

# Evaluation of Spinning Disk Reactor Technology for the Manufacture of Pharmaceuticals

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A continuously operating spinning disk reactor (SDR) displayed distinct advantages over batch processing techniques when several commercially relevant processes for the manufacture of pharmaceuticals as test reactions were investigated. It proved to be a useful tool for revealing intrinsically fast kinetics as well as for optimizing processes with such kinetics. Very encouraging results were achieved for a phase-transfer-catalyzed (ptc) Darzen's reaction to prepare a drug intermediate and the recrystallization of an active pharmaceutical ingredient (API). In comparison to presently used batch processes, the ptc reaction resulted in a reaction with 99.9% reduced reaction time, 99% reduced inventory, and 93% reduced impurity level. The recrystallization yielded particles with a tight particle size distribution and a mean size of around 3  $\mu\text{m}$ . Reactor modeling was in good agreement with the experimental results and highlighted the advantages of the process-intensified equipment with a production capacity of around 8 tonnes/year.

## Introduction

Recently, the spinning disk reactor (SDR) was brought forward as an alternative to traditional stirred tank processing technology,<sup>1,2</sup> claiming to offer distinct advantages with respect to mixing characteristics, heat transfer, and residence time distribution. Following an industrial/academia collaboration sponsored by the Innovative Manufacturing Initiative in the United Kingdom, the Process Chemistry Department, at SmithKline Beecham (SB) Chemical Development, Tonbridge, evaluated with support from Newcastle University the applicability of this continuous processing technology to drug manufacturing processes currently in development. The aim of the study was to determine whether this novel reactor would prove to be of advantage over presently applied manufacturing techniques. A prototype of the equipment was constructed by Newcastle University and then loaned to and later purchased by SB. It was installed at SB pilot plant premises at Tonbridge for the duration of the evaluation study.

In this report, we will describe the results of this evaluation, determining whether the spinning disk reactor proved to be an attractive and commercially viable alternative to conventional batch processing.

## Theory

**Background.** Most pharmaceuticals and fine chemicals are manufactured in stirred vessels which are simply scaled-up versions of the beaker in which the process was originally devised. Unfortunately, the heat-

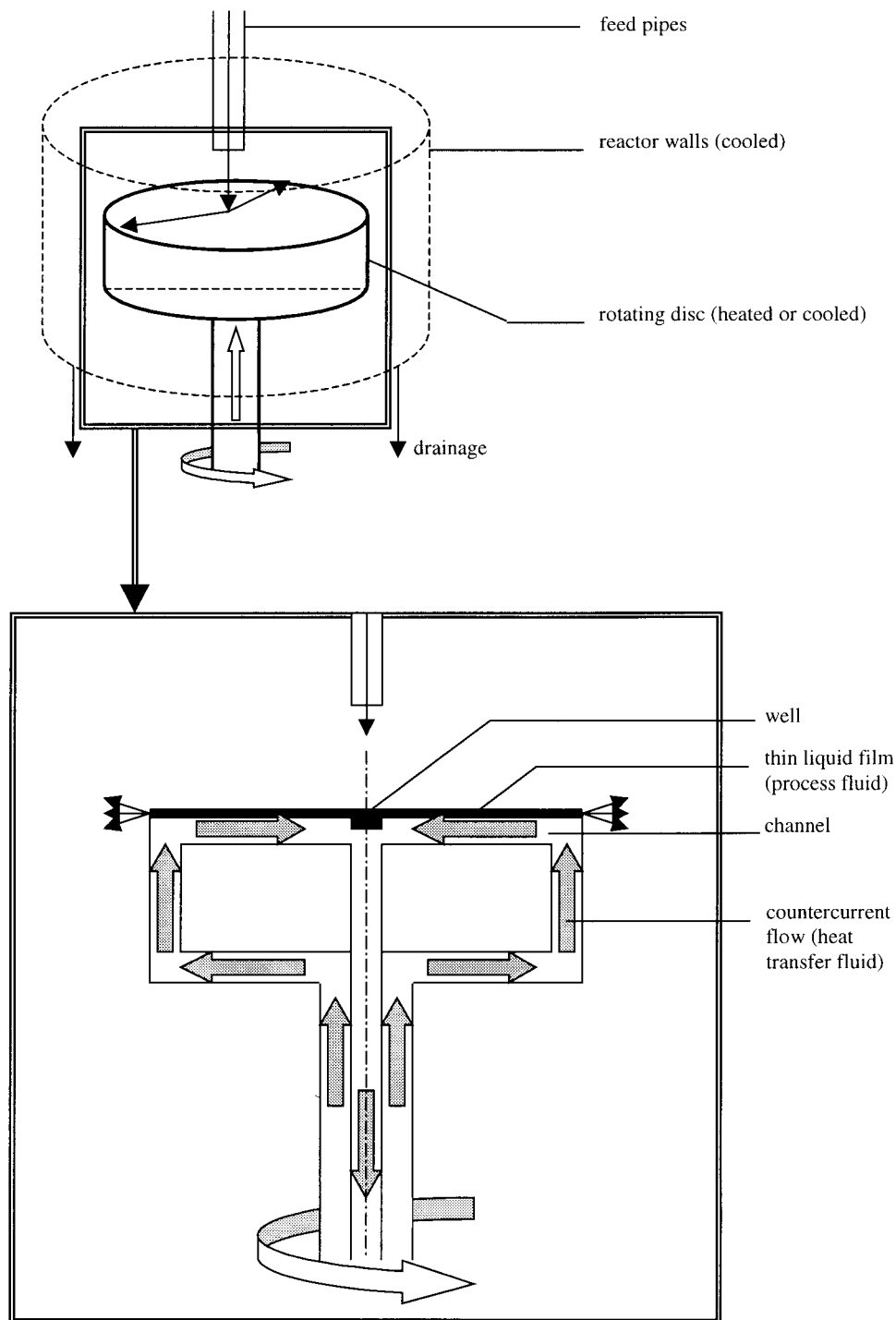
mass-transfer and mixing characteristics of a stirred vessel deteriorate rapidly at larger sizes because the surface-to-volume ratio decreases and the circulation time of contents increases while the corresponding mixing intensity decreases at constant impeller tip speed. Thus, large vessels will tend to impede reactions which may be intrinsically fast and highly exothermic. If a more intense fluid dynamic environment could be created, the intrinsic reaction kinetics can be given free rein. Where these are fast, the reaction can in principle be completed within a few species half-lives, provided heat-/mass-transfer and mixing limitations are relaxed. In practice, the fluid residence times on an SDR are in the range of 1–5 s compared with a few hours in a stirred vessel. Hence, reactions with half-lives in the 0.1–1 s range may be expected to be completed on the disk. Noting the qualitative equivalence of mixing intensity and fluid shear stress, the SDR is capable of generating a far higher mixing intensity than a stirred vessel and should therefore be capable of maintaining uniform concentration profiles within a rapidly reacting fluid. Thus, better control should be exerted over the reaction trajectory than that achieved in a conventional stirred tank. Bearing in mind the pharmaceutical industry's drive to shorten development times, it is apparent that the SDR, with its high potential productive capacity may allow the laboratory scale to be the full scale and hence avoid the inevitable delays in authenticating various levels of scale-up. In addition, the small reactor holdup (<100 mL) and the excellent fluid temperature control make the SDR particularly suited for highly hazardous reactions.

