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Preparation techniques for racemic and optically pure ibuprofen, evaluation of resulting active substance qualities

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Racemic ibuprofen and S(+)-ibuprofen show unfavourable galenic properties (bad flow behaviour, no direct tabletting). As a rule, substances available on the market have an identical crystal morphology, which among other methods, can be precisely determined by scanning electron microscopy. Investigations of a representative sample of conventional RS- or S(+)-ibuprofen have shown that in spite of the occurrence of some acceptable parameters no substance can be evaluated positively from a pharmaceutic-technological point of view. Special recrystallisations and reduction procedures bring no satisfactory qualities either. Only granulation techniques can transform ibuprofen into a galenically favourable form, especially fluid bed granulation.

Präparationstechniken für racemisches und optisch reines Ibuprofen und Prüfung der resultierenden Wirkstoffqualitäten

Racemisches Ibuprofen und S(+)-Ibuprofen zeichnen sich durch ungünstige galenische Eigenschaften aus (schlechtes Fließverhalten, nicht direkt tablettierbar). Die am Markt befindlichen Wirkstoffe besitzen in der Regel eine übereinstimmende Kristallmorphologie, die unter anderem durch Rasterelektronenmikroskopie genau determiniert werden kann. Untersuchungen an einer repräsentativen Auswahl von herkömmlichem RS- bzw. S(+)-Ibuprofen zeigten, daß trotz vereinzelt auftretender akzeptabler Parameter kein Wirkstoff pharmazeutisch-technologisch positiv zu beurteilen ist. Spezielle Umkristallisationen und Zerkleinerungsprozesse führen ebenfalls nicht zu befriedigenden Qualitäten. Allein Granulierungstechnologien, insbesondere die Wirbelschichtgranulierung, sind in der Lage, Ibuprofen in eine galenisch günstige Form zu überführen.

1. Introduction

Since its introduction in the form of its racemate in the late 1960's ibuprofen has been widely applied in rheumatism- and pain therapy. The insufficient pharmaceutic-technological properties of the substance (eventually not suitable for direct tabletting) have made it necessary to use rather costly procedures in order to transform it into compact pharmaceutical forms (tablets, coated tablets) [1]. The pharmacologically effective S(+)-antipode is particularly affected by this negative galenic characteristic, among other things, due to its lower melting point of approx. 52 °C (vs. approx. 73 °C) compared to the racemate and due to thermodynamic differences [2, 3] and a differing crystal structure [4, 5]. This paper deals with the characterisation of the material properties of substances produced and distributed by means of preparation techniques commonly used for ibuprofen. In addition to this, alternative methods for the improvement of the bed properties are discussed and investigated with respect to their suitability.

2. Investigations, results and discussion

2.1. Pharmaceutic-technological characterisation of conventional raw materials

The production techniques for ibuprofen or S(+)-ibuprofen available on the world market are only vaguely known for the respective products; it can be assumed, however, that at the end of the synthesis there is at least one purification step that includes recrystallisation from an organic solvent [6, 7]. Apart from a few exceptions the active substance qualities offered therefore have identical physical qualities or show identical features of the crystal habit. This can be seen from the results summarized in Tables 1–3 (we investigated active substances of the most important ibuprofen manufacturers). The flow property of ibuprofen can almost exclusively be considered as insufficient; both with racemate and the optically pure substance only one exception each occurred. The water content of the individual samples – here the water activity = equilibrium humiditys was chosen as the more relevant basis of evaluation [8] – is practically identical. Only the compression qualities show greater differences between the individual batches (Table 2). The bulk- and tapped volumes sometimes differ considerably, a correlation with size of particles or crystal habit, however, could not be established.

Table 1: Flow properties of conventional ibuprofen

Racemic ibuprofen		S(+)-Ibuprofen	
Batch number	Angle of repose (°)	Batch number	Angle of repose (°)
RS 1	>46	S 1	>46
RS 2	>46	S 2	>46
RS 3	29	S 3	>46
RS 4	>46	S 4	>46
		S 5	37

Table 2: Bulk and tapped volume of conventional ibuprofen

Batch number	Bulk-/tapped volume (ml/100 g)	Hausner factor
S 1	224/194	1.15
S 2	190/168	1.13
S 3	174/156	1.11
S 4	184/168	1.09
RS 1	252/208	1.21
RS 2	219/177	1.23
RS 3	183/168	1.08
RS 4	290/239	1.21

Table 3: Equilibrium humidity of conventional ibuprofen

Batch number	Equilibrium humidity (%)
S 1	36.8
S 2	36.8
S 3	36.6
S 4	38.1
RS 1	36.9
RS 2	36.7
RS 3	36.8
RS 4	37.2

It is also noticable that the particle size distribution of the racemic as well as of the optically pure substances investigated is practically identical (s. Figs. 1 and 2). Conventionally produced ibuprofen is marked by a distinct fine portion (100 to 250 µm). This unfavourable particle size distribution could be a major cause of the bad flow behaviour of the substance. A further characteristic of RS- and S(+)-ibuprofen of the various suppliers is the phenotype of the single crystals (s. Fig. 3a). The scanning electron microscope picture is dominated by columnar to pole-like crystals with a distinct length: breadth relation and a smooth non-structured surface. These factors make it possible for the single crystals to attach themselves to their lateral surfaces and to develop great cohesion forces which result in a lasting negative effect on the flowability of the fluid bed. Occasionally, however, the rule is broken by substances with more or less modified macro-crystalline structure. These morphological differences can be explained by effects of the solvent. That means that depending on the polarity of the solvent used for purification, extremely different crystal forms develop [9]. Fig. 3b, for instance, shows ibuprofen-racemate, which due to its almost cubic structure, is at least capable of flowing freely. Due to the form of single crystals illustrated in the SEM-photographs the results of the sieve analysis mentioned above must be examined critically, since the material could as well pass through the meshes of the sieve lengthwise and therefore falsify the results.

