Organic Process Research & Development **2011,** *15,* 84–90

An Alternative Method to Isolate Pharmaceutical Intermediates

Frans L. Muller and Brian Whitlock*

AstraZeneca, Pharmaceutical Development, Macclesfield SK10 2NA, U.K.

Abstract:

A robust crystallisation process can be resource intensive to develop, but simpler isolation alternatives such as evaporation to dryness can have thermal stability issues and result in a difficult to handle solid residue. This contribution presents Solid Supported Evaporation as an equally simple alternative to evaporation to dryness but which goes some way to overcome the thermal stability issue and results in an easy to handle solid product.

Introduction

Early in development, drug substance quantities required are small. Given that a significant number of potential New Chemical Entities (NCEs) fail during phase I, minimising cost and time prior to this attrition point is important. The focus in development at this stage is therefore on manufacturing trial quantities that are "fit for purpose", and that are delivered against very tight timelines. Manufacture typically takes place in multipurpose batch reactors. As outlined by Double, Gourlay, and Atherton (2005),[1] batch reactors have a degree of flexibility unsurpassed when executing partially developed, often multiphase (typically solid−liquid) processes.

Once the route is established, process development starts on all stages. The initial focus of the development team is of course on the reactive part. This is usually established relatively quickly. To develop a workup procedure that results in the isolated stage product can however be a significant challenge. Figure 1 outlines several possible operations in a workup process. Of course, not every workup process requires each possible operation, but unless the reaction is "telescoped" the intermediate-stage product needs to be isolated as a solid.

Muller and Latimer (2009)[2] reviewed the outcome of 16 Scale-Up Risk Evaluations (SURE) that were executed on manufacturing processes for pharmaceutical intermediates and active ingredients that had not yet been scaled up. They identified that more than 25% of scale-up scenarios were associated with the workup. In addition, an internal review of the frequency of application of workup operations, and the development time required, identified that *crystallisation* and *solvent swapping* command significant development resources.

In an "ideal" process (charge raw materials and solvent, heat up, cool down, and filter the product off) the reaction temperature is 60 °C greater than the isolation temperature, and the reaction mass becomes saturated with the product. In such case

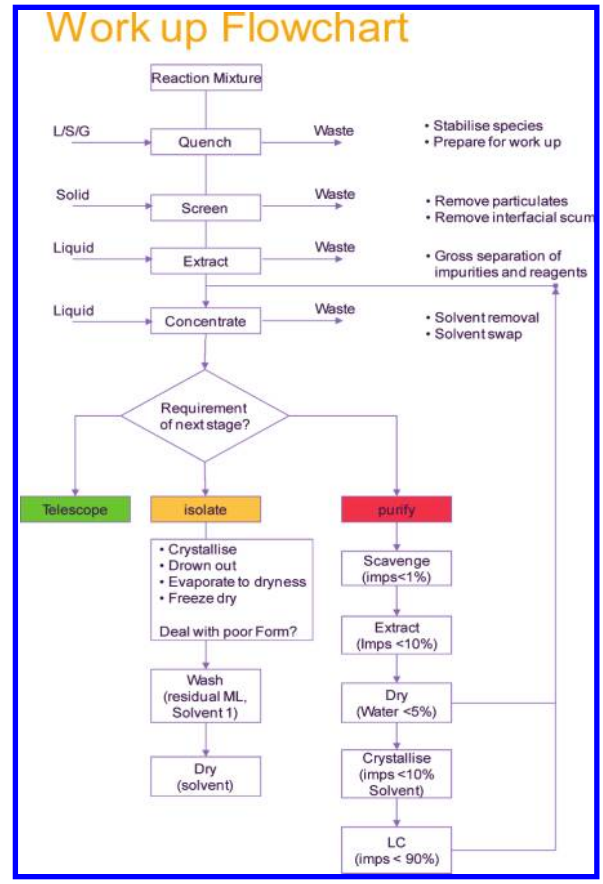


Figure 1. **Workup options.**

Black's rule (In analogy with the rule of thumb that reaction rates double every 10 °C, Black's rule states that solubility doubles every 20 °C. This means that after cooling a solution saturated at 80−20 °C the amount that has precipitated is $(2^3 - 1)/2^3 = 87.5\%$ of the Product (Muller et al. 2009)[3]) suggests simply cooling the reaction mass is likely to give more than 80% recovery of the product. In reality the reaction mass is often not saturated at the reaction temperature. One of the reasons for this is that isolations typically require a "poor" solvent (5−20 mg/mL solubility at room temperature see Muller et al 2009[3]), but reactions require a "good" solvent (~100 mg/mL solubility at room temperature) so that workup operations like for instance scavenging, catalyst filtration and extractions can easily be completed prior to isolation.

Isolations can be split into two broad categories: purification and isolation (such as crystallisation followed by filtration), or just isolation (such as evaporation to dryness). In general, crystallisation is the preferred option in the pharmaceutical

* Author to whom correspondence may be sent. E-mail: Brian.Whitlock@AstraZeneca.com.

