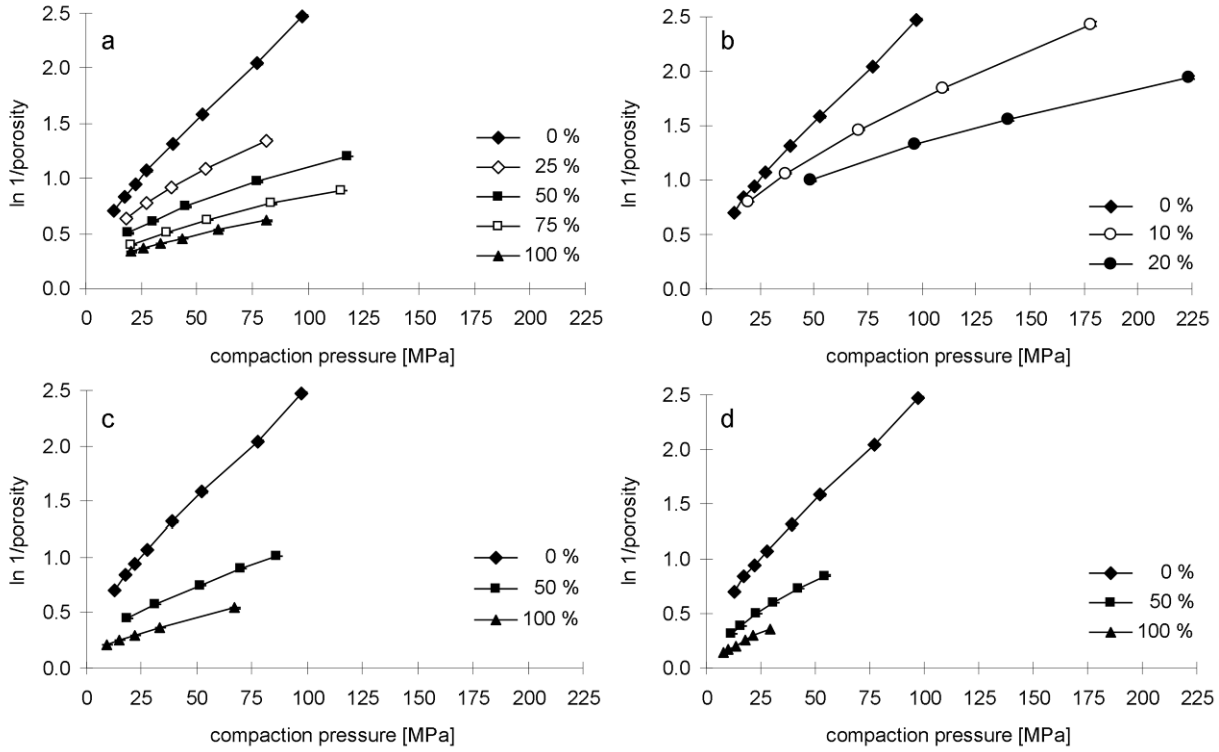

Fig. 12: Heckel plots of the Avicel® / silicate powder blends with varying silicate concentrations (means ± SD; n = 6)
a) Aerogel, b) Aerosil®, c) Neusilin®, d) Florite®

It is obvious with all blends that the slope of the Heckel plot decreases with increasing silicate concentration indicating a loss of plastic deformation behavior. However, this decrease was pronounced differently with the respective silicate blends. The influence of the silicate concentration on the mean yield pressure is displayed in detail in Fig. 13 for the different silicate blends.

Avicel® as microcrystalline cellulose shows a high degree of plastic deformation [128] manifesting itself in a low mean yield pressure (50 MPa). The addition of silicate led to a reduction of plastic deformation of the blends, which was most pronounced with Aerosil®, followed by Silica Aerogel and Neusilin®, whereas the addition of Florite® showed the lowest reduction. A relationship was found for the investigated silicates between the tensile strength of the tablets and the mean yield pressure (Figs. 11, 13): the higher the mean yield pressure and thus the lower the degree of plastic

deformation, the lower the resulting tablet hardness. Hardest tablets were obtained with Florite® which exhibited the lowest mean yield pressure, followed by Neusilin® and Aerogel, whereas tablets containing Aerosil® showed the highest mean yield pressure resulting in the lowest tablet strength.

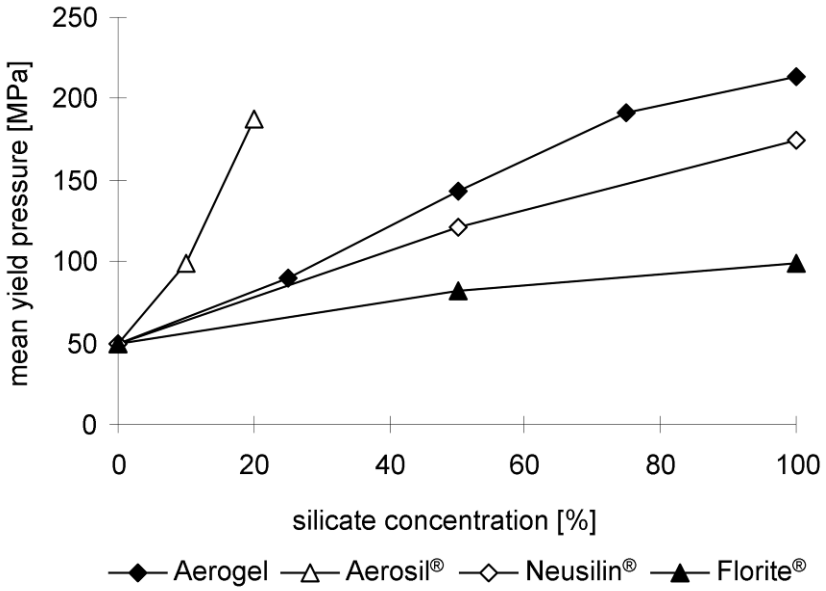

Fig. 13: Influence of the silicate concentration on the mean yield pressure of the Avicel® / silicate powder blends

However, the results also show that in addition to plastic deformation other bonding mechanisms within the silicates must be present. For instance, the tensile strength of Florite®-containing tablets was higher than that of plain Avicel® tablets although the mean yield pressure increased slightly with rising Florite® concentration. Further possible bonding mechanisms are mechanical interlocking of irregular particles, forces of attraction including Coulomb forces, hydrogen bonds, and van der Waals forces [145, 146].

3.4 Conclusion

The physical properties and the structures of the investigated silicates differed significantly from each other. Silica Aerogel exhibited by far the largest specific surface area and Florite® the lowest. Silica Aerogel and Neusilin® showed free flowability due to the larger particle size in comparison to Florite® and Aerosil®. Moreover, Neusilin® and Silica Aerogel were more sensitive to moisture sorption than the other investigated silicates. The tabletability of the silicates improved in the following order: Aerosil® < Silica Aerogel < Neusilin® < Florite®, whereas plastic deformation of all powder blends decreased with increasing silicate concentration. It was shown that compaction of plain Silica Aerogel, Neusilin® and Florite®, respectively, result in acceptable tablet hardness. Thus, these silicates are most suitable as tableting excipients, e.g. as carrier materials for liquid drugs or for amorphisation of drugs.

4. Suitability of various excipients as carrier and coating materials for liquisolid compacts

Suitability of various excipients as carrier and coating materials for liquisolid compacts

Abstract

The liquisolid technology is a promising technique for release enhancement of poorly soluble drugs. With this approach liquids such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are transformed into acceptably flowing and compressible powders. As fast release liquisolid compacts require a high amount of liquid vehicle more effective tableting excipients for liquid adsorption are needed to reduce tablet weight.

The aim of this study was to investigate the suitability of various novel tableting excipients as carrier and coating materials for liquisolid compacts.

Liquisolid compacts containing the liquid drug tocopherol acetate as model drug and various excipients were prepared. The effect of liquid drug content on the flowability and tabletability of the liquisolid powder blends as well as the disintegration of the liquisolid compacts was studied. From this data, the maximum liquid adsorption capacity of the respective mixtures of carrier and coating materials could be determined.

It was shown that the liquid adsorption capacity depends on the specific surface area of the investigated excipients. Fujicalin® (spherically granulated dicalcium phosphate anhydrous) and especially Neusilin® (magnesium aluminometasilicate) are more effective carrier materials for liquid adsorption than Avicel® (microcrystalline cellulose) which is often used for liquisolid systems. Moreover, Florite® (calcium silicate) and Neusilin® turned out to be more suitable as coating materials than the commonly used Aerosil® (colloidal silica) due to their better tableting properties.

In conclusion, if Neusilin® is used as carrier and coating material instead of Avicel® (carrier material) and Aerosil® (coating material) the tocopherol acetate adsorption capacity is increased by a factor of seven.

4.1 Introduction

Poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent a technological challenge as their poor bioavailability is only caused by poor water solubility resulting in low drug absorption [147]. Numerous methods for increasing water solubility and drug release, respectively, are used such as micronization [48], adsorption onto high surface area carriers [52, 53], co-grinding [56], formulation of inclusion complexes [61], solid dispersions [65, 66, 70] and lipid based formulations [71] for instance self-emulsifying drug delivery systems (SEDDS). One of the most promising approaches is the liquisolid technology [11, 14, 29].

The concept of “liquisolid systems“ as defined by Spireas [1] may be used to convert a liquid into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles is incorporated into the porous carrier material (Fig. 14). Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles [2]. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as the carrier material and amorphous silicon dioxide as the coating material.

