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Published in:
Organic Process Research & Development

DOI:
[10.1021/op1001116](https://doi.org/10.1021/op1001116)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Noorduyn, W. L., Asdonk, P. V. D., Bode, A. A. C., Meekes, H., Enckevort, W. J. P. V., Vlieg, E., Kaptein, B., Meijden, M. W. V. D., Kellogg, R. M., & Deroover, G. (2010). Scaling Up Attrition-Enhanced Deracemization by Use of an Industrial Bead Mill in a Route to Clopidogrel (Plavix). *Organic Process Research & Development*, 14(4), 908-911. <https://doi.org/10.1021/op1001116>

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Scaling Up Attrition-Enhanced Deracemization by Use of an Industrial Bead Mill in a Route to Clopidogrel (Plavix)

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Abstract:

The recently discovered technique of deracemization by means of grinding a racemic conglomerate in contact with a solution wherein racemization occurs has been scaled up using an industrial bead mill to demonstrate the practical applicability. The time needed to reach the enantiopure end state is drastically reduced as a result of the efficient grinding that can be achieved using bead mills.

Recently, a remarkably simple way to transform racemic mixtures of conglomerates into an enantiomerically pure crystalline phase was discovered.^{1–11} The process involves subjection of the crystals in a slurry to continuous grinding under conditions whereby racemization in solution takes place. The practical execution is very easy and offers an attractive route to enantiomerically pure compounds including those of interest for the production of pharmaceuticals. Although this deracemization process has been explored for various racemizable conglomerates, thereby confirming its general applicability, so far most of the experiments as described above have been conducted with no more than 8–20 mL total volumes. To

demonstrate the practical value of this method, scale-up is therefore a key requirement. Here, we show that by employment of industrial mills attrition-enhanced deracemizations can be scaled up readily with dramatically shorter times needed to reach the enantiopure end state.

In general, scale-up of chemical processes from the small amounts of material and volumes that are used in the initial stages of research to the large volumes that are required for commercially beneficial processes is not straightforward.^{12,13} Mixing properties and heat control are notoriously troublesome parameters in scale-up of chemical processes, although there are also advantages in increasing the size of reaction systems.¹³ For the deracemization process, we were particularly interested in the high abrasion that can be achieved in large-scale bead mills (or bead mill reactors), since we know from previous results that the intensity of the abrasive grinding of the crystals is a crucial factor in the time it takes to transform all the solid material of an almost racemic solid phase into the enantiomerically pure form.³ The grinding causes the ablation of small fragments from the crystals. According to the Gibbs–Thomson effect the smaller crystals have a higher solubility than the larger crystals.¹⁴ As a result the smaller crystals dissolve, thereby nurturing the larger crystals, a process called Ostwald ripening.¹⁵ However, the incorporation of molecules alone is not sufficient to explain the asymmetric transformation during grinding. Uwaha already postulated that the reincorporation of subcritical clusters in the crystals of the same handedness might be crucial.¹⁶ The cluster reincorporation results in an experimentally measurable accumulation in the solution of the enantiomer that forms the minor population in the solid phase.¹⁷ The solution phase racemization reaction erodes this solution phase enantiomeric excess, resulting in a net flux of molecules from crystals of the minor handedness towards crystals of the major one. The rate at which the initially enriched solid phase enantiomeric excess, $ee(0)$, increases as a function of the time t is determined by the rate constant k , according to the relation:^{3,18}

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$$ee(t) = ee(0) \exp(kt) \quad (1)$$

The rate constant k is strongly dependent on the attrition intensity.³ A search for methods for more efficient attrition brought us to the pigment and coating industries, which have long experience in the grinding of solids, both on small and large scale.¹⁹ One of the devices that is often used for this purpose is a so-called bead mill (see Figure 1). The high number of revolutions per minute (up to 4000 rpm) in combination with very hard yttrium-stabilized ZrO₂ beads should allow more intense grinding.