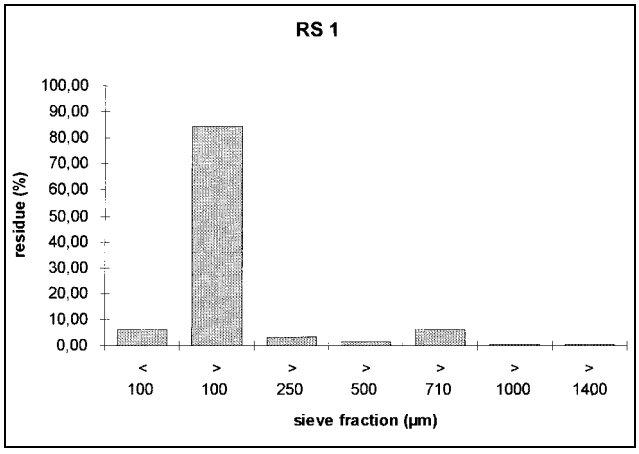


Fig. 1: Particle size distribution of racemic ibuprofen (batch RS 1)

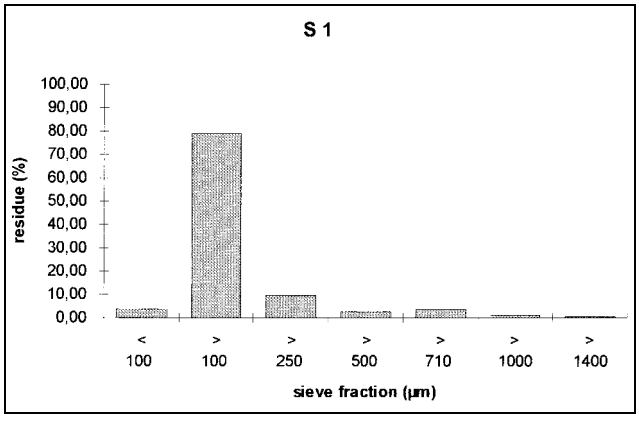
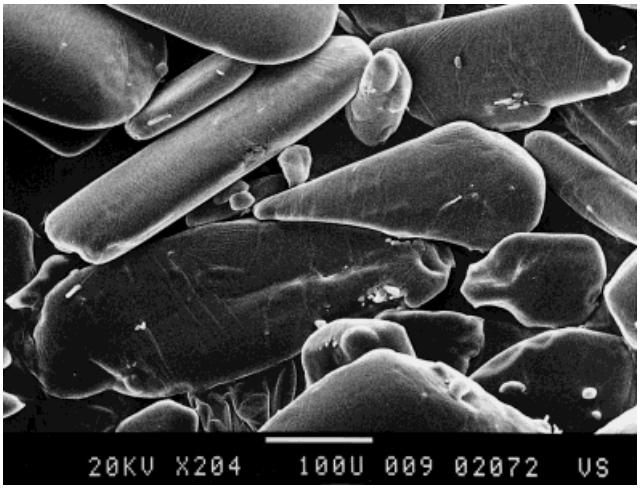


Fig. 2: Particle size distribution of racemic ibuprofen (batch S 1)



a

b

Fig. 3: Scanning electron micrographs of commercial ibuprofen, 200fold (a: batch S 2; b: batch RS 3)

The generally identical physical properties of conventionally produced iburofen-substances primilarily influence the tabletting behaviour. Mainly due to the marked crystalline structure and the resulting mechanical anisotropy, racemic and optically pure substances cannot be compressed directly. During the tabletting process ibuprofen shows elastic behaviour which eventually results in massive lidding [10]. The pharmaceutic-technological features also influence the dissolution behaviour. In artifical intestinal juice the weak acid ibuprofen is readily soluble. Therefore the differences between the individual batches as well as between the racemate and the optically active substance are comparatively small; as a rule 90% of the substance are in solution after five minutes (Figs. 4 and 5).

S(+)-ibuprofen is significantly better soluble in neutral and acid environment than the racemate [11]. As expected, the dissolution in artificial gastric juice shows corresponding differences. In comparison approx. 50% more of optically pure substance is dissolved after 30 min (Figs. 6 and 7). Apart from one exception (batch p.5, spe-

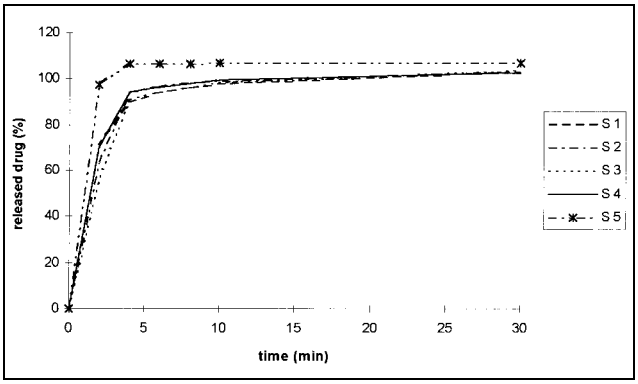


Fig. 4: Dissolution of conventional S(+)-ibuprofen in artificial intestinal juice

