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RESEARCH ARTICLE

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

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Abstract

Context: The liquisolid technology is a promising technique for the 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.

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

Materials and methods: Liquisolid compacts containing the liquid drug tocopherol acetate (TA) 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.

Results and discussion: The liquid adsorption capacity depends on the specific surface area of the investigated excipients. Fujicalin® and especially Neusilin® are more effective carrier materials for liquid adsorption than Avicel®, which is often used for liquisolid systems. Moreover, Florite® and Neusilin® turned out to be more suitable as coating materials than the commonly used Aerosil® due to their better tableting properties.

Conclusion: If Neusilin® is used as carrier and coating material instead of Avicel® (carrier material) and Aerosil® (coating material), the TA adsorption capacity is increased by a factor of 7.

Keywords: Liquisolid compacts, carrier/coating material, tocopherol acetate, liquid adsorption, Fujicalin®, Neusilin®, Florite®

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[1]. Numerous methods for increasing water solubility and drug release, respectively, are used such as micronization[2], adsorption onto high surface area carriers[3,4], co-grinding[5], formulation of inclusion complexes[6], solid dispersions[7–11], and lipid-based formulations[12] for instance self-emulsifying drug delivery systems (SEDDS). One of the most promising approaches is the liquisolid technology[13–17].

The concept of "liquisolid systems" as defined by Spireas[18] 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 (Figure 1). 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[19]. Thus, a dry looking, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as the carrier

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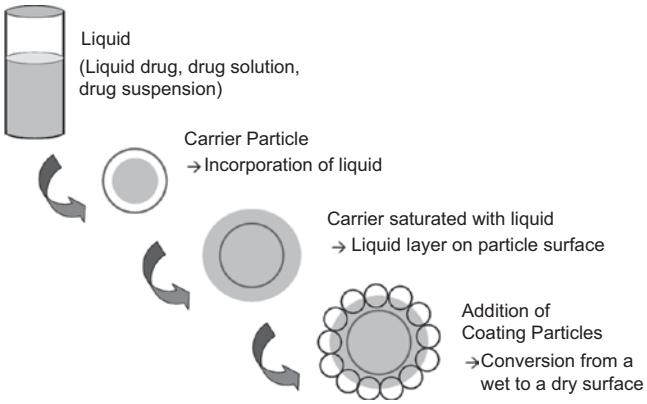

Figure 1. Schematic representation of liquisolid systems[19].

material and amorphous silicon dioxide is used as the coating material.

Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilizing vehicle provide enhanced drug release characteristics due to an increased surface area of drug available for release, an increased solubility of the drug, and an improved wettability of the drug particles[20–23]. Accordingly, this improved drug release allows a higher drug absorption in the gastrointestinal tract and thus an improved oral bioavailability[24,25].

The liquisolid technology may also be used to prolong drug release[26–28]. 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 or by addition of a matrix former such as hydroxypropyl methylcellulose, sustained release systems may be obtained.

The liquisolid technology for release enhancement has been successfully applied to low dose poorly soluble drugs[15,17]. However, the formulation of a high dose poorly soluble drug is one of the limitations of this technology. The release rates are directly proportional to the fraction of molecularly dispersed drug in the liquid portion[15,16]. 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 although 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[29] or by using carrier and coating materials with a high specific surface area (SSA). The higher the SSA of an excipient, the higher the liquid load factor. For instance, the liquid adsorption capacity of the experimental grade of granular amorphous cellulose (SSA: 24.22 m^2/g) is higher than that of microcrystalline cellulose Avicel PH 102 (SSA: 1.10 m^2/g) and microcrystalline cellulose Avicel PH 101 (SSA: 1.07 m^2/g)[19].

Of course, the physicochemical characteristics of the liquid such as polarity, viscosity, chemical structure, and lipophilicity may also affect the adsorption capacity of the carrier and coating materials. Consequently, the liquid adsorption capacity of a blend of carrier and coating material is dependent on the respective liquid[18].

