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Research paper

Interaction of Bay t 3839 coprecipitates with insoluble excipients ☆

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Abstract

Bay t 3839 is an extremely sparingly soluble drug and results in severe problems with regard to oral bioavailability. In order to improve the dissolution performance a coprecipitate formulation approach was investigated and the necessary ratio polyvinylpyrrolidone (pvp) to drug substance was found to be approximately 15 in order to achieve a sufficient supersaturation in 900 ml 0.1 N HCl, which is considered to be an appropriate as well as challenging in vitro test method. Surprisingly substantial differences in the dissolution characteristics of coprecipitate granulates were revealed when the coprecipitate was formed on excipients which was not the case when pure pvp/drug coprecipitates were submitted to dissolution testing. As substantial deterioration of the supersaturation capability was detected only in the case of insoluble excipients it is concluded that solid/liquid interfaces during the dissolution step act as recrystallization inducers. In case of soluble fillers/adsorbents, like mannitol, the supersaturation capability could be maintained also after the granulation step. Therefore, it is likely that in the case of extremely challenging drug candidates like, e.g. Bay t 3839, the supersaturated solution is less stable than in the case of more soluble compounds. These more susceptible coprecipitates can be stabilized by proper selection of the granulation excipients. Additionally the admixture of crystallization inhibiting agents like sodium dodecyl sulfate (SDS) offers the opportunity to decrease the necessary ratio pvp/Bay t 3839 considerably (to a ratio of ~7).

Keywords: Coprecipitate; Solubility of filler material; Recrystallization of supersaturated solutions; Sparingly soluble drug substance; Polyvinylpyrrolidone

1. Introduction

Sparingly soluble drug substances frequently possess problems with regard to oral bioavailability. An estimation whether a bioavailability risk exists or not can be done by taking into account dose and aqueous solubility [1,2].

Another very simplified empirical approach is to check whether the administered dose is soluble in 2000 ml of water or not: dose (mg)/solubility (mg/ml) ≤2000 ml.

If the dose divided by the aqueous solubility is less than 2 l, solubility is judged to be not the limiting factor for oral bioavailability. A similar stricter approach was taken for the biopharmaceutical classification system in order to define highly soluble drug substances [3].

In reality–of course–oral bioavailability is determined by a series of additional factors, like:

- permeability [1,4];
- absorption windows [5–7];
- active secretion/absorption processes [4,8,9];
- food intake [10–12]

.

As these factors are hard to control or modifying these mechanisms will lead to a risk of imbalancing biological processes and thus bear an immanent risk, Pharm. Technology will focus on dissolution rate and/or solubility enhancing measures, e.g.:

- micronization [13];
- wetting [14,15];
- sand milling [12,16];
- nanosuspensions [17–19];
- complexation [20]

.

In this article solubility enhancement by coprecipitation will be described for a very sparingly soluble drug: Bay t 3839 [21] (Fig. 1). The dose/solubility ratio is 100.000 ml, which indicates that severe oral bioavailability problems are to be expected.

☆ Dedicated to Professor B.C. Lippold on the occasion of his 60th birthday.

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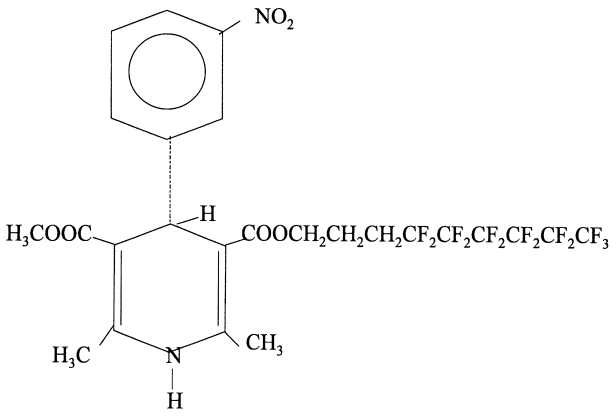

Fig. 1. Bay t 3839; target dose/unit: 1 and 2 mg; solubility in water: ≪0.02 mg/l (37°C); molecular weight: 692.