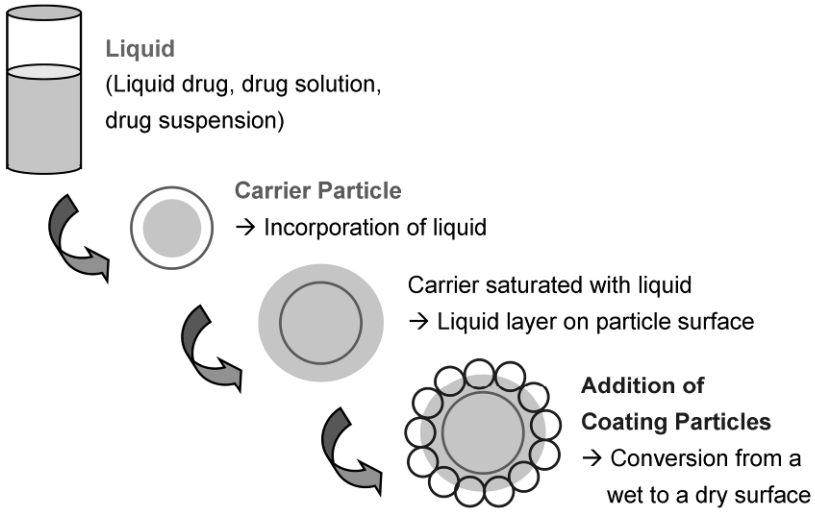

Fig. 14: Schematic representation of liquisolid systems [2]

Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle provide enhanced drug release characteristics due to an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles [3-6]. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus an improved oral bioavailability [9, 10].

The liquisolid technology has been successfully applied to low dose poorly soluble drugs [14, 29]. However, the formulation of a high dose poorly soluble drug is one of the limitations of this technique. The release rates are directly proportional to the fraction of molecularly dispersed drug in the liquid portion [11, 14]. Thus, a higher drug dose requires a higher amount of liquid vehicle to obtain a faster drug release. As a powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties, high amounts of carrier and coating materials are needed. This results in an increase in tablet weight ultimately leading to an unacceptably high tablet size.

A potential approach to minimize tablet weight is to increase the liquid adsorption capacity by either adding binders such as povidone or hypromellose to the liquid portion [18] or by using carrier and coating materials with a high specific surface area (SSA). The higher the specific surface area of an excipient, the higher the liquid load factor [2]. For instance, the liquid adsorption capacity of microcrystalline cellulose (SSA: 1.18 m^2/g) is higher than that of lactose (SSA: 0.35 m^2/g), starch (SSA: 0.6 m^2/g) and sorbitol (SSA: 0.37 m^2/g) [4].

The aim of this study was to investigate novel porous tableting excipients with a high specific surface area with regard to their suitability of liquid adsorption while maintaining acceptable flow and tableting properties. The following excipients were compared to the commonly used carrier and coating materials Avicel® and Aerosil®: Fujicalin®, a spherically granulated dicalcium phosphate anhydrous [105, 106] with a high porosity and high specific surface area resulting in good flowability and tabletability, Neusilin® US2, a synthetic amorphous form of magnesium alumino-metasilicate [141] prepared by spray drying with an extremely high specific surface

area and good flowability and tabletability, and Florite®, a calcium silicate [142] with large micropores and excellent tabletability.

In the present study the influence of liquid drug content on the flowability and tabletability of various liquisolid powder blends was analyzed. Tocopherol acetate was used as the liquid model substance. The objective was to identify the most effective carrier and coating material for liquid uptake while maintaining acceptable flow and tableting properties. Therefore, in the first part of the study various carrier materials were investigated and compared to Avicel® and in the second part the commonly used coating material Aerosil® was replaced by novel excipients to further optimize the liquid adsorption capacity.

4.2 Materials and methods

Materials

Tocopherol acetate, BASF, Ludwigshafen, Germany; Avicel® PH200 (microcrystalline cellulose), FMC BioPolymer, Cork, Ireland; Neusilin® US2 (magnesium aluminometasilicate), Fuji Chemical Industry, Toyama, Japan; Fujicalin® (spherically granulated dicalcium phosphate anhydrous), Fuji Chemical Industry, Toyama, Japan; Aerosil® 200 (colloidal silica), Evonik, Darmstadt, Germany; Florite® (calcium silicate), Tokuyama, Tokyo, Japan; Kollidon® CL (crospovidone), BASF, Ludwigshafen, Germany; Magnesium stearate, Baerlocher, Unterschleissheim, Germany. All other reagents used were of analytical grade.

Methods

Determination of the specific surface area of the excipients

The specific surface area of the excipients was determined by gas adsorption using a Sorptomatic 1990 (Carlo Erba Instruments, Rodano, Italy). The samples were degassed under vacuum for 24 h and exposed to nitrogen at 77.4 K. According to the Brunauer-Emmet-Teller (BET) equation [108] the specific surface area of the excipients was evaluated within a relative pressure range p/p_0 between 0.05 and 0.3. Each excipient was measured in triplicate.

Scanning electron microscopy of the excipients

The excipients were coated with a thin carbon layer and analyzed using a LEO 1525 scanning electron microscope (LEO Elektronenmikroskopie, Oberkochen, Germany) and an accelerating voltage of 5 kV.

Preparation of the liquisolid powder blends

Liquisolid powder blends of varying content of tocopherol acetate (TA) (expressed as percent [w/w] referred to the total weight of TA, carrier and coating materials) were prepared with a Bohle Mini Granulator (BMG, Bohle, Ennigerloh, Germany). The liquid

drug was added as acetonic solution to binary mixtures of carrier and coating materials (Table 8). Carrier and coating materials were used in a ratio of 20 : 1 (*R*-value) according to the recommendation of Spireas et al. [29]. Mixing was performed until the powder appeared visibly dry. To remove solvent residues, the blends were subsequently oven-dried (2 h, 40 °C) and stored at 21 °C / 45 % R. H. before use.
Prior to tableting Neusilin® blends were mixed with Kollidon® CL (6 % [w/w]) for 5 min in a Turbula blender (T2F, Willy A. Bachofen, Muttenz, Switzerland) to ensure tablet disintegration.

Table 8: Excipient composition of various tocopherol acetate liquisolid compacts

Carrier material	Coating material	*R*	Disintegrant
Avicel®	Aerosil®	20 : 1	–
Fujicalin®	Aerosil®	20 : 1	–
Neusilin®	Aerosil®	20 : 1	Kollidon® CL*
Neusilin®	Florite®	20 : 1	Kollidon® CL*
Neusilin®	Neusilin®	20 : 1	Kollidon® CL*

R - Excipient ratio (carrier material : coating material)
*6 % [w/w] referring to the weight of the liquisolid formulation

Flowability of the liquisolid powder blends

Flow properties of the liquisolid powder blends were characterized by measurement of the Hausner ratio and the powder flow rate. The Hausner ratio was calculated as the quotient of tap and bulk density. Bulk and tap densities were determined with a jolting volumeter (STAV 2003, J. Engelsmann, Ludwigshafen, Germany) equipped with a 50 ml measuring cylinder according to the Pharmacopoeia Europaea. The powder flow rate was measured by recording the weight change over time with a precision balance

(BL 1500 S, Sartorius, Göttingen, Germany). The orifice diameter of the funnel was 7 mm.

Tableting of the liquisolid powder blends

Tablets were produced with an instrumented eccentric press (EXI, Fette, Schwarzenbek, Germany) equipped with flat faced punches of 10 mm diameter. External lubrication was performed with magnesium stearate. The required amount of powder was filled manually into the die and compressed at a compaction speed of 16 strokes / min. All experiments were performed at 21 °C / 45 % R. H..

Characterization of the liquisolid compacts

Tablets were characterized after a relaxation time of at least 24 hours after tablet manufacture. Crushing force, tablet diameter and tablet thickness were determined using a hardness tester (TBH30, Erweka, Heusenstamm, Germany). The tensile strength was calculated according to Fell et al. [109]. Tabletability of the liquisolid compacts was evaluated by plotting tensile strength versus compaction force. A minimum tensile strength of 1.5 MPa was regarded as sufficient tablet hardness. Disintegration time was measured with a disintegration tester (ZT 72, Erweka, Heusenstamm, Germany) according to the conditions of the Ph. Eur. for uncoated tablets.

4.3 Results and discussion

Characterization of the excipients

The specific surface area (SSA) and the structure of the investigated excipients differ significantly from each other. For instance, the specific surface area of Fujicalin® (SSA: 32 ± 1 m²/g) is 32 times higher than that of Avicel® (SSA: 1 ± 0 m²/g). This difference becomes apparent in Fig. 15. Whereas the spherically granulated dicalcium phosphate anhydrous (Fujicalin®) shows a high porosity, microcrystalline cellulose (Avicel®) exhibits a smooth surface. From the excipients investigated in this study the silicates provide by far the highest specific surface areas. Florite® with its petaloid crystal structure and large micropores exhibits a SSA of 142 ± 7 m²/g, whereas Aerosil® with its loose agglomerates formed by the nanometer-sized primary particles exhibits a SSA of 201 ± 7 m²/g. The highest specific surface area by far shows Neusilin® (SSA: 339 ± 1 m²/g) which is prepared by spray drying resulting in spherically shaped, porous, ultra light granules.