The aim of this study was to investigate novel porous tableting excipients with a high SSA with regard to their suitability of liquid adsorption while maintaining acceptable flow and tableting properties. The following excipients were compared with the commonly used carrier and coating materials Avicel® and Aerosil®: Fujicalin®, a spherically granulated dicalcium phosphate anhydrous[30,31] with a high porosity and high SSA resulting in good flowability and tabletability, Neusilin® US2, a synthetic amorphous form of magnesium aluminometasilicate[32] prepared by spray-drying with an extremely high SSA and good flowability and tabletability, Florite®, a calcium silicate[33] 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 (TA) was used as the liquid model substance. The objective was to identify the most effective carrier and coating material for liquid uptake although maintaining acceptable flow and tableting properties. Therefore, in the first part of the study various carrier materials were investigated and compared with Avicel® and in the second part the common coating material Aerosil® was replaced by novel excipients to further optimize the liquid adsorption capacity.

Materials and methods

Materials

The following drugs and excipients were used: TA, 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.

Determination of the SSA of the excipients

The SSA of the excipients was determined by gas adsorption using a Sorptomatic 1990 (Carlo Erba Instruments, Rodano, Italy). The samples were degassed in vacuum for 24 h and exposed to nitrogen at 77.4 K. According to the

Brunauer–Emmet–Teller (BET) equation[34], the SSA 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 contents of 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 1). Carrier and coating materials were used in a ratio of 20:1 (*R*-value) according to the recommendation of Spireas et al.[17] Mixing was performed with a chopper speed of 500 rpm and an impeller speed of 200 rpm 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% relative humidity (RH). before use.

Prior to tableting, Neusilin® blends were mixed with Kollidon® CL (6% [w/w]) for 5 min in a Turbula blender at 72 rpm (T2F; Willy A. Bachofen, Muttenz, Switzerland) to ensure tablet disintegration.

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 tapped and bulk density. Bulk and tapped densities were determined with a jolting volumeter (STAV 2003; J. Engelsmann, Ludwigshafen, Germany) equipped with a 50-mL measuring cylinder according to the Ph. Eur. 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 by polishing the surface of the upper and lower punch as well as the die wall using a felt bob (micromotor Bravo TD equipped with contra-angle; Hager & Werken, Duisburg, Germany) with a sufficient amount of magnesium stearate necessary to cover all surfaces. The required amount of powder was filled manually into the die and compressed at a compaction speed of 16 strokes per minute. All experiments were performed at 21°C/45% RH.

Table 1. 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®		Kollidon® CL*

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

Characterization of the liquisolid compacts

Tablets were characterized after a relaxation time of at least 24 h 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 and Newton[35]. 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 according to the Ph. Eur. in purified water with a disintegration tester (ZT 72; Erweka, Heusenstamm, Germany) at 37°C.

Results and discussion

Characterization of the excipients

The SSA and the structure of the investigated excipients differ significantly from each other. For instance, the SSA of Fujicalin® (SSA: 32 ± 1 m^2/g) is 32 times higher than that of Avicel® (SSA: 1 ± 0 m^2/g). This difference becomes apparent in Figure 2. The spherically granulated dicalcium phosphate anhydrous (Fujicalin®) shows a high porosity, whereas microcrystalline cellulose (Avicel®) exhibits a smooth surface. From the excipients investigated in this study, the silicates provide by far the highest SSA. Florite® with its petaloid crystal structure and large micropores exhibits an SSA of 142 ± 7 m^2/g, whereas Aerosil® with its loose agglomerates formed by the nanometer-sized primary particles exhibits an SSA of 201 ± 7 m^2/g. The highest SSA by far shows Neusilin® (SSA: 339 ± 1 m^2/g), which is prepared by spray-drying resulting in spherically shaped, porous, ultralight granules.