(1) Double, J. M.; Gourlay, B.; Atherton, J. H. *Seventh World Congress of Chemical Engineering Conference Proceedings*; IChemE: Glasgow, UK, 2005; pp O156−003; ISBN: 0 85295 494 8.

(2) Muller, F. L.; Latimer, J. *Comput. Chem. Eng.* **2009**, *33*, 1051–1055.

(3) Muller, F. L.; Fielding, M.; Black, S. N. *Org. Process Res. Dev.* **2009**, *13*, 1315–1321.

Published on Web 11/24/2010

10.1021/op100207e

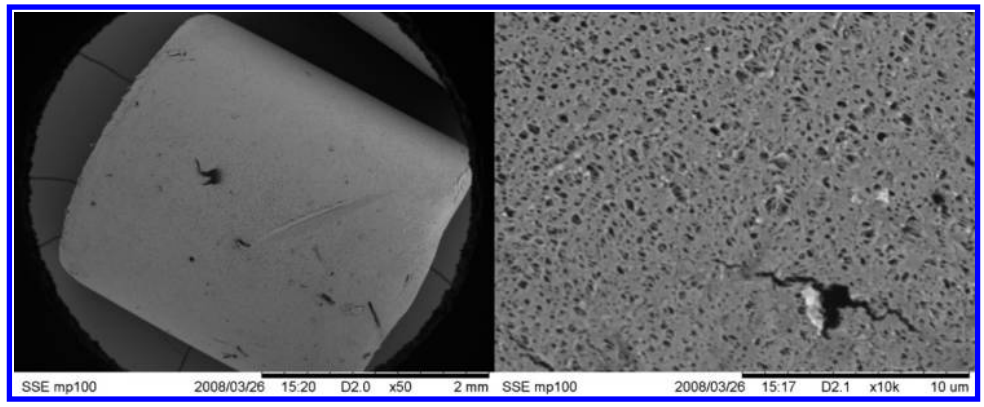


Figure 2. **SEM photographs of Accurel MP100 at 50× and 1000× magnification.**

industry due to the high purity requirements of the industry regulators. Use of evaporation to dryness is less favored, as on top of the lack of purification, the residue can have thermal stability issues and it can be difficult to handle. (See the Health and Safety Executive (HSE) report about the investigation into the fire at Hickson and Welch 1992.[4]) However, robust crystallisations are sometimes too resource intensive to develop, and as explained above, in the early stages of development, time is of the essence. Therefore, there is an opportunity for an isolation method that is an alternative to evaporation to dryness that is as quick and simple to develop, but which overcomes its thermal stability and handling issues. This paper presents such a method.

Solid Supported Evaporation (SSE)

In this paper we present a method to isolate intermediates: *Solid Supported Evaporation*. The reaction mass is sprayed on adsorbent solid particles in a vacuum. The solvent evaporates and all nonvolatile species are deposited ***inside*** the absorbent. A similar technique is used by formulation scientists who aim to deposit drugs on porous carriers. A detailed example of this is given by Sher et al (2007)[5] who deposited ibuprofen onto porous polypropylene particles by mixing 100 mg of the porous particles with 1−5 mL of an ibuprofen solution in either methanol or DCM. The mixture was left to evaporate under ambient conditions. The resulting solids contained ibuprofen at 1−3 grams per gram of polypropylene support.

The advantages of the proposed method are (i) good recovery yields as the product does not build up on the wall of the evaporation equipment, (ii) the solid does not form a dust as it is contained within the absorbent, and finally (iii) the thermal stability is improved as there is an inert mass of solid that slows down the heatup rate (larger thermal mass), and improves the heat removal (larger surface area). SSE thus removes the key issues associated with evaporating to dryness, whilst maintaining its wide applicability; even liquid products with a high boiling point can be isolated as a "solid" in this manner as liquid product will remain absorbed within the solid support.

Key to the success of SSE is the identification of a highly porous absorbent material that can be used in a pharmaceutical environment. Such materials need to be cheap, acceptable for use by the regulatory authorities, and chemically inert. We have focussed on polypropylene beads that are commonly used to generate additive concentrates via physical absorption of the additive into the bead. (Membrana 2010).[6] The concentrate is subsequently used for the incorporation in a polymer blend by conventional extrusion compounding. These polypropylene beads have been used to demonstrate the applicability of the SSE technique in the pharmaceutical environment.

Materials Used in This Study

Properties of Polypropylene Beads. The physical properties of the polypropylene beads make them a very suitable substrate for solid supported evaporation. Several types of beads are available (e.g., Accurel MP1000, MP100). These differ in their physical size and shape and in the features of their external surface (see Figures 2 and 3 for scanning electron microscope (SEM) pictures). For instance MP100 beads are half cylindrical in shape (approximately 2 mm diameter and 3 mm long). Its surface is punctured with evenly spaced <0.5 μm diameter holes. MP1000 beads are approximately spherical in shape (about 1 mm diameter). Its surface is covered with approximately 20 μm diameter holes to create a structure comparable with honeycomb.

