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Lecture Transcripts

Evaluation of a Spinning Disc Reactor for Continuous Processing[1]

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Abstract:

As part of an evaluation of equipment aimed at process intensification, use of a continuously operating spinning disc reactor (SDR) was investigated. Results obtained for two organic reactions and one crystallisation are discussed. The SDR was found to be a useful tool for reveալling intrinsically fast kinetics as well as for optimising a process with such kinetics. Control of particle size distribution was demonstrated with the crystallisation investigated.

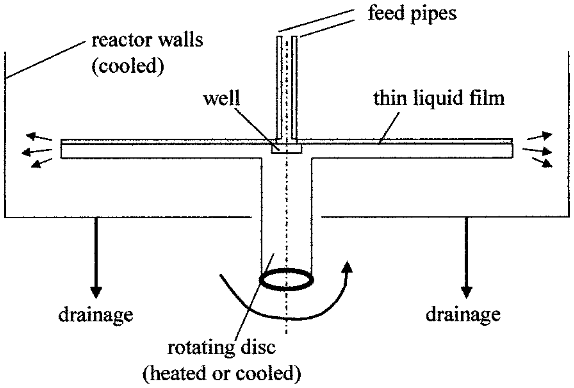

Figure 1. **Schematic drawing of the SDR.**

Introduction

Many challenges are faced by Process Research and Development groups, and the major challenges revolve around control of purity and physical form to ensure that a consistent quality product is produced. Success in these areas has to be achieved in ever decreasing timelines. These apparently incompatible requirements can be met if chemists and chemical engineers collaborate to develop smarter ways of working. One area of considerable interest in pharmaceutical and fine chemical industries over the past few years has been process intensification. Although process intensification equipment and methods have been used successfully for years in the oil industry where processes are often continuous, very little practical demonstration of process intensification has occurred in the pharmaceutical and fine chemical industries. There are many attractive features of intensified processes, not least of which is dramatically reduced capital investment required for commercial-scale operation. This approach can also embrace the concept of scaling out rather than scaling up, which has the potential for reduced lead times to commercialisation of processes. Many approaches have been made to intensifying processes, and one is continuous processing, where there is an additional benefit of offering better control of product quality. Recently, the spinning disc reactor (SDR) was proposed as an alternative to traditional stirred tank processing technology.[2−4] Interest in the SDR at SmithKline Beecham (SB) arose from a collaboration with Professor Colin Ramshaw, and an evaluation of the capabilities of this equipment was part of a DTI-funded collaboration, the Innovative Manufacturing Initiative (IMI) involving SB, Glaxo-Wellcome, Hickson and Welch, and Courtaulds Coatings. In this lecture initial results in the area of organic synthesis and crystallisation from this collaboration will be discussed.

Description of Equipment and Mathematical Model. Figure 1 shows a schematic diagram of the spinning disc reactor. The SDR is constructed in 316 stainless steel and has two feed streams to enable reactive reagents and substrates to be mixed in the centre well of the spinning disc. Reactants and solvents are pumped onto the disc using peristaltic or positive displacement pumps at a maximum rate of 4.5 mL/s. The horizontally oriented spinning disc is

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15 cm in diameter, and it can be heated or cooled by a heat transfer fluid (Dowcal 10, a glycol/water mixture was found to be most effective). A practical operating temperature range of −20−170 °C was achieved. The disc is rotated by means of an air-driven motor at rotational speeds up to 5000 rpm. The walls of the vessel can also be heated or cooled, and the process materials leave the reactor via two drain pipes. In practice a residence time on the disc of 1−5 s is achievable; thus, reactions with half-lives in the range of 0.1−1 s are anticipated to be particularly suitable for the SDR.

When reaction fluids are applied to the spinning disc, a film thickness in the range 50−600 μm is formed, depending on the viscosity of the fluid. The SDR subjects the thin film to very high shear stress, and this leads to very high heat and mass transfer rates between the film/disc and the liquid streams, respectively. In addition, photographs of the SDR in action show that ripples are formed in the fluid on the disc, leading to further enhanced mass transfer.