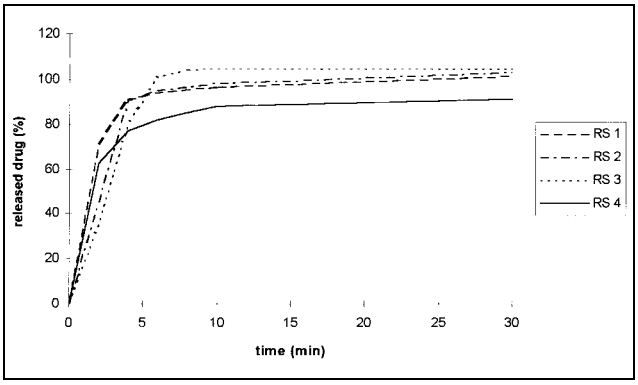


Fig. 5: Dissolution of conventional RS-ibuprofen in artificial intestinal juice

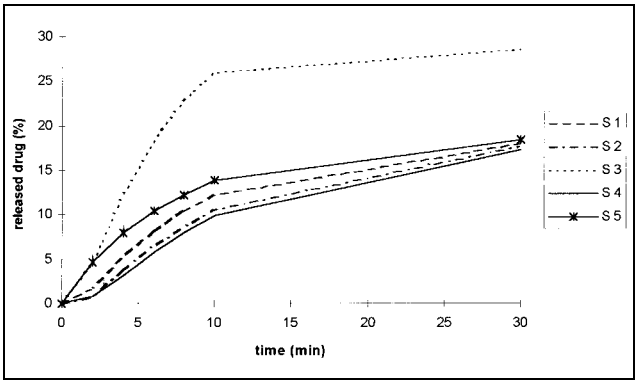


Fig. 6: Dissolution of conventional S(+)-ibuprofen in artificial gastric juice

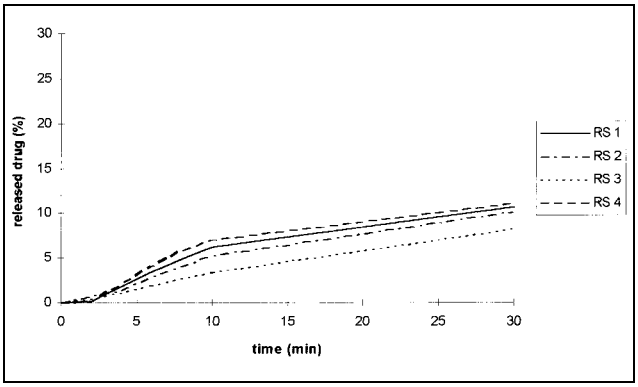
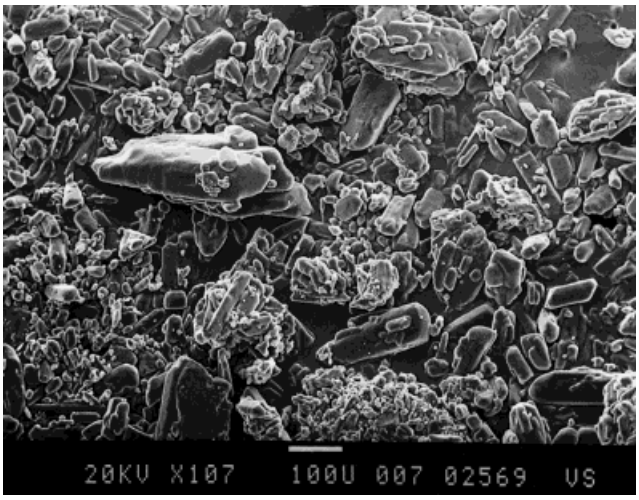


Fig. 7: Dissolution of conventional RS-ibuprofen in artificial gastric juice

cial fine-grained quality) the dissolution rates of S(+)-ibuprofen are on the same level; the racemic substance shows the same behaviour.

2.2. Characterisation of alternatively recrystallised substances

Apart from the commercial products mentioned above, optically pure substances conventionally recrystallised from organic solvents were produced on a laboratory scale and tested for their substance properties. Although the discussion about the ideal morphology of ibuprofen-crystals has not yet been concluded it seems to be undisputed that the physical and galenic properties can be changed significantly through changes of the crystallisation-medium [16–18]. Our analytical determination (content, purity, degradation product) has shown that the chemical properties of the substances correspond to those of the production-batches mentioned above and therefore meet the pharmacopeial demands of the product. The variation of the solvent used should eventually yield a freely flowing substance that can be tabletted directly. Thus substances were recrystallised from 90% or rather 75% hexane, methanol, 50% acetone and a mixture of ethanol/methanol/water and comparative investigations were carried out. Scanning electron microscopic (SEM) pictures show that the respective choice of the crystallisation medium partly results in morphological changes (Fig. 8).



a

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Fig. 8: Scanning electron micrographs of modified recrystallized S(+)-ibuprofen, 250fold (a: batch SEU 2; b: batch SEU 3)

Table 4: Angle of repose of recrystallised S(+)-ibuprofen

Batch number	Angle of repose (°)
SEU 1	46
SEU 2	32
SEU 3	32
SEU 4	>46
SEU 5	>46
standard (S 1)	>46

In S(+)-ibuprofen, which is recrystallised from 90% hexane, one can see a large portion of smaller particles, but also here as in single crystals, the batches mentioned above prevail, which show a cerain "melting" together (Fig. 8a). When recrystallised from methanol there are no changes compared to S(+)-ibuprofen batches produced commercially on a large scale (Fig. 8b). Massive columnar crystals determine the microscopical picture of this substance.

This modified recrystallisation, however, partly resulted in a clear improvement of the flow behaviour (Table 4). This result is partly due to a portion of smaller crystallites which were not present in the starting material. The effect of solvents could also be a reason for the reduced angle of repose observed in some samples.

The resolving behaviour of the substances recrystallised from modified crystallisation media in phosphate buffer did not show any significant changes. The solution velocity of S(+)-ibuprofen and the absolute amount of the resolved substance are within the same range as the corresponding values of conventionally produced batches (Fig. 9). In dilute hydrochloric acid one can observe a more or less distinct decline in solubility compared to conventionally recrystallised substances (Fig. 10). As against nearly 20% only 13–15% of resolved substance

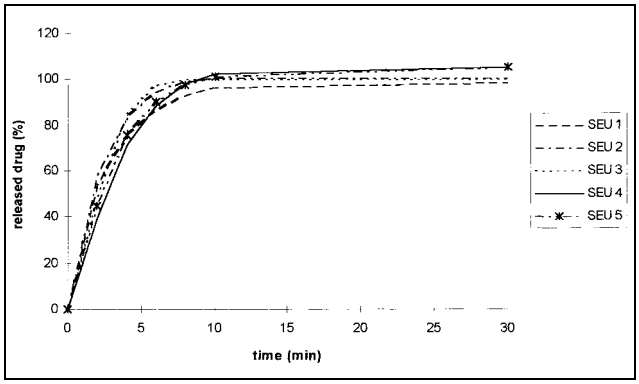


Fig. 9: Dissolution of modified recrystallized S(+)-ibuprofen in artificial intestinal juice

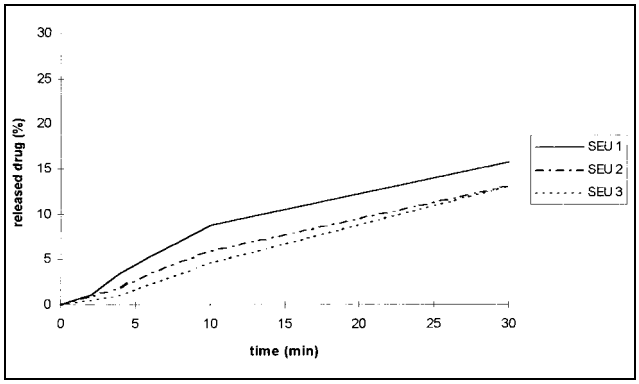


Fig. 10: Dissolution of modified recrystallized S(+)-ibuprofen in artificial gastric juice

could be determined for modified recrystallised samples. Apparently the altered resolving behaviour have its origin, if only slight, structural changes brought about by the different recrystallisation media. Solvent effects seem to play a decisive role. IR-spectroscopic and DSC-investigations have shown that crystallisation techniques have no effect on the crystal structure of ibuprofen and its thermal behaviour. Thus neither changes in the IR-spectrum nor significant differences in the thermo-analytic parameters could be determined (Table 5).