Both beads have a highly porous structure with about 75% voidage, giving them a high capacity to absorb solutions and a large surface area for deposition of solids. Their size makes them easy to handle as they are not dusty and have good flow properties. They are physically strong enough to retain their shape and structure without disintegrating during physical handling operations such as tumbling in a rotary evaporator. Polypropylene has good resistance to a range of solvents. The polypropylene used in the beads has detailed FDA compliance statements (available from the suppliers) and is suitable for use in pharmaceutical manufacturing processes.

Solvents. The following range of solvents from different classes was used in this work to demonstrate the technique's broad applicability: acetonitrile, ethanol, toluene, 2-methyl-tetrahydrofuran, ethyl acetate, methyl-*tert*-butyl-ether, and meth-

(4) The fire at Hickson & Welch Limited - A report of the investigation into the fatal fire at Hickson & Welch Limited, Castleford, on 21st September 1992. In Health and Safety Executive ; 1994; ISBN 0 71 760 702 X; http://www.hse.gov.uk/comah/sragtech/casehickwel92.htm.

(5) Sher, P.; Ingavle, G.; Ponrathnam, S.; Pawar, A. P. *Int. J. Pharm.* **2007**, *331* (1), 72–83.

(6) Membrana. http://www.membrana.de/polymers/center.htm (accessed Nov 2, 2010).

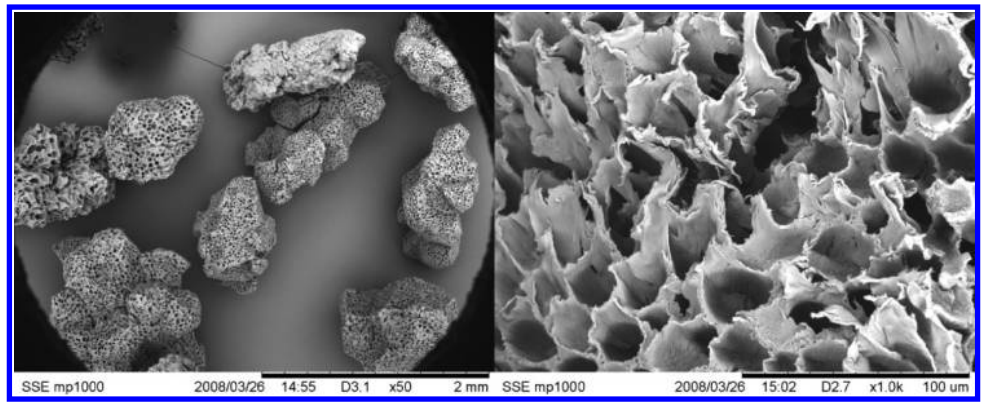


Figure 3. **SEM photographs of Accurel MP1000 at 50× and 1000× magnification.**

yl-isobutyl-ketone. Solvents that are physically incompatible with polypropylene were not used.

Solutes. Maleic acid was chosen as the solute as its physical and chemical characteristics are broadly similar to those of a typical pharmaceutical intermediate.

Results and Discussion

Method Development. The equipment used for solid supported evaporation is a rotary evaporator (rotavap). Initially, the polypropylene beads were simply loaded into a round-bottom flask, an aliquot of liquid was added, and the rotary evaporator was used to evaporate off the solvent under vacuum. Further aliquots of liquid were applied by breaking the vacuum, removing the round-bottom flask, charging the aliquot, refitting the round-bottom flask, and then reapplying the vacuum.

In addition to the time-consuming nature of this process, it was difficult to ascertain when the aliquot had evaporated, and therefore when the time was right to charge the next aliquot.

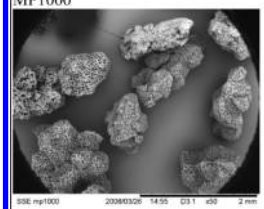
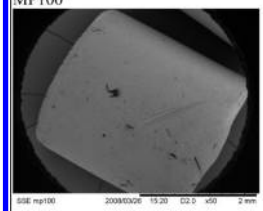
Consequently, the equipment was modified to allow continuous addition of the liquid. This was achieved by inserting a long metal tube into the rotavap such that one end of the tube was in the round-bottom flask suspended vertically above the bed of beads. The other end of the tube was connected to a valve and a flexible tube that was immersed into the container of liquid to be evaporated. The vacuum within the rotavap was used to suck in the liquid and feed it directly onto the beads. The valve was used to control the rate such that the polypropylene beads remained free from a separate liquid phase. Large-scale rotary evaporators can have this feed arrangement as a standard.