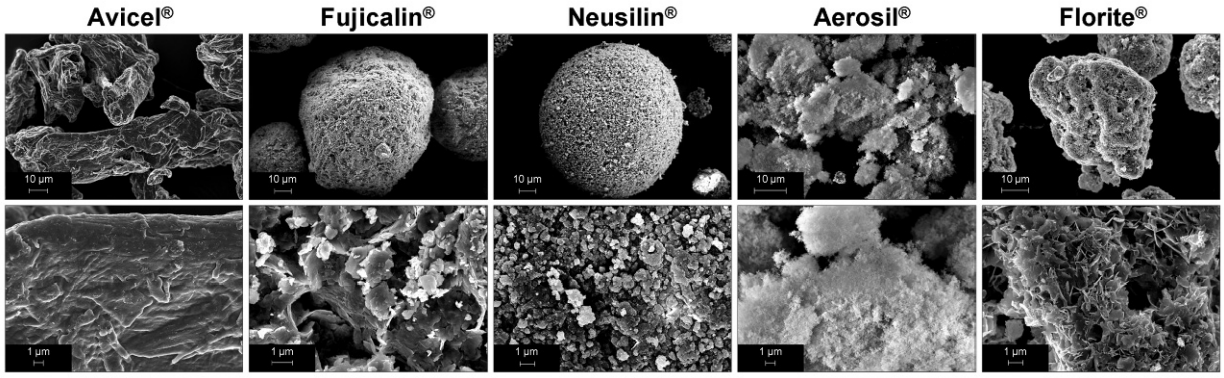

Fig. 15: SEM pictures of the excipients

Variation of the carrier material

In the following subchapters the results of the flowability, tabletability, and tablet disintegration of the formulations containing Aerosil® as coating material, Avicel®, Fujicalin® or Neusilin® as carrier material (Table 8) and tocopherol acetate as liquid drug are presented.

a. Flowability

In Fig. 16 the influence of liquid drug content on the flowability of the liquisolid powder formulations is shown. The flowability of the investigated blends was affected differently by the increase in liquid drug content.

For all three formulations the blends without TA show poor flowability manifesting itself in a high Hausner ratio and a low powder flow rate. This can be attributed to the high amount of very fine Aerosil® coating particles leading to large cohesive and adhesive forces caused by the high specific surface area of these fine particles. It is shown for all formulations that the addition of the liquid drug improves the flowability (decrease of the Hausner ratio and increase in powder flow rate). The liquid drug is initially adsorbed by the carrier surfaces and subsequently covered by the fine Aerosil® coating particles resulting in particles with better flowability due to a decrease of interparticle forces.

For Avicel® blends this flowability improvement could only be observed with up to 8 % liquid drug content (Fig. 16a). With higher liquid drug contents (12 and 16 %) the flowability decreases because the liquid drug content was too high. The high amount of liquid could not be completely adsorbed by the carrier and coating materials and thus, sticky agglomerates were formed. The blend with 20 % TA was not measurable because of pronounced sticking. Therefore, best flowability of the Avicel® blends is observed with a liquid drug content of 8 %.

In contrast to Avicel®, Fujicalin® and Neusilin® blends show improved flowability far beyond 8 % liquid drug content (Figs. 16b and 16c). The high porosity and high specific surface area of these excipients allow penetration of the liquid into the particle pores and thus, a high liquid load. The flowability improvement can be attributed to a sponge-like liquid uptake into these porous excipients resulting in a weight gain of the individual particles accompanied by better flow properties.
The liquid oversaturation is not yet reached for the Fujicalin® blends and the Neusilin® blends with a TA content of 20 % and 55 %, respectively.

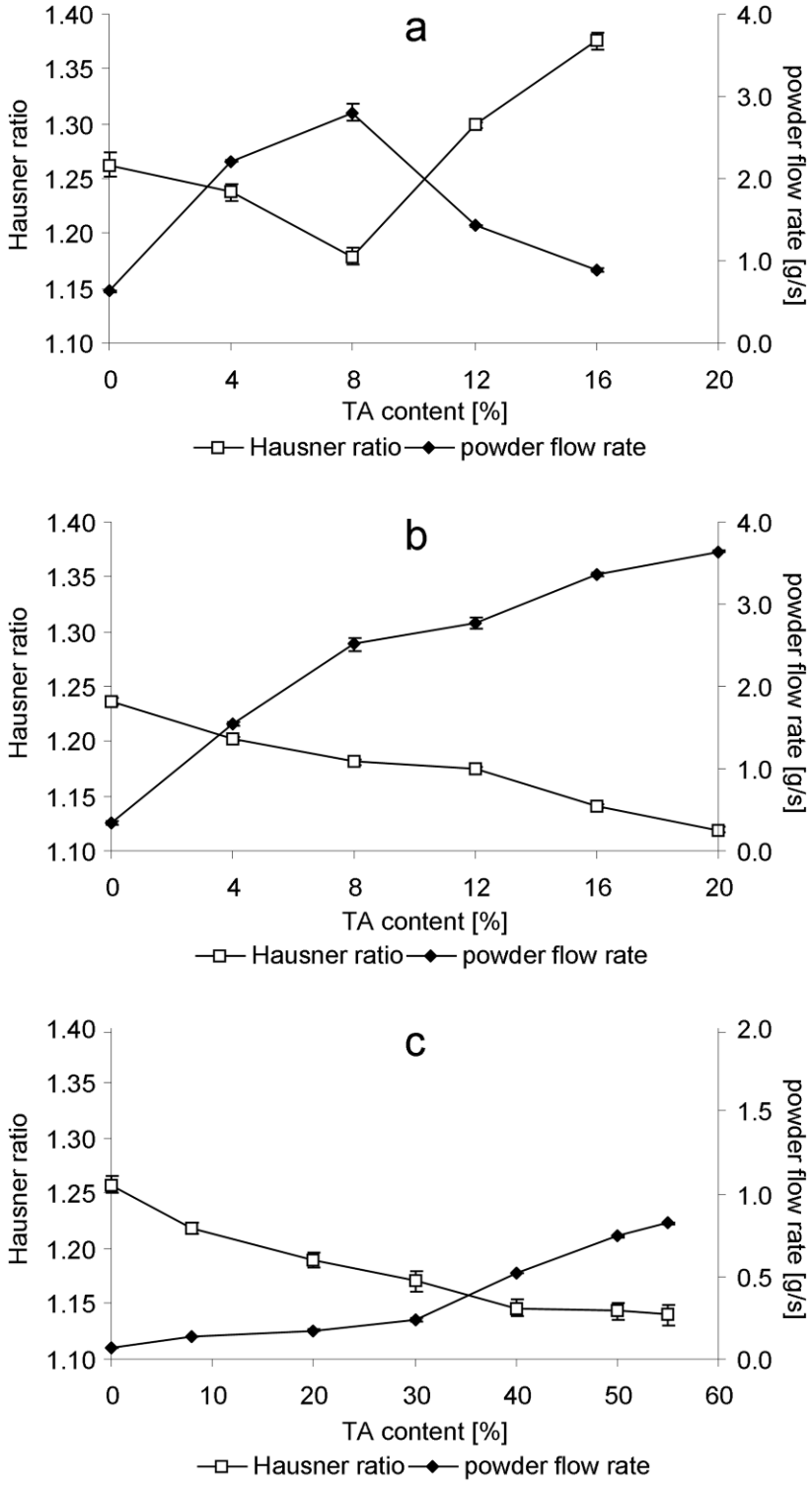

Fig. 16: Flowability of TA liquisolid powder blends containing Aerosil® as coating material (means ± SD, Hausner ratio: n = 3, powder flow rate: n = 5)
a) Avicel® blends, b) Fujicalin® blends, c) Neusilin® blends

b. Tabletability

The influence of tocopherol acetate on the tableting properties of the investigated blends is shown in Fig. 17. Obviously, the tableting properties of the blends are affected differently by the increase in liquid drug content.

The tensile strength of the Avicel® compacts continuously decreases with increasing liquid drug content (Fig. 17a), whereas the tableting properties of Fujicalin® blends remain almost unaffected by the addition of liquid drug up to 12 % (Fig. 17b). This may be explained by the different deformation characteristics of these two excipients: Avicel® as microcrystalline cellulose shows plastic deformation [128] whereas fragmentation is the main deformation mechanism of the dicalcium phosphate Fujicalin® [105]. With a brittle excipient new contact areas form instantaneously during compaction and thus, the liquid drug does not influence the tabletability at a low liquid content.

As with Fujicalin®, Neusilin® formulations are insensitive to liquid addition up to a certain liquid content. With the Neusilin® formulations this insensitivity is even extended up to 40 % liquid content (Fig 17c).

In conclusion, tablets with acceptable mechanical properties are obtained with a maximum TA content of 8 % for the Avicel® compacts, 12 % for the Fujicalin® compacts and 50 % for the Neusilin® compacts.

With higher liquid drug contents the tablet hardness decreases significantly and the tensile strength is independent of the compaction force. The adhesive properties of the drug itself cause sticking of the compressed particles resulting in a constant low tensile strength.

These results show that with the investigated novel carrier materials a higher liquid drug content of the liquisolid compacts can be achieved while maintaining good tableting properties. The superior liquid adsorption capacity of Neusilin® and Fujicalin® can be explained by their porous structure and high specific surface area.