An operating model of the reactor has been developed where a highly simplified version of the film flow is used (refer to ref 11 where the model is described in more detail). It is assumed that the film is laminar and circumferentially uniform and stable, with local film thickness being determined by a modified “Nusselt” approach to take account of radial acceleration.[5,6] The effects predicted by this model are expected to be underestimated owing to the simplifications used. A qualitative measure of mixing efficiency can be obtained from the shear stress as depicted in eq A.

$$\tau = -1.5\eta\frac{v_{\mathrm{rel}}}{\delta} = -1.5\sqrt[3]{\frac{\eta\rho^2 Q_{\mathrm{v}}\omega^4 \mathrm{r}}{18\pi}} \qquad \text{(A)}$$

$$\omega = \frac{2\pi N}{60} \qquad \text{(B)}$$

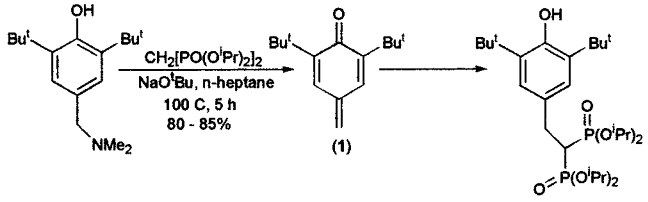
$$t_{\mathrm{res}} = \left(\frac{81\pi^2\eta}{16\omega^2 Q_{\mathrm{v}}^{\,2}\rho}\right)^{1/3}\left(r_{\mathrm{o}}^{4/3} - r_{\mathrm{i}}^{4/3}\right) \qquad \text{(C)}$$

where

τ = shear stress (N/m^2)
η = dynamic viscosity (mPa•s)
ν_{rel} = mean film velocity (mm/s)
δ = film thickness (m)
Q_{v} = volumetric feed rate (m^3/s)
r_{i} = radial distance of inlet from centre of disc (m)
ω = angular velocity (s^{-1})
r = disc radius (m)
N = rotation speed of the disc (rpm)
ρ = density (kg/m^3)
r_{o} = radius at exit from disc (m)
t_{res} = residence time (s)

Equation A shows a predominant relationship between shear stress (τ) and angular velocity (ω) and hence the rotational speed of the disc (N)—see eq B. Thus, it can be expected that mixing efficiency on the disc increases with increased rotational speed. The residence time of reactants on the disc is expressed by eq C where it can be seen that residence time (t_{res}) is inversely proportional to angular velocity $(\omega)^{2/3}$.

Scheme 1. **Thermal generation of a quinone methide**



Evaluation of the Reactor. At the time evaluation of the SDR was undertaken the only experience of organic reactions was with polymerisation reactions.[6−9] It was not clear whether the SDR would be viable for organic reactions of interest to the pharmaceutical industry. As a starting point, optimised batch reactor conditions were used on the SDR and then modified to establish the most effective conditions for the equipment. The anticipated benefits of the SDR were 2-fold: use as a tool to reveal intrinsically fast kinetics as well as to optimise processes displaying such kinetics. It was envisaged that optimisation would be carried out against criteria such as conversion (yield), selectivity, and cost compared with standard batch processes.

(A) Organic Reaction with Removal of a Gaseous By-Product. The first reaction to be evaluated on the SDR was thermal generation of a reactive quinone methide (**1**) as shown in Scheme 1.

This reaction had been successfully demonstrated in a batch process, but the yield was limited by the efficiency of removal of dimethylamine. A complex series of equilibria are formed in this reaction as shown in Scheme 2, and from this the importance of removing the dimethylamine is apparent. It was thought that the SDR would offer advantages of efficient mixing for generating the reactive quinone methide (**1**), a short contact time to minimise decomposition of (**1**) and efficient removal of dimethylamine through good mass-transfer properties.

Disappointingly, no conversion to the desired product was observed by HPLC analysis of the reaction mixtures emerging from the SDR under a variety of conditions. The reason for this has been ascribed to the kinetics of this reaction not being intrinsically fast.

(B) Phase-Transfer-Catalysed Process. Within SB we had an interest in a phase-transfer-catalysed Darzens’ reaction as a key stage in the preparation of a drug candidate, shown in Scheme 3.