In very small-scale experiments it can be hard to establish the appropriate flow rate. In such cases, the same system could be used to suck in aliquots of liquid. The volume of the aliquots was equivalent to 1 g of solvent per 1 g of polypropylene beads. This is significantly less than the solvent capacity of the beads and, thus, a conservative rule of thumb that applies even when some of the capacity of the beads is taken up by the solute.

The dry beads can build up static, causing the particles' behaviour to change from free-flowing to sticking together and moving as a single block. If that is the case, it is advisible to break the vacuum with nitrogen.

Solvent Capacity of the Polypropylene Beads. The solvent capacity of each of the two types of polypropylene beads was determined for acetonitrile, ethanol, toluene, 2-methyl-tetrahydrofuran, ethyl acetate, methyl-*tert*-butyl-ether (MTBE), and methyl-isobutyl-ketone (MIBK). These solvents were selected to give a range of solvent properties. The full results are tabulated in Table 1.

Table 1. **Solvent capacity of polypropylene beads**

Support	Solvent	Solvent Loading g solvent per g support	% of solvent added left in beads after drying
MP1000 			
	Acetonitrile	4.69	-0.004
	Ethanol	4.84	0
	Toluene	5.54	0
	Ethyl Acetate	5.65	0.004
	Methyl tert butyl ether	5.17	0.004
	2-Me THF	5.75	0.02
	MIBK	5.04	0.01
MP100 			
	Acetonitrile	0.89	0.09
	Ethanol	2.79	0.02
	Toluene	3.47	0.02
	Ethyl Acetate	3.02	0.02
	Methyl tert butyl ether	3.07	-0.24
	2-Me THF	3.48	0.26
	MIBK	2.34	0.04

The polypropylene beads type MP1000 had a significantly higher solvent capacity and retained the least solvent after drying (<1%). None of the solvent-bead combinations displayed any difficult handling behaviour. The MP100 beads had a lower solvent capacity and, as a result of a flat face, were prone to sticking to a glass surface.

Solute Capacity of the Polypropylene Beads. The solute capacity was evaluated for four different solvents: ethanol, 2-methyl-tetrahydrofuran, acetonitrile, and ethyl acetate. For the first two solvents, scanning electron microscope (SEM) pictures were taken after each aliquot of solution to try to get a picture of how the solids build up in the beads.

The SEM photos (Figure 4) demonstrate that for up to 0.5 g of solute per gram of bead, little of the maleic acid is present on the outside of the beads, indicating that the solvent has been

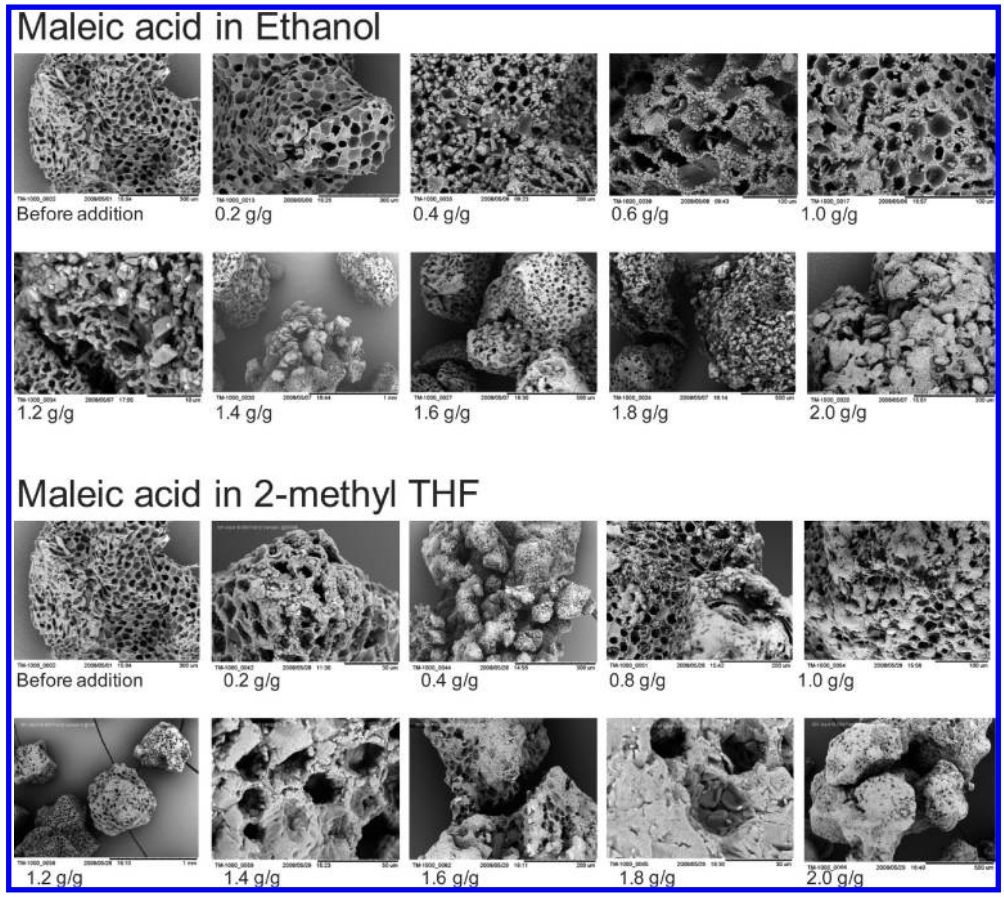


Figure 4. **Determination of the solute capacity: deposition of solute on the beads at a range of SEM magnifications.**