Solubility enhancement by coprecipitation with polyvinylpyrrolidone (pvp) is widely used and some products based on this technology are on the market place, e.g. for Nifedipine (Adalat T10®) and Nimodipine (Nimotop®). In the latter case sufficient oral bioavailability can be achieved only by solutions or solid dispersions, i.e. amorphous drug.

Comparing dose and solubility of these three dihydropyridines, it becomes obvious, that in the case of Bay t 3839 a new challenge with regard to solubility enhancement arises (Table 1).

2. Materials and methods

2.1. Materials

Drug substance: Bay t 3839, batch nos. 518009 and 320168, Bayer AG, Leverkusen.

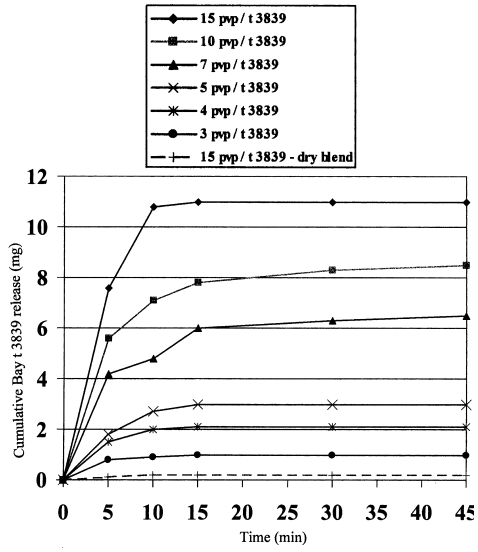

Fig. 2. Bay t 3839 dissolution in 0.1 N HCl from pure drug/pvp – coprecipitates. All samples tested correspond to 10 mg Bay t 3839.

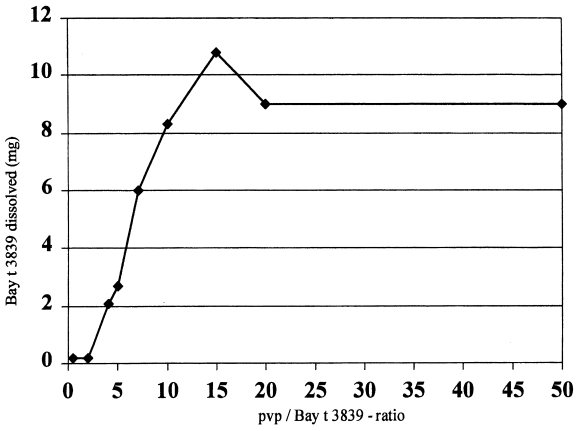

Fig. 3. Solubility of Bay t 3839/pvp – coprecipitates in 0.1 N HCl in dependency of the pvp/drug ratio. All samples tested correspond to 10 mg Bay t 3839.

Kollidon® K 25 (BASF, Ludwigshafen, Germany, further referred to as 'pvp'); mannitol is D-(−) mannitol (Merck, Darmstadt, Germany, further referred to as 'mannitol'); sodium dodecylsulphate is Texapon® K 12 (Henkel, Düsseldorf, Germany, further referred to as 'SDS'). All other excipients used were also of standard quality.

2.2. Preparations

2.2.1. Physical mixtures

Physical mixtures were prepared by intensive manual mixing in a mortar for 2 min.

2.2.2. Pure pvp/drug coprecipitates

Pure pvp/drug coprecipitates were prepared by dissolving the drug and the pvp in sufficient acetone to achieve a clear solution at room temperature and afterwards evaporating the solvent under vacuum at elevated temperatures. Final solvent removal was done after manual grinding of the coprecipitate in a vacuum dry oven at 90°C overnight. The residual acetone concentration was less than 1%. Batch size was in the range of 10 g.