Variation of the carrier material

In the following sections, 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 1), and TA as liquid drug are presented.

Flowability

In Figure 3, 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 SSA 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 fine Aerosil®-coating particles resulting in particles with better flowability due to a decrease of interparticulate forces.

For Avicel® blends, this flowability improvement could only be observed with up to 8% liquid drug content (Figure 3A). 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 (Figure 3B and 3C). The high porosity and high SSA 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.

Tabletability

The influence of TA on the tableting properties of the investigated blends is shown in Figure 4. Obviously, the tableting properties of the blends are affected differently by the increase in liquid drug content.

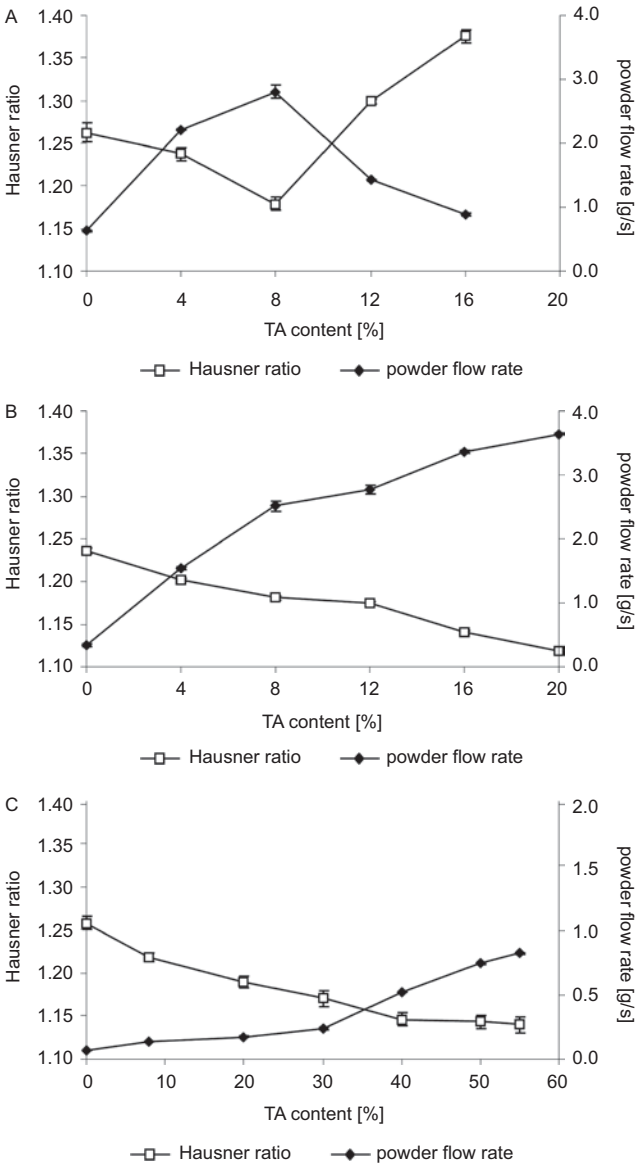

Figure 3. Flowability of tocopherol acetate (TA) liquisolid powder blends containing Aerosil® as coating material (means ± SD, Hausner ratio: $n=3$, powder flow rate: $n=5$). (A) Avicel® blends; (B) Fujicalin® blends; and (C) Neusilin® blends.