Table 5: Evaluation of the DSC spectra of modified recrystallised S(+)-ibuprofen

Parameter	Batch SEU 2	Batch SEU 3	Standard (batch S 1)
Endothermal peak (°C)	48.8–60.4	47.5–62.1	45.6–62.8
Onset (°C)	53.0	52.9	52.5
Peak maximum (°C)	55.6	56.5	56.2
Melting enthalpy (J/g)	86.9	87.4	89.8

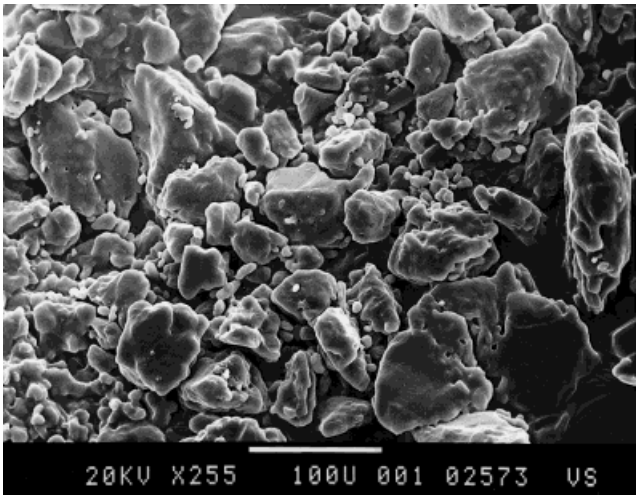
From all the information collected about specially recrystallised ibuprofen one can conclude that the variation of recrystallisation media can only have certain effects on the crystal habit and the flow behaviour of the substance, but that it does not lead to basic improvements of the pharmaceutic-technological properties and therefore cannot be regarded as a preparation technology for racemic or S(+)-ibuprofen.

2.3. Granulated substances

With ibuprofen granulation is still considered to be the method to be chosen for substance processing. Although not all of the compression problems can be eliminated by granulation ("delayed elasticity"), the interparticulate binding of the substance is significantly improved and the required viscoplastic flow is made possible. The following granulation technologies were applied in the production of processed S(+)-ibuprofen:

- Fluid bed granulation (method 1)
- Dry granulation (briquetting, method 2)
- Coating/granulating with own melt (method 3).

Naturally, method 1 was carried out using adjuvants, for methods 2 and 3 principally no additional adjuvants are necessary. The macroscopical picture of the final product varies greatly depending on the granulation technology. Fluid bed granulates have a very fine appearance in common, the particles look kind of roundish. Briquetted batches that have been granulated with their own melt look like coarse-grained agglomerates; the crystalline lustre typical of conventional S(+)-ibuprofen has partly disappeared. Whereas with the racemic substance [20, 21] dry granulation can well be taken into consideration it must be considered to be of limited value with optically pure ibuprofen because of its low melting point (53 °C). Coating with the own melt is said to make a simple compression possible, but it should also be looked at critically. The briquetted batches investigated (exact production conditions are unknown), under the scanning electron microscope show a not clearly defined structure of the single crystals, which combine into larger anomalous formations (Fig. 11a). The side effect that due to the high mechanical pressure the substance melts together, is used indirectly for agglomeration. S(+)-Ibuprofen, coated with its own



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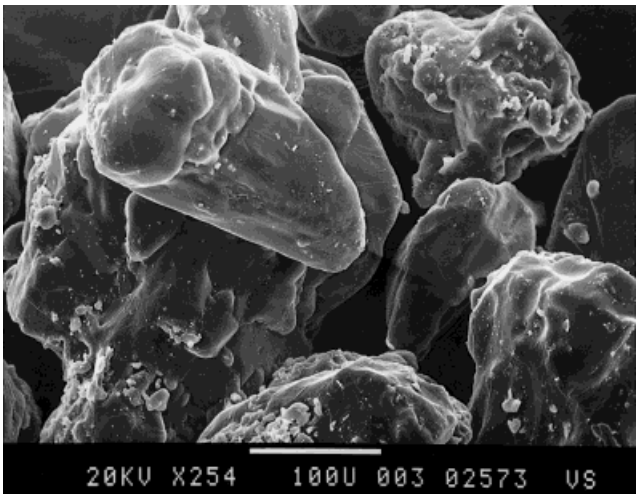

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Fig. 11: Scanning electron micrographs of S(+)-ibuprofen, 250fold (a: dry granulated, batch K1; b: spray-coated with the own melt, batch SB 3)

melt, still shows the crystalline structure of the starting material. The congealed melt, as can also ben seen clearly, combines with or partly coats the single crystals (Fig. 11b).

Fluid bed granulated (binding material HPMC) do not show any changes of the form of the S(+)-Ibuprofen crystals. The binding materials used coat the crystal with a more or less complete or even layer (Fig.12). In the determination of the bed qualities granulated of substances, fluid bed granulated substances were clearly superior to the remaining batches, especially with regard to the flow characteristics. Also compared to classically or modified shock-agglomerated ibuprofen, the fluid bed granulates showed the best flowability. Briquetted substances which are coated with their own melt do not show any free flow (exception: batch SB 3). Nearly all granulated batches share a low density, which is a disadvantage for subsequent tabletting. Exceptions are two "melt-granulated" substances (batches SB 1 and SB 3, Table 6).

The favourable range of the Hausner factor characterising the compressibility of a bed (with the exception of batch SB 2) lies between 1.06 and 1.0, independent of the preparation technology. Only with some fluid bed granulated batches the water activity falls out of the range below 40% GF. Due to the watery procedure higher water-activity values were to be expected right from the beginning.

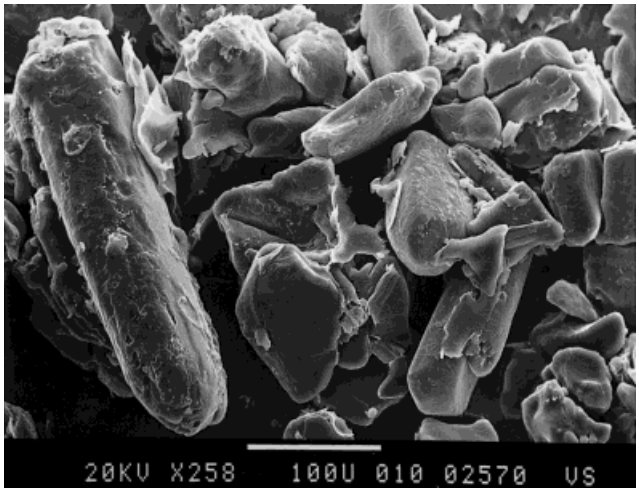

Fig. 12: Scanning electron micrographs of fluid bed granulated S(+)-ibuprofen, 250fold (batch SG 6)

Since dry granulated and melt coated substances were produced without water their equilibrium humidity contents are similar to those of conventional starting materials.

The evaluation of the sieve analyses carried out did not show any features characteristic of the individual granulation techniques. The grain spectra were manifold and batch spezific (Figs. 13–16). Dry granulated S(+)-ibuprofen has a wide grain spectrum, but the size of the individual sieve fractions differs considerably (batch K1 is on average much coarser than batch K2). Like with dry granulated material one has to proceed from the specific production conditions when dealing with substances coated with their own melt, since the results of the sieve analyses are highly variable. Whereas batch SB 2 shows a relatively constant particle size distribution in the range from 250 μm to 1.0 mm, batch SB 3 is characterized by a high proportion of fine particles.