It was known from experience of the batch process that efficient mixing was required for high conversion to the desired product and from evaluation of a continuous process that the kinetics of this reaction are fast. In addition it was desirable to control the by-product (**3**) formation to a low level. It was therefore felt that the properties of the SDR were ideally suited to this reaction. Initial work identified

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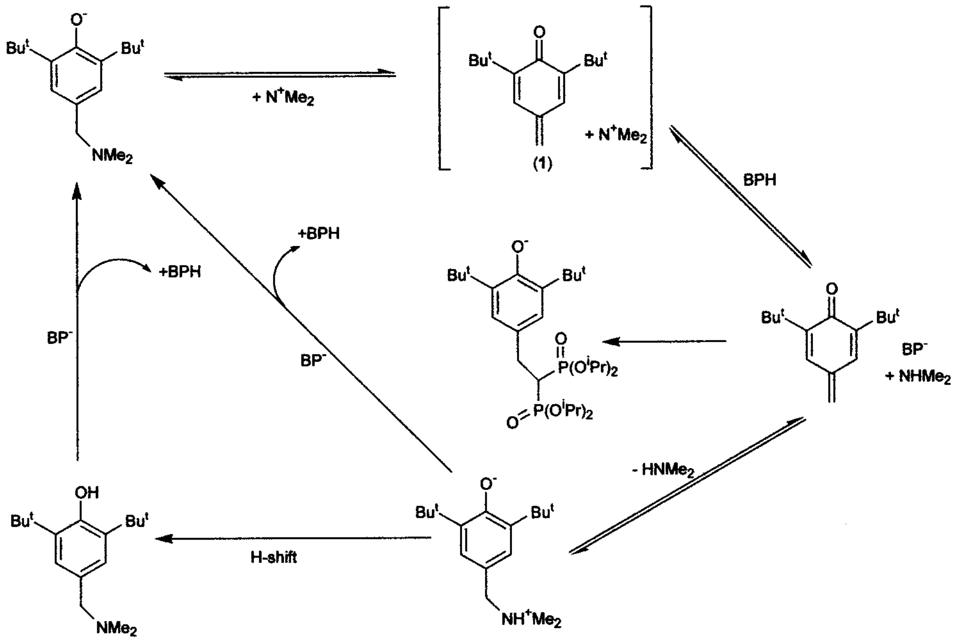
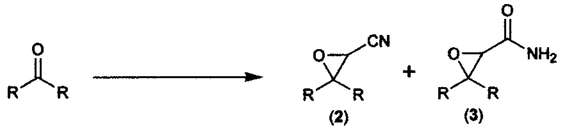
Scheme 2. **Equilibria in formation and reaction of 1**



Scheme 3. **Phase-transfer-catalysed Darzen's reaction**



that a reaction temperature of 20 °C (rather than 0 °C used in the batch process) was required for efficient conversion on the disc. Results obtained are presented graphically in Figure 2.

From Figure 2 it can be seen that the degree of conversion to the desired epoxide (**2**) was linearly related to rotational speed of the disc and, from eq A, the shear stress. The degree of conversion to the desired product (**2**) also increased with base strength, but with a smooth disc, conversion was limited to 72%. Adding texture to the disc in the form of a counterclockwise spiral machined in the surface of the disc further increased conversion to 88% at 4500 rpm. Using a higher temperature of 40 °C led to inferior results, presumably due to increased decomposition of the chloroacetonitrile by potassium hydroxide. In all reactions, the amount of amide by-product (**3**) produced was less than 0.1% compared with 1.4% in the batch process.

From the mathematical model shown in eq A it is expected that greater conversion would be achievable using a disc with a larger diameter, and higher rotational speeds. These results show that optimised conditions for the SDR are substantially different from optimised batch conditions. The conversions obtained in the reactions carried out on the SDR would equate to a throughput of 8 tonnes per year of product (**1**).[10]

(C) Crystallisation of an Active Pharmaceutical. As stated earlier, the main requirement of processes to be