**Operating Principle.** The working principle of the continuously operated SDR can be taken from Figure 1. The spinning disk is a horizontally oriented plate that can be heated or cooled and rotated via an air motor at speeds up to 5000 rpm. Liquid feed streams, supplied to a well in the center of the plate, travel rapidly across

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**Figure 1.** SDR operating principle.

the surface and form a thin film with thickness  $\delta$ . Liquid leaves the disk at its edge after which it can be collected. The SDR is capable of subjecting this film to very high shear stress,  $\tau$ , promoting very high heat-transfer rates between the film and the disk and high mass-transfer rates between the liquid streams or between the film and the gas in the surrounding atmosphere.

**Model Concept.** The flow of the liquid film as it moves from the center of the disk to the periphery is intrinsically unstable and extremely complex. The film instability results in minor disturbances being amplified to generate an increasingly chaotic array of ripples, which are known to enhance the film transport properties via their associated flow field. A highly simplified

version of the film flow is used here as the basis of the operating model. It is assumed that the film is laminar and circumferentially uniform and stable, with the local film thickness being determined by a "Nusselt" approach, modified to take account of the varying radial acceleration.<sup>3,4</sup> As implied above, the model predictions are expected to be very conservative.

The two main factors of interest in this investigation were mixing intensity and the liquid residence time,  $t_{res}$ , as they had a dominant influence on the degree of conversion,  $X$ , on the disk (for chemical reactions) and the particle size,  $d_p$  (for crystallizations).

A qualitative measure of the mixing efficiency in the liquid film can be obtained by calculation of the shear

stress,  $\tau$ , which is imposed on the liquid film by the rotational force as it moves over the disk surface. The higher the shear stress, the more efficient the mixing. From the correlations described in refs 3 and 4, which involve a modification of Nusselt's condensation theory, and from the fact that the film surface velocity is 50% greater than the mean velocity, the shear stress can be defined as

$$\tau = -1.5\eta\frac{v_{\text{rel}}}{\delta} = -1.5\sqrt[3]{\frac{\eta\rho^2Q_V\omega^4r}{18\pi}} \quad (1)$$

Equation 1 immediately makes it clear that the shear stress is predominantly influenced by the angular velocity,  $\omega$ , and therefore, by the rotational speed of the disk,  $N$ :

$$\omega = \frac{2\pi N}{60} \quad (2)$$

This indicates that—as might be expected—the mixing characteristics on the disk improve with increasing spin speed. However, it has to be pointed out again that when the definition for  $Re$  and the flow regime given in ref 4 are followed, this is strictly valid for laminar flow only ( $Re < 4$ ) and does not take into account the increase in mixing efficiency by turbulent film flow ( $Re > 20$ ). So shear stress can be regarded as a good quantitative mixing efficiency indicator for laminar flow and a qualitative indicator providing conservative estimates for a turbulent flow regime.