To demonstrate the practical importance we turned to compound **1**, recently used by us as an intermediate in a total resolution process towards clopidogrel by preferential crystallization under deracemization conditions.⁹ The blockbuster drug (*S*)-clopidogrel (Plavix, Figure 2) was developed and commercialized by Sanofi-Aventis for the treatment of cardiovascular diseases and launched in 1993.²⁰ The intermediate compound **1** is a racemic conglomerate and can be readily racemized in solution with the organic base diaza(1,3)bicyclo[5.4.0]undecane (DBU). It is interesting to compare the deracemization rates between the ‘standard’ small-scale experimental procedure and the process using the bead mill. For the small-scale experiment, to a 12-mL reaction vial were added 8.0 g of glass beads (2.5 mm diameter), 0.3 g of (*RS*)-**1**, and 4.7 g of acetonitrile (MeCN). This solution/solid mixture was ground in an ultrasonic cleaning bath thermostatted at 23 °C. After 10 min of intense grinding, 0.1 g of the solution-phase racemization catalyst DBU was added. The progression of the solid-phase enantiomeric excess (*ee*) was followed by filtering samples taken from the slurry and analyzing the composition of the solid phase using chiral HPLC. As can be observed in Figure 3, within 6 h the solid phase deracemizes to an enantiomerically pure state.

For the milling experiments a Netzsch MINICER bead mill (110 mL free volume) filled with 0.4-mm-diameter yttrium-stabilized ZrO₂ beads (660 g) was used. The setup is shown in Figure 1. We start with a small *ee* in order to have a rapid conversion that still allows an accurate determination of the rate. To overcome blocking of the mill by large crystals, a slurry was first prepared by partially dissolving 20 g (*RS*)-**1** and 2 g of (*S*)-**1** in 320 mL of MeCN in a separate reaction vessel. This mixture was vigorously stirred for 20 min and then poured in the bead mill that already contained 110 mL of MeCN. After 5 min of grinding at 2000 rpm, 5 g of DBU was added to initiate the solution-phase racemization. To follow the process, we continuously sampled the solid phase. As can be seen from Figure 3, within 45 min the racemate is completely converted into the desired (*S*)-**1** enantiomer.

To compare quantitatively the deracemizations in the ultrasonic cleaning bath and in the bead mill, the rate constants for the process were calculated using eq 1. As can be seen from Table 1, the deracemization process is approximately 6–7 times

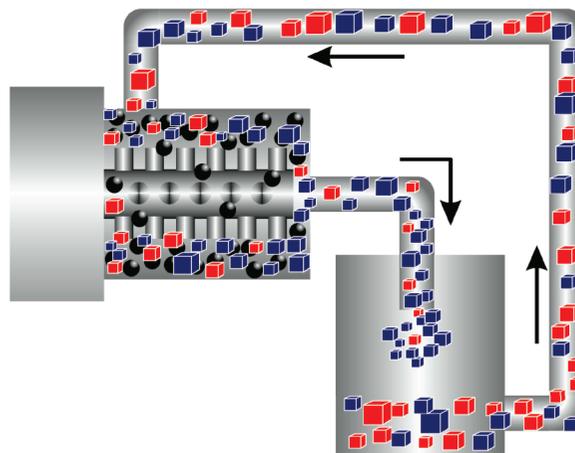


Figure 1. Schematic drawing of the deracemization setup. A slurry containing a mixture of (*R*)- and (*S*)-**1** crystals is circulated through the bead mill. As a result of the vigorous grinding in the mill, in combination with the cyclic process, in the end all crystals are converted into a single enantiomer via the solution-phase racemization reaction.

faster in the bead mill compared to that in the ultrasonic cleaning bath. However, we should realize that in the bead mill the slurry is continuously circulated through the system and, hence, spends only a fraction of the time in the milling chamber (110 mL free volume) where it is subjected to grinding. If we take the total solution volume (430 mL) and the free volume in the mill into account (110 mL), the difference in the rates is even more pronounced. Ignoring further effects of the differences in volume of the setup, the overall deracemization rate of the bead mill is more than 25 times faster as compared to the rate for deracemizations performed in the ultrasonic cleaning bath.