completely adsorbed into the beads before it evaporated. Increasing the loading to 1−1.2 g/g shows the beginning of crystal growth on the outside of the beads, but the pore structure is largely unaffected. Further increases of the loading result in complete covering of the surface of the support, thus closing the pores. Comparison of the series for Me/THF to those for ethanol shows that the outside is reached at lower loading for Me/THF. Sher et al. (2007) also observed that different solvents behave differently. This is likely to be due to the different surface tension and wetting behaviour of the different solvents.

If a significant amount of solid is present on the outside of the bead, the fresh liquid added may remain as a free liquid phase outside the support. On evaporation, the support particles can then agglomerate as the solid forming on the surfaces forms bridges between adjacent particles. To ensure the product is free-flowing it is therefore recommended to keep the loading under 1 g of solute per gram of beads.

Uniformity of Solute Distribution. This loading recommendation was used in a scale-up experiment in which 20 g of maleic acid was loaded onto 20 g of MP1000 support. To investigate the uniformity of solute distribution on the beads, six samples of about 2.5 g each were taken from final loaded beads (1 g/g). One of the six samples was scraped off the walls of the round-bottom flask that was used to load the beads. For each of the six samples the loading was analysed by differential scanning calorimetry (DSC) as well as gravimetrically by dissolution of the solute from the beads in ethanol.

As shown in Table 2, the loading on the sample of the beads that was scraped off the wall was significantly higher, indicating

Table 2. **Variation of solute loading for a range of samples of the same SSE batch**

sample	loading based on DSC data (g/g)	loading based on loss of mass (g/g)	loading based on mass dissolved (g/g)
6 (walls)	3.46	3.46	4.88
1	1.12	1.02	1.37
2	0.95	0.97	1.49
3	1.06	1.00	1.48
4	1.06	0.96	1.82
5	1.18	0.96	2.44
average	1.07	0.98	1.72
standard deviation	0.09	0.02	0.44

that even though no wetting of the wall was observed there is enrichment. The bead loading as measured by mass lost and by DSC was very consistent: the average was close to the value of 1 g/g. However, the gravimetric recovery of the material dissolved on the beads show that this technique gives inconsistent recoveries. We have not attempted to identify the experimental error that led to this variability.

From the evidence described above, it appears that the nonuniformity in the distribution of maleic acid onto the beads can be explained by the presence of higher levels of maleic acid in the beads scraped off the walls. This is probably caused by the equipment configuration and operating parameters used to load the beads in this instance. Alternative processing equipment could be used to overcome some of the limitations of the rotavap setup used in this work. Carefully controlling the solution addition rate to prevent free solution getting to the vessel walls could prevent beads sticking to the walls.

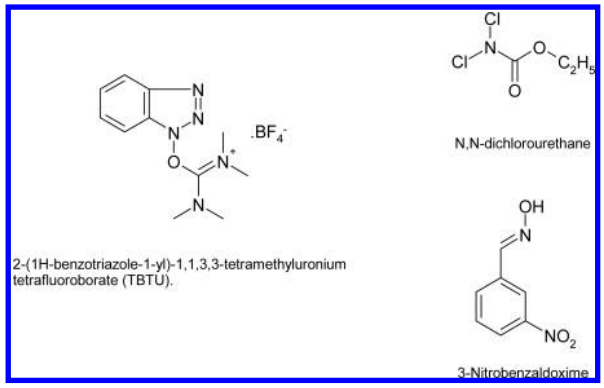


Figure 5. **Thermally unstable compounds.**

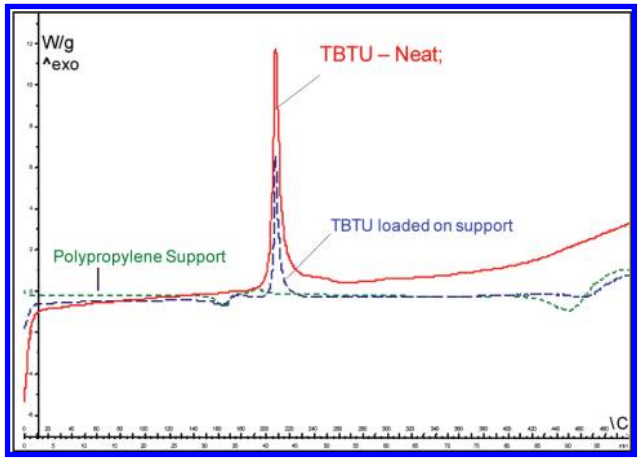


Figure 6. **DSC for TBTU showing that the beads do not alter the onset temperature of the thermal event. Note the endotherm at 150 °C is due to the polypropylene matrix.**

Thermal Stability Enhancement by the Polypropylene Beads. Together with the lack of purification, the main drawback of evaporation to dryness is the risk of thermal instability of the concentrated residue. This thermal instability can be due to the much higher concentration of reactive reagents and catalysts in the reduced liquors. One of the key advantages that we envisaged was the reduction of this risk in the SSE process due to the fact that the residue is distributed over an equivalent mass of inert solid.