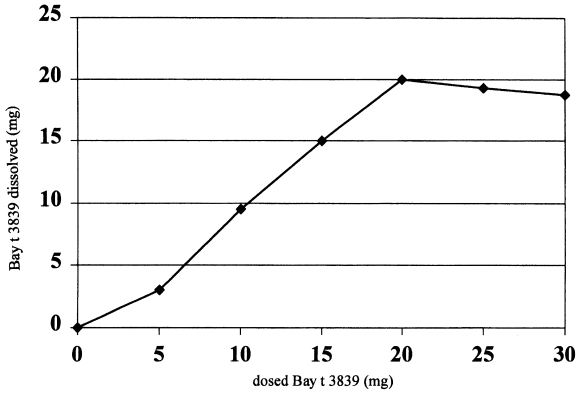

Fig. 4. Maximum dissolved amount of Bay t 3839 from pure coprecipitates with a pvp/drug ratio of 15 dependency of the dosed Bay t 3839.

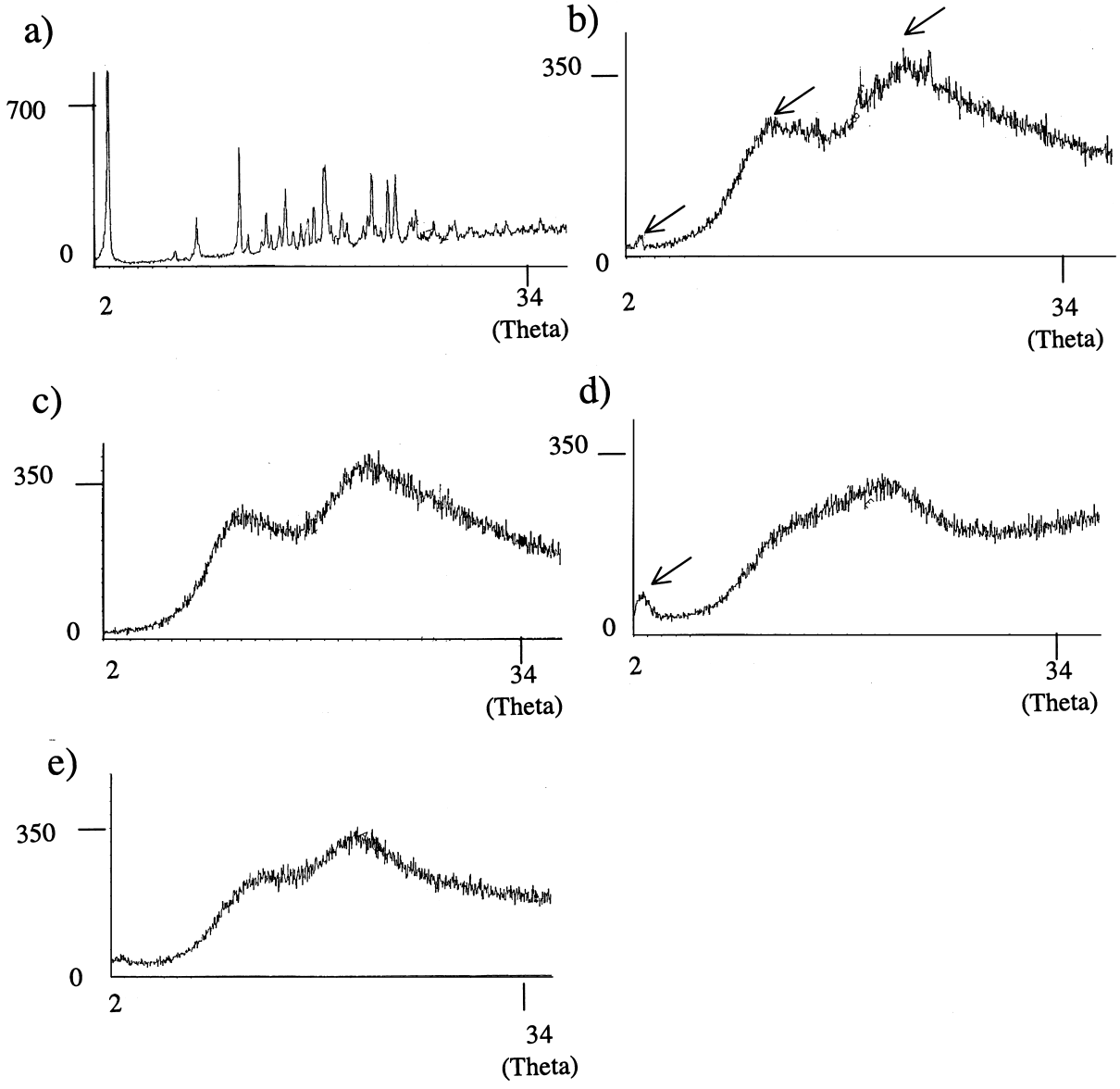

Fig. 5. X-ray diffractograms of Bay t 3839 coprecipitates in comparison to drug, pvp and physical mixtures: (a) drug; (b) phys. mixture pvp/t 3839 15/1; (c) pvp; (d) pvp/t 3839 1/2; (e) pvp/t 3839 2/1.

2.2.3. Coprecipitate granules

The acetonic solution of the drug and pvp was used for wet granulation of mannitol in a lab scale planetary mixer. The wet mass was passed through a 0.8 mm sieve and dried under vacuum at 90°C overnight. After drying the granulate was passed through a 0.8 mm sieve in order to deagglomerate it. In case SDS was admixed, it was dry blended with mannitol in the laboratory scale planetary mixer for 5 min or added to the clear pvp/drug solution to form a suspension.

Table 1
Dose/solubility ratios of dihydropyridine drug substances

Drug	Dose per unit (mg)	Solubility in water (mg/l)	Ratio (ml)