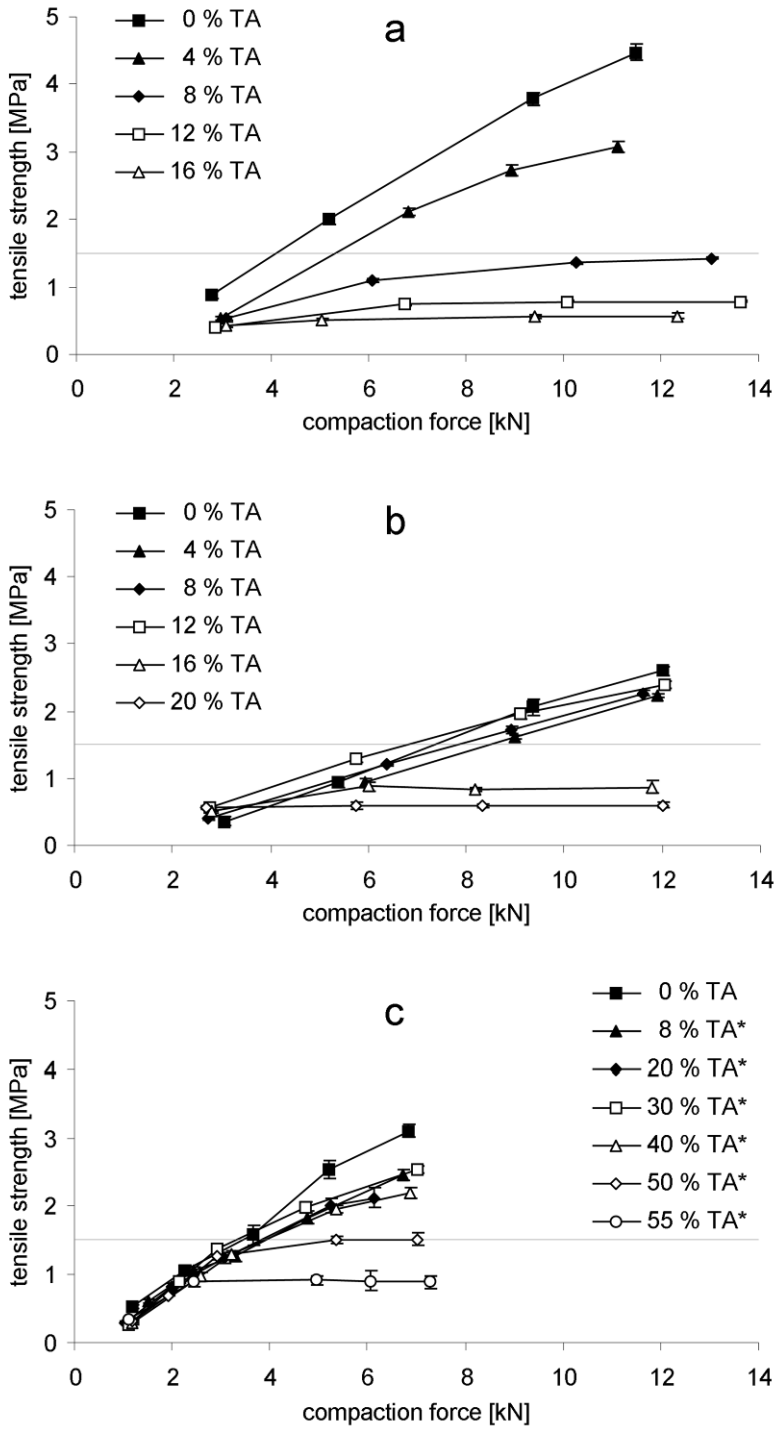

Fig. 17: Tabletability of TA liquisolid compacts containing Aerosil® as coating material (means ± SD, n = 5)
a) Avicel® compacts, b) Fujicalin® compacts, c) Neusilin® compacts
*containing additional 6 % Kollidon® CL

c. Disintegration

In Fig. 18 the disintegration of the Avicel® and Fujicalin® compacts is shown. As expected, all tablets show an increase in disintegration time with increasing drug content due to the lipophilic nature of TA and thus, a decreased wettability of the compacts. Moreover, the disintegration time is strongly dependent on the excipient used. In comparison to Fujicalin® (Fig. 18b), Avicel® compacts disintegrate much faster (Fig. 18a). This may be explained by an extremely fast water penetration into microcrystalline cellulose tablets caused by wicking and subsequent widening of the pores [148]. The very fast disintegration of Neusilin® compacts (< 1 min) is solely caused by the addition of the superdisintegrant Kollidon® CL.

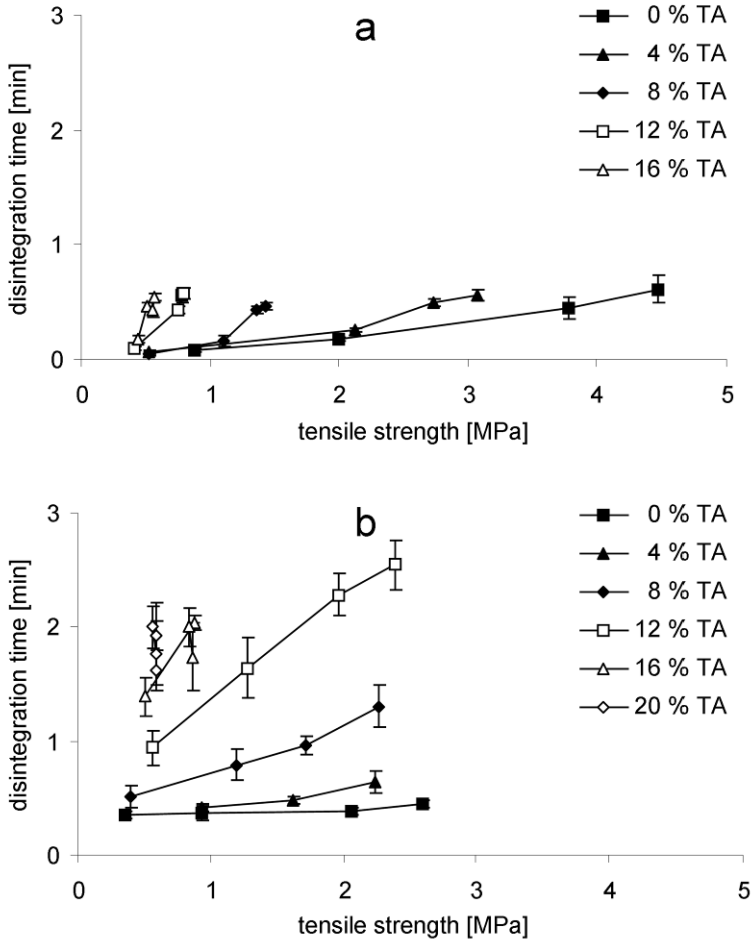

Fig. 18: Disintegration of TA liquisolid compacts containing Aerosil® as coating material (means ± SD, n = 6)
a) Avicel® compacts, b) Fujicalin® compacts

Variation of the coating material

As Neusilin® turned out to be the most effective carrier (Figs. 16 and 17) this silicate was used for further studies as carrier material to look for the most effective coating material. In the following subchapters the results of the flowability and tabletability of the formulations containing Neusilin® as carrier material, Aerosil®, Florite® or Neusilin® as coating material (Table 8) and tocopherol acetate as liquid drug are presented. The disintegration times of the compacts are not discussed because of the very fast disintegration of the Neusilin®-containing compacts (see above).

a. Flowability

All blends containing Neusilin® as carrier material show good flowability at high TA contents of 50 and 55 % (Table 9). Moreover, a slight improvement of the powder flow rate is observed with all blends with an increasing drug content from 50 to 55 %. This can be explained by the above mentioned sponge-like liquid uptake of Neusilin® and thus, a weight gain of the individual particles. Among these free flowing powder blends the formulation containing Neusilin® as carrier as well as coating material exhibits the best flow properties with the lowest Hausner ratio and the highest powder flow rate resulting from the spherical shape of this silicate.

Table 9: Flowability of TA liquisolid powder blends containing Neusilin® as carrier material (means ± SD, Hausner ratio: n = 3, powder flow rate: n = 5)

	Hausner ratio		Powder flow rate [g/s]	
	50 % TA	55 % TA	50 % TA	55 % TA
Aerosil® blends	1.14 ± 0.01	1.14 ± 0.01	0.74 ± 0.00	0.82 ± 0.01
Florite® blends	1.16 ± 0.00	1.16 ± 0.00	0.59 ± 0.00	0.60 ± 0.01
Neusilin® blends	1.13 ± 0.01	1.13 ± 0.01	0.87 ± 0.00	0.90 ± 0.00

b. Tabletability

In Fig. 19 the tabletability of tocopherol acetate liquisolid compacts containing Neusilin® as carrier material is shown. As mentioned above for the Neusilin®- and Aerosil®-containing compacts, tablets with acceptable mechanical properties are obtained with a maximum TA content of 50 % (Figs. 17c, 19a). The replacement of Aerosil® by Florite® or Neusilin® as coating material allows a higher liquid loading capacity. With Neusilin® and Florite® as coating material an increase of the liquid content up to 55 % is possible resulting in acceptable tablet hardness (Figs. 19b and 19c). Therefore, Florite® and Neusilin® turned out to be more suitable as coating materials than the commonly used Aerosil®. This higher liquid loading capacity is accompanied by better tableting properties of Florite® and Neusilin® than Aerosil®: The tensile strength of the Aerosil® compacts is considerably lower than that of the respective Florite® and Neusilin® compacts.

In conclusion, compared to the commonly used carrier and coating materials Avicel® and Aerosil® (Fig. 17a) the liquid adsorption capacity of the formulation containing Neusilin® as carrier as well as coating material (Fig. 19c) is increased by a factor of seven (from 8 to 55 % TA).