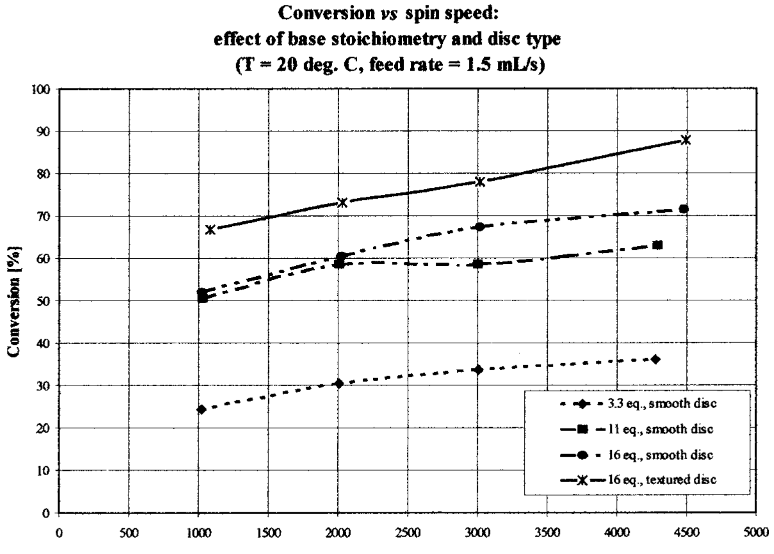


Figure 2. **Conversions achieved with the Darzen's reaction.**

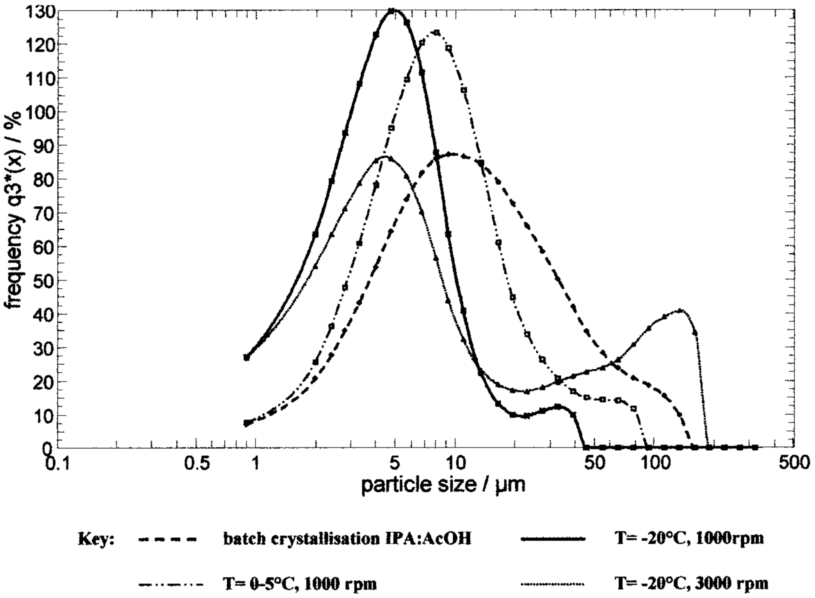


Figure 3. **Figure 3. Particle size distribution following crystallisation on the SDR.**

successful on the SDR is to have fast kinetics. In general, cooling crystallisations show slower kinetics compared with precipitations owing to the level of supersaturation achievable on cooling. The active pharmaceutical chosen was a mesylate salt which could be precipitated from acetic acid by the addition of *tert*-butyl methyl ether. The objective of this crystallisation was to control the particle size distribution to a narrow range. Using the stainless steel disc, crystallisation was not successful because the crystallised material adhered to the disc, leading to severe encrustation problems. Applying a layer of PTFE to the surface of the disc overcame problems with encrustation and, therefore, allowed the crystallisation parameters to be explored. Results from particle size distribution measurements are shown in Figure 3.

From Figure 3 it can be seen that batch crystallisation leads to a wide particle size distribution, whereas the SDR led to formation of a narrow particle size distribution. A certain amount of optimisation of disc temperature and rotational speed was found to be possible, although at high rotational speeds loss of control of the particle size distribution was observed, presumably because the solution/slurry film of product broke down into rivulets so that uncontrolled crystal growth occurred in the collection vessel. Thus, we were able to demonstrate that the SDR can be used for a precipitation reaction leading to a product with a narrow particle size distribution. The throughput calculated for this precipitation was 8.2 tonnes per year.

Conclusions

The SDR has been demonstrated to offer some advantages over traditional batch processing equipment for intrinsically fast reactions. Throughput for a 15 cm diameter disc has been calculated to be in the region of 8 tonnes per annum for the reactions evaluated. In addition, from the evaluation of the two reactions discussed, success was achieved on the SDR when intrinsic reaction kinetics are fast. Conversely, the SDR can therefore be used as a tool to reveal that the kinetics of a transformation are intrinsically fast. The SDR also shows promise in the control of particle size distribution for fast crystallisations. Further evaluation of the utility of this novel equipment has been carried out, and comprehensive results have been published recently in a full paper.[11]

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