Equation 3 shows that the residence time on the disk is inversely proportional to the angular velocity,  $\omega^{0.67}$ :

$$t_{\text{res}} = \left(\frac{81\pi^2\eta}{16\omega^2Q_V^2\rho}\right)^{1/3} (r_0^{4/3} - r_i^{4/3}) \quad (3)$$

Thus, it is evident that increased mixing efficiency (i.e., high shear stress) can only be realized at very short contact times, which has important consequences for reactions limited by mass transfer. To observe effective conversion on the SDR, a high degree of conversion has to be achieved in reaction times shorter than 0.5 s.

## Experimental Methods

**Setup.** The experimental rig was installed in pilot-plant premises at Tonbridge, to make use of existing ancillary plant facilities (e.g., vacuum, nitrogen, scrubber, steam, etc.). The prototype unit, fabricated in 316 stainless steel (316SS), comprised a 15-cm-diameter disk mounted on a hollow assembly and housed in a jacketed cylinder of about 2-L volume. Interchangeable disks were fabricated from different materials (316SS or naval brass) with different surface textures (smooth, counterclockwise spiral groove, or PTFE-coated). Heat-transfer fluid from an external, heated or cooled reservoir ( $-20$  to  $180$  °C) was pumped into the hollow disk assembly through a narrow channel (channel width 1 mm) directly beneath the disk to achieve the required disk-operating temperature (see Figure 1). The fluid then entered a collector, which drained back into the external heat exchanger. A lip seal between the collector and the rotating shaft assured complete separation of process and heat-transfer side. Rotation of the disk up to 5000 rpm was achieved by use of an air motor and special rolling bearings, allowing for vertical and horizontal

contraction/expansion of the shaft material with variation in operating temperature. Materials were fed onto the disk by two variable flow pumps, both peristaltic-type and positive displacement Micropumps being used. The reactor allowed a maximum throughput of 4.5 mL/s. Processed material left the reactor via two outlet drain pipes and could be sampled at two points immediately after exiting the SDR. The output was then collected in a cooled tank reservoir. Vapor formation was controlled by a condenser, which could either be arranged to collect condensate separately or be returned to the SDR as required. Any reactor off-gas was contacted in a suitable scrubber before release to the environment. Reactions were usually carried out under a nitrogen atmosphere. The system was not rated for operation above atmospheric pressure.

Two separate feed solutions were supplied to the central well on the disk which had undercut sides, thereby creating a small annular liquid reservoir as the disk rotated. Liquid flowed out of the well via the circular lip in a circumferentially uniform flow. While some initial mixing may be expected in the well, most will occur in the subsequent thin liquid film on the disk. Critical stoichiometric ratios were controlled by measurement of the concentrations of the feed solutions and adjustment of the relative flow rates of each pump into the reactor.

Collected reaction samples were quenched immediately to halt further reaction and were analyzed by HPLC. Samples for the crystallization study were filtered on the reactor exit, washed, and dried to preserve the particle size information. Particle size measurements were performed on a Sympatec particle size analyzer.

The materials used were of *pro analysi* quality and obtained either from proprietary chemical supply companies (e.g., Aldrich, Lancaster, Acros) or, in the case of pharmaceutical intermediates, from existing SB inventory.

**Mode of Operation.** The typical mode of operation of the SDR was as follows: The disk type was chosen and fitted, the reactor lid then closed, and the whole setup purged with nitrogen. The required temperature was set at the external heat exchanger and heat-transfer fluid was pumped through the disk assembly at about 6 L/min. The disk speed was set by regulation of the air motor and determination of the speed with a hand-held optical tachometer. The desired feed ratios were identified and the pumps calibrated and set. Once material was detected leaving the reactor, the experiment commenced. A run lasted up to 10 min with three samples being obtained during the experiment at regular time intervals. This was done to determine whether a steady state had been achieved during the run and also to obtain a degree of confidence in the reproducibility of the results. After this, the feed pumps were stopped. If necessary, the reactor was cleaned at this stage with a suitable solvent. The rotational speed was adjusted and another run commenced. Upon completion of this, either temperature, feed ratios, total feed rate, or disk texture would be adjusted and the effect of disk speed re-evaluated.

## Results and Discussion

**Reaction Screening.** From the description of the operating principle above, it is clear that only reactions/processes with intrinsically fast kinetics would prove

**Table 1. Reactions Investigated on the SDR**

	reaction type	presumed rate-limiting issues
1	phase-transfer Darzen's process	liquid-liquid mixing (mass transfer)
2	crystallization study	liquid-liquid mixing (mass transfer)
3	Knoevenagel reaction	gaseous product removal (mass transfer)
4	condensation process	gaseous product removal (mass transfer)
5	elimination reaction	heat transfer to reaction
6	exothermic condensation	liquid-liquid mixing, heat transfer from reaction

to be operable on the SDR. As information on chemical reaction kinetics were not readily available, several reactions/processes were screened for compatibility with the SDR. These processes are listed in Table 1 and were chosen because of their assumed fast kinetics hindered by heat- or mass-transfer limitations in traditional stirred tank equipment. Process details for these reactions are as follows:

1. The phase-transfer-catalyzed Darzen's reaction involves the reaction of a ketone with chloroacetonitrile in tetrahydrofuran promoted by aqueous potassium hydroxide in the presence of a phase-transfer catalyst. The reaction rate was thought to be limited by the degree of mixing of the two phases.