Table 6: Bulk parameters of granulated S(+)-ibuprofen

Batch number	Angle of repose (°)	Bulk-/tapped volume (ml/100 g)	Hausner factor	Equilibrium humidity (%)
Fluid bed granulate (batch SG 1)	29	260/245	1.06	57.3
Fluid bed granulate (batch SG 2)	31	225/208	1.1	35.8
Fluid bed granulate (batch SG3)	28	226/214	1.05	38.8
Fluid bed granulate (batch SG 4)	28	254/239	1.1	41.6
Fluid bed granulate (batch SG5)	27	228/210	1.1	64.2
Fluid bed granulate (batch 6)	29	220/204	1.05	40.7
Dry granulated S(+)-Ibuprofene (batch K1)	32	no value	#NV	40.2
Dry granulated S(+)-Ibuprotene (batch K2)	>46	no value	#NV	39.9
Coated with melt (batch SB 1)	>46	197/180	1.09	39.4
Coated with melt (batch SB 2)	>46	242/206	1.17	37.9
Coated with melt (batch SB 3)	29	186/176	1.06	37.5

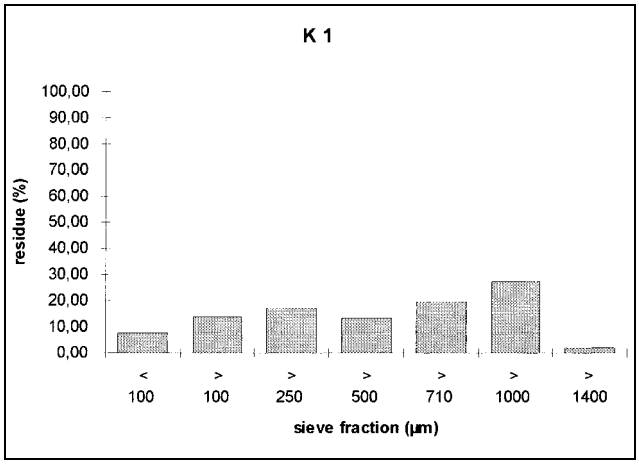

Fig. 13: Particle size distribution of dry granulated S(+)-ibuprofen (batch K 1)

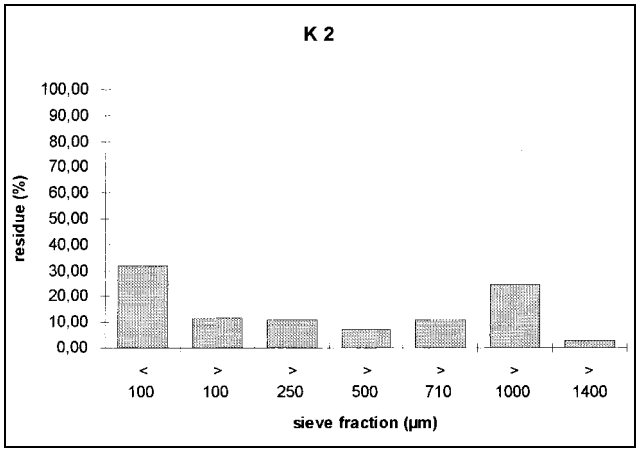

Fig. 14: Particle size distribution of dry granulated S(+)-ibuprofen (batch K 2)

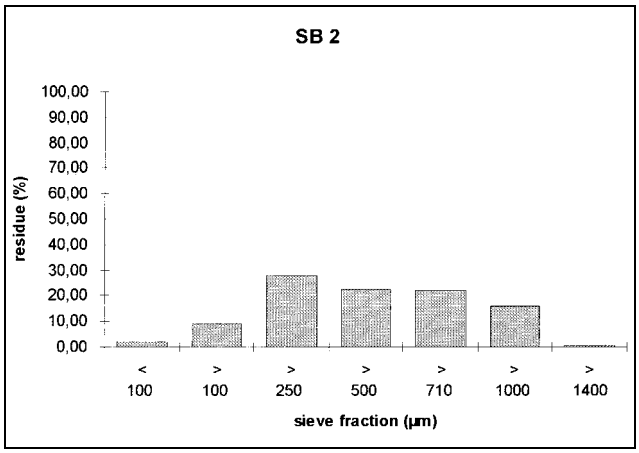

Fig. 15: Particle size distribution of S(+)-ibuprofen coated with the own melt (batch SB 2)

Briquetted and melt granulated substances normally do not show an optimal distribution, which could at least partly explain the unsatisfactory flow characteristics. Fluid bed granulated ibuprofen usually shows small particles, that is a marked fine grain portion. Individual particle diameters of more than 710 µm are relatively rare. Fig. 17 shows an untypical particle spectrum ("coarse" granulate). It shows a nearly optimal bell distribution and therefore offers favourable conditions for good flowability.

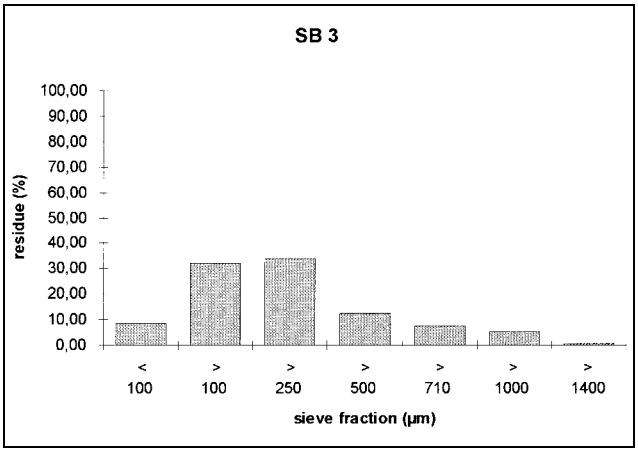

Fig. 16: Particle size distribution of S(+)-ibuprofen coated with the own melt (batch SB 3)

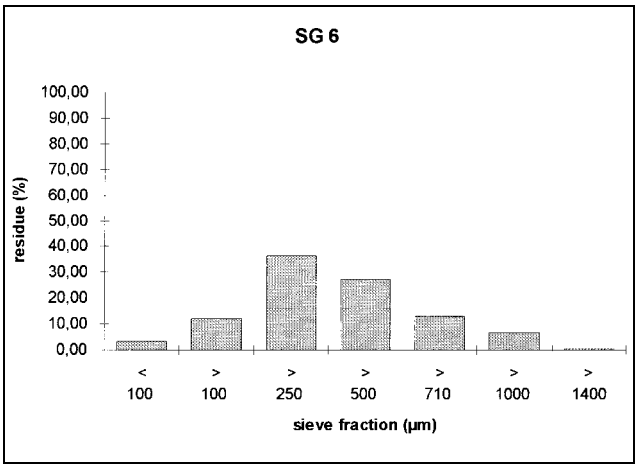

Fig. 17: Particle size distribution of fluid bed granulated S(+)-ibuprofen (batch SG 6)

The analyses of the solubility behaviour in phosphate buffer brought the result that granulation, independent of the technology chosen, has no impact on the dissolution properties of S(+)-ibuprofen. The good solubility of the substance in alkaline environment causes in all batches that the total amount of active substance has gone into solution at the latest after ten minutes, but as a rule already after six minutes (Fig. 18). These results are identical with those of conventional S(+)-ibuprofen, which means that the quality of the active substance has not changed. Marginal differences concerning the values of the first minutes have no relevance.