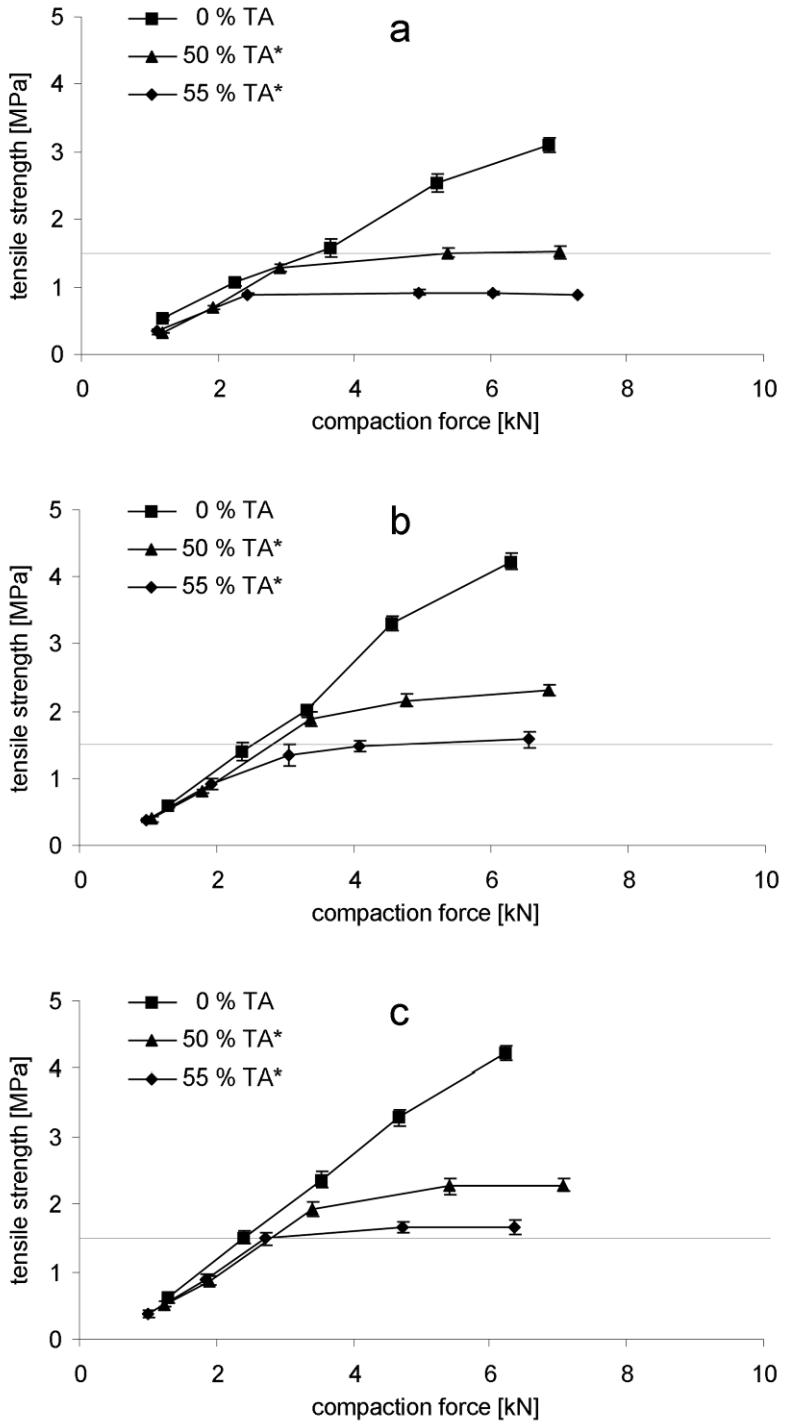

Fig. 19: Tabletability of TA liquisolid compacts containing Neusilin® as carrier material (means ± SD, n = 5)
a) Aerosil® compacts, b) Florite® compacts, c) Neusilin® compacts
*containing additional 6 % Kollidon® CL

4.4 Conclusion

It could be shown that the selection of the carrier and coating materials strongly affects the liquid adsorption capacity of liquisolid formulations. Replacement of the commonly used carrier and coating materials by excipients with high specific surface areas and good flow and tableting properties allows considerably higher liquid adsorption capacities. If Neusilin® is used as carrier as well as coating material instead of Avicel® and Aerosil®, the tocopherol acetate adsorption capacity is increased by a factor of seven. This higher liquid adsorption capacity leads to a significant improvement of the liquisolid technology: the use of this effective excipient enables the preparation of liquisolid compacts of high dose, poorly soluble drugs where high amounts of liquid vehicle are needed. Thus, tablet weights are reduced in comparison to the commonly used carrier and coating materials. Furthermore, Neusilin® simplifies the preparation of liquisolid formulations as it acts as carrier as well as coating material.

Moreover, as solid dosage forms are preferred over liquid preparations due to improved patient compliance, dosage uniformity, and stability highly adsorptive tableting excipients provide a wide field of application for liquid drugs, liquid nutritional supplements or liquid SEDDS.

5. Enhancement of griseofulvin release from hydrophilic aerogel formulations and liquisolid compacts

Enhancement of griseofulvin release from hydrophilic aerogel formulations and liquisolid compacts

Abstract

The potential of hydrophilic aerogel formulations and liquisolid systems to improve the release of poorly soluble drugs was investigated using griseofulvin as model drug. The in vitro release rates of this drug formulated as directly compressed tablets containing crystalline griseofulvin were compared to aerogel tablets with the drug adsorbed onto hydrophilic silica aerogel and to liquisolid compacts containing the drug dissolved or suspended in PEG 300. Furthermore, the commonly used carrier and coating materials in liquisolid systems Avicel® and Aerosil® were replaced by Neusilin®, an amorphous magnesium aluminometasilicate with an extremely high specific surface area to improve the liquisolid approach.

Both the liquisolid compacts containing the drug dissolved in PEG 300 and the aerogel tablets showed a considerably faster drug release than the directly compressed tablets. With liquisolid compacts containing the drug suspended in PEG 300 the release rate increased with rising percentage of dissolved drug in the liquid portion. It could be shown that Neusilin® with its extremely high liquid adsorption capacity allows the production of liquisolid formulations with lower tablet weights.

5.1 Introduction

Since the implementation of combinatorial chemistry and high throughput screening for the investigation of new chemical entities the molecular weight and lipophilicity of drugs increase and this in turn decreases water solubility [149]. Especially poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent a technological challenge, as their poor bioavailability is solely caused by poor water solubility resulting in low drug absorption [147]. Therefore, new technologies increasing the solubility and thus drug release are looked for. Release enhancement of poorly soluble drugs may be achieved by an increase of the drug solubility, the drug surface area, or by formulating the drug in its dissolved state: Several methodologies such as micronization [48], co-grinding [55, 56], formulation of inclusion complexes [61], solid dispersions [65, 70] and lipid based formulations [71] such as self-emulsifying drug delivery systems (SEDDS) have been introduced with different success.

Adsorption of drugs onto hydrophilic silica aerogels has been shown to be a promising technique for drug release enhancement [52, 53]. This methodology also allows a long-time stabilization of amorphous drugs. Upon contact with fluids, the structure of hydrophilic aerogels collapses and a fast release of the loaded drug takes place.
One of the most promising approaches for release enhancement is the liquisolid technology [3, 5, 11, 14, 19, 30]. Liquisolid systems are composed of a non-volatile, water soluble liquid vehicle, solid drug particles and selected excipients, named the carrier and coating materials. The drug may be dissolved or suspended in the liquid vehicle. Subsequently, this liquid portion is transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with the carrier and coating materials. Liquisolid compacts of poorly soluble drugs containing the drug dissolved or suspended in a solubilising liquid vehicle provide enhanced drug release due to an increased aqueous solubility of the drug, an increased surface area of the drug, and an improved wettability of the drug particles [4, 6]. Accordingly, this optimized drug release allows an improved drug absorption in the gastrointestinal tract and thus a higher oral bioavailability [9, 10].

Besides drug release enhancement, the liquisolid approach is a promising technique because of the simple manufacturing process, low production costs and the possibility of industrial manufacture due to good flow and compaction properties of the liquisolid formulations.

To calculate the required amount of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquisolid systems has been developed by Spireas [1].
Depending on the excipient ratio *R* of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load, named "liquid load factor" (L_f), is not exceeded.
The terms "acceptable flow" and "acceptable compressibility" imply the desired and thus preselected flow and compaction properties, which must be met by the final liquisolid formulation.
R represents the ratio between the mass of the carrier (*Q*) and the coating (*q*) materials present in the formulation:

$$R = Q / q \qquad \text{Eq. (8)}$$

L_f represents the ratio between the mass of the liquid portion *W* and the carrier materials *Q*:

$$L_f = W / Q \qquad \text{Eq. (9)}$$

With the desired amount of liquid, the amount of carrier and coating material can be calculated if the liquid load factor L_f is known.

The aim of the present study was to compare drug release from several griseofulvin tablet formulations. The poorly soluble antifungal drug was formulated as conventional tablets containing crystalline griseofulvin, as aerogel tablets containing the drug adsorbed to hydrophilic silica aerogel and as liquisolid compacts containing the drug dissolved in PEG 300. Liquisolid compacts containing the drug suspended in PEG 300 were investigated with regard to the influence of drug content in the liquid portion on drug release. Furthermore, the commonly used carrier and coating materials in

liquisolid systems Avicel® and Aerosil®, respectively, were replaced by Neusilin® to improve the liquisolid approach. Due to its extremely high specific surface area as well as its good flow and tableting properties this magnesium aluminometasilicate was assumed to allow a considerably higher liquid load factor, thereby enabling the preparation of liquisolid compacts with lower tablet weights.

5.2 Materials and methods

Materials

Griseofulvin, Fagron, Barsbüttel, Germany; Carbon dioxide (purity 99.9 %), AGA Gas, Hamburg, Germany; hydrophilic silica aerogel microspheres, mean particle size 300 µm [144]; polyethylene glycol 300 (PEG 300), glycerol, and propylene glycol, Fagron, Barsbüttel, Germany; Avicel® PH200 (microcrystalline cellulose), FMC BioPolymer, Cork, Ireland; Aerosil® 200 (colloidal silica), Evonik, Darmstadt, Germany; Neusilin® US2 (magnesium aluminometasilicate), Fuji Chemical Industry, Toyama, Japan; Kollidon® CL (crospovidone), BASF, Ludwigshafen, Germany. All other reagents used were of analytical grade.