2. A solution of a mesylate salt is mixed with antisolvent to induce crystallization. A number of solvent/antisolvent combinations were tried. The production of small particles as well as the control of particle size and distribution by intimate mixing was of interest.

3. The Knoevenagel reaction requires the condensation of a malonate-type reactant with an aldehyde. The reaction proceeds with concomitant loss of water. This equilibrium process is moved in favor of the product by azeotropic removal of water from the system by the solvent, which is slow in the batch process.

4. The preparation of a quinone methide requires the condensation of a methylene bisphosphonate anion with a benzylamine under the loss of dimethylamine. The loss of dimethylamine from the system was a proposed rate-limiting step.

5. The preparation of this pyrrolidine derivative is carried out at high temperature and proceeds by elimination of a carboxylic acid. Prolonged reaction at elevated temperature in batch mode leads to loss of selectivity due to byproduct accumulation.

6. A previously prepared reactive intermediate generated by the interaction of *N*-chlorosuccinimide with an indole reacts with an alcohol in a highly exothermic fashion. Control of the exotherm and of the reaction selectivity was of interest.

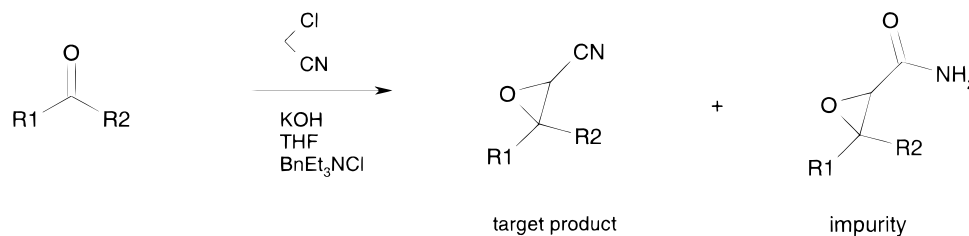
The optimized batch reactor conditions were used as a starting point for the development work of a continuous process. Generally, the process was briefly evaluated on the SDR and process adjustments were investigated in the laboratory, or on the SDR, to establish the most effective reaction conditions for the equipment.

Thus, the use of the SDR was 2-fold: It was applied as a tool to reveal intrinsically fast kinetics as well as to optimize fast processes. From Table 1 above, only reactions (1), (2), and (6) were found to display intrinsic kinetics that were fast enough to exploit the attributes of the SDR. Reactions (3)–(5) displayed low conversions in the range of 0%–10%, which leads us to conclude that in these cases neither heat or mass transfer exert a

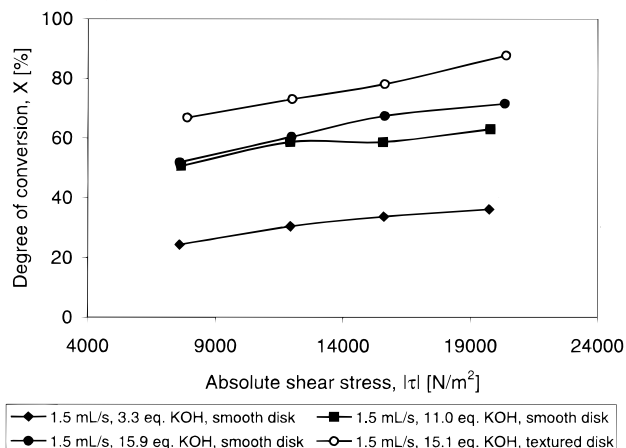
limiting influence on the observed overall rate of reaction. The highly exothermic reaction (6), which features a heat of reaction in excess of  $-250$  kJ/mol, could be safely performed on the SDR with excellent temperature control. However, product selectivities were, despite several optimization attempts, significantly lower than those in the batch process; therefore, this reaction was not investigated further. In the following, we will focus our discussion on reactions (1) and (2).

**Process Optimization.** *ptc Darzen's Reaction.* The general chemistry of this reaction can be taken from Figure 2. The target product is an important intermediate in the manufacture of an active pharmaceutical currently in development. The batch process requires a solution of the ketone and chloroacetonitrile in tetrahydrofuran to be stirred with aqueous potassium hydroxide and a catalytic quantity of benzyltriethylammonium chloride at  $0$  °C. The reaction is complete in 30 min to 2 h, depending on scale. On the SDR, solutions of the ketone and chloroacetonitrile in tetrahydrofuran and benzyl triethylammonium chloride in aqueous potassium hydroxide were mixed at various temperatures and stoichiometries while the rotational speed and disk texture were varied.<sup>5</sup> Initial studies determined that a temperature of  $20$  °C was more effective than the typical batch process temperature of  $0$  °C. When operated at this higher temperature, the reaction proceeded very rapidly, with a high conversion of the ketone occurring during the short contact time on the disk. Investigation showed that the extent of reaction is directly proportional to the rotational speed of the disk and thus the mixing efficiency noted by shear stress, as shown in Figure 3. Reaction at  $40$  °C produced inferior results compared with that at  $20$  °C, possibly because of degradation of chloroacetonitrile by potassium hydroxide.