In contrast to the results in alkaline environment, the studies of the solution behaviour in artificial gastric juice, showed comparatively strongly deviating dissolution profiles for the individual batches. A dependence on the granulation method could not be determined; both the particle distribution and the dissolution behaviour are batch specific.

In fluid bed granulated S(+)-ibuprofen, amount and velocity of the relase of granular particles seem to be influenced primarily by the kind of auxiliary agents used (Fig. 19a). Granulates that contain micro-crystalline cellulose or pre-gelatinised starch go into solution particularly quickly (batches SG 1, SG 2, SG 5). Carboxymethylcellulose as disintegrant cannot positively influence the release of the substance. Here the profiles are on the level of shock agglomerated S(+)-ibuprofen as with substances only granulated with a binding agent (HPMC). The same is true for the briquetted product K2. Although on average

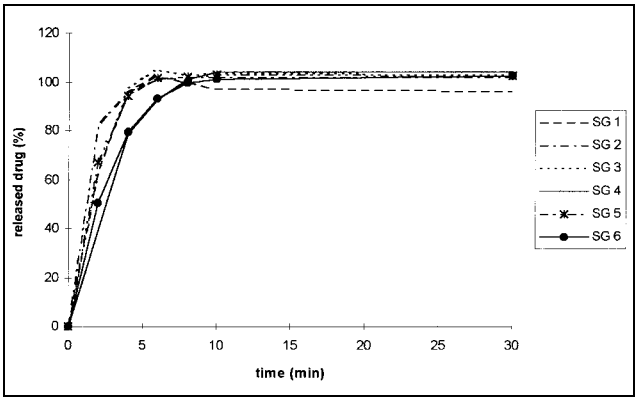

Fig. 18a: Dissolution of some granulated S(+)-ibuprofen batches in artificial intestinal juice

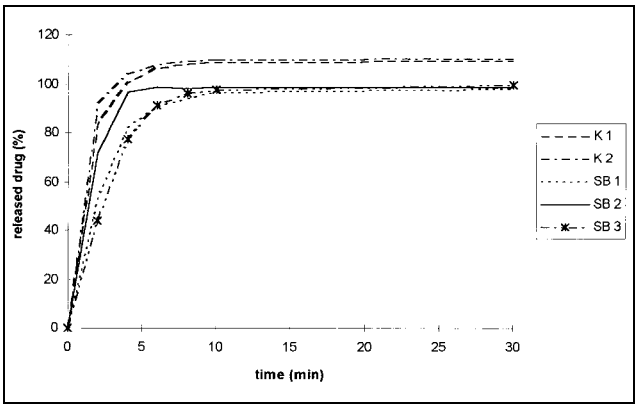

Fig. 18b: Dissolution of some granulated S(+)-ibuprofen batches in artificial intestinal juice

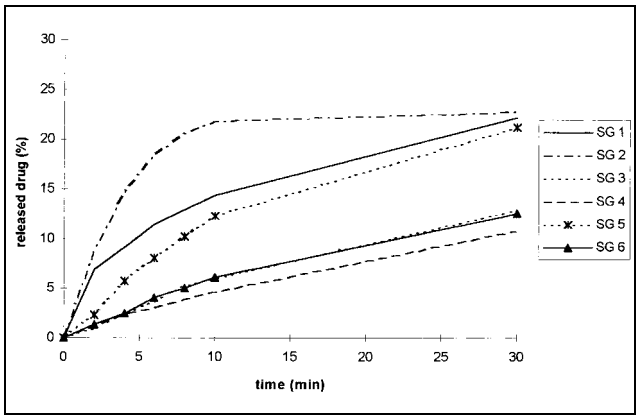

Fig. 19a: Dissolution of some granulated S(+)-ibuprofen batches in artificial gastric juice

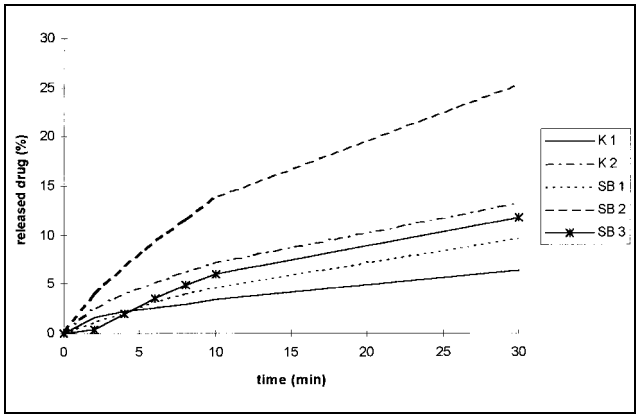

Fig. 19b: Dissolution of some granulated S(+)-ibuprofen batches in artificial gastric juice

the particle size is much smaller, the batch K1 that was also dry granulated goes into solution clearly slowlier and about 50% less than K2. Here the work up process seems to determine the dissolution properties decisively.

In the same way as with dry-granulated S(+)-ibuprofen, with substances that have been granulated with their own melt, neither the particle size nor particle distribution but technologically conditioned special features are responsible for the solubility in acid environment. The "coarsest" batch SB 2 shows by far the best dissolution properties. The finer grained products have a solubility on or slightly under the level of shockagglomerated substances (Fig. 19b).

To sum up it can be said that the present high rank of S(+)-ibuprofen granulation is justified since above all the bed properties are improved considerably and the active substance can be tabletted. This applies in particular to fluid bed granulation; dry granulation and melt granulation procedures that are used more rarely for S(+)-ibuprofen, do not lead to similarly convincing results. The dissolution behaviour is only influenced significantly in artificial gastric juice. Here mainly formulation-conditioned (fluid bed granulation) and technology specific dependences are of importance. Thermoanalytical and IR-spectrophotometric studies confirm existing results [23, 24] that the inner structure of the substance (crystal lattice structure) is not influenced through work up procedures.