Nifedipine	10	~9	1.100
Nimodipine	30	~4	7.500
Bay t 3839	2	<0.02	100.000

2.2.4. Dissolution testing

USP-Paddle, 900 ml 0.1 N HCl, 50 rev./min, 37°C, UV-detection after sampling through a 0.45 μm filter. Samples were diluted with methanol 1:1 prior to measurement in order to prevent recrystallization after sampling. Each data point was run in triplicate. As no substantial variability was observed, mean values are presented in the corresponding figures.

2.2.5. X-ray

Diffractometer D 500–DACO–MP, data provided by central research, Bayer AG.

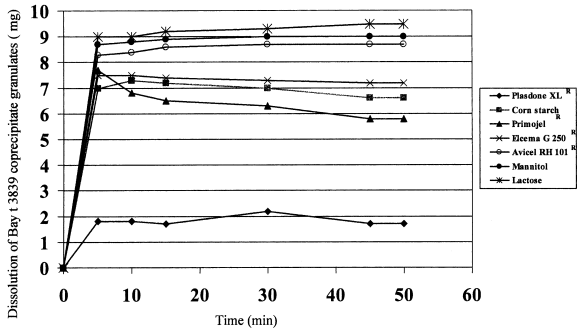

Fig. 6. Impact of excipient type on the supersaturation capability of pvp/Bay t 3839 coprecipitate granulates (pvp/drug ratio of 15). All samples tested correspond to 10 mg Bay t 3839.

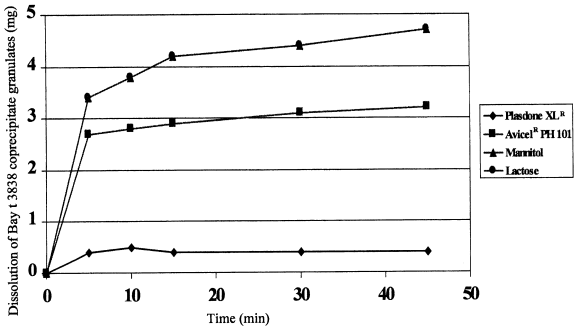

Fig. 7. Impact of excipient type on the supersaturation capility of pvp/Bay t 3838 coprecipitate granules (pvp/drug ratio 10). All samples tested correspond to 5 mg Bay t 3838.