The relationship between conversion and shear stress shown in Figure 3 is consistent with the reaction rate being limited by the degree of mixing. This is a well-known feature of phase-transfer reactions and demonstrates the ability of the SDR to impart high mass transfer through high shear at high rotational speeds, even at low Reynolds numbers (for this process, calculated  $Re \approx 4$ ). The reduced contact time at high spin speeds is more than compensated for by the increased mixing and the rate can be further enhanced by an increase of the base stoichiometry. The data suggests that the anion formation and reaction are extremely fast once the reactants in the organic phase are exposed to hydroxide anion at the interface with the rate-limiting effect being directly related to the interfacial area between the aqueous and organic phases. Adding texture to the disk, in the form of a counterclockwise spiral machined into the disk's surface, further increased the extent of reaction, as a textured surface promotes turbulent flow and, therefore, enhances mass transfer. The best result of nearly 90% conversion was achieved at a high rotational speed of 4500 rpm with  $\approx 15$  mol equiv of potassium hydroxide using the textured disk. The batch process, carried out at  $0$  °C, with 3 mol equiv of base is complete in  $\approx 1$  h. This process also gives rise to an amide impurity at  $\approx 1.5\%$  caused by prolonged contact of the target product with potassium hydroxide. With a contact time on the disk of under 1 s,  $<0.1\%$  of the amide impurity is formed using the SDR. Operated in continuous mode, under ideal conditions, the throughput of this "bench top"-scale reactor (disk diameter, 15



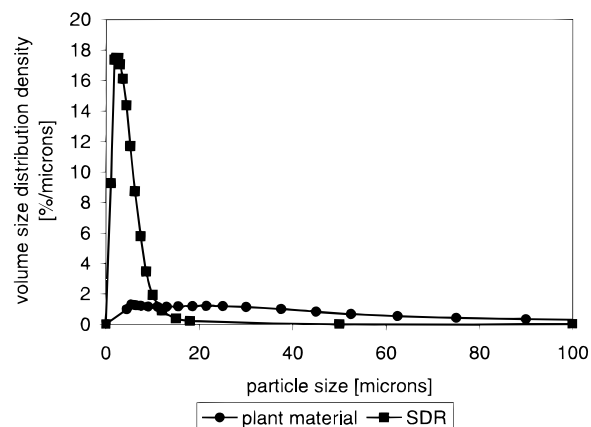
**Figure 2.** Chemistry of the investigated ptc Darzen's reaction.



**Figure 3.** Effect of variation of mixing efficiency, base stoichiometry, and disk surface upon conversion.

cm), for this process, is calculated to be in the region of 8 tonnes/year. Summarizing this, in comparison to the batch process at identical production height per year, the SDR here offers distinct advantages: Reaction time is reduced by 99.9%, reactor volume by 99%, and impurity level by 93%.

*Recrystallization of an Active Pharmaceutical Ingredient (API).* It has been general knowledge in the pharmaceutical industry for quite some time that producing an API by fast crystallization methods would result in small-sized particles with a tight size distribution, which would in return have favorable consequences for the formulation and pharmacological profile.<sup>6</sup> For successful "crash" crystallization to occur on the SDR, the identification of a solvent system capable of inducing such rapid crystallization was essential. A system for carrying out a rapid cooling crystallization could not be found because of the very broad metastable zone width of the evaluated API (>50 °C), so attention was focused on a solvent/antisolvent approach, which is also common practice in the pharmaceutical industry.<sup>7,8</sup> Mixing a solution of the API in hot acetic acid with *tert*-butyl methyl ether was found to induce rapid crystallization under a wide range of conditions within the SDR. However, the use of a stainless steel disk proved to be a serious drawback because the crystallized material adhered to the surface of the disk, leading to severe encrustation. Application of a layer of PTFE to the disk's surface overcame the adhesion problem while the thin coating still allowed good heat transfer between the disk and the film. This allowed the crystallization process to be explored by adjustment of the temperature (-20 to 35 °C), spin speed (1000 to 5000 rpm), feed rate (1.5 to 4.5 mL/s), and solvent-to-antisolvent ratio (1:3 to 1:10). The crystallization always gave very high recovery of material (>95%), and for every set of variables employed, the products showed remarkable similarities