To demonstrate this, 4 g of each of the thermally active compounds shown in Figure 5 was loaded onto 4 g of beads (1 g/g loading). The thermal stability of the loaded beads was assessed using differential scanning calorimetry (DSC) and accelerating rate calorimetry (ARC).

Comparing the DSC traces for TBTU and 3-nitrobenzaldoxime (see Figure 6 for TBTU) indicated that the extent of a thermal event is not affected by loading the compounds onto the beads; i.e. 1 g of compound releases the same amount of energy as it decomposes whether it is diluted by the beads or not. It also shows that the onset temperature is not affected by the presence of the beads. This is of course not unexpected as the beads only provide an inert matrix.

The beads that were loaded with *N*,*N*-dichloro-urethane had the same thermal activity as the neat beads, despite the fact that the beads had gained weight. This suggests that either the compound had already decomposed during the bead loading operation, leaving behind a residue that was thermally stable in the temperature range examined by the DSC, or that the compound had somehow reacted with the beads and formed a thermally stable species.

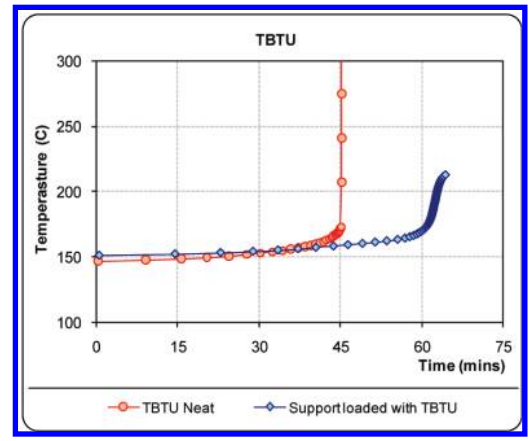


Figure 7. **Output from the ARC test for TBTU. The material on the loaded beads has a significantly longer induction time for the adiabatic run away.**

The ARC works by heating up the sample by 5 K and then holding for 30 min or until a thermal event has completed. The sample is then heated again by 5 K and held, and the process is repeated until either the sample is destroyed or the maximum temperature is reached. Figure 7 shows the responses for neat TBTU and for TBTU loaded onto beads. Similar results were seen with 3-nitrobenzaldoxime. The ARC results show that the compounds are significantly less likely to suffer thermal runaway as the beads act as a heat sink, thus, lowering the temperature rise and slowing down the rate of decomposition compared to that with compound alone. Again, the onset temperature is not significantly affected.

Recovery of Solutes from the Polypropylene Beads. Maleic acid has been recovered off the loaded beads (2.5 g/g) using (i) water, (ii) 10 vol % ethanol in water, and (iii) 5 vol % water in acetonitrile. The beds were filtered off only after the pH of the solution stabilised. This took about 20 min. The total amount of maleic acid recovered compared with the expected maleic acid content varies from one solvent to the next. This is probably due to the variability in the gravimetric method as discussed before. In any case, it appears that almost all the available maleic acid is recovered into the first two or three solvent washes. The full results are tabulated in Table 3.

In an alternative study, the dissolution of 3-nitrobenzaldoxime from the support was followed using an in situ UV probe. The normalised absorbance at 250 nm as a function of time is plotted in Figure 8. The graph shows 80% has dissolved after 75s, increasing to 90% after 10 min and >95% after 25 min. These time scales are comparable with the dissolution time for maleic acid loaded beads as was observed from the stabilisation of the pH.

Experimental Section

Materials. ACCUREL MP1000 Microporous PP homopolymer powder and ACCUREL MP100 Microporous PP homopolymer pellets (Membrana GmbH, Obernburg, Germany). Laboratory grade maleic acid and solvents were used. The thermally unstable compounds were 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) dissolved in acetone, *N*,*N*-dichlorourethane dissolved in ethanol, and

Table 3. **Recovery of material for a series of support washes**

	mass of maleic acid recovered (g/g support)		
aliquot no.	water	water/ethanol (90:10)	acetonitrile/ water (95:5)
1	1.013	1.476	1.506
2	0.084	0.124	0.301
3	0.011	0.018	0.045
4	0.010	0.004	0.003
5	0.014	0.002	0.002
6	0.017	0.002	0.006
7	0.002	0.003	0.001
8	0.002	0.002	
9	0.002	0.002	
10	0.002		
11	0.004		
total (g/g)	1.161	1.631	1.865
expected content	2.500	2.500	2.500
	46%	65%	75%

3-nitrobenzaldoxime dissolved in acetone. Note that *N*,*N*-dichloro-urethane is an oil.