2.2.6. Water content of excipients

Karl Fischer Titration, System DL 18 Karl Fischer Titrator, Mettler, Gießen, Germany.

3. Results and discussion

3.1. Optimum pvp/drug ratio evaluation

In order to evaluate the optimal pvp/drug ratio pure coprecipitates were manufactured covering a ratio of 0.5 up to 50. These coprecipitates were submitted to dissolution testing by pouring an amount representing 10 mg drug substance onto the medium's surface. Considering the drug's solubility this test is judged as very challenging in terms of the required solubility enhancement.

Fig. 2 shows that a ratio of 15 turns out to be sufficient for 100% dissolution. In view of the anticipated dose strength of 1–2 mg/d this drug/excipient ratio still is acceptable in terms of the resulting tablet size. The maximum release of about 11 mg observed from a coprecipitate containing only 10 mg drug substance (Fig. 2) is considered to be due to a constant deviation in the detection method (correlation factor) for this experiment.

As the concentration of 10 mg/900 ml 0.1 N HCl is maintained throughout 45 min thus indicating that no recrystallization of this highly supersaturated solution occurs, the coprecipitate 15/1 is considered to be acceptable in order to yield high oral bioavailabilities. Fig. 3 shows the dependency of the achieved solubility of Bay t 3839 in dependence on the pvp/drug ratio, based on the data of Fig. 2 and supplemented by pvp/drug ratios of 0.5, 2, 20 and 50.

Fig. 4 shows the maximum concentration which could be achieved with the 15/1 coprecipitate in the dissolution test by increasing the sample size: up to 20 mg Bay t 3839 could be dissolved (new dissolution data were generated for the dose of 10 mg Bay t 3839 also, compare with Fig. 2). Thus solubility in comparison to that of crystalline drug substance could be enhanced by a factor of >1100.

The coprecipitate 15/1 was characterized with respect to crystallinity grade by X-ray (Fig. 5). In a physical mixture 15 pvp/1 drug substance interference signals are detectable whereas the coprecipitate 1/2 displays nearly no signals and is similar to the spectrum of pure pvp. Therefore, it is concluded that X-ray allows a rough estimation of amorphicity of coprecipitates but that no conclusion can be drawn with regard to the supersaturation performance. This is in line with the empirical experience with other drug

Table 2
Physico-chemical characteristics of excipients employed for granulation

Excipient	Soluble in water	Residual water (%)
Mannitol	Yes	~0.1
Lactose	Yes	0.2 [22]
Elcema® G 250	No	~5
Avicel® PH 101	No	~6.6 [22]
Primojel®	No	~12.6 [22]
Corn starch	No	~13.2 [22]
Plasdone XL®	No	~22.2 [22]

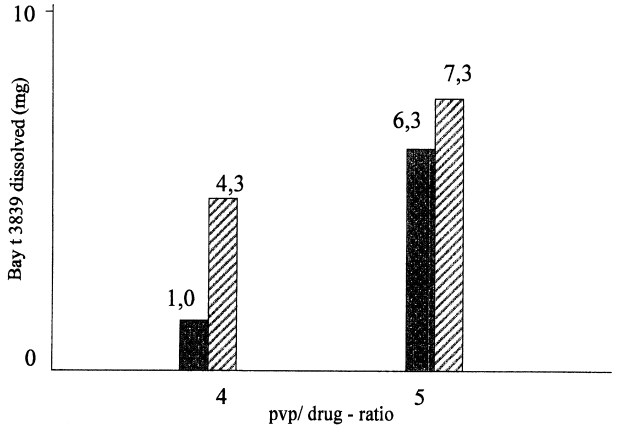

Fig. 8. Enhancement of supersaturation in 0.1 N HCl by addition of sodium dodecylsulfate (SDS) to Bay 3839/pvp–coprecipitates. First bar represents pure pvp/drug coprecipitate, second bar the coprecipitate admixed with 1 part SDS per 1 part drug. Each sample represents 10 mg drug substance.