**Figure 4.** Recrystallization of an API, comparison of particle size distributions.

to each other when analyzed for particle size distribution. Each sample contained particles of a primary size of 1–15 μm and, present in varying amounts, were agglomerated particles ranging from 15 to 200 μm in size. Particles larger than 200 μm were present in only a very few instances (the Sympatec instrument routinely measured for particles up to 350 μm in size). Generally, products obtained at lower spin speed contained, predominantly, particles of the primary size. At the higher spin speeds the proportion of particles in the primary range diminished to give mixtures of the smaller particles and agglomerates. The evidence that the larger particles are agglomerates comes from microscopic observation as well as method development work carried out with the Sympatec equipment. The rotational speed of the disk had the most distinct effect on the particle size distribution. At 1000 rpm, in a high proportion of cases, the particles were predominantly of the primary range with a  $d_{50}$  value of around 3 μm and a  $d_{90}$  value of 7–15 μm not being unusual. Figure 4 shows the best result obtained with the SDR in comparison to plant material obtained by normal batch crystallization. It is evident that the material recrystallized from the SDR is much finer and also features a much tighter particle size distribution. At 3000 rpm a second distribution, sometimes dominating, spanned from 15 to 200 μm, with  $d_{90}$  values of 100–120 μm. Increasing the spin speed to 5000 rpm usually produced material indistinguishable from product obtained from the 3000 rpm run. It appears that although the PTFE coating was highly successful in allowing crystallization to be studied on the SDR, its "nonstick" nature did have a negative effect on this type of investigation. In the use of a PTFE coating, the wettability of the disk was profoundly changed. This caused eventually—in conjunction with the relatively low flow rates and high spin speeds—the thin liquid film (calculation predicted  $\delta < 20 \mu\text{m}$ ) to break down into rivulets, which adversely

affected the quality of the crystallized product. The fluid dynamics occurring on the PTFE disk during the crystallization process are complex and not well understood. The experimental data suggests that as long as the film is still stable (in this instance at low spin speeds), then mainly small particles of a well-defined particle size are formed and agglomeration is suppressed. As soon as the film breaks down and the mixing efficiency deteriorates (at higher spin speeds, due to poor wettability of the coated disk), agglomeration of the primary particles exerts a dominating influence. In this study, mixing and residence time appear to be near the optimum at around 1000 rpm and less favorable at higher speeds. Finding the optimum point for this system with respect to contact time and mixing efficiency as well as identifying the best-suited disk surface material leave ample room for optimization investigations.

Despite the problems associated with the nature of disk material, we have been able to demonstrate that the SDR can be used to study the crystallization of an API. In addition, operating conditions were identified which yielded product with superior particle size definition over the batch process. The maximum calculated throughput of this equipment was 8.2 tonnes/year.

**Reactor Modeling.** To ensure optimum performance of the SDR as well as to gain a deeper understanding of the reactor characteristics, several modeling calculations have been carried out, which are described below.

**Heat Transfer.** One of the features of the SDR is excellent heat transfer through the disk, which is ensured by turbulent flow of the heat-transfer fluid through a thin channel directly underneath the disk (see Figure 1). Experimental evidence from evaporation studies with alcohols and alkanes suggested that the degree of the heat transfer achieved was dependent on the disk material, the channel width underneath the disk, and the type of heat-transfer fluid used. The SDR was originally designed for the use of water as the heat-transfer fluid. As some of the reactions described above have an operating temperature below 0 °C and above 100 °C, alternative heat-transfer media had to be identified. Investigations were made using water, Therminol 59 (silicone oil-based<sup>9</sup>), and Dowcal 10 (glycol-based<sup>10</sup>) as heat-transfer fluids and disk tops made of 316SS as well as naval brass ( $\lambda_{316SS} < \lambda_{naval\ brass}^{11}$ ). Correlations such as eq 4 for turbulent flow in tubes were used to calculate heat-transfer coefficients,  $\alpha_i$  and  $\alpha_o$ :<sup>12</sup>

$$\frac{\alpha d_e}{\lambda_{fluid}} = j_h Re Pr^{0.33} \left( \frac{\eta_{bulk}}{\eta_{wall}} \right)^{0.14} \quad (4)$$

For the equivalent hydraulic diameter  $d_e$ , the channel width and film thickness were chosen to calculate  $\alpha_i$  and  $\alpha_o$ , respectively. In the case of the narrow channel underneath the disk as well as the thin liquid film on the disk, the differences in the bulk and wall viscosities can be disregarded, which simplifies eq 4:

$$\frac{\alpha d_e}{\lambda_{fluid}} = j_h Re Pr^{0.33} \quad (5)$$

Knowing the flows and properties of process and heat-transfer fluids as well as the characteristics of the disk used, the overall heat-transfer coefficient can then be

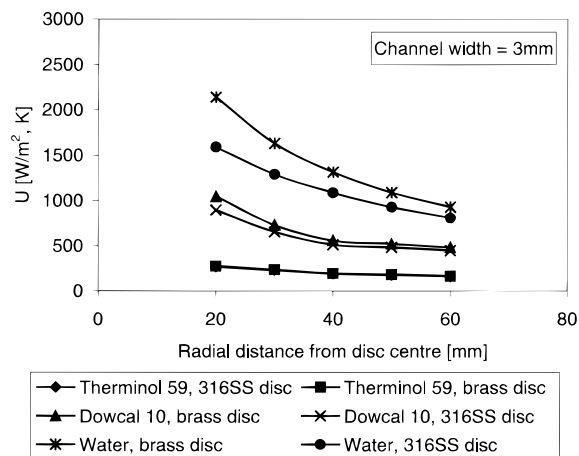


Figure 5. Variation of  $U$  with radial distance (channel width = 3 mm).