The acceleration of the deracemization is attributed to the efficient grinding that can be achieved using the bead mill. To investigate this effect further we varied the stirring rate in the bead mill, keeping all other conditions constant. Surprisingly, the rate of the deracemization scarcely increases between 1000 and 2000 rpm and even decreases going to the highest stirring rate of 3000 rpm (Table 1). This may be attributed to increasing damage to the crystal packing at these high stirring rates, resulting in the formation of a substantial amount of amorphous material, a phenomenon well-known for these industrial mills.²¹ The formation of amorphous material is indeed observed in the background of the X-ray powder diffraction patterns (Figure 4). The amorphous surfaces may slow down the deracemization since the enantioselective crystal growth by Ostwald ripening is expected to be hampered. An additional effect of the increase of the grinding intensity may be that the formation of clusters that dissolve in monomers will start to dominate over the reincorporation of clusters back into the crystal, thereby decreasing the overall deracemization rate.

Thus far, most deracemizations have been performed on a 10-mL scale in a single vessel. However, we have previously described an alternative manner to deracemize larger volumes. A clear homogeneous solution in which racemization of **1** takes place is cooled with grinding. The mechanism of deracemization

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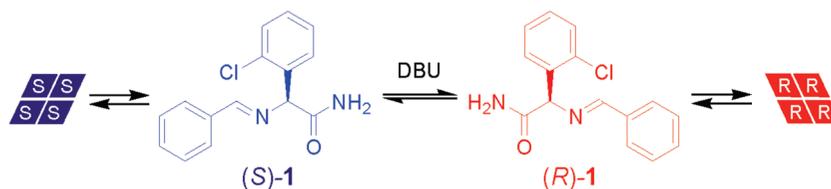


Figure 2. Chemical and physical equilibria during the attrition-enhanced asymmetric transformation of **1**.

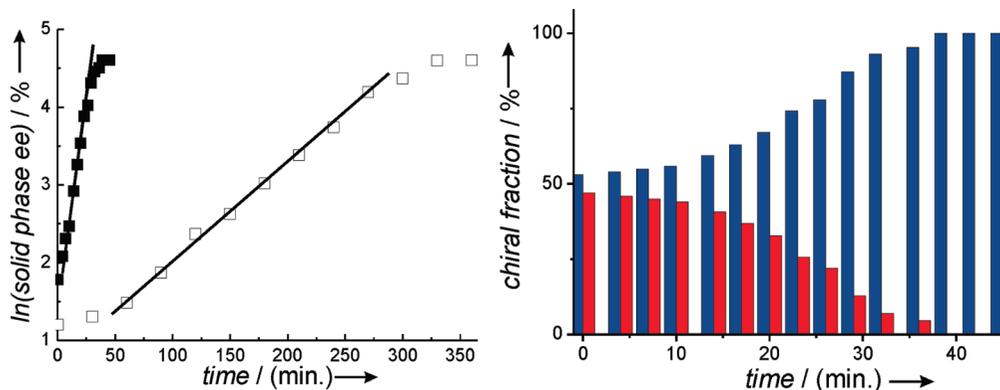


Figure 3. Progression of the enantiomeric excess in the solid phase during the grinding-induced transformation on a 10-mL scale using a thermostatted ultrasonic cleaning bath (open symbols) and on a 400-mL scale using the bead mill (closed symbols). The straight lines are a fit of the data to eq 1. The right graph shows the increase of the chiral purity in the solids of the latter experiment (blue (S)-1, red (R)-1). The initial ee values after dissolution were 3.40% for the ultrasonic and 5.96% in the beadmill experiment.