Table 3
Granulate compositions of Bay t 3839 coprecipitates

Mannitol granulate[a]	pvp/drug ratio	SDS (2 parts)
A	7.5	Yes
B	7.5	No
C	15	Yes
D	15	No

[a] As to the mannitol amount used please refer to Table 4.

substance/pvp coprecipitates: the most sensitive parameter for testing the coprecipitate performance is dissolution testing in media which require supersaturation capability in order to dissolve 100% of the drug.

3.2. Impact of tablet excipients on the performance of the coprecipitate

As the pure coprecipitate usually cannot be transformed to a dosage form but needs additional excipients, e.g. fillers, superdisintegrants and lubricants, the impact of various conventional excipients on the dissolution characteristics of the coprecipitate 15/1 was investigated (Fig. 6). In contrast to former experiences with pvp-coprecipitates (Nifedipine, Nimodipine) which in comparison to Bay t 3839 have ratios of pvp/drug of only 2.5 to 4, a pronounced impact of the excipient type on supersaturation capability was observed. Excipients which are insoluble in water lead to a breakdown with regard to the solubilization capability of the coprecipitate. The most pronounced effect was observed with Plasdone XL®. Table 2 lists the excipients tested in terms of residual water and aqueous solubility.

Deterioration of the supersaturation capability occurs with the insoluble excipients only. This finding could be reproduced with Bay t 3838 coprecipitate granulates (ratio pvp/drug 10; Bay t 3838 is the enantiomer of Bay t 3839)

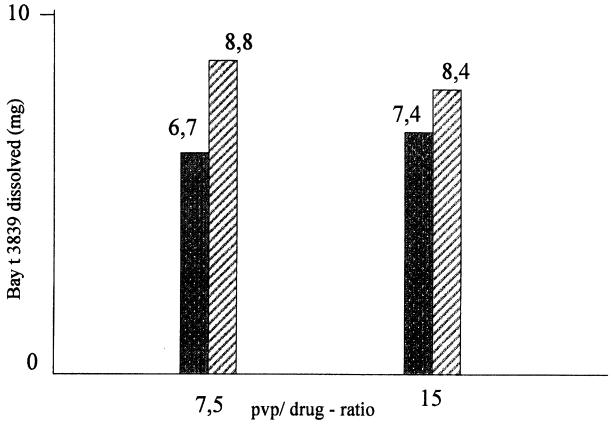

Fig. 9. Enhancement of supersaturation in 0.1 N HC1 by addition of sodium dodecylsulfate (SDS) to Bay t 3839 coprecipitate granulates based on mannitol. First bar represents granulates without addition of SDS, the second bar plus addition of 2 parts of SDS per 1 part of drug. Each sample represents 10 mg drug substance.

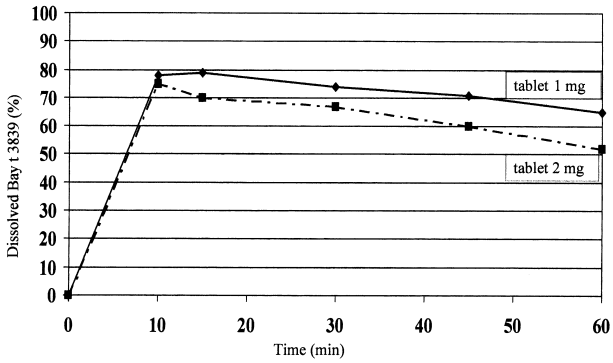

Fig. 10. Dissolution of Bay t 3839 from coprecipitate tablets 1 resp. 2 mg in 0.1 N HCl (each sample corresponds to 10 mg Bay t 3839: 10 × 1 mg tablet/sample and 5 × 2 mg tablet/sample).

In this case the effect of Avicel® PH 101 was even more pronounced than with the Bay t 3839 granulates (see Fig. 7).