Methods

Loading of silica aerogel microspheres with griseofulvin

A weighed amount of drug and aerogel microspheres, each wrapped in a filter paper were placed in an autoclave (250 ml, built at the Hamburg University of Technology, Germany). The autoclave was sealed, heated to 40 °C and carbon dioxide was pumped inside until a pressure of 180 bar was reached [143, 150]. After 48 hours under these conditions the pressure was released and the drug-loaded aerogel microspheres (300 µm) were removed. To determine the drug concentration in the loaded aerogel a weighed amount of aerogel microspheres was dispersed in methanol. The solution was stirred for at least 20 min to ensure complete dissolution of the drug. The concentration of the drug in methanol was analyzed spectrophotometrically at 291 nm (1 cm quartz cells, 8453, Agilent Technologies, Santa Clara, USA). Based on these data the drug concentration in the loaded aerogel was calculated. Each experiment was carried out in triplicate.

Solubility studies

The solubility of griseofulvin in three non-volatile liquid vehicles which are commonly used for the formulation of liquisolid compacts, namely, propylene glycol, polyethylene

glycol 300 (PEG 300), and glycerol were determined by preparation of saturated solutions of the drug in these solvents and measuring their drug concentration: excess griseofulvin was stirred in the above mentioned solvents for 48 h at 21 °C. Accurately weighed quantities of the filtered supernatants were further diluted with methanol and analyzed spectrophotometrically at 291 nm for their drug content. From these results the solubility of griseofulvin (in percent [w/w]) in the respective liquid vehicle was calculated. Each experiment was carried out in triplicate.

Preparation of directly compressed tablets

A conventional tablet formulation with micronized griseofulvin and an aerogel tablet formulation with griseofulvin adsorbed to hydrophilic silica aerogel were prepared with each tablet containing Kollidon® CL as disintegrant, Avicel® as binder, and 1.5 mg of drug. The drug concentration of the hydrophilic silica aerogel microspheres was determined to 3.0 ± 0.1 % [w/w] and therefore each tablet contained 50 mg of drug-loaded silica aerogel. To ensure that tablet disintegration is not the rate-limiting step and drug release is not hindered by slow disintegration of the dosage form, 5 % [w/w] Kollidon® CL were added to all formulations. All ingredients were mixed for 5 min in a Turbula blender (T2F, Willy A. Bachofen, Muttenz, Switzerland) and compressed into tablets with an instrumented single punch press (EXI, Fette, Schwarzenbek, Germany) equipped with flat faced punches of 10 mm diameter. For each tablet 300 mg of the powder blends were filled manually into the die and compressed at a compaction speed of 16 strokes / min. The compaction force was adjusted to achieve a minimum tensile strength of 1 MPa [109]. All experiments were performed at 21 °C / 45 % R.H..

Preparation of liquisolid compacts

Several liquisolid formulations with each sample unit containing 3 mg of griseofulvin (corresponding to 2 – 5 tablets) were prepared by addition of the liquid portion (0.9 – 2.3 % drug in PEG 300) to the carrier and coating material and mixing in a mortar (Table 10). Finally, Kollidon® CL was added and the formulations were mixed for 5 min in a Turbula blender. The liquisolid formulations LS-1 – LS-10 consisted of Avicel® as carrier and Aerosil® as coating material. Carrier and coating materials were used in a weight ratio of 20 : 1 (= *R*-value) according to the recommendation of Spireas et al. [29]. A liquid load factor of 0.22 was used in these formulations resulting in acceptable

flowability of the blends (maximum angle of slide 33 °C) and sufficient tablet hardness (minimum tensile strength 1 MPa). For the liquisolid formulation LS-N with Neusilin® as carrier as well as coating material a liquid load factor of 1.58 was used. Despite such a high liquid load factor, the formulation fulfills the required flowability and tablet hardness. The high liquid loading capacity of this magnesium aluminometasilicate may be explained by its extremely high specific surface area of 339 ± 1 m²/g as well as its good flow and tableting properties [107].

The liquisolid formulations were compacted as described for the directly compressed tablets. However, for the liquisolid compacts the required amount of powder blend for one tablet was between 300 and 434 mg (Table 10).

Formulations LS-2 – LS-10 contained drug suspensions as liquid portion in contrast to LS-1and LS-N which contained a drug solution. For suspensions the percentage of dissolved drug in the liquid portion is calculated by the ratio of the drug's solubility in the liquid vehicle PEG 300 and the total drug content in the liquid portion present in each formulation (Table 10).

Disintegration studies

Disintegration time of the investigated tablets was measured with a disintegration tester (ZT 72, Erweka, Heusenstamm, Germany) according to the conditions of the Ph. Eur. for uncoated tablets.

Drug release studies

Drug release of the tablets was measured according to the Ph. Eur. in phosphate buffer (pH 6.8) using a paddle apparatus (Sotax AT7, Allschwil, Switzerland) at 100 rpm and 37 °C. In each vessel containing 900 ml dissolution medium one sample unit corresponding to 3 mg of griseofulvin was analyzed. Because of the slightly different UV spectrum in phosphate buffer drug release profiles were recorded spectrophotometrically at 295 nm.

Table 10: Formulation characteristics of the investigated liquisolid compacts with each sample unit containing 3 mg of griseofulvin

Liquisolid Formulation	Total drug content in liquid portion [g/100 g]	Dissolved drug in liquid portion [% w/w][1]	Amount of liquid portion [mg]	Carrier / Coating material (20 : 1)	Amount of carrier and coating blend [mg]	Disintegrant [% w/w]	Sample unit weight [mg][2]
LS-1	0.9	100	333	Avicel® / Aerosil®	1591	5	2026 (5 tablets)
LS-2	1.0	95	300	Avicel® / Aerosil®	1432	5	1823 (5 tablets)
LS-3	1.1	86	273	Avicel® / Aerosil®	1302	5	1657 (4 tablets)
LS-4	1.2	79	250	Avicel® / Aerosil®	1193	5	1519 (4 tablets)
LS-5	1.3	73	231	Avicel® / Aerosil®	1101	5	1402 (4 tablets)
LS-6	1.5	63	200	Avicel® / Aerosil®	955	5	1215 (3 tablets)
LS-7	1.7	56	176	Avicel® / Aerosil®	842	5	1072 (3 tablets)
LS-8	1.9	50	158	Avicel® / Aerosil®	754	5	959 (3 tablets)
LS-9	2.1	45	143	Avicel® / Aerosil®	682	5	868 (2 tablets)
LS-10	2.3	41	130	Avicel® / Aerosil®	623	5	793 (2 tablets)
LS-N	0.9	100	333	Neusilin® / Neusilin®	222	7.5	600 (2 tablets)

[1] Solubility of griseofulvin in PEG 300: 0.95 [g/100 g]

[2] Each sample unit consisted of several tablets with a weight of 300 - 434 mg each.

5.3 Results and discussion

Solubility of griseofulvin in various non-volatile liquid vehicles

Griseofulvin was found to be poorly soluble in glycerol (0.004 ± 0.000 [% w/w]) and propylene glycol (0.13 ± 0.00 [% w/w]). Its solubility in PEG 300 (0.95 ± 0.00 [% w/w]) was much higher. Thus, to minimize the required amount of liquid, PEG 300 was chosen as liquid vehicle for preparation of griseofulvin liquisolid compacts.

Disintegration of the investigated tablets

The disintegration times of the liquisolid and the directly compressed tablets are shown in Table 11. Obviously, all formulations (except for formulation LS-N) disintegrated within less than 15 seconds. This very fast tablet disintegration may be explained by the presence of the superdisintegrant Kollidon® CL [151] as well as the microcrystalline cellulose Avicel® leading to an extremely fast water penetration into the tablets caused by wicking and subsequent widening of the pores [148]. Thus, drug release was not hindered by slow disintegration of the dosage form. Tablets containing Neusilin (LS-N) disintegrated within 4.5 min because of the poor disintegration properties of this silicate.

Table 11: Disintegration times of the investigated tablets (means ± SD, n = 3)

Formulation	conv. tablet	aerogel tablet	LS-1 compact	LS-2 compact	LS-3 compact	LS-4 compact	LS-5 compact
Disintegration time [s]	2 ± 1	5 ± 1	3 ± 3	3 ± 0	11 ± 4	7 ± 0	3 ± 2

Formulation	LS-6 compact	LS-7 compact	LS-8 compact	LS-9 compact	LS-10 compact	LS-N compact
Disintegration time [s]	7 ± 4	8 ± 5	4 ± 1	7 ± 4	10 ± 3	270 ± 27

Drug release from the investigated tablet formulations

Drug release profiles of the conventional and the aerogel tablets as well as the liquisolid compact formulation LS-1 are shown in Fig. 20. It is obvious that drug release from the liquisolid compacts was much faster than that from the conventional tablets although both formulations disintegrated rapidly (Table 11): within 5 min, only 37 % of griseofulvin were released from the conventional tablets as compared to the LS-1 compacts with 95 % drug release. Even though the liquisolid compacts LS-1 represent solid dosage forms, the drug is dissolved in the liquid vehicle within the powder matrix. Thus, drug release from LS-1 compacts was solely dependent on the disintegration of the tablets and the miscibility of the liquid portion with the dissolution medium. The comparatively slow drug release from conventional tablets may mainly be explained by the poor water solubility of griseofulvin and thus a low drug dissolution rate.