Determination of Beads Solvent Loading Capacity. The solvent capacity of polypropylene beads was determined by putting approx. 500 mg of dry polypropylene beads in a vial. Solvent was added dropwise, allowing time for the drops to be adsorbed. Whilst adding solvent, the beads were carefully observed for signs of stickiness or other behaviour that could cause handling difficulties. Solvent addition was stopped when the beads started to agglomerate, indicating liquid remained on the outer surface. The total weight of solvent was recorded.

Determination of Beads Solute Loading Capacity. The solute capacity of the beads was determined by loading 2 g of MP1000 beads into a rotary evaporator. The pressure was then reduced to 250 mbar, and the temperature of the heater bath was set at 40 °C. A 2-mL aliquots of 210 and 185 mg/mL maleic acid in ethanol and 2-methyl-tetrahydrofuran, respectively, were charged, and 10 min was allowed for the solvent to be distilled off. A sample was taken for SEM, and the addition was repeated until a total of 18 and 20 mL of solution, respectively (1.9 g maleic acid/g beads), was added. Afterwards the beads loaded with solvent were dried overnight in a vacuum oven to assess the ease of removal of the solvent from the beads. For solvents acetonitrile and ethyl acetate, the maleic acid solution strengths were 30 and 36 mg/mL, respectively; the solution was added continuously unless a separate liquid phase was observed at which point the addition was interrupted until the separate liquid phase had been adsorbed or evaporated; a total of 5 g of maleic acid was added; the bath was set at 50 °C, and the vacuum was set at 200 mbar; no samples were taken for SEM.

Small-Scale SSE. A predetermined weight of MP1000 beads was charged to a round-bottom flask of sufficient volume that the particles formed a shallow bed with a volume of up to approx 25% of the flask volume. The flask was then connected to the rotary evaporator (rotavap) set up for continuous addition. After the pressure was lowered to 200 mbar, the bath temperature was raised to the distillation temperature (typically 50 °C). The total volume of liquid was charged either via slow continuous flow or via aliquots of approximately 1 g of solvent per gram of polypropylene beads charged.

Product Loading by DSC. The bead loading was derived by measurement of the heat of melting of the pure solute ($\Delta H_{m.solute}$) and of the dry loaded beads ($\Delta H_{m.beads}$). The bead loading is the ratio $\Delta H_{m.beads}/\Delta H_{m.solute}$

Product Loading by Gravimetric Determination. A 1-g sample of loaded beads was shaken in 10 mL of solvent for 2−3 min, and the beads were filtered off. The beads were then given a second wash by shaking in 10 mL of fresh ethanol. The isolated beads were dried, and the bead loading was determined from mass of the beads before and after contact with ethanol. The two lots of ethanol filtrates were combined, and the solute content was determined gravimetrically by complete evaporation of the solvent.

Thermal Stability by ARC Test. The ARC is a commercially available adiabatic calorimeter that provides information on the heat and pressure released during a reaction/decomposition and thus the potential likelihood of a runaway reaction occurring. The sample, usually 3−4 g, is contained in a metal sphere, 2.5 cm in diameter, typically of titanium. From the data it is possible to get adiabatic temperature rise data, self-heat rate data against time or temperature, the pressure, and the pressure rate data.

Recovery of Material by Repeated Washes. To determine the quantity of solvent required to wash the solute of the beads, 1 g of loaded beads was stirred in 10 mL of solvent at ambient temperature for about 20 min. The beads were separated from the solvent, and the amount of maleic acid in the solvent was measured gravimetrically (total evaporaton). This was repeated 10 times with fresh solvent each time in order to determine when solute removal is complete.

Dissolution Rate of Solute on the Support. The dissolution of solute from the support was followed using an in situ UV probe. Two grams of loaded support (loaded at 1 g/g) was stirred into 75 mL of acetone at 20 °C in a jacketed vessel equipped with an in situ UV probe. The probe was programmed to take a spectrum every 15 s for 40 min. The absorbance at 250 nm has been normalised against the absorbance of 1 g of solute in 75 mL of acetone.

Scale-Up of Solid Supported Evaporation

The work presented in this paper is done at scales up to 20 g solute or 40 g of loaded support. The technology is simple, however, and it is easy to see how larger 20-L rotavaps commonly available in kilo-scale laboratories can be used to accommodate solid supported evaporation. In the pharmaceutical industry the SSE technique can have a significant impact on the development time of potential products where fast delivery is important. However, as long-term processes are being developed and there is time and resource to develop crystallisation processes that yield high-purity product, this technology, at larger scale, may be less attractive.