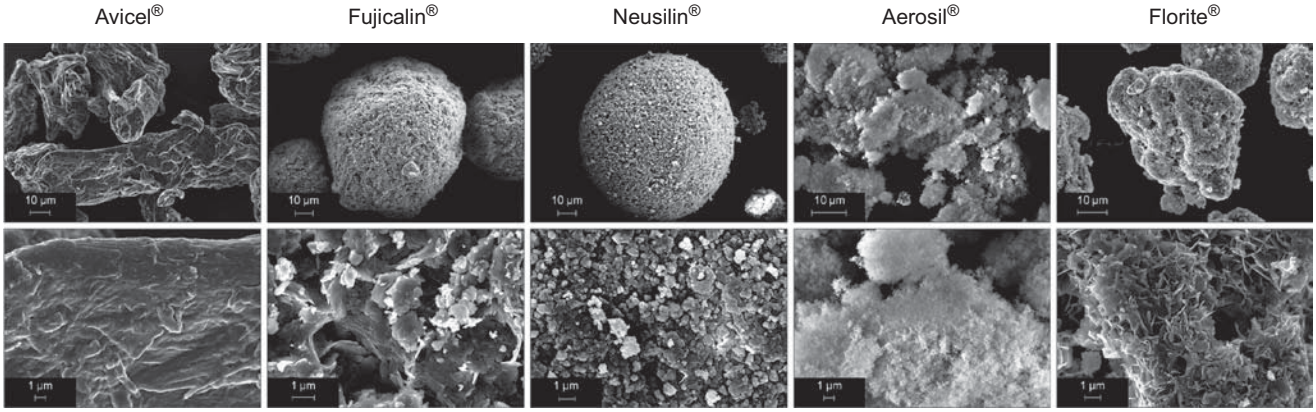

Figure 2. Scanning electron microscopy (SEM) pictures of the excipients.

The tensile strength of the Avicel® compacts continuously decreases with increasing liquid drug content (Figure 4A), whereas the tableting properties of Fujicalin® blends remain almost unaffected by the addition of liquid drug up to 12% (Figure 4B). This may be explained by the different deformation characteristics of these two excipients: Avicel® as microcrystalline cellulose shows plastic deformation[36] whereas fragmentation is the main deformation mechanism of the dicalcium phosphate Fujicalin®[30]. 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 evenly extended up to 40% liquid content (Figure 4C).

Moreover, it is obvious from Figure 4 that the difference in tabletability between the TA contents becomes more apparent at high compaction forces. At low compaction forces, the porosity and void between the particles, respectively, is comparably high. Thus, it is assumed that there is enough space for the different amounts of liquid to be adsorbed and the liquid does not hinder bonding of the carrier and coating material. At high compaction forces, the void between the particles is very low and therefore the amount of liquid strongly affects bonding of the carrier and coating material.

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 SSA.