Table 7: Bulk parameters of untreated and ground ibuprofen

Batch	Angle of repose (°)	Bulk-/tapped volume (ml/100 g)	Hausner factor
S 4	>46	184/164	1.12
S 4-G	>46	193/172	1.12
RS 4	>46	196/146	1.34
RS 4-g	>46	260/214	1.21

2.4. Substances obtained through grinding and classification

Through grinding we tried to change the crystalline morphology of conventional ibuprofen (racemic and optically pure) in order to reduce the marked length-width ratio and thus optimize the fluid bed properties. Besides that we wanted to make use of the finding that a micronisation of racemic and optically pure ibuprofen can have very different effects on the solubility behaviour [25]. For this purpose, the substances were processed for 20 min in a ballmill together with dry ice. Afterwards the relevant technological properties and the dissolution were investigated. In comparison to the starting material no improvement in the flowability could be found; the cohesive properties of ibuprofen were even intensified and therefore, due to their inconclusive nature, sieve analyses were dispensed with from the outset.

The compression properties worsened in so far as bulk- and crush volumes increased as a result of the milling process and that with the racemic substance the Hausner-factor rose significantly (Table 7). Therefore the grinding of ibuprofen is not suitable to influence the fluid bed properties positively.

Due to the achieved reduction of the particle size an improvement in solubility was to be expected in the different test media. This assumption could be confirmed experi-

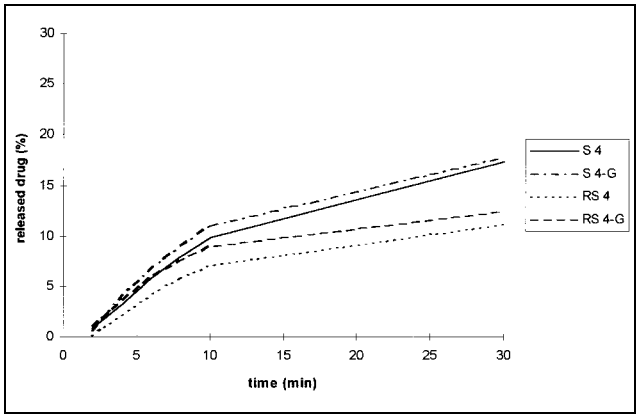

Fig. 20: Dissolution of untreated and grinded ibuprofen in artificial gastric juice

mentally. In diluted hydrochloric acid the amount of dissolved substance increased only insignificantly, but there was a slight rise of the solubility velocity (Fig. 20). Due to the good solubility of ibuprofen no difference in the dissolution behaviour of ground and unground substance in artificial intestinal juice could be found.

The analysis of the present investigations shows that the processes are not to be considered useful since on the one hand they require a comparatively great deal of effort and on the other hand the achieved improvements in dissolution are only small and do not serve the purpose.

In conclusion we must state that, irrespective of its optical activity, ibuprofen available on the market shows insufficient pharmaceutic-technological properties and therefore, as a rule, must be fluid bed granulated. By varying the recrystallisation-conditions or through mechanical work-up steps, no improvement of the bed properties can be achieved. Therefore, in particular for the low melting S(+)-ibuprofen new conceptions for the development of innovative and cost-saving preparation technologies are necessary.

3. Experimental

3.1. Chemicals

Ibuprofen-racemate and S(+)-ibuprofen see batch-key; Aerosil® 200, Degussa (Ph. Eur.); Acivel® PH 101, FMC, (Pharm. Eur.); Acivel® PH 102 SCG, FMC (Pharm. Eur.); ECG® 505, Nichivin, (Pharm. Eur.); Tylose® H 4000, Hoechst; Nymcel® ZSB 10, Nyma; Polyglykol 20000; Hoechst; Starch® 1500 Colorcon, (Spec. Colorc.); Uvasol® (potassium bromide), Merck; potassium dihydrogenphosphate, Merck; sodium hydroxide (pastilles) p.a., Merck.

3.2. Work-up methods for ibuprofen (fluid bed granulation)

3.2.1. Laboratory scale

The fluid bed granulation on laboratory scale was carried out in the fluid bed spray granulation unit WSG 5 of the firm Werner Glatt Lufttechnischer Apparatebau Haltingen.The substance to be granulated – if necessary auxiliary ingredients were added – was heated in the fluid bed and then the granulating solution or granulating suspension was applied. Due to the low melting ranges of racemic and especially S(+)-ibuprofen lower working temperatures than usual had to be chosen (see procedure parameters). In order to prevent excessive moistening of the material, the spraying of the granulating liquid was carried out successively. For the same reason the final after-drying in the fluid bed could only be performed without the addition of thermic energy. When lumpy agglomerates emerged the granulate was ground in the dry granulator.

Procedure parameters:

- incoming air temperature: 45–55 °C
- outgoing air temperature: 35–40 °C
- product temperature: approx. 30 °C
- incoming air lid: position 1.5
- outgoing air lid: 80%
- working air: 5 bar
- spraying air: 2 bar
- pumping power: 20 Upm
- Batch size: 4 to 5 kg ibuprofen or S(+)-ibuprofen
- granulating liquid: watery
- binding substance: hydroxypropylmethylcellulose, pregelatinised starch.

3.2.2. Production scale

On the production scale the fluid bed granulation was carried out with a fluid bed granulator WSG LT 60 of the firm Werner Glatt Lufttechnische Apparaturen, Haltingen. The procedure is almost identical with the granulation described above. Only the granulate drying was carried out by adding temperature (20 min at 30–35 °C).

Procedure parameters:

- incoming air temperature: 20–30 °C
- outgoing air temperature: 20 °C
- incoming air lid: 80%
- outgoing air lid: 80%
- working air: 4.2 bar
- pumping power: 20–30 Upm
- batch size: 22 kg S(+)-ibuprofen
- granulating liquid: watery
- binding substance: hyydroxypropylmethylcellulose

3.3. Analysis

3.3.1. Scanning electron microscopy (SEM)

The SEM tests performed with substances, mixtures and pharmaceutical preparations were carried out at a SEM type 100 A of the firm Leitz. The tabletted samples were broken and then mounted to preparation carriers with conductive carton cement. Powdery samples were attached to the preparation carrier by means of a double adhesive tape. Then the samples to be examined were sputtered with gold in a gas discharge apparatus GEA 005 for 60 s. The thickness of the gold layer was about 150 Å.Depending on the samples the enlargement of the SEM photographs varied between 20 and 2000.

3.3.2. Thermoanalysis (DSC)

Equipment: Perkin Elmer Differential Scanning Calorimeter DSX-4; Perkin Elmer Thermo Analysis Data Station model 3600 (The Perkin Elmer Corp. Norfolk).

The thermo-analytical investigations were carried out with samples in a closed pan. For that purpose about 4.0 g of the sample were exactly weighed into the aluminium pan, which was then closed with a lid. The sample was introduced into the apparatus and then analysed. The heating rate was 10 K/min. Measurement was carried out within the range of 30–100 °C, in racemic substances and preparations respectively within a range of 60 to 100 °C and samples containing S(+)-ibuprofen within a range of 40 to 80 °C were investigated. The following test results have been established and documented: curve diagram, melting point, onset, enthalpy of melting.