Another area in which this technology may find application is continuous processing. Due to current trends in "flow chemisty", chemistry departments are working on production processes that rely on control of the reaction zone that can only be achieved in continuous reactors. Several of such reactors

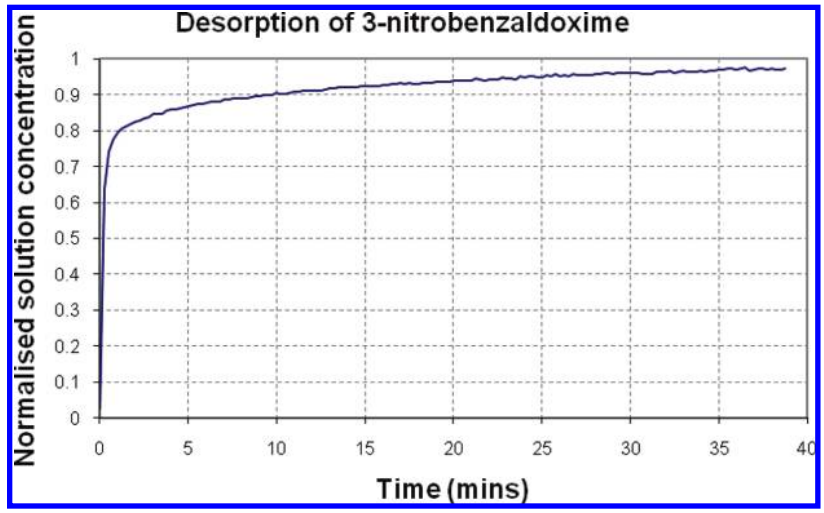


Figure 8. **Dissolution from the loaded solid support followed by an in situ UV probe.**

are now available at a range of scales (Vapourtec (2010),[7] Uniqsys (2010),[8] Alfa Laval (2010)[9]). Workup of these processes is typically still done in batch mode. Solid supported evaporation is an isolation technology that fits seamlessly with the continuous reactors. One can now envision an equipment train consisting of (i) feed vessels and pumps, (ii) continuous reactor, (iii) in-line filter, and (iv) solid supported evaporator. Such a train promises a wholly continuous process that has a general applicability and, as such, is a viable alternative to the conventional batch reactor.

If in the future such processes become generally established, then scale-up to pilot-plant scale is also not inconceivable, although here one would be looking at systems that continuously feed in fresh support and remove the solute-loaded particles. A continuous granulator is an example of a system that has a very similar function.

This process is also similar to the impregnation and drying method for the synthesis of supported catalysts described by Dillon et al. (2003):[10] porous support bodies are impregnated with a solution of the metal (oxide) precursor followed by evaporation of the solvent. They state that this is the most used synthesis route with the most attractive feature being its simplicity in practical execution on both laboratory and industrial scales. This confirms our view that scale-up of SSE is relatively easy; the unit operation is similar to granulation, or even a drying operation for which equipment is readily available. At 0.1−100 L scale the operation can be done in rotary evaporators.

Conclusions

Solid supported evaporation is a new concept for the isolation of pharmaceutical and fine chemical intermediates. A solution is absorbed onto a porous solid support, and the solvent is distilled off under vacuum, resulting in isolation of the solute inside the porous support. The equipment required is simple and commonly available in R&D laboratories which facilitates scale down and development.

We identified a suitable support and determined (i) the maximum solvent loading and (ii) the optimal solute loading, the maximum loading without excessive buildup of solute on the surface of the support. Thermal analysis of the loaded support indicates that the onset temperature and magnitude of thermal events are not altered. This suggests the absence of interaction between the polymer support and the solute for the cases studied. Isothermal tests, however, indicated that the induction time for degradation was significantly longer than that for neat material. This is due to the inert beads acting as a heat sink which lowers the temperature rise and hence slows down the rate of decomposition compared to that for compound alone. Isolating thermally unstable mixtures via solid supported evaporation is a safer alternative to evaporation to dryness.

Recovery of the solute from the support is accomplished simply by washing the beads with a suitable solvent. Two or three washes are sufficient to remove more than 95% of the material.

Acknowledgment

We thank Saurabh Chitre for his assistance in the experimental work, Paul Gillespie for the safety assessment, and Andy Godfrey for his comments and support. We also thank Nicola Hubbard from Plastic Technology Service for the information and samples of the solid supports that have been supplied.

Received for review July 27, 2010.

OP100207E

(7) Vapourtec. http://www.vapourtec.co.uk/publications (accessed Nov 2, 2010).
(8) Uniqsys. http://www.uniqsis.com/applications (accessed Nov 2, 2010).
(9) Alfa Laval. http://www.alfalaval.com/campaigns/stepintoart/downloads-links/pages/downloads-links.aspx (accessed Nov 2, 2010).
(10) van Dillen, A.J.; Terörde, R. J. A. M.; Lensveld, D. J.; Geus, J. W.; de Jong, K. P. *J. Catal.* **2003**, *216*, 257–264.