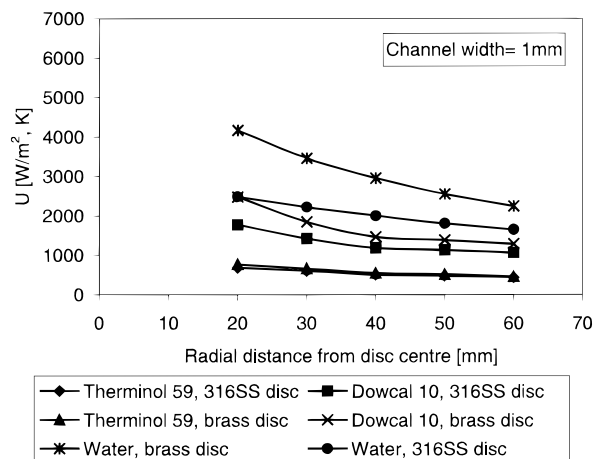


Figure 6. Variation of  $U$  with radial distance (channel width = 1 mm).

calculated as a function of the radial distance from the disk center,  $z$  (because of channel width variation due to SDR geometric arrangement,  $d_e$ ,  $j_h$ , and  $Re$  vary with radial distance  $z$ )<sup>12</sup>:

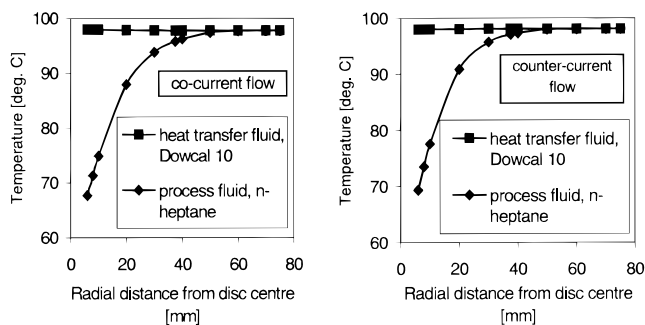
$$\frac{1}{U(z)} = \frac{1}{\alpha_i(z)} + \frac{x}{\lambda_{disc}} + \frac{1}{\alpha_o} \quad (6)$$

The results of these calculations agree with experimental observations during a heat-transfer study using *n*-heptane as the process fluid. They are shown in Figures 5 and 6 and allow the following deductions:

1. Thermal conductivity of the heat-transfer fluid and the geometric arrangement underneath the disk are the two main factors governing effective heat transfer. To promote effective heat transfer, a heat-transfer fluid with high thermal conductivity ( $\lambda_{Therminol\ 59} < \lambda_{Dowcal\ 10} < \lambda_{Water}^{9-11,13}$ ) and a narrow channel underneath the disk (to promote turbulent flow) is essential.

2. When a heat-transfer fluid with low thermal conductivity (such as Therminol 59) is used, the choice of the disk material does not affect the  $U$  value greatly because the fluid property is limiting.

3. If a heat-transfer fluid with good thermal conductivity (such as Dowcal 10 or water) is used, the choice of disk material has an influence on the overall heat transfer.



**Figure 7.** Calculated temperature vs radial distance for Dowcal 10 (heat-transfer fluid, 6 L/min) and *n*-heptane (process fluid, 1.67 mL/s) with 316SS disk, for cocurrent (left) and countercurrent flow (right).

4. Use of a heat-transfer fluid and a disk material with respective high thermal conductivities (water/naval brass for  $\approx 10\text{--}90\text{ }^{\circ}\text{C}$  and Dowcal 10/naval brass for  $\approx -30\text{ to }170\text{ }^{\circ}\text{C}$ ) appears to be the best choice for optimum heat transfer.

With knowledge of the heat-transfer coefficients at different radii on the disk, the temperature profiles of the heat-transfer and process fluids have been estimated and plotted using the differential Newton equation,<sup>12</sup>

$$d\Phi = U dA (T_i - T_o) \quad (7)$$

which was then integrated numerically, assuming that the process fluid properties remain constant during disk contact. Initial conditions for the integration were taken from experimental data. The inlet and outlet temperatures of the heat-transfer fluid as well as the inlet temperature of the process fluid were measured. It was not possible to measure the temperature of the fluid on the disk with the equipment available (contact thermocouples) because of the thinness of the film. Therefore, these calculations provide only estimates of the true temperature regime on the disk. Figure 7 shows the computed temperature profiles for co- and countercurrent flow. It can be seen that the flow mode does not affect heat transfer significantly, but that it is slightly better for countercurrent flow, which is to be expected from theory. Therefore, countercurrent flow was chosen for the SDR.

**Process Characterization.** To gain insight into how the spinning disk reactor compares with traditional continuous reactors, reaction engineering calculations were carried out using the earlier-described ptc Darzen's reaction as a case study. Because at present no quantitative model for the SDR exists, a standard reactor model was chosen. The model which matches the SDR characteristics best was identified as the plug flow reactor model because of the similarities in flow mode (continuous, no back-mixing) and the high degree of mixing (in the plug flow reactor achieved by turbulent flow and in the SDR by high shear stress).