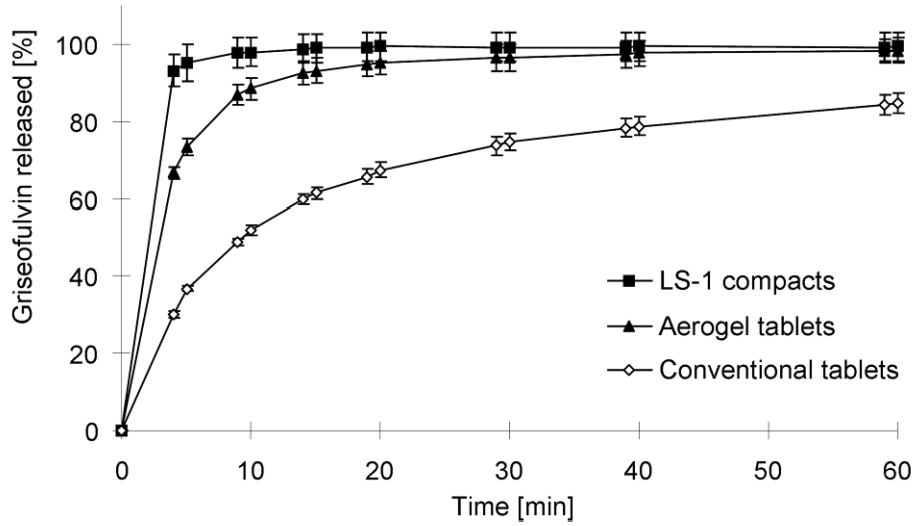

Fig. 20: Drug release profiles of the conventional tablets, the aerogel tablets, and the liquisolid compacts LS-1 (means ± SD; n = 3)

In comparison to the liquisolid compacts LS-1, the aerogel tablets showed a slightly slower drug release. However, compared to the conventional tablets the drug release rate from the aerogel tablets was much higher with more than 73 % within 5 min. This faster drug release from hydrophilic aerogels was also observed by Smirnova et al. [52] who investigated different methods for drug release enhancement of griseofulvin, namely micronization of drug by milling, by rapid expansion from supercritical

solutions (RESS), and drug adsorption to hydrophilic aerogels. The faster drug release of the aerogel tablets may be explained by both an increase in the specific surface area of the drug resulting from the adsorption to the aerogel microspheres and possibly an amorphous state of the drug. X-ray diffraction patterns confirmed the hypothesis that no crystalline structures of the drug are present in drug-loaded aerogel formulations and no long-range order is established upon adsorption of the drug to silica aerogels [51, 53]. The faster drug release from aerogel tablets may also be caused by fast wetting of the hydrophilic aerogel and an immediate collapse of its structure in aqueous media [51, 52].

In Fig. 21 drug release profiles of several liquisolid compacts with varying drug contents in the liquid portion are shown. It is apparent that the drug content in the liquid portion had an effect on drug release from liquisolid compacts.

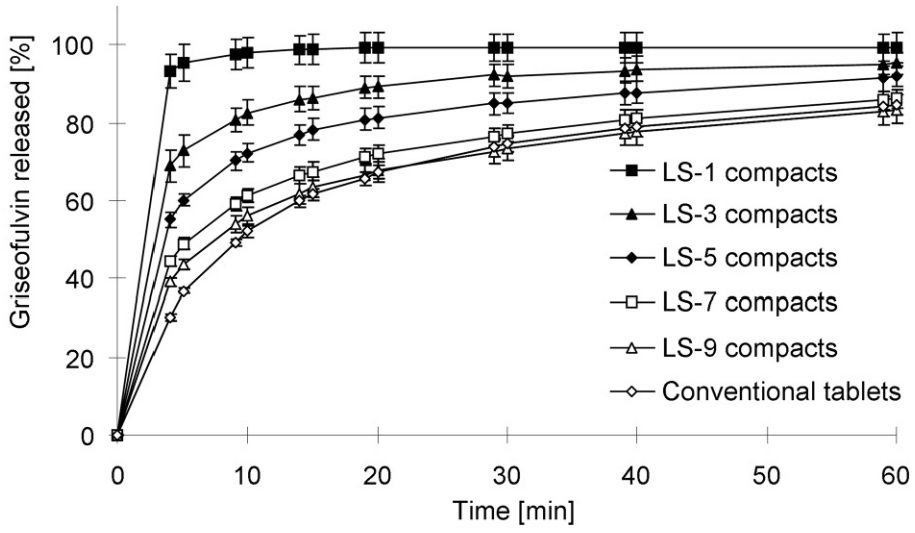

Fig. 21: Drug release profiles of several liquisolid compacts and the conventional tablets (means ± SD; n = 3)

With increasing drug content in the liquid portion exceeding the solubility limit and thus a decreasing percentage of dissolved drug in the liquid portion the release rate decreased. This effect is illustrated in detail in Fig. 22 where the drug content in the liquid portion of the compacts LS-1 – LS-10 is plotted versus drug release at 20 min. This decrease of drug release is attributed to the increasing amount of undissolved drug.

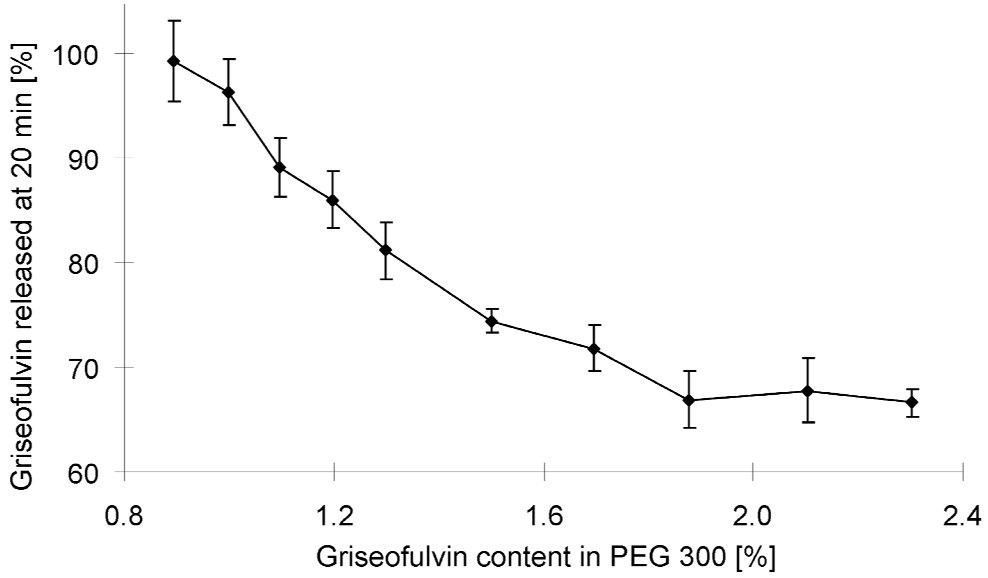

Fig. 22: Influence of the drug content in the liquid portion of liquisolid compacts on the released drug at 20 min (means ± SD; n = 3)

In Fig. 23 the percentage of released drug from the liquisolid compacts LS-1 – LS-10 and the conventional tablets at 20 min are plotted versus the corresponding percentage of dissolved drug in the liquid portion. It is obvious that there was no difference in the percentage of released drug at 20 min between the conventional tablets and the liquisolid compacts LS-8 – LS-10 with all formulations showing a release of about 67 %. Accordingly, the rising percentage of dissolved drug in these three liquisolid compacts did not lead to the expected increase in drug release. With higher percentages of dissolved drug in the liquid portion above 50 % the released drug at 20 min increased linearly (slope = 0.64, R^2 = 0.995). Therefore, the percentage of released drug from liquisolid compacts may be predicted, a fact that was also observed by Spireas et al. [11, 14].

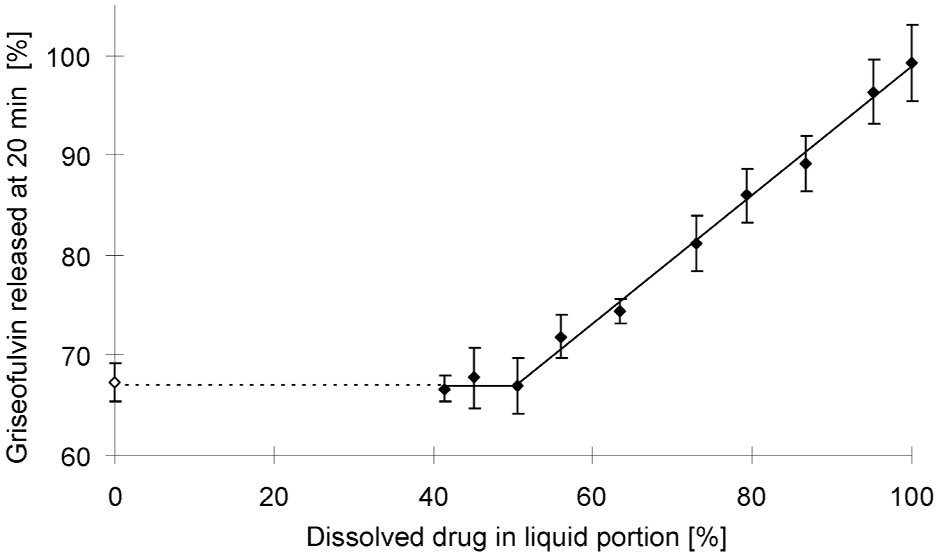

Fig. 23: Influence of the percentage of dissolved drug in the liquid portion of liquisolid compacts on the released drug at 20 min (means ± SD; n = 3);
◇ data of the conventional tablets

In summary, if fast release rates are desired, the liquid portion of liquisolid compacts must contain a high percentage of dissolved drug. However, a liquid portion with a high percentage of dissolved drug might require a high amount of liquid vehicle depending on the solubility of the drug in the liquid vehicle and the required drug dose. As the powder excipients can only adsorb limited amounts of liquid while maintaining good flow and tableting properties, tablet weight will increase with higher amounts of liquid vehicle (Table 10). For instance, the sample unit weight of the fast release formulation LS-1 was more than 2 g, whereas that of LS-10 was only about 800 mg. However, this lighter formulation contained a comparatively high percentage of undissolved drug in the liquid portion and thus showed a significantly lower drug release compared to the heavy formulation LS-1.