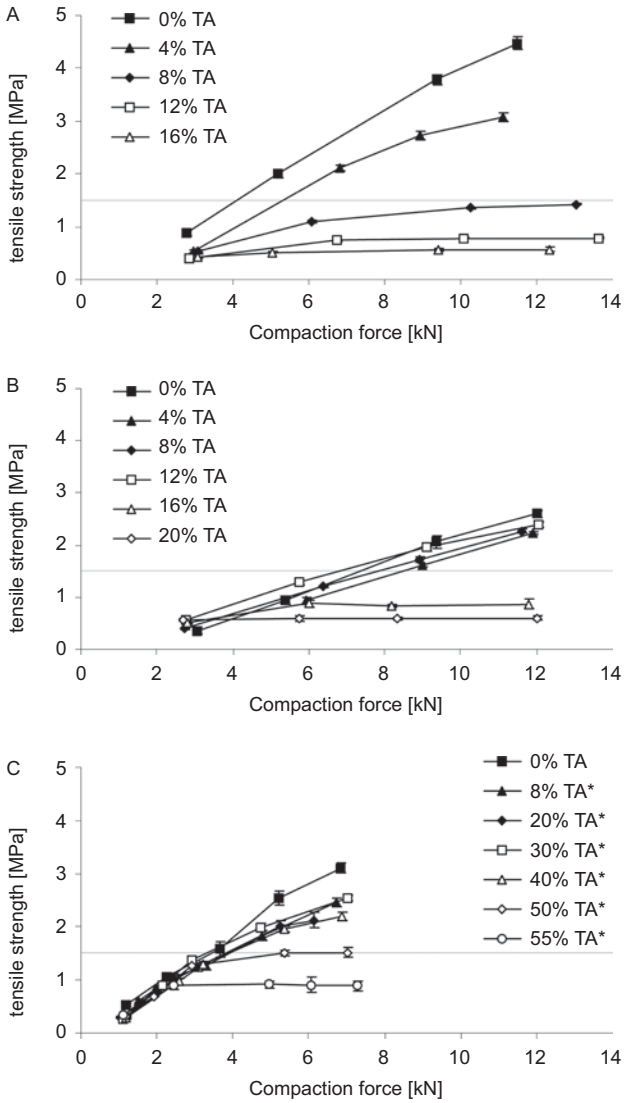

Figure 4. Tabletability of tocopherol acetate (TA) liquisolid compacts containing Aerosil® as coating material (means ± SD, $n=5$). (A) Avicel® compacts; (B) Fujicalin® compacts; and (C) Neusilin® compacts; *containing additional 6% Kollidon® CL.

Disintegration

In Figure 5, 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,

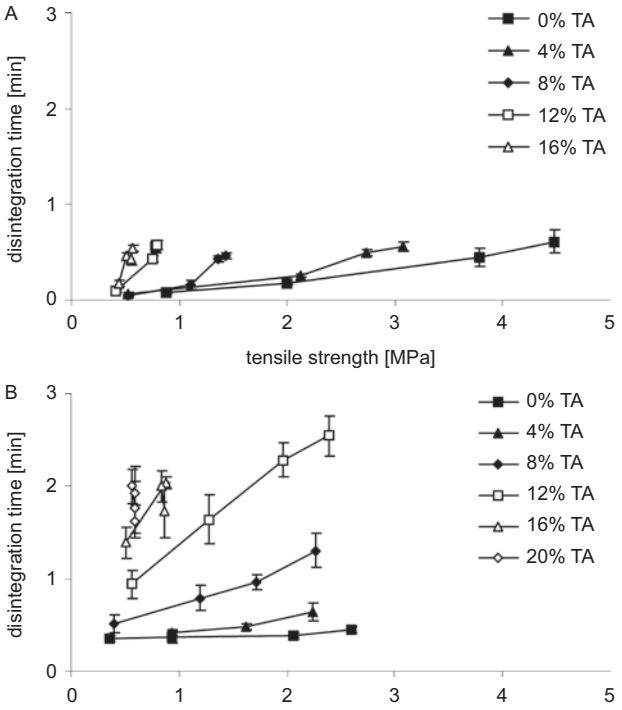

Figure 5. Disintegration of tocopherol acetate (TA) liquisolid compacts containing Aerosil® as coating material (means ± SD, $n=6$). (A) Avicel® compacts and (B) Fujicalin® compacts.

Table 2. Flowability of tocopherol acetate (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/sec]	
	50% TA	55% TA	50% TA	55% TA
Aerosil® blends	1.14 ± 0.01	1.14 ± 0.01	0.743 ± 0.004	0.820 ± 0.009
Florite® blends	1.16 ± 0.00	1.16 ± 0.00	0.589 ± 0.003	0.597 ± 0.008
Neusilin® blends	1.13 ± 0.01	1.13 ± 0.01	0.867 ± 0.004	0.895 ± 0.002

the disintegration time is strongly dependent on the excipient used. In comparison with Fujicalin®, Avicel® compacts disintegrate much faster. This may be explained by an extremely fast water penetration into microcrystalline cellulose tablets caused by wicking and subsequent widening of the pores[37]. The very fast disintegration of Neusilin® compacts (<1 min) is solely caused by the addition of the superdisintegrant Kollidon® CL.

Variation of the coating material

As Neusilin® turned out to be the most effective carrier (Figures 3 and 4), this silicate was used for further studies as carrier material to look for the most effective coating material. In the following sections, the results of the flowability and tabletability of the formulations containing Neusilin® as carrier material, Aerosil®, Florite®, or Neusilin® as coating material (Table 1), and TA 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 the section "Disintegration").