3.3.3. UV-detection and interpretation of dissolution results

3.3.3.1. Release from artificial intestinal juice

Apparatus: photometer: diodearray-spectrophotometer HP 8452A (Hewlett-Packard Ltd., Waldbronn); Sample Changer/Controller: model 222 (firm Gilson Villier le Bel); Evaluation software Hewlett-Packard Dissolution Software Division 03.01 (Hewlett-Packard, Waldbronn).

Analytical parameters: measuring cuvette: 0.1 cm thickness; wavelength: 221 nm; integration time: 2.0 s.

The calibration curve was drawn up with phosphate buffer used as solvent and standards with 0.333; 0.222; 0.111 mg/ml ibuprofen content were established. Phosphate buffer was used as blank measure.

3.3.3.2. Release from artificial gastric juice

With respect to methods and apparatus the studies of dissolution in acid environment went according to the conditions mentioned above. The calibration curve was drawn up with phosphate buffer as solvent and was prepared with standards of 10, 40 and 80 µg/ml (corresponds to a weighed portion of 4, 5, 18 and 36% of 200 mg iburofen). Gastric juice was used as a blank measure. The measurement was carried out in a cuvette of 1.0 cm thickness.

3.4. Pharmaceutic-technological test methods

3.4.1. Determination of bulk and tapped volume

The investigations were carried out with a crush volumeter (constructed by Gebro Broschek Ltd., Fieberbrunn) in accordance with DAB 10 V.5.5.4. For this procedure a sample of 100 g was poured into a 250 ml-measuring cylinder without condensing the material. If this was not possible a smaller amount was chosen, which was later used for calculation. The bulk volume was read off with an accuracy of 1 ml. Afterwards 1250 crush-move-

ments were performed and the crush volume was read off with a accuracy of 1 ml. If a difference of <2 ml occurred, another 1250 crush-movements were performed.

3.4.2. Determination of angle of repose

The flow behaviour of substances and substance-preparations was tested and quantified with of the angle of repose. The investigations were carried out with an apparatus constructed by Gebro Broschek Ltd., Fieberbrunn, in accordance with DAB 10. Due to their inconclusive nature the results were determined with an accuracy of $>2°$.

3.4.3. Determination of particle size distribution of fluid beds

Substances and substance preparations were classified at a sieve tower with regard to their particle size. In individual cases light disagglomeration was necessary, since (above all untreated substance) ibuprofen tends to agglomerate, especially after a certain storage-period. This moderate fragmentation could be achieved by pressing the substance through a 2.0 mm-sieve. The substance (100.0 g) was weighed exactly and then put on the sieve tower. The following sieves were used (indication of mesh-size): 0.1 mm/0.25 mm/0.5 mm/0.71 mm/1.0 mm/1.4 mm. For comparative tests of special fluid beds an additional sieve of 0.125 mm mesh size was used. The classification of the fluid bed was carried out with a shaking sieve Retsch RV of the firm Retsch, Haan. The shaking lasted 20 min, the vibratory intensity was 80% and the shaking intervals were 20 s. The classification results, i.e. the particle size distributions, followed from the difference between the gross and net sieve weights. They were documented as diagrams.

Table 8: Batch number coding

Batch	Manufacturer	Compression/remarks
S 1	Sekhsaria, India	Conventional bulk material, S(+)
S 2	Boots, GB	Conventional bulk material, S(+)
S 3	Albemarle, USA	Conventional bulk material, S(+)
S 4	Albemarle	Conventional bulk material, S(+)
S 5	Francis, Italy	Conventional bulk material, S(+)
RS 1	Francis	Conventional racemic bulk material
RS 2	Boots	Conventional racemic bulk material
RS 3	Glaxo, India	Conventional racemic bulk material
RS 4	Albemarle	Conventional racemic bulk material
SEU 1	Ethyl, USA	S(+)-Ibuprofen, recrystallised from hexane (75%)
SEU 2	Ethyl	S(+)-Ibuprofen, recrystallised from hexane (90%)
SEU 3	Ethyl	S(+)-Ibuprofen, recrystallised from methanol
SEU 4	Ethyl	S(+)-Ibuprofen, recrystallised from acetone (50%)
SEU 5	Ethyl	S(+)-Ibuprofen, recrystallised from EtOH/MetOH/water
S 4-G	TM	S 4, ground with dry ice
RS 4-G	TM	RS 4, ground with dry ice
S 1-Hex 1	TM	S 1; shockagglomerated from hexane
S 1-Hex 2	TM	S 1; shockagglomerated from hexane
SG 1	TM	S(+)-Ibuprofen granulate (MCC, HPMC)
SG 2	TM	S(+)-Ibuprofen granulate (MCC, HEC)
SG 3	TM	S(+)-Ibuprofen granulate (HPMC, Ca-CMC)
SG 4	TM	S(+)-Ibuprofen granulate (HPMC)
SG 5	TM	S(+)-Ibuprofen granulate (Starch R 1500, HPMC)
SG 6	Gebro, Austria	S(+)-Ibuprofen granulate (HPMC)
SB 1	Albemarle	S(+)-Ibuprofen, coated with the own melt
SB 2	Albemarle	S(+)-Ibuprofen, coated with the own melt
SB 3	Albemarle	S(+)-Ibuprofen, coated with the own melt
K 1	Albemarle	S(+)-Ibuprofen, dry granulated
K 2	Albemarle	S(+)-Ibuprofen, dry granulated

TM = manufactured by the authors

3.4.4. Determination of equilibrium humidity (water activity)

The equilibrium humidity was established with the rotronic hygroscope DT of the firm rotronic AG, Zürich. The sample (2.0 g) was introduced into the measuring chamber and the measuring head containing the humidity- and temperature donors was mounted on it. The measurement was finished when the measurement reading was sufficiently stable (variation $<0.02\%$ rF and $<0.02\,°C$/min). The equilibrium humidity was established in %rF and documented.

3.4.5. Investigations of the dissolution and the release of substance from the preparation

3.4.5.1. Dissolution of substances and tablets/coated tablets in artificial gastric juice

– Method:	USP paddle
– Apparatus:	dissolution-tester Sotax AT 7 (Sotax, Allschwil); fraction collector Sotax C 613; reciprocating pump Sotax CY 7-50.
– Test medium:	hydrochloric acid 0.1 N pH 1.2; 900 ml
– Mixing velocity:	150 Rpm
– Test temperature:	37 °C.

3.4.5.2. Dissolution of substances and tablets/coated tablets in artificial intestinal juice

Test medium:	degased phosphate buffer pH 7.2; ingredients: KH_2PO_4 156.52 g; NaOH-pastille 31.92 g; Aqua dest. ad 23.0 kg. pH adjustment with NaOH or H_3PO_4, all other parameters see above.

3.5. Batch number coding

For batch number coding see Table 8.

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