As the liquid load factor is dependent on the carrier and coating materials used, a further aim of this study was to optimize the liquisolid technology by replacing the commonly used carrier and coating materials Avicel® and Aerosil® by Neusilin® US2. This magnesium aluminometasilicate with its extremely high specific surface area allowed a considerably higher liquid load factor of 1.58 and thus the production of

liquisolid formulations with lower tablet weights. Replacement of Avicel® and Aerosil® by Neusilin® led to a reduction of the weight of the sample unit containing 3 mg of griseofulvin dissolved in PEG 300 from 2026 mg to 600 mg (Table 10).

In Fig. 24 drug release from the liquisolid compacts LS-N and the conventional tablets are shown. It is obvious that the release from the liquisolid compacts LS-N was much faster than that from the conventional tablets. This may be attributed to the above mentioned dissolved state of the drug in these liquisolid compacts. However, in comparison to the liquisolid compacts LS-1 (Fig. 20) containing Avicel® and Aerosil® as carrier and coating materials, respectively, it is interesting, that the release from LS-N compacts was slower than that from LS-1 compacts within the first 10 min, although both formulations contained a 0.9 % drug solution in PEG 300 as liquid portion. The percentage of griseofulvin released from LS-1 compacts reached 95 % already after 5 min, while with LS-N compacts only a release of 82 % was observed within this time period. This initially slower release rate from LS-N compacts may be explained by the slower disintegration of LS-N compacts (Table 11) compared to LS-1 compacts, which disintegrated instantaneously. With LS-N compacts disintegration was the rate-limiting step and thus, drug release may be accelerated by increasing the amount of disintegrant in the formula resulting in faster disintegration.

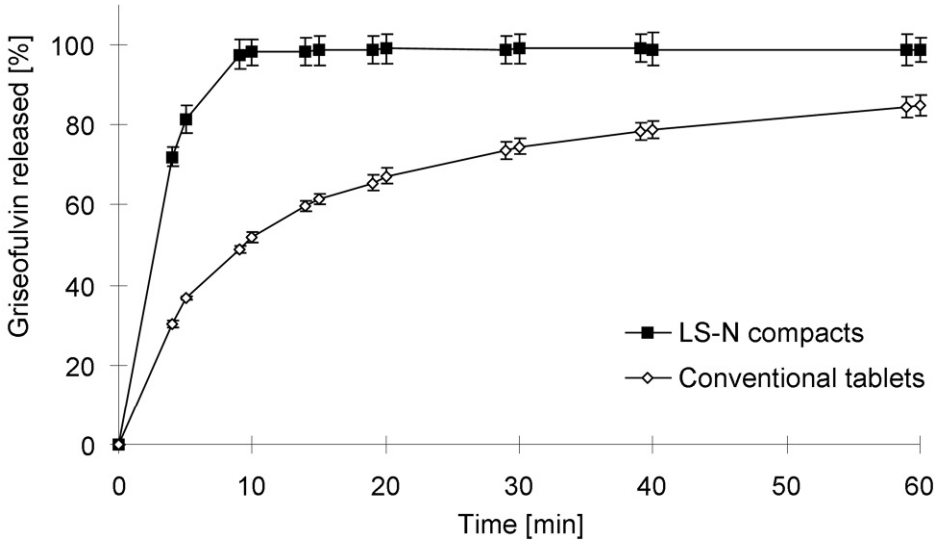

Fig. 24: Drug release profiles of the liquisolid compacts LS-N and the conventional tablets (means ± SD; n = 3)

5.4 Conclusion

Griseofulvin release from silica aerogel tablets and from liquisolid compacts is faster than that from conventional tablets containing the crystalline drug. Moreover, with liquisolid compacts containing the drug suspended in PEG 300 the release rate increases with rising percentage of dissolved drug in the liquid portion. Highest drug release rates are observed with liquisolid compacts containing a drug solution as liquid portion. Therefore, if the desired drug dose is high and/or the drug solubility in the liquid vehicle is low, a high amount of liquid vehicle is needed which in turn requires high amounts of carrier and coating materials. This results in an increase in tablet weight usually leading to an unacceptably large tablet size. Replacement of the commonly used carrier and coating materials Avicel® and Aerosil®, respectively, by the highly adsorptive silicate Neusilin® allows a considerably higher liquid loading capacity ultimately resulting in lower tablet weights.

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Eur. J. Pharm. Biopharm. 68: 277-282 (2008)

7. Appendix

Curriculum vitae

Personal Data:

Name:	Christina M. Hentzschel
Date of birth:	October 2nd, 1981
Place of birth:	Würzburg
Maritial status:	unmarried

Job History	since 11/2010	Assistant for Pharmaceutical Technology, Solida Production, Berlin-Chemie AG, Berlin
	since 11/2006	Ph.D. student, Pharmaceutical Technology, University of Hamburg; supervisor: Prof. Dr. C.S. Leopold
Job Specialization	since 01/2007	Training as Pharmaceutical specialist for Pharmaceutical Technology
Education	12/2006	Pharmacist Licensure
	11/2005-10/2006	Internship: Pharmacy: Leonardo Apotheke, Hamburg R & D, Lilly Forschung GmbH, Hamburg
	10/2001-10/2005	Pharmaceutical studies, Universities of Würzburg and Hamburg
School	06/2001	A-level diploma, St. Ursula-Schule, Würzburg

Publication List

Publications

Nokhodchi, A., Hentzschel, C.M., Leopold, C.S.
Drug release from liquisolid systems: speed it up, slow it down.
Expert Opin. Drug Del. 8: 191-205 (2011)

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Drug Dev. Ind. Pharm., in press (2011)

Hentzschel, C.M., Alnaief, M., Smirnova, I., Sakmann, A., Leopold, C.S.
Enhancement of griseofulvin release from hydrophilic aerogel formulations and liquisolid compacts.
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Hentzschel, C.M., Alnaief, M., Smirnova, I., Sakmann, A., Leopold, C.S.
Tableting properties of silica aerogel and other silicates.
Drug Dev. Ind. Pharm., submitted (2011)

Hentzschel, C.M., Sakmann, A., Leopold, C.S.
Comparison of traditional and novel tableting excipients – physical and compaction properties.
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Alnaief, M., Antonyuk, S., Hentzschel, C.M., Leopold, C.S., Heinrich, S., Smirnova, I.
A novel process for coating of silica aerogel microspheres for controlled drug release applications.
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Conference contributions – oral presentations	Hentzschel, C.M., Sakmann, A., Leopold, C.S. Influence of liquid drug content on the flow properties of liquisolid powder blends. Annual meeting of the DPhG, Bonn, Germany (2008) Hentzschel, C.M., Alnaief, M., Smirnova, I., Sakmann, A., Leopold, C.S. Tableting properties of silica aerogel and various silicates. Annual meeting of the DPhG, Jena, Germany (2009) Hentzschel, C.M. Interpretation of the data recorded during tableting. In-house training at KORSCH AG, Berlin, Germany (2009)
Conference contributions – poster presentations	Hentzschel, C.M., Saniocki, I., Sakmann, A., Leopold, C.S. Particle size, surface area and flowability of novel tableting excipients. XIV. Workshop Porotec, Bad Soden, Germany (2008) Hentzschel, C.M., Sakmann, A., Leopold, C.S. Flowability of liquisolid powder blends. AAPS Annual Meeting & Exposition, Atlanta, USA (2008) Hentzschel, C.M., Sakmann, A., Leopold, C.S. Influence of the magnesium stearate concentration on the tabletability of various excipients. 36th Annual Meeting & Exposition of the Controlled Release Society, Copenhagen, Denmark (2009) Hentzschel, C.M., Sakmann, A., Leopold, C.S. Comparison of physical and tableting properties of traditional and novel excipients. AAPS Annual Meeting & Exposition, Los Angeles, USA (2009)

Conference contributions – poster presentations	Hentzschel, C.M., Sakmann, A., Leopold, C.S. Suitability of various tableting excipients as carriers for liquisolid systems. 7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Malta (2010) Alnaief, M., Smirnova, I., Antonyuk, S., Heinrich, S., Hentzschel, C.M., Conradi, R., Leopold, C.S. Aerogel based solid dosage forms for targeted drug delivery. 7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Malta (2010) Hentzschel, C.M., Alnaief, M., Smirnova, I., Sakmann, A., Leopold, C.S. Hydrophilic silica aerogels and liquisolid systems - Two drug delivery systems to enhance dissolution rates of poorly soluble drugs. 37th Annual Meeting & Exposition of the Controlled Release Society, Portland, USA (2010) Hentzschel, C.M., Sakmann, A., Leopold, C.S. Enhancement of griseofulvin release from liquisolid tablets and optimization thereof. Annual meeting of the DPhG, Braunschweig, Germany (2010)

Hazardous materials

Substance	Supplier	Danger symbol	Code letter	Risk phrases	Security phrases
Acetone	Merck, Darmstadt, Germany		F, Xi	11-36-66-67	9-16-26-46
Carbon dioxide	AGA Gas, Hamburg, Germany	-	-	-	9-23
Griseofulvin	Fagron, Barsbüttel, Germany		T	61-40-43	53-45
Methanol	Merck, Darmstadt, Germany		T, F	11-23/24/25-39/23/24/25	7-16-36/37-45
Sodium hydroxide	Carl Roth, Karlsruhe, Germany		C	35	26-37/39-45

Eidesstattliche Versicherung

Hiermit versichere ich an Eides statt, die vorliegende Arbeit selbstständig und ohne fremde Hilfe sowie nur mit den angegebenen Hilfsmitteln und Quellen erstellt zu haben. Ich versichere zudem, keinen weiteren Promotionsversuch an einer anderen Einrichtung unternommen zu haben.

Hamburg, den

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Christina M. Hentzschel