Flowability

All blends containing Neusilin® as carrier material show good flowability at high TA contents of 50% and 55% (Table 2). 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 highest powder flow rate resulting from the spherical shape of this silicate.

Tabletability

In Figure 6, the tabletability of TA liquisolid compacts containing Neusilin® as carrier material is shown. As mentioned above for the Neusilin®- and Aerosil®-containing compacts (Figure 4C), tablets with acceptable mechanical properties are obtained with a maximum TA content of 50% (Figure 6A). 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 (Figure 6B and 6C). Therefore, Florite® and Neusilin®

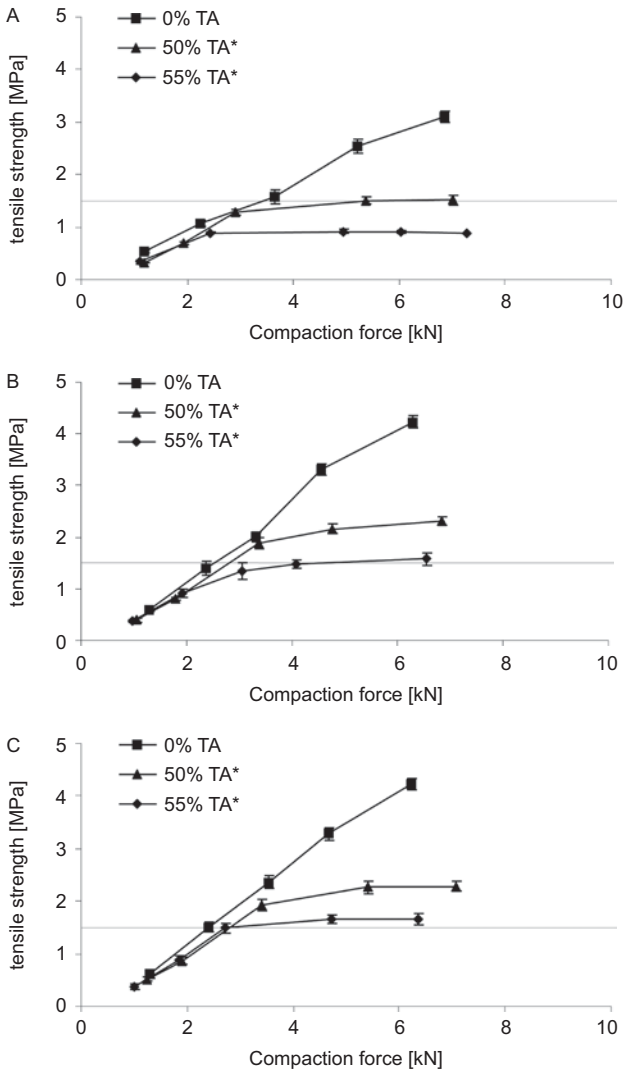

Figure 6. Tabletability of tocopherol acetate (TA) liquisolid compacts containing Neusilin® as carrier material (means ± SD, $n = 5$). (A) Aerosil® compacts; (B) Florite® compacts; and (C) Neusilin® compacts; *containing additional 6% Kollidon® CL.

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 with the commonly used carrier and coating materials Avicel® and Aerosil® (Figure 4A), the liquid adsorption capacity of the formulation containing Neusilin® as carrier as well as coating

material (Figure 6C) is increased by a factor of 7 (from 8% to 55% TA).

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 SSA and good flow and tableting properties allows considerably higher liquid adsorption capacities. In conclusion, if Neusilin® is used as carrier as well as coating material instead of Avicel® and Aerosil® the liquid adsorption capacity is increased by a factor of 7 in the case of TA. 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 with 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.

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Declaration of interest

The authors report no declarations of interest.

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