Table 1. Deracemization rates in the various experiments

experiment	grinding process	rpm	k (min ⁻¹)	overall k (min ⁻¹) ^a
1	ultrasonic bath (10 mL)	—	0.012	0.01
2	bead mill (400 mL)	1000	0.076	0.30
3	bead mill (400 mL)	2000	0.080	0.31
4	bead mill (400 mL)	2500	0.081	0.32
5	bead mill (400 mL)	3000	0.069	0.27

^a Final column lists the overall k value that corrects for the fraction of the time that the slurry is actually ground by the beads, ignoring further effects of the differences in volumes of the setups.

is analogous to that described for NaClO₃.^{22,23} The solution may be seeded during the cooling process with crystals of the desired handedness. In this way it took about 17 h to reach complete deracemization of 35 g of **1** in a volume of 315 mL.⁹ Here we demonstrate that the severe grinding achieved in an industrial mill can be employed to drastically reduce the deracemization time, even at constant temperature. Moreover, we show that the transformation is still effective when the slurry is pumped through a network of tubes. This should also allow one to pump the slurry through a cascade of mills and to use a backfeed of enriched material. As the enantiomeric enrichment follows an exponential law, the rate is slowest at the onset of the process. Therefore, it may be attractive to remain in the steep part of the exponential increase of the ee. To achieve this one can, for instance, envision a setup with a partial backfeed, such that enantiomerically highly enriched crystals are used to enrich the racemic starting material, thus avoiding the slow onset. Recently, we demonstrated that the racemization reaction for the grinding process need not be performed in the presence of the crystals.¹⁷ Since one can now pump the slurry through a network, this might allow one to use different racemization conditions (such

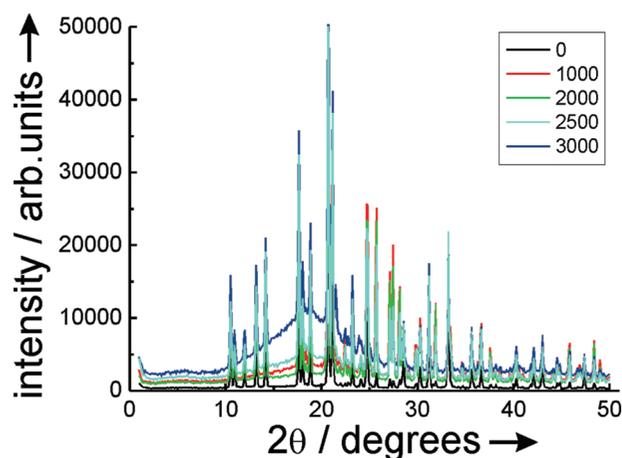


Figure 4. X-ray powder diffraction patterns of the solids collected after 20 min of grinding at various stirring rates (expressed in units of rpm in the inset/legend). The patterns show a trend of increasing background intensity, indicating the formation of amorphous material at higher stirring rates.

as high temperatures, which would dissolve the crystals) or to use enzymes (which cannot be used in combination with severe grinding). For instance, this may be implemented by using two containers (one with crystals that are ground and one container in which the racemization takes place) that are separated by a semipermeable membrane that only allows solute molecules to pass.

In summary, these results demonstrate that scaling up of the grinding of a slurry of racemic conglomerate crystals with low enantiomeric excess under racemizing conditions as a route to

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enantiomerically pure compounds is possible. Furthermore, we observe that this route becomes even more efficient on a larger scale. Using the efficient grinding that can be achieved with an industrial bead mill, we have explored the limits of the rate at which this process can be performed.

Experimental Section

Determination of the ee by Chiral HPLC Analysis of the Solids Samples. Sample preparation 0.5 mg solid in 1.5 mL of eluent, injection volume 20 μ L, HPLC column Chiralpak AD-H (250 mm \times 4.6 mm ID), eluent *n*-hexane/2-propanol, 85:15 v/v%, flow 1 mL/min, r.t., detection λ = 254 nm. Retention times (*S*)-**1** 9.3 min, (*R*)-**1** 10.5 min.

Acknowledgment

We kindly acknowledge Ivan Vanderhaeghe, Sonny Wynants and Liesbeth Vranckx (AGFA-Gevaert NV) for their assistance during the bead mill experiments. The SNN agency (Cooperation Northern Netherlands) and the European Fund for Regional Development (EFRO) are acknowledged for partial financial support of this work. The group from Radboud University Nijmegen thanks COST Action CM0703 for support.

Received for review April 20, 2010.

OP1001116