Again Plasdone® XL lead to a complete breakdown with respect to supersaturation capability whereas the soluble excipients lactose and mannitol resulted in nearly complete dissolution. It is suggested, therefore, that the very sparingly soluble drug substance Bay t 3838 (and Bay t 3839 as well) recrystallizes 'in statu nascendi' after dissolving from the coprecipitate catalyzed by solid/liquid interfaces. Drying of the excipients prior to granulation does not alter the supersaturation capability. This is to be expected as all coprecipitate granulates are dried under vacuum at elevated temperatures in order to remove the residual acetone thereby also removing residual water of the excipients. Thus, it is concluded that the residual water is not the primary reason for the deterioration of supersaturation capability.

3.3. Impact of crystallization inhibiting agents

If the supersaturation achieved by the pvp/drug coprecipitate is susceptible towards solid/liquid interfaces crystallization inhibitors should improve the performance of Bay t 3839 coprecipitates. This approach was evaluated by the addition of sodium dodecyl sulfate (SDS) to the coprecipitate. As X-ray diffractograms indicated that pvp/drug copre-

Table 4
Bay t 3839 coprecipitate tablet formulations

	Tablet A (mg)	Tablet B (mg)
Bay t 3839	1	2
Pvp	15	15
SDS	2	2
Mannitol	60	59
Magnesium stearate	2	2
Tablet weight	80	80
pvp/drug ratio	15	7.5

cipitates are amorphous when the pvp/drug ratio exceeds 3–5, SDS was admixed in form of a physical mixture to coprecipitates with a pvp/drug ratio of 4 resp. 5 in order to challenge this approach. The comparative solubilities are presented in Fig. 8. As expected the supersaturation capability is enhanced markedly at low pvp/drug ratios.

3.4. Optimization of the composition of Bay t 3839 pvp-coprecipitates

In the case of this extremely sparingly soluble drug coprecipitate compositions are advantageous which avoid insoluble excipients and contain some SDS as a recrystallization-inhibiting agent. Thus, the formulation selected for further investigations was based on mannitol as filler and 2 parts of SDS per 1 part of drug.

Comparative dissolution studies were performed with the formulations listed in Table 3. Fig. 9 demonstrates the superiority of formulation A with respect to the dissolution performance: In spite of a low pvp/drug ratio of 7.5 the supersaturation was enhanced by means of SDS to a value equal to coprecipitates with a pvp/drug ratio of 15 containing no SDS.

The effect of SDS could not be achieved in the case of physical mixtures drug/pvp/SDS and, therefore, is considered to be mainly due to the avoidance of recrystallization. There is no difference whether SDS is admixed with the mannitol prior to granulation by the pvp/drug solution in acetone or SDS is suspended in the pvp/drug acetonic solution.

The dissolution profiles of the resultant Bay t 3839 tablets 1 and 2 mg are shown in Fig. 10.

The corresponding compositions are listed in Table 4. The supersaturation capability of the coprecipitate tablets is inferior to that of the granules but is still considered to be sufficient. The deterioration may be explained by the reduced surface of the tablet in comparison to the granules and the better dispersion of the granules in the medium. Another reason may be the impact of the low amounts of insoluble magnesium stearate for lubrication.

As generally observed with Bay t 3839/pvp coprecipitates the duration of supersaturation lasted at least 60 min in vitro and only a slight trend to recrystallization could be seen (in case of pure coprecipitates and granulates no trend within 60 min, see Figs. 2 and 6). Thus, it is concluded that supersaturation is stable over a period sufficiently long for the absorption of drug substance in vivo.

4. Conclusions

The dissolution performance of coprecipitates of very sparingly soluble drugs may be impacted by the choice of the excipients for granulation. In the case of Bay t 3839 insoluble excipients lead to a deterioration of the supersaturation capability. By utilization of soluble fillers (mannitol) and by addition of recrystallization inhibitors (SDS) well performing coprecipitates could be achieved which could be compressed to tablets.

Overall the dissolution performance and the drug/excipient ratio of these coprecipitate tablets were favourable and these formulations were judged to be appropriate for further clinical development.

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