Kinetic parameters of the reaction were approximated by assuming a simple first-order reaction with respect to the base concentration (which is the kinetic equation recommended for fast ptc reactions<sup>14</sup>) and matching conversion with the calculated residence time. For this, data was taken for the "optimized" reaction on the disk: spin speeds over 4000 rpm, textured disk, and temperatures at 20 and 40  $^{\circ}\text{C}$ . The rate of conversion,  $dX/dt_{\text{res}}$ , was estimated from these data, which were

**Table 2. Determined Kinetic Parameters for the ptc Darzen's Reaction**

kinetic rate law	$r = k_0 \exp(-E/RT) c_{\text{base}}$
activation energy $E$ [kJ/mol]	27.8
frequency factor $k_0$ [ $\text{s}^{-1}$ ]	5500

used with the design equation for plug flow reactors<sup>15</sup> to estimate the specific reaction rate:

$$r_s = -c_{\text{base}} \frac{dX}{dt_{\text{res}}} \quad (8)$$

The so-obtained kinetics are listed in Table 2. Because of the fact that residence time was calculated using eq 3 and not measured and because only two different temperature levels were taken into account, these kinetics represent only a rough approximation of the true parameters. Therefore, they were only used, as in the procedure described below, for trend analysis, not for quantitative calculations. To represent the excellent mixing achieved on the disk, a high Reynolds number of 12 500 was chosen for the tube model. To achieve the same conversion and throughput level, it was found that a tubular reactor with a diameter of 0.26 mm and a length of 12 m would be necessary. This would in fact be a long capillary tube (length-to-diameter ratio  $> 40\,000:1$ ), which as a capillary reactor would be very difficult to implement and more cost-intensive to operate than the equivalent SDR. In summary, these calculation results highlight the advantages of small-scale "process-intensified" equipment over traditional large-scale reactor technology.

## Conclusion

The study described above demonstrates that the SDR is attractive and viable technology for drug manufacture in a continuous operation mode because of its unique characteristics and its capability of being tailored to a wide range of important applications. In detail, we conclude the following:

1. Fast organic reactions and precipitations, with species half-lives up to 5 s, can be performed much more effectively in an SDR than in a stirred vessel. In the investigated Darzen's reaction, reactant inventory and impurity level were reduced by 99% and 93%, respectively.

2. Rotational speed confers an extra variable for reaction optimization, with higher speeds giving better mixing, heat/mass transfer, and shorter residence times.

3. The SDR is capable in principle of producing fine crystals ( $d_{50} \approx 3\text{ }\mu\text{m}$ ) with a very narrow size distribution.

4. A 15-cm-diameter SDR will manufacture around 8 ton of product/year, so that laboratory scale may become full scale.

Summarizing this, it is our belief that SDR technology represents a major step toward achieving the desktop pharmaceutical process.

## Acknowledgment

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### Nomenclature

$\alpha$ : heat-transfer coefficient,  $\alpha_o$  for process fluid and  $\alpha_i$  for heat-transfer fluid ( $\text{W}/\text{m}^2, \text{K}$ )  
 $A$ : area of the disk ( $\text{m}^2$ )  
 $c$ : concentration ( $\text{kmol}/\text{m}^3$ )  
 $\delta$ : film thickness (m)  
 $d_{50}$ : characteristic particle size for 50% of the measured sample ( $\mu\text{m}$ )  
 $d_{90}$ : characteristic particle size for 90% of the measured sample ( $\mu\text{m}$ )  
 $d_e$ : equivalent hydraulic diameter (m)  
 $d_p$ : particle size ( $\mu\text{m}$ )  
 $E$ : activation energy (kJ/mol)  
 $j_h$ : heat-transfer factor  
 $\eta$ : dynamic viscosity (mPa·s)  
 $\Phi$ : heat flux through the disk (W)  
 $k_0$ : frequency factor ( $\text{s}^{-1}$ )  
 $\lambda$ : thermal conductivity ( $\text{W}/\text{m}, \text{K}$ )  
 $N$ : rotational speed of the disk (rpm)  
 $Q_V$ : volumetric feed rate ( $\text{m}^3/\text{s}$ )  
 $Pr$ : Prandtl number  
 $R$ : universal gas constant ( $\text{J}/\text{K}, \text{mol}$ )  
 $Re$ : Reynolds number  
 $r$ : disk radius (m)  
 $r_i$ : radial distance of inlet tube from the center of the disk (m)  
 $r_o$ : radius at exit from the disk (m)  
 $r_s$ : specific reaction rate ( $\text{kmol}/(\text{m}^3\cdot\text{s})$ )  
 $\rho$ : density ( $\text{kg}/\text{m}^3$ )  
 $t_{res}$ : residence time on disk (s)  
 $\tau$ : shear stress ( $\text{N}/\text{m}^2$ )  
 $T$ : temperature, index i for inlet and o for outlet ( $^\circ\text{C}$  or  $\text{K}$ )  
 $U$ : overall heat-transfer coefficient ( $\text{W}/\text{m}^2, \text{K}$ )  
 $v_{rel}$ : mean film velocity ( $\text{mm}/\text{s}$ )  
 $x$ : disk thickness (m)  
 $X$ : degree of conversion (%)

$z$ : radial distance from disk center (mm)  
 $\omega$ : angular velocity ( $\text{s}^{-